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# Section 1. Biology

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## DISTRIBUTION OF *HELICOBACTER PYLORI* GENOTYPES IN TWO AREAS OF UZBEKISTAN WITH DIFFERENT GASTRIC CANCER RISK

**Abstract.** Genotyping of *H.pylori* from the region of Aral Sea, a zone of ecological disaster with a high prevalence of gastric cancer, was compared with Tashkent – region with low gastric cancer rate. PCR analysis revealed that 66,1% samples from the Aral Sea and 84.2% samples from Tashkent was CagA positive. In Tashkent, we found the prevalence of VacAs1 m2 alleles and VacAs1 m1 alleles from Khorezm region. In most samples from Khorezm had mixed genotype of IceA1/IceA2 (80%), whereas in Tashkent mostly IceA1 allele was distributed. The predominant genotypes in high-risk of gastric cancer area (Aral Sea) were cagA+/vacAs1m1/iceA1/iceA2 and in low-risk Tashkent, the district was cagA+/vacAs1m2/iceA1, which correspond to the less aggressive strains. Comparison of *H.pylori* virulence genes distributed in high- and low-risk area of gastric cancer in Uzbekistan showed the differences between genotypes, more aggressive form of *H.pylori* was revealed in the Aral Sea region.

**Keywords:** *Helicobacter pylori*, the gene of virulence, CagA, VacA, IceA, gastric cancer, genotypes.

**Background**

*Helicobacter pylori* is a gram-negative pathogen that colonizes the human stomach. *H. pylori* colonization results in a persistent, lifelong infection if left untreated [1]. The infection of *H. pylori* is associated with duodenal ulcer, gastric ulcers, adenocarcinoma of the distal stomach and MALT- lymphoma [2].

Each year, at least 7 million cases of these diseases occur worldwide, resulting in hundreds of thousands of deaths. 754000 people around the world died from gastric cancer in 2015 and 70% of those makes to poor countries. In 2016 alone, 900000 people were diagnosed with gastric cancer. By 2035, almost 15 million cancer-related deaths per year are forecast to occur. More than half of the world population is infected with *H. pylori*, but not all individuals develop associated diseases. This may be related to a complex of environmental factors, host characteristics, and bacterial virulence determinants. Several virulence-associated factors of *H. pylori* were associated with clinical outcomes of the infection [3]. Previous studies in Uzbekistan showed a significant relationship between gastric diseases including gastric cancer or precancerous lesions and *H. pylori* infection [4]. Consequently, it is important to know the genetic diversity of H. pylori strains in Uzbekistan, a region with a high frequency of *H. pylori*-induced gastric disease.

Aral Sea region of Uzbekistan become a zone of ecological disaster and known as a high-risk area of gastric cancer. The case of gastric cancer in this region is three times more than in Tashkent – low cancer risk area. But whether the high

incidence of gastric cancer in the high-risk area has a relationship with specific *H. pylori* genotype is unclear. The aim of this study was to compare the distribution of *H pylori* genotypes in the two areas with different cancer risk and furthermore explore its geographic characteristics.

**Methods**

For this study, gastric biopsies were collected from 147 individuals including 109 cases from Aral Sea region (58 men and 51 women, 25–62 years, mean age: 42.5 years) and 38 cases from Tashkent (20 men and 18 women, 21–59 years, mean age: 44.33 years). Their biopsies were obtained during endoscopy with informed consent.

**DNA extraction from the biopsy and PCR analysis**

Isolation of DNA was obtained using the kits of Ampli Prim RIBO-PREP reagent kit (Inter Lab Service, Russia). Genotyping was performed for CagA, VacA и IceA genes, and subtypes of these genes. Genotypes were determined by polymerase chain reaction [5; 6; 7].

**Statistical analyses**

Data were analyzed using SPSS for windows version 11.0. The $\chi^2$ test or Fisher's exact test was used to assess the relationships between different areas. $P < 0.05$ was considered statistically significant.

**Results and Discussion**

A total of 147 *H.pylori* clinical isolates from two geographic areas in Uzbekistan were obtained. The high-risk group comprised 109isolates from Khorezm (Aral Sea region). The low-risk group comprised 38 strains from Tashkent.

*Detection of the cagA gene in two geographical areas*

CagA positive genotypes were found in 109 cases from total analyzed 147, that corresponds to 70%, and geographical distribution in Uzbekistan regions was: 66.1% samples from Khorezm was CagA positive, in Tashkent region, 84.2% of samples have CagA gene. CagA gene is considered as a marker for the presence of Cag PAI, which is associated with the most virulent *H.pylori* strains [8]. High prevalence of cagA-positive *H. pylori* is 90–95 % in Asian countries and 50–60% in western countries [9]. Bravo et al., also reported that a higher frequency of cagA is in patients from high risk areas of gastric cancer than in those from low risk areas of gastric cancer [10]. Some persons showed that cagA positive strains are associated with higher gastric cancer risk [11]. But in our study, there was no significant difference in cagA status between the two areas of Uzbekistan. Study of association of CagA genotype with the different type of diseases showed that in the case of gastric ulcer percent of CagA positive strains (87%) was higher compared with gastric cancer – 60.5%.

*Detection of the vacA gene in two areas*

The vacuolating cytotoxin (VacA) induces the formation of intracellular vacuoles in epithelial cell lines. Besides its direct cell-damaging effect in vitro, VacA also plays a major role in inducing cytoskeletal changes, apoptosis, suppression of epithelial proliferation, and migration [12; 13; 14; 15]. VacA also causes cell death by mitochondrial damage, via signaling pathways that are not fully defined [16]. VacA gene is present in all *H. pylori* strains and the three most extensively studied regions of heterogeneity correspond to the signal "s" region, the intermediate "i" region, and the middle "m" region. Type s1/i1/m1 forms of VacA are more active in assays of cell- vacuolating activity than are forms of VacA designated s2, i2, m2 [17; 18]. The s-region, which encodes the signal peptide, coexists as either s1 or s2 allelic types. The m-region (middle) occurs as m1 or m2 allelic types. Production of VacA is related to the mosaic structure of vacA [19]. In human stomach, strains with vacA m1 allele are associated with severe epithelial damage compared to those with m2 allele.

The presence of VacA gene was found in all samples, and distribution of VacA subtypes was s1 variant was found in 112 (76.2%) cases, s 2 in 26 (17.7%) cases. From this 84 (77.1%) samples from Khorezm region have s1 allele, and 16 (14.7%) have s2 allele of VacA gene. In Tashkent this distribution was different – s1 genotype was determined in 73.7% cases, little lower than in Khorezm and in 26.3% was found s2 variant. In 9 cases all from Khorezm "s" allele wasn't typed, probably because high mutation rates of this gene and used primers have not specificity in these cases.

In 31 cases (20.2%) we found m1 allele of VacA gene, and 82 (55.8%) samples have an m2 subtype of this gene. Among geographic area percent amount of this alleles was different and consist of 49.5% for the Khorezm region and it was much higher in Tashkent – 73.7%. In addition, we did not find vacA m genotype in 33 isolates. This is currently unexplained and may be due to the existence of additional vacA. The frequency of predominant VacA alleles found in our study was close to revealed in Thailand and China [20] but different from allele distribution in isolates from East Asia.

Studies of association of VacA genotypes with clinical outcomes showed the prevalence of s1 and m1 alleles in strains isolated from patients with gastric cancer, and in the cases of gastric ulcer was found s1 and m2 genotypes.

The results of our study demonstrate that *vacA*s1 is very common among *H. pylori* strains in Uzbekistan (76.2%), and the most frequent *H. pylori vacA* genotypes in Uzbekistan are s1/m2 (41.5%) and s1/m1/m2 (26%). In different studies, it was shown that patients infected with vacA s1m1 strains have a higher risk of carcinogenesis [21]. Type s1-m1 forms of VacA promote the death of gastric epithelial cells in vitro [22; 13; 23]. In our study, distribution of the vacA s1m1 genotype was found in the high risk areas, this may be a factor

contributing to the higher gastric cancer incidence in the Aral Sea region.

Since the *H. pylori* genome contains only one copy of the *vacA* gene, detection of multiple genotypes is indicative of the presence of several strains in one sample [24; 25]. We found a very high proportion of mixed genotypes (36%) with respect to the *vacA* gene in clinical isolates. In addition, a high incidence (up to 30%) of multiple *H. pylori* strains in single biopsy specimens was noted.

The risk of coinfection or superinfection is known to be higher in countries where the general level of infection is higher. In Uzbekistan, 90% of the adult population is infected with *H. pylori* and, in some areas, the incidence reaches 100%. However, it remains unclear whether mixed infection with several strains of *H. pylori* increases the risk of severe clinical manifestations, such as gastric ulcer or cancer. The presence of multiple-strain colonization should be considered when planning therapeutic strategies, as well as when studying the pathogenesis of *H. pylori* infection.

*Detection of IceA gene alleles*

The iceA gene has two main allelic variants, iceA1 and iceA2. IceA gene could be genotyped as iceA1 and iceA2 with specific primers. *IceA1* is upregulated upon contact of *H. pylori* with the gastric epithelium and has also been suggested as a marker for peptic ulcer disease [20; 25]. In our study IceA2 genotype was found in 9 cases, IceA1 genotype in 28 cases (19%) and mainly in 65.3% cases was found IceA1/A2 genotype, however in Tashkent region percent of mixed IceA1/A2 variant was much lower than in Khorezm and consist of 23.7% and 65.3% correspondingly.

**Conclusion**

In our study, the predominant genotypes in high-risk of gastric cancer area (Aral Sea) were cagA+/vacAs1m1/iceA1/iceA2 and in low-risk Tashkent district was cagA+/vacAs1m2/iceA1, which correspond to the less aggressive strains. Combined analysis of vacA, cagA, and iceA genotypes may permit identification of high-risk patients infected with more pathogenic *H. pylori* strains. Eventually, patients infected with such strains could be selected for prophylactic anti-*H.pylori* treatment to prevent associated gastric diseases later in life. Further studies are required to determine the epidemiological and clinical importance of *H.pylori* virulence-associated genotypes in different geographic areas in Uzbekistan.

**Competing interests**

The authors declare that they have no competing interests.

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# THE DYNAMICS OF AMYLOLYTIC ENZYME ACTIVITY IN THE CONTENT OF BLOOD AND LIVER HOMOGENATE IN RATS OF DIFFERENT AGE IN EXPERIMENTAL HYPOKINESIA CONDITION

**Abstract.** The purpose of this research is to study the dynamics of amilolytic activity changes in blood and liver homogenate in different age rats under experimental hypokinesis conditions. It was determined that on the 1–day of hypokinesia amylolytic activity in the blood of mature rats rapidly decreased relatively to the control, on the 3–, 10–day it remained in high value and on the 60–day restored at value close to the control, and also on the first day of hypokinesis amylase activity and liver homogenate of mature rats rapidly increased relatively to the control, on the 3–, 10– and 20–day it remained at high value and on the 30–, 60–day it approximated to the value of control. It was found out that on the 1st day of hypokinesia in the old rats, a sharp reduction in amilolytic activity in the blood is significantly higher than that of the control group, on the 3–, 10–day it is significantly higher than that of the control, on the 20–day it reduced again and on the 30–day it changed in restoration and on the 60–day it is at value close to the control. Besides, it was found out that on the first day of hypokinesia in the old rats, the value of amylolytic activity in the liver homogenate decreased in comparison with the control, on the 3–day it approximated to the control, on the 10–day it was higher than that of the control and on the 20–, 30, 60–day it nearly remained at value of control. It was found out that the correlation coefficient between dynamics of changing depending on hypokinesia duration of amylase activity in liver homogenate of young rats is equal to $r = 0.29$; mature rats: $r = 0.32$ an old rats: $r = 0.58$.

**Keywords**: Hypokinesia, α – amylase activity, blood, liver homogenate.

**Introduction**

It is known that fermental homeostasis is one of the major reactions to various stress factors in the body [1, p. 25–30]. Combined action of stress agents (γ–radiation, hypokinesia, etc.) indicates significant changes in the functional activity of the hemostasis system [2, p. 286–289]. Hypokinesia is one of the most common stress factors in the body, causing specific and nonspecific structure/functional changes in the body [3, p. 40]. Specifically, hypokinesis has revealed dysfunction in the nervous system, gumoral regulator, cardiovascular, respiratory, immune, antioxidant, digestive system [4, p. 5–307; 5, p. 3–10; 6, p. 10–224; 7, p. 198–205; 8, p. 3–20; 9, p. 255–267]. In turn, the study of mechanisms of hypokinesis is one of the topical issues in clinical practice [9, p. 255–267]. The research has revealed that pathogenic morpho–functional changes in the cardiovascular system were influenced by hypokinesia [4, p. 25–320]. In addition, the disorder state of the antioxidant system is influenced by hypokinesis [10, p. 387–389; 11, p. 15–462]. Especially hypokinesia of duration has proven to have a broad spectrum of complex structures/functional changes in the body [12, p. 991–998; 13, p. 2165–2176; 14, p. 845–875].

Thus, it is crucial to develop adequate approaches to study and correction of the medical/biochemical mechanisms of dysfunctional changes in the body under hypokinized conditions [12, p. 991–998; 10, p. 387–389]. Based on the information given above, the purpose of this research is to study the dynamics of amilolytic activity changes in blood and liver homogenate in different age rats under experimental hypokinesis conditions.

**Materials and methods**

Experimental hypokinesis was performed using standard methods in rats [9, p. 255–267; 15, p. 10–270; 16, p. 3; 17, p. 111–114; 18, p. 117–184; 19, p. 58–65].

The preparation of rats homogenate was carried out using standard methods [18, p. 117–184; 20, p. 351–358] (Fig. 1).

A B C D

Figure 1. Experimental hypokinesia model (A), preparation of liver homogenate (B), amylolytic activity study (C, D)

Effect of α –amylase activity in experiments was determined by means modified by Ugolev A. M., developed by Smithson-Roy [21, p. 345–544; 22, p. 192–196; 23, p. 86–89]. The amylolytic activity was determined by photoconductor method based on the amount of starch dissolved over the given time [24; p. 1228].

**Statistical analysis.** The outcomes achieved were statistically retreated by means of Excel 2003 (Microsoft Office; USA) and special program packages OriginPro v. 8.5 SR1 (EULA, Northampton, MA 01060–4401, USA). The results were given in the form of $M \pm m$ of the results experiments carried out repeatedly $n$ times and indicate $M$ – average arithmetic value and $m$ – standard mistake value. The statistical reliability of the control and experimental group values was calculated on the basis of Student $t$–scores and was statistically evaluated as reliable at < 0.05 [25, p. 12–351; 26, p. 23–284; 27, p. 15–144; 28, p. 24–459; 29; p.106; 30, p. 54–260]. In the experiments, the likelihood of a link between the dynamics of changes in the amilolytic activity in the structure of the blood and liver homogenates in the hypokinesis environment was discussed in Excel 2003 (Microsoft Office, USA) and OriginPro v. 8.5 SR1 (EULA, Northampton, MA 01060–4401, USA) the Pyron Correlation coefficient was calculated using the following formula with the mathematical statistical program (Coefficient correlation of Pirson // [Electronic resource]. URL: http://www.machinelearning.ru /wiki/index.php?title… Date of application: 20/01/2019)

$$r = \frac{n\sum xy - (\sum x) - (\sum y)}{\sqrt{\left[n\sum x^2 - (\sum x)^2\right]\left[n\sum y^2 - (\sum y)^2\right]}}$$

**Results and Discussion**

Amylolytic enzymes in the blood are one of the most important indicators of the functional activity of the digestive system in terms of clarity in physiological norms/pathological conditions [31, p. 17–25; 32, p. 17–22]. The experiments showed that amilolytic activity of hypokinesia in the bloodstream in young rats increased in 1–, 3–, 10–, 20– and 30–days for 12.1 ± 0.1; 122 ± 1.2; 257 ± 3.7; 24 ± 2.3% and 143 ± 2.6% respectively. In addition to this, in the 60$^{th}$ day of experimental hypokinesia, amylolytic activity in the bloodstream in young rats was restored to the initial state (97 ± 2.7%), which was close to the control group (Tabl. 1).

The subsequent experiments showed that in the liver homogenate of young rats increased in 1–, 3–, 10–, 20– and 30–days of experimental hypokinesia amylolytic activity increaded to 16 ± 3; 35 ± 2.1; 1 ± 0.8% respectively with the control. Also, in the 20–, 30–, and 60–day experimental hypokinesia – 22 ± 2.6, respectively; 9 ± 1.2; A decrease of 7 ± 1.2% was observed (Tabl 1).

Table 1. – Effects of hypokinesia on amylase activity in the structure of young rats and their liver homogenate ($M \pm m$)

| Hypokinesia duration (day) | Blood content (mg/min./g) | | Liver homogenate (mg/min./g) | |
|---|---|---|---|---|
| | Control group | Experimental group | Control group | Experimental group |
| *1* | *2* | *3* | *4* | *5* |
| 1 | $\frac{111 \pm 0,7}{100}$ | $\frac{101 \pm 0,7}{12,1 \pm 0,9(0,001)}$ | $\frac{2372 \pm 20}{100}$ | $\frac{2757 \pm 679(0,01)}{116 \pm 3(0,01)}$ |
| 3 | $\frac{71,9 \pm 2,0}{100}$ | $\frac{160 \pm 1,2(0,001)}{222 \pm 1,0(0,001)}$ | $\frac{2469 \pm 41}{100}$ | $\frac{3338 \pm 70(0,001)}{135 \pm 2,1(0,001)}$ |
| 10 | $\frac{87,0 \pm 1,1}{100}$ | $\frac{311 \pm 3,3(0,001)}{357 \pm 3,7(0,001)}$ | $\frac{2736 \pm 11}{100}$ | $\frac{2766 \pm 22(0,1)}{101 \pm 0,8(0,1)}$ |

| *1* | *2* | *3* | *4* | *5* |
|---|---|---|---|---|
| 20 | $\frac{106 \pm 1,5}{100}$ | $\frac{131 \pm 3,3(0,001)}{124 \pm 2,3(0,001)}$ | $\frac{2965 \pm 15}{100}$ | $\frac{2330 \pm 60(0,01)}{78 \pm 2,6(0,001)}$ |
| 30 | $\frac{108,3 \pm 2,0}{100}$ | $\frac{155 \pm 4,0(0,001)}{143 \pm 2,6(0,001)}$ | $\frac{2323 \pm 17}{100}$ | $\frac{2112 \pm 26(0.01)}{91 \pm 1,2(0,01)}$ |
| 60 | $\frac{111,2 \pm 3,0}{100}$ | $\frac{108 \pm 3,2(0,1)}{97 \pm 2,7(0,1)}$ | $\frac{2407 \pm 12}{100}$ | $\frac{2229 \pm 27(0,01)}{93 \pm 1,2(0,01)}$ |

*Note: The numerators show amylase activeness (absolute value); the denominators show their indicators in percentage; statistic reliability degree of experimental group value (p) versus control groupis in the brackets (In all cases $p < 0.05$; $n = 3–6$)*

Based on the results of the study, it was noted that the dynamics of changes in the duration of hypokinesis (1–60 days) of amylase activity in the young rats blood and liver homogenates have specific characteristics (Fig. 2. A, B). At the same time, in the 1$^{st}$, 3$^{rd}$, and 10$^{th}$ days of hypokinesia, an increase in amylolytic activity in the bloodstream was observed with a linear description in the rats (maximal up to about 3.5 times in control), and 20–, 30–, and 60–days (Fig. 2 A).

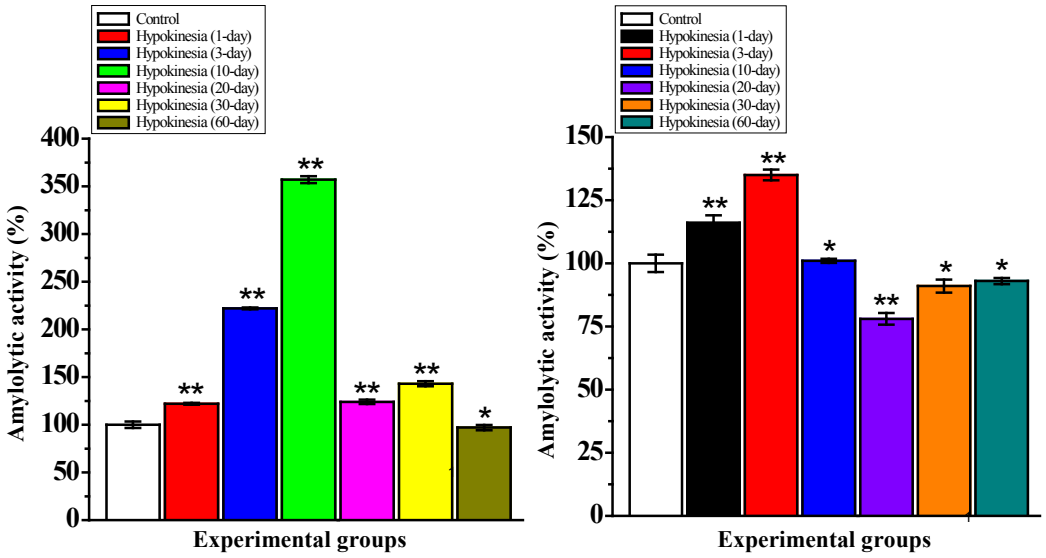


Figure 2. Dynamics of change in amylase activity hypokinesis duration (1–60 days) in the blood (A) and liver homogenat of young rats (B). The ordinate axis shows the percentage of amylase expressed in percentage to 100% controlled. * – relatively to the control $p < 0.001$, ** – $p < 0.01$ ($n$ =3–6)

Also, it was noted that in the young rats, the amilolytic activity in the liver has a dynamics of change due to the hypokinesis duration. In particular, the increase in the amylolytic activity in the liver homogenate within the 1$^{st}$, 3$^{rd}$ and 3$^{rd}$ days (maximally up to ~16–35% in control), return to the control group for 10 days, decrease to 22 ± 2.6% in the 20–day period and 30– and approximated to control values for 60 days, but lower (9 ± 1.2 and 7 ± 1.2% respectively) in the control (Fig. 2 B).

Also, the coefficient of correlation between the change in the amilolytic activity value of hypokinesis in the liver homogenate in young rats was $r = 0.29$ (Fig. 3).

Amylolytic activity in the liver or gastrointestinal tract; abscissa axis is the amilolytic activity of the blood ($n = 3–6$).

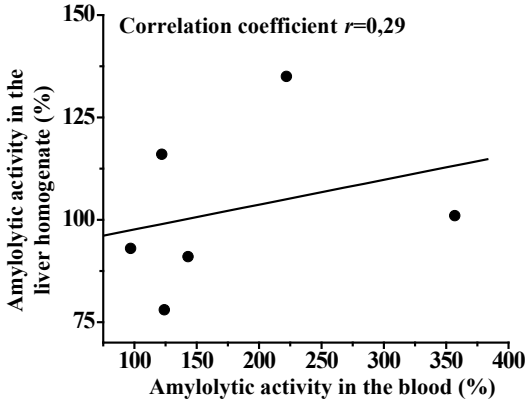


Figure 3. The coefficient of correlation between the dynamics of change due to the hypokinesis duration of the amilolytic activity in the liver structure of the young rats

In the experimental experimental group, it was determined that amylolytic activity of mature rats was ~8.3 times higher in the blood of mature rats and ~1.7 times less in the liver. The experiments showed that amylolytic enzyme activity in blood of mature rats decreased by 60 ± 1% than the control on the 1–day, on 3–, 10–day increased by 27 ± 1.4 and 17 ± 0.8%, on 20–day it returned to the control value and on 30–day and 60–day it came close to the control value (respectively – 99 ± 0.7; 101 ± 1%) (Tabl. 2).

Table 2. – The effect of hypokinesia on amylase activity in blood structure and liver homogenate of mature rats ($M \pm m$)

| Hypokinesia duration (day) | Blood content (mg/min./g) | | Liver homogenate (mg/min./g) | |
|---|---|---|---|---|
| | Control group | Experimental group | Control group | Experimental group |
| 1 | $\frac{784,2 \pm 6,2}{100}$ | $\frac{468,8 \pm 3(0,001)}{60 \pm 1,0(0,001)}$ | $\frac{1401,8 \pm 14}{100}$ | $\frac{3233 \pm 12(0,001)}{230 \pm 0,1(0,001)}$ |
| 3 | $\frac{780 \pm 6,4}{100}$ | $\frac{992,8 \pm 14(0,001)}{127 \pm 1,4(0,001)}$ | $\frac{1500 \pm 6}{100}$ | $\frac{2214 \pm 18(0,001)}{148 \pm 0,8(0,001)}$ |
| 10 | $\frac{790 \pm 7}{100}$ | $\frac{923,8 \pm 6(0,001)}{117 \pm 0,8(0,001)}$ | $\frac{1519,8 \pm 7}{100}$ | $\frac{3240 \pm 16(0,001)}{213 \pm 1,1(0,001)}$ |
| 20 | $\frac{750 \pm 6}{100}$ | $\frac{745 \pm 7(0,1)}{100 \pm 0,8(0,1)}$ | $\frac{1526 \pm 8}{100}$ | $\frac{1861 \pm 9(0,001)}{122 \pm 0,6(0,001)}$ |
| 30 | $\frac{730 \pm 4}{100}$ | $\frac{722 \pm 6(0,1)}{99 \pm 0,7(0,1)}$ | $\frac{1604 \pm 10}{100}$ | $\frac{1500 \pm 6(0,001)}{93 \pm 1,0(0,001)}$ |
| 60 | $\frac{730 \pm 6}{100}$ | $\frac{738,6 \pm 10(0,1)}{101 \pm 1(0,1)}$ | $\frac{1670 \pm 11}{100}$ | $\frac{1617 \pm 7(0,05)}{97 \pm 0,9(0,05)}$ |

*Note: The numerators show amylase activeness (absolute value); the denominators show their indicators in percentage; statistic reliability degree of experimental group value (p) versus control group is in the brackets (In all cases p < 0.05; n = 3–5)*

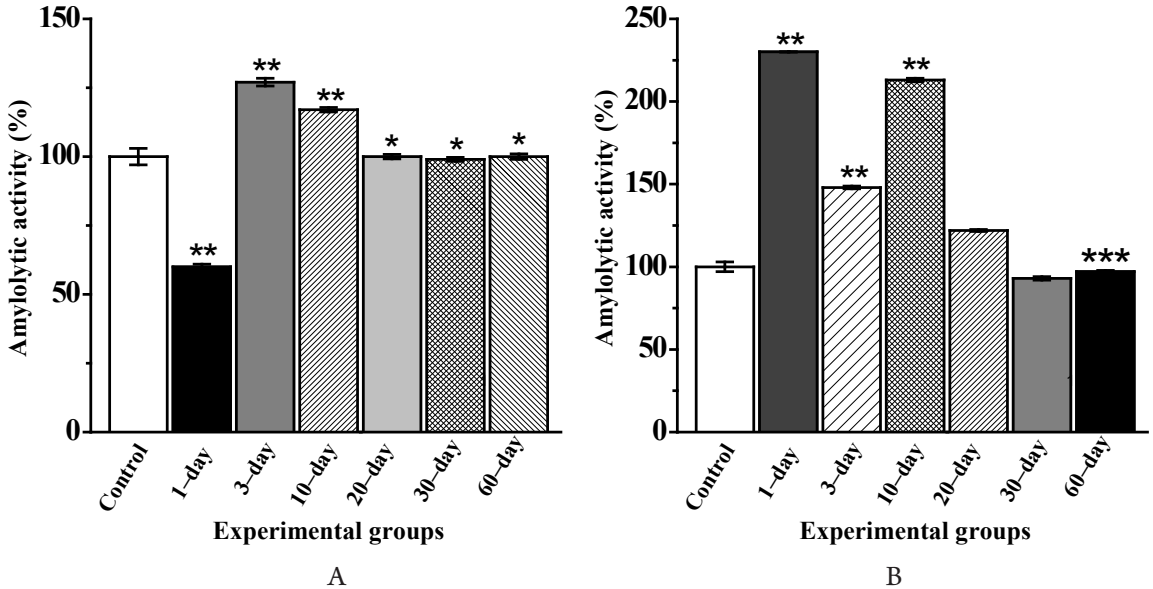


Figure 4. Dynamics of changing depending on hypokinesia duration (1–60 day) of amylase activity in blood and liver homogenate of mature rats. The ordinate axis shows the percentage of amylase expressed in percentage to 100% in those in control group. * – relatively to the control $p < 0.001$, ** – $p < 0.01$ ($n = 3–5$)

The following experiments showed that on 1–, 3–, 10– and 20–days of experimental hypokinesia amylolytic enzyme activity in liver homogenate of mature rats increased by 130 ± 0.1; 48 ± 0.8; 113 ± 1.1; 22 ± 0.6% respectively to the control, and also on 30– and 60–days it decreased by – 7 ± 7 ва 3 ± ± 0.9% respectively to the control (Tabl. 2).

At the next stage, the dynamics of changes in the duration of the hypokinesis duration (1–60 days) of amylase activity in blood of the mature rats and liver hepatic system were analyzed (Fig. 4 A, B). In particular, it was observed that hypokinesia had a significant decrease in amilolytic activity in the bloodstream on day 1, significantly high on 3–, 10–day and restored at a controlled rate on 60–day (Fig. 4 A).

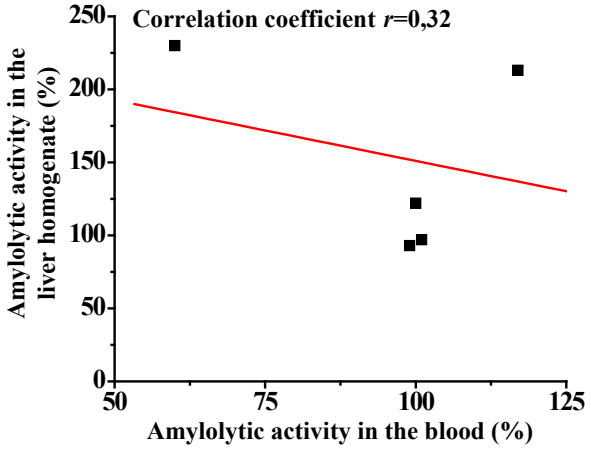


Figure 5. The coefficient of correlation between the dynamics of change due to the hypokinesis duration of the amilolytic activity in the liver structure of mature rats

Amylolytic activity in the liver or gastrointestinal tract; abscissa axis is the amilolytic activity of the blood ($n$ = 3–5)

Also, it was found that amylase activity in the blood and liver of mature rats was significantly higher on the first day of hypokinesia than those in control groups, and it was found to be high on 3–, 10– and 20–day and approximated to control value on 30–60$^{th}$ day (Fig. 4 B).

The correlation coefficient between the change in the amylolytic activity value in the liver homogenate of mature rats and the dynamics of change due to the hypokinesis duration is $r$ = 0.32 (Fig. 5).

The experiments showed that the value of amilolytic activity in blood of old rats in the control group is ~7.7 times higher, amilolytic activity in the liver homogenate is ~1.4 times higher in comparison with young rats. In the experiments it was found out that on the 1–day of experimental hypokinesia amylolitic activity in blood of old rats is 61 ± 0.9% lower than the control, and on the 3–, 10–day it increased in –12 ± 1.1 and 11 ± 1.1% in comparison with the control, on the 20–, 30–day it changed up to – 59 ± 1.2; 73 ± 1,1 respectively to those in control group and on the 60–day it approximated to the control value in 96 ± 0.8% (Tabl. 3).

Further experiments showed that on the 1– and 3–days amylolytic enzyme activity in the liver homogenate of old rats decreased from – 70 ± 1.1 up to 95 ± 0.6% respectively to those in control group, on the 10–days it increased in 20 ± 1.7% than those in control group, on the 20–, 30–day it equalized with the control value and on the 60–day it was higher in 5 ± 1.1% (Tabl. 3).

Table 3.– The effect of hypokinesia on amylase activity in blood and liver homogenate of old rats ($M \pm m$)

| Hypokinesia duration (day) | Blood content (mg/min./g) | | Liver homogenate (mg/min./g) | |
|---|---|---|---|---|
| | Control group | Experimental group | Control group | Experimental group |
| 1 | $\frac{800 \pm 19}{100}$ | $\frac{48,5 \pm 7,0(0,001)}{61 \pm 0,9(0,001)}$ | $\frac{3630 \pm 45}{100}$ | $\frac{5214 \pm 46(0,001)}{70 \pm 1,1(0,001)}$ |
| 3 | $\frac{815 \pm 17}{100}$ | $\frac{913,0 \pm 10(0,01)}{112 \pm 1,1(0,001)}$ | $\frac{3670 \pm 63}{100}$ | $\frac{3487 \pm 19(0,05)}{95 \pm 0,6(0,001)}$ |
| 10 | $\frac{836 \pm 18}{100}$ | $\frac{928,6 \pm 9,0(0,001)}{111,0 \pm 1,1(0,001)}$ | $\frac{3665 \pm 60}{100}$ | $\frac{4409 \pm 60(0,001)}{120 \pm 1,7(0,001)}$ |
| 20 | $\frac{717 \pm 16}{100}$ | $\frac{4292 \pm 9,0(0,001)}{59 \pm 1,2(0,001)}$ | $\frac{3710 \pm 56}{100}$ | $\frac{3714 \pm 27(0,1)}{100 \pm 0,8(0,1)}$ |
| 30 | $\frac{720 \pm 15}{100}$ | $\frac{527,0 \pm 8,0(0,001)}{73 \pm 1,1(0,001)}$ | $\frac{3620 \pm 60}{100}$ | $\frac{3644 \pm 25(0,1)}{100 \pm 0,7(0,1)}$ |
| 60 | $\frac{710 \pm 18}{100}$ | $\frac{684,2 \pm 6,0(0,1)}{96 \pm 0,8(0,1)}$ | $\frac{3567 \pm 60}{100}$ | $\frac{3739 \pm 40(0,1)}{105 \pm 1,1(0,1)}$ |

*Note: The numerators show amylase activeness (absolute value); the denominators show their indicators in percentage; statistic reliability degree of experimental group value (p) versus control group is in the brackets (In all cases p < 0.05; n = 4)*

Based on the achieved results, when the dynamics of changes in the duration of the hypokinesis duration (1–60 days) of amylase activity in blood and liver hepatic system of the old rats were analyzed, it was observed that hypokinesia had a significant decrease in amilolytic activity in the bloodstream of old rats on day 1, significantly high on

3–, 10–day and it decreased again on 20–day and restored on 30–day and it is at a controlled rate on 60–day (Fig. 6 A).

Also, it was found that amylase activity in the blood and liver of old rats decreased on the first day in hypokinesia condition than those in control groups, and it approximated to those in control on 3–day and it was higher than those in control on 10–day and it at a controlled rate on 20–, 30, 60–day (Fig. 6 B).

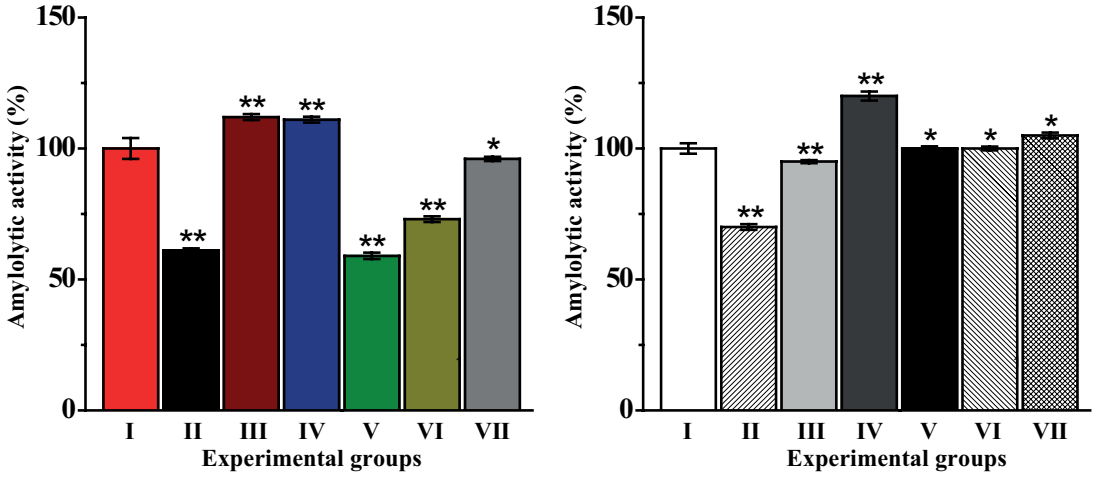


Figure 6. Dynamics of changing depending on hypokinesia duration (1–60 day) of amylase activity in blood (A) and liver homogenate (B) of old rats. The ordinate axis shows the percentage of amylase expressed in percentage to 100% controlled. The abscissa axis expresses experiment groups (I – control; II – 1–day; III – 3–day; IV – 10–day; V – 20–day; VI – 30–day; VII – 60–day). * – relatively to the control $p < 0.001$, ** – $p < 0.01$ ($n = 4$)

It is determined that the correlation coefficient between dynamics of changing depending on hypokinesia duration of amylase activity liver homogenate of old rats is equal to $r = 0.58$. (Fig. 7).

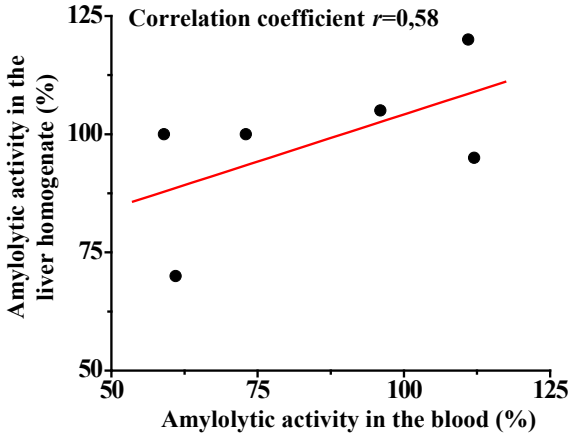


Figure 7. The correlation coefficient between dynamics of changing depending on hypokinesia duration of amylase activity in liver homogenate of old rats

The ordinate axis shows amylase activity in liver homogenate; The abscissa axis shows amylase activity in blood ($n = 4$).

It is recorded that significant changes occur in the structure/functional state of the liver in pathological cases in the body [29, p. 8].

Specifically, it is determined that in the initial study of hypokinesis, the activity of the dehydrogenase enzymes in the liver in the citrate cycle increased, and the activity of liver enzymes in the subsequent stages decreased [33, p. 309–315].

The effect of hypokinesis on the liver and myocardium tissue was determined by the diminished antioxidant system enzymes and glycogen levels (energy deficiency) and the dysfunction of antioxidant system enzymes [17, p. 11–114; 18, p. 17–184].

In general, the effect of hypokinesis on the activity of almost all functional systems in the body is noted [34, p. 4–18; 35, p. 3–40]. In its turn, biological organisms are characterized by various stress–factors, including hypokinesis response, with the function of stress–relieving and stress–limiting systems [36, p. 20–452].

In hypokinesia, the hypothalamic–hypophysic–corticoid system, which is activated by stress is activated and the organism reacts to the condition. The increase in corticosterone concentration in blood determines the specific condition of the rate of hypersus in hypochinized conditions. Also, the influence of endogenous opioids directed against hypokinesis ($\alpha$ –, $\beta$ –endorphins, methenephaline, etc.) in the body is activated [19, p. 58–65].

The experimental hypokinesia (1–60 days) may be explained by the difference in the dynamics of amilolytic activity in the blood and liver in the heifoglobin of various age rats, depending on the physiological age and the degree of development of functional systems in the body, as well as the functional activity of compensatory mechanisms.

**Conclusion**

Thus, it has been established that amylolytic activity in the blood and liver homogenate of the various age rats has specific characteristics of change due to the hypokinesis duration. Moreover, it was found out that hypokinesia increased in linear classification relatively to the control of amylolytic activity in the blood of young rats on 1–, 3–, 10–days (maximal ~3,5 times than the control), and it restored in close value to the control on 20–, 30– and 60–days. In addition, Also in the young rats, it was noted that the amylolytic activity of the liver has a dynamics of change due to the hypokinesis duration, ie increase in control over the $1^{st}$, $3^{rd}$, $10^{th}$, $20^{th}$ and $30^{th}$ days, and 20–, 30–$60^{th}$ day decrease in control.

It was determined that on the 1–day of hypokinesia amylolytic activity in the blood of mature rats rapidly decreased relatively to the control, on the 3–, 10–day it remained in high value and on the 60–day restored at value close to the control, and also on the first day of hypokinesis amylase activity and liver homogenate of mature rats rapidly increased relatively to the control, on the 3–, 10– and 20–day it remained at high value and on the 30–, 60–day it approximated to the value of control.

It was found out that on the 1st day of hypokinesia in the old rats, a sharp reduction in amilolytic activity in the blood is significantly higher than that of the control group, on the 3–, 10–day it is significantly higher than that of the control, on the 20–day it reduced again and on the 30–day it changed in restoration and on the 60–day it is at value close to the control. Besides, it was found out that on the first day of hypokinesia in the old rats, the value of amylolytic activity in the liver homogenate decreased in comparison with the control, on the 3–day it approximated to the control, on the 10–day it was higher than that of the control and on the 20–, 30, 60–day it nearly remained at value of control.

It was found out that the correlation coefficient between dynamics of changing depending on hypokinesia duration of amylase activity in liver homogenate of young rats is equal to $r = 0.29$; mature rats – $r = 0.32$ an old rats – $r = 0.58$.

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# STUDY ON SOME PARAMETERS OF LIPID METABOLISM IN THE CEREBRAL TISSUES OF RATS WITH THE ROTENONE – INDUCED MODEL OF PARKINSON'S DISEASE

**Abstract.** The work was initiated to study the role of lipids, lipid peroxidation processes and antioxidant enzymes of the cerebral tissues of rats with the rotenone–induced model of Parkinson's disease. An attempt to find correlations between the behavioral performance of rats and changes in lipid compositions of the brain regions within the various periods of experimentally induced Parkinson's disease was made. Changes in the behavioral performance of the animals were established to take place on the 2$^{nd}$ day after administration of rotenone, to increase peaking on the 4$^{th}$ day, and to decrease on the 9$^{th}$ day. The changes in the behavioral performance of the animals with the neurodegenerative disease in question was found to correlate with changes in lipid composition of their cerebral tissues within the various periods of the experimentally induced neurodegenerative disease.

**Keywords:** neurodegeneration, Parkinson's disease, behavioral tests, corpus striatum, lipids, phospholipids, cholesterol, lipid peroxidation, antioxidant enzymes.

**Introduction.** Today, degenerative nerve diseases, also called neurodegenerative diseases, are figuring larger among underlying causes of work decrement and mortality increase. However, regardless of the enormous aggregation of data on the factors underlying the onset of the diseases, understanding of mechanisms accounting for the processes is far from perfect. The extracellular deposition of amyloid–beta protein followed by formation of the senile plaques inducing apoptosis, causing pathological activation of the microglia and initiation of the immune inflammation is suggested as a key aspect [1; 2; 3]. At the moment, the role of sphingomyelin cycle in apoptosis and a neurodegenerative disease's onset is under discussion [4; 5; 6]. Meanwhile, there is no the single viewpoint of the root cause for neurodegenerative diseases ultimately resulting in the death of brain cells. In our opinion, a disorder in lipid metabolism causing secondary changes in the biochemistry of amyloid–beta

protein and tau protein, as well as in reactions of oxidative stress, is a potential cause for the onset of neurodegenerative diseases.

In the view of the aforesaid, the work was initiated to study the role of lipids, lipid peroxidation processes and antioxidant system of the cerebral tissues in the rotenone–induced model of Parkinson's disease.

**Materials and methods**

The experiment was conducted on the outbred rats weighing 250–300g kept on a standard diet. Prior to administration of rotenone, all rats were subjected to the cognitive tests [7; 8]. For the purposes of experiment, all animals were divided into three groups, to name the group including intact animals (IG), the exposure group (EG) consisting of animals receiving rotenone in the vegetable oil intraperitoneally in the dose of 2.5 mg per kg of animal's weight for 7 days and the control group consisting (CG) of animals intraperitoneally receiving the vegetable oil. The McGraw Stroke Index Scale was used to evaluate the neurological status of the animals; behavioral activity was assessed be means of the open field test on the 2nd, 4th and 9th day after rotenone administration. Materials for biochemical and histological investigation from the striatum were taken on the 12th day after rotenone administration. The Bligh and Dyer method was used for total lipid extraction [9]. Fractionation of lipids was performed by the thin–layer chromatography according to M. Kates [10]. Phospholipid quantification was performed as described elsewhere [11]. The cholesterol was determined as described elsewhere [12]. The total protein was determined with modified Lowry method according to Hartree [13]. Initial levels of the substrates reactive with thiobarbituric acid were determined as described elsewhere [14]. Activity of antioxidant enzymes, such as catalase, superoxide dismutase and glutathione reductase was estimated as describes elsewhere [15; 16; 17]. Cary 60 spectrophotometer (Agilent Technologies, USA) was used to make optical measurements. Student's t–test was used to process the data.

**Results and discussion**

Prior to Parkinson's disease (PD) modeling, behavioral performance of animals was tested to evaluate main PD symptoms, such as hypokinesia, bradykinesia and oligokinesia, postural instability, unsteadiness of gait, and the accessory ones, to name muscle rigidity and tremor, which are not always present in experimental PD [18]. Total symptom intensity was scored (from 1 to 18), as well [19].

The 7–day administration of rotenone was demonstrated to cause some changes in the behavioral performance of the animals in the open field test (Table 1, Fig. 1).

Table 1.– Behavioral performance of animals in the open field test

| Behavioral activity | Groups of animals | | |
|---|---|---|---|
| | Intact (n = 5) | Control (n = 5) | Exposure (n = 15) |
| Latent period (s) | 52.3 ± 15.3 | 44.5 ± 20.3 | 90.6 ± 25.6 |
| Distance traveled (м) | 13.4 ± 7.8 | 12.5 ± 8.5 | 4.3 ± 2.1 |
| Line crossings (n) | 19.2 ± 2.0 | 17.3 ± 1.6 | 4.6 ± 1.1** |
| Squares transversed (n) | 54.5 ± 16.4 | 52.3 ± 8.3 | 8.6 ± 4.2** |
| Groomings (n) | 2.5 ± 0.5 | 2.4 ± 0.3 | 1.6 ± 0.2 |
| Frequency of head–dipping | 25.2 ± 5.4 | 20.3 ± 6.3 | 7.4 ± 3.1* |

*** statistically significant differences, significance level p < 0.05;*

** significance level p ≥ 0.05.*

Confirming the presence of PD symptoms, our findings in the open field test are consistent with the literature data reporting an elongation of the latent period in adaptation of animals to new conditions, and a reduction in the distance traveled in the playpen and as a consequence, the number of the line crossings, of the squares transversed and of the frequency of hear-dipping.

Our findings demonstrated that the main PD symptoms, such as retardation of motion and reduction in its frequency, as well as postural instability and unsteadiness of gait manifested as late as on the 2nd day after rotenone administration. The accessory ones, the rigidity, in particular, appeared on the 4th day; as to the resting tremor, the symptom could be seen in 10% of the animals on the late PD stages.

The dynamics of behavioral performance in the animals early in the course of the rotenone – induced model of Parkinson's disease seems to be a result of changes in lipid compositions of dopamine receptors' (DR) rafts and synaptic compartments with the functional properties strongly determined by the lipid compositions of the nerve cell membranes.

In the view of the above, the lipid composition, lipid peroxidation and antioxidant enzymes' activity in the brain of animals from the control and the exposure group were studied. Table 2 demonstrated changes in lipid composition of the brain tissues of rats with the rotenone – induced model of Parkinson's disease on the 2nd, 4th and 9th day of rotenone administration.

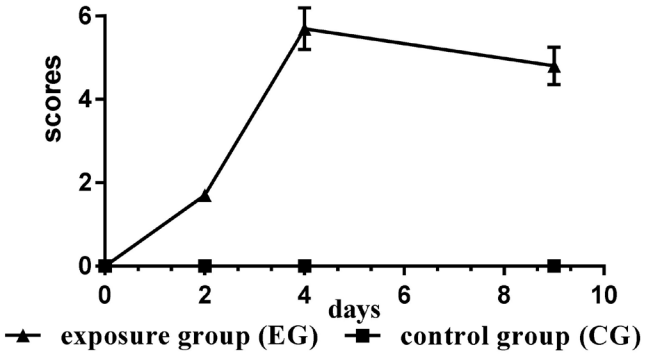


Figure 1. Changes in behavioral activity of rats according to the McGraw Stroke Index Scale on the 2nd, 4th and 9th day after administration of rotenone: *x* axis – scores in the cognitive test, *y* axis – days of experiment

As our findings demonstrated, on the 2nd day after rotenone administration concentrations of cholesterol, lysophospholipids and phosphatidic acid (PA) tended to increase while those of sphingomyelin (SPH) fractions, phosphatidylserine (PS) and phosphatidylinositol (PI) appeared to decrease. Total phospholipids changed insignificantly. On the 4th day after rotenone administration, the tendency above seemed to preserve, but the range of changes was more significant than of those seen on the 2nd day (Table 2). Thus, cholesterol, lysophospholipids and PA can be seen to increase by 8%, 50% and 14%, respectively, both SPH and PS decreased by 15%, while PI reduced by 14%. There was 8% reduction in the total phospholipids.

Table 2.– Lipid composition of striatum regions of the rat brain on the 2nd, 4th and 9th day after rotenone administration

| Phospholipids and lipids | Control group | Exposure group (n=15) | | |
|---|---|---|---|---|
| | Time after administration | 2nd day | 4th day | 9th day |
| | μg of rotenone/g of tissue | μg of rotenone/g of tissue | μg of rotenone/g of tissue | μg of rotenone/g of tissue |
| Lysophospholipids | 10.9 ± 0.5 | 12.5 ± 0.6 | 16.4 ± 0.3** | 13.1 ± 0.4** |
| SPH | 131.2 ± 3.8 | 120.7 ± 3.3 | 111.5 ± 3.2** | 118.1 ± 3.1** |
| PC | 589.38 ± 28.6 | 571.6 ± 25.6 | 554.0 ± 21.3 | 560.0 ± 20.6 |
| PS | 197.4 ± 9.5 | 177.7 ± 6.5 | 167.8 ± 5.6** | 156.4 ± 5.1** |
| PI | 91.7 ± 4.8 | 85.3 ± 3.2 | 78.9 ± 2.5 | 82.5 ± 3.1 |
| PE | 506.6 ± 22.4 | 491.4 ± 20.3 | 476.2 ± 15.6 | 486.3 ± 19.1 |
| Cardiolipin | 61.2 ± 3.1 | 60.0 ± 3.5 | 55.1 ± 2.5 | 58.1 ± 2.1 |
| PA | 15.4 ± 0.8 | 16.9 ± 1.0 | 17.6 ± 1.1 | 17.2 ± 1.2 |
| Total phospholipids | 1604.2 ± 32.6 | 1536.1 ± 30.3 | 1477.4 ± 35.2** | 1491.8 ± 36.3* |
| TC (mg/g of tissue) | 19.3 ± 0.3 | 19.8 ± 0.2 | 21.9 ± 0.1** | 21.0 ± 0.3 |

*Abbreviations: SPH – sphingomyelin, PC – phosphatidylcholine, PS – phosphatidylserine, PI – phosphatidylinositol, PE – phosphatidylethanolamine, PA – phosphatidic acid, TC – total cholesterol*

*** statistically significant differences, significance level $p < 0.05$;*

** significance level $p \geq 0.05$.*

Cholesterol was found to increase by 6% on the 9th day after rotenone administration. As compared to those in the control animals, concentrations of lysophospholipids and PA were increased, while those of SPH, PS and PI appeared to reduce, but their absolute values were lower than those observed on the 4th day after rotenone administration. Less significant changes in lipid composition of the brain tissues could be attributed to lower accessibility of the substrates by phospholipases and LPO.

The role of cholesterol, phospholipids and lipid peroxidation in the functioning of the nerves remains obscure. Some authors demonstrated the crucial role of cholesterol, phospholipids and other components in the neuroplasticity, neurility and apoptosis of the nerve cells [20; 21; 22]. According to Isakina [23], concentrations of PI and PE reduced by 30.3 and 8.4%, respectively, in the stimulated nerve as compared with those in the non–stimulated one, and the data could be the evidence for close relationship between lipid components of nerve cell membranes and neurility.

The changes we have found in phospholipids seem to affect the neuroplasticity of the synaptic part and neurility and to be a cause for changes in the behavioral performance of the animals with the rotenone–induced Parkinson's disease. LPO and antioxidant enzymes are known to have a significant effect on the lipid composition of cell membranes. With that in mind, we studied LPO products and activity of some

antioxidant enzymes in the brain regions of interest within the various periods of rotenone administration. Changes in LPO parameters and activity of antioxidant enzymes in the regions of interest on the 2nd, 4th and 9th day after administration of rotenone (in %) can be seen in (Fig. 2).

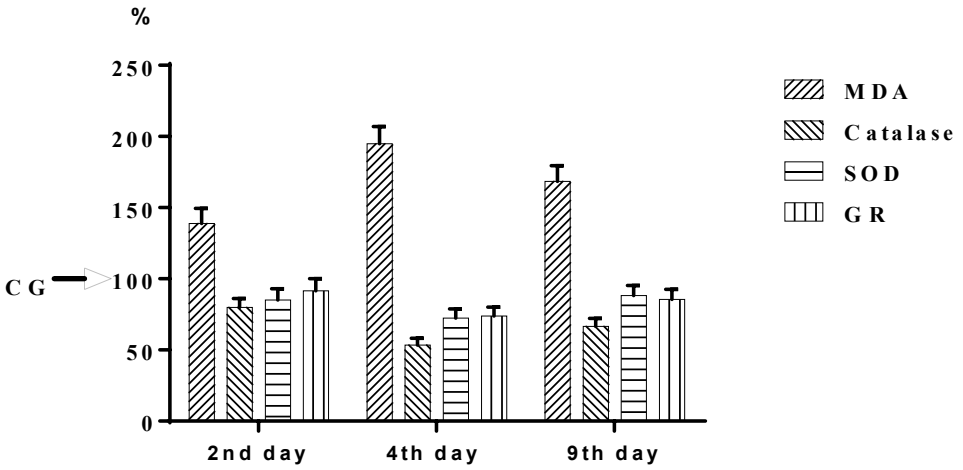


Figure 2. Changes in LPO parameters and activity of antioxidant enzymes in the striatum regions of interest on the 2nd, 4th and 9th day after administration of rotenone (in percentage of control)

MDA – malondialdehyde;
SOD – superoxide dismutase;
GR –glutathione reductase;
CG – control group.

The LPO activation could be seen as late as on the 2nd day after rotenone administration with more significant stimulation on the 4th day and slight reduction on the 9th day. Presumably, this can be explained by lower accessibility of the substrates to LPO. In the context of reduction in total phospholipids upon experimental induction of Parkinson's disease, levels of phospholipids rich with the unsaturated fatty acids seem to reduce too.

According to Isakina [23], upon nerve stimulation LPO products increased, while concentrations of diene conjugates and malondialdehyde are 20.4 and 27.7% higher, respectively, than the control ones. This can be the evidence for the fact that certain levels of LPO products is constantly present in the nerve tissue, and only a concentration threshold crossing results in neurodegenerative diseases.

In accordance with our findings, changes in lipid composition of the brain regions of interest appear as late as on the early stages of experimentally induced PD. Intensification of the changes seems to have a significant effect on the signal reception and transduction by the nerve cells to result in changes of behavioral performance of the animals with experimentally induced PD. The increase in the levels of cholesterol in the cerebral tissues upon the PD model of interest seems to be associated with its unique property to impact and maintain the microviscosity of cell membranes.

Thus, levels of cholesterol and phospholipids, as well as LPO activity and the one of antioxidant system are the most significant factors having an impact on physical properties of cell membranes facilitating optimal conditions for the receptor and synaptic parts of neurons. Changes in the parameters upon experimentally induced model of the disease seem to be a cause for changes in the behavioral activity of the animals.

**Conclusions**

To sum up, concentrations of cholesterol and phospholipids, as well as activity of the LPO and antioxidant system are the factors producing the most significant effect on physical properties of cell membranes facilitating optimal conditions for the function of receptor and synaptic parts of a neuron. Changes of the parameters generated upon experimentally induced neurodegenerative disease in animals seem to be a cause for changes in their behavioral performance.

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# INHERITANCE AND VARIABILITY OF THE TYPE OF BRANCHING WITH GEOGRAPHICALLY DISTANT AND INTERSPECIFIC HYBRIDIZATION

**Abstract.** This article provides data on the inheritance and variability of the trait "type of branching of cotton" in $F_1$ and $F_2$ hybrids of geographically distant and interspecific forms of the species G.*hirsutum* L. and G. *Mustellinum*.

**Keywords:** Inheritance, hybrids, unterminated types, geographically distant, hybridization.

There are three types of cotton branching, to name: 1) monopodial branching essentially typical of wild species, but occurring in some cultivated, monocyclic tropical samples of cotton; 2) sympodial branching with terminated and unterminated types of fruit spurs; forms with the unterminated types of sympodial branches depending on length of internodes can be subdivided into I, II, III and IV subtypes; 3) null branching where sympodial branches do not form, and bolls are developed directly in the leaf base.

The "branching type" trait changes in which are easily discernable in works on cotton taxonomy can serve as an example [1]. Presence of transitional forms by any trait should have made us conclude of polymeric character of its inheritance [3; 5], but multiple genetic studies of branching type trait, in particular, as a rule, demonstrate its monohybrid character with few exceptions when the trait is inherited by polymery [4; 8]. Based on our previous studies, we concluded that inheritance of sympodia (terminated versus unterminated) is controlled by S-s genome. I, II and III subtypes of the unterminated type of sympodia are determined by polymeric, that is, additive genes, genes promoters of simpodia growth. The branching type inheritance apparently involves 4 independent combined S-s gene alleles, such as $S_1$-$s_1$, $S_2$-$s_2$ and $S_3$-$s_3$ interacting by epistasis and polymery type [6].

Aiming at study on inheritance and variability of branching type, we included forms of the terminated and unterminated types of sympodial branches. By types of branching the hybridized forms are stark contrast, to name L-6161 line having the terminated type of branching and Yulduz breed with the 1st type of branching, 146.75003–7 breeds and L-2689 line having the 2nd type of branching and L-2777 line with the 3rd type of sympodial branching. Our findings demonstrated that upon hybridization of terminated type (L-6161) with the unterminated one (75007–3, L-2689, L-27777) samples with the unterminated type of sympodial branches specifically dominate in $F_1$ regardless of branching type they had. Upon hybridization of the unterminated and terminated types of branches in $F_2$ branching type ratio was 1: 2: 1 (where 1, unterminated type making 25%, 2, unterminated II–III type making 50%, 1, terminated I type making 25%). Hybridization of two breeds with similar types of sympodial branches yielded hybrids with the sympodial branches similar to their parent forms. Hybrid combinations resulting from hybridization of L-2777 line with the 3rd type of sympodial branching and 146 breed with the 2nd type of sympodial branching had the 3rd type of sympodial branching. However, other hybrid combinations resulting from hybridization of L-2777 line having the 3rd type of branching with other samples of cotton (Yulduz breed having the 1st type of sympodial branches, 75007–3 and L-2689 breeds having the 2nd types of sympodial branches) the domination of the latter was observed. Thus, in hybrids resulting from hybridization of breeds having the terminated type of sympodial branches with those having unterminated types of fruit spurs domination of the unterminated

sympodial type could be seen, but regardless of sympodial branching type (I st, II nd, III rd and IV th subtypes of sympodial branches), the hybrids have compact habitus of bush. In hybrid combinations resulting from hybridization between breeds having I st, II nd, III rd and IV th subtypes of sympodial branches domination of breeds having shorter sympodial branches could be observed.

Invariable genetic basis, only form of trait manifestation is established to change. Number of genes in a genotype necessary for determination of a trait is well within the limits of ploidy. Sometimes differences in manifestation forms create an illusion of polymeric inheritance, while essentially it is monomeric. Our experiments on "branching type" trait demonstrated that practically in all hybrid combinations with involvement of forms both similar and different in origin and manifestation of the trait in $F_1$ into hybridization complete domination of breeds with the unterminated branching could be seen. $F_2$ plants could be divided into distinctly different phenoclasses, the unterminated and terminates branching types in the ratio 3: 1 (Table 1).

Of note, in all $F_2$ hybrids resulting from hybridization of L-6161 lines having terminated branching type with those having the unterminated type of fruit spurs a plant having transitional types of branching could be seen.

Table 1.– Splitting ratio in $F_2$ based on sympodia types

| № | Material | Total number of plants | The number of plants with sympodia | | $X^2$ | Ratio |
|---|---|---|---|---|---|---|
| | | | unterminated type | terminated type | | |
| 1. | Л-2689 × Л 6161 | 252 | 191 | 61 | 0.08 | 3.1: 1 |
| 2. | Л-6161 × Л-2689 | 320 | 243 | 77 | 0.15 | 3.1: 1 |
| 3. | 75007–3 × Л 6161 | 210 | 160 | 50 | 0.16 | 3.2: 1 |
| 4. | Л-6161 × 75007–3 | 165 | 118 | 47 | 0.80 | 2.5: 1 |
| 5. | Л-2777 × Л-6161 | 158 | 121 | 37 | 0.21 | 3.2: 1 |
| 6. | Л-6161 × Л 2777 | 185 | 140 | 45 | 0.2 | 3.1: 1 |
| 7. | 146 × Л-6161 | 120 | 94 | 26 | 0.64 | 3.6: 1 |
| 8. | Л-6161 × 146 | 180 | 138 | 42 | 027 | 3.2: 1 |
| 9. | Юлдуз × Л-6161 | 355 | 266 | 89 | 0.13 | 2.9: 1 |
| 10. | Л-6161 × Юлдуз | 350 | 259 | 91 | 0.24 | 2.8: 1 |

The findings allow concluding of polymeric character of a trait inheritance when the distribution of transitional and other forms by classes is taken into account or of monomeric one when the diversity can be neglected to unite all plants having terminated branching in one class, and those having unterminated and mixed types of branching (which can be categorized as the recessive) into another to have ratios close to 3: 1 [7; 2].

$F_1$ hybrids obtained from crossing unterminated types of sympodial branches (AN-Bayaut-2-G. *hirsutum* L × G. *Mustellinum*) among themselves were mainly observed compressed bush form, that is, the dominance of the form related to the first type or one-and-a-half type of branching, the ratio the splitting is equal to 1: 2: 1.

Thus, in hybrid combinations obtained by crossing between the forms of the I, II, III, and IV types of sympodial branches, the dominance of forms with a shorter type of sympodial branches is mainly observed. We think that the latter is more consistent and natural because the trait inheritance is essentially monomeric; transitional and other forms result from changes in manifestation form of permanent genetic basis. Consequently, general consistencies in the ratios of classes of alternative traits in $F_2$ are preserved, rather extensive diversity of gene- and phenotypes formed as a result of gametal linkage with various potential capabilities for development of the trait can be seen. For that very reason in most cases we obtained heterogeneous populations of various forms preserving genotypic status upon prolonged self-fertilization.

Thus, number of genotypic and phenotypic classes in the trait manifestation increases by several times along with the respective reduction in percent of identical copies of initial forms practically without any changes in the genetic basis and increase in number of traits in the group of genetic factor to result in nonstandard conclusions.

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# HERITABILITY OF A RAW COTTON BOLL MASS IN GEOGRAPHICALLY SEPARATED $F_2$ HYBRID POPULATIONS

**Abstract.** The article presents analysis of heritability estimate by a raw cotton boll mass in a population of geographically separated cotton $F_2$ hybrids. Efficacy of selection by a raw cotton boll mass was demonstrated to depend on individual peculiarities of the genotypes hybridized.

**Keywords:** Cotton, heritability, genotype, selection, population, cotton mass.

Cotton breeding at the final stage is based on selection, which is a continuation of genetic studies, that is, hybridologic analysis of $F_1$ and $F_2$ hybrid swarms. Analytical selection is based on individual selection from genetically heterogeneous populations of cotton older generation hybrids, lines and cultivars. In natural settings the cultivar heterogeniety results from natural hybridization between genotype populations, natural mutations and their crossing. One and the same culture is known to have various environment dependence traits. Some traits more depend on growth environment; the others are governed by a genotype. Heritability estimate is routinely calculated by fractional value from 0 to 1 or in percent from 0 to 100. The higher the heritability estimate, the stronger is heritable dependence of the trait [5; 6].

The three main components of the genotypic variation proposed by Wright (according to Brubeyker) [3] are: 1) additive genetic variation; 2) dominancy related deviation; 3) interaction or epistatic deviation. Estimates of heritability for various traits, in addition to estimates of their genetic correlations, can be used to identify indirect selection patterns which appear more efficient than the direct selection for trait to be improved [1; 2; 4]. Thus, as most authors report, heritability estimate is a real value to be used as sustainable method for selection, and prediction of the process efficacy, which is essential for selection process planning.

Quantitive traits of cotton in the second generation have a complex nature of heredity. On the one hand, it is connected with the genetic variability, on the other, with the paratypic one. Paratypic variability makes study on hereditary variability of traits difficult.

To assess selection value of the polymorphic and polygenic $F_2$ hybrids, we studied heritability estimate of economically valuable trait of cotton, such as mass of a raw cotton boll in $F_2$ hybrids. Types of cotton of various origins, such as Namangan-77 (a product of individual selection from natural hybrid of C-6526 genotype population obtained in its turn by crossing 159-f with (05152) punctatum subspecies), Kupaysin (a product of radiation and multiple individual selection), Kelajak (a product made on the basis of L-38 line, obtained by crossing of intraspecific geographically separated L-6161 *G.hirsutum* and Bulgaria *G.hirsutum* 146 breeds), UzFA-705 and UzFA-713 (made by radiation of dry seeds of L-38 line by $^{60}$CO gamma-rays and multiple individual selection), and Australian selection 75007–11 breed served as materials for study.

Heritability value in the hybrid combinations by a raw cotton boll mass, as it can be seen in (table 1), has different variability. In hybrids heritability estimate by size of cotton bolls ranged from 0.18 to 0.53 (from 18 to 53%), indicating that by the size of cotton boll some hybrid swarms undergo significant environmental effect, the others have high heritable character.

Table 1.– The coefficient of heritability of the mass of raw cotton of one box in hybrid populations of $F_2$

| ♀ \ ♂ | **Namangan –77** | **Kupaysin** | **Kelajak** | **75007–11** | **UzFA-705** | **UzFA-713** |
|---|---|---|---|---|---|---|
| Namangan –77 | – | 0,44 | 0,52 | 0,18 | 0,33 | 0,27 |
| Kupaysin | 0.50 | – | 0.41 | 0.36 | 0.45 | 0.36 |
| Kelajak | 0.44 | 0.42 | – | 0.43 | 0.44 | 0.39 |
| 75007–11 | 0.33 | 0.53 | 0.48 | – | 0.38 | 0.35 |
| UzFA-705 | 0.31 | 0.40 | 0.45 | 0.30 | – | 0.38 |
| UzFA-713 | 0.21 | 0.46 | 0.28 | 0.30 | 0.35 | – |

The highest genotypic character of variability by the trait above was demonstrated by hybrid swarms 75007–11 x Kelajak (0.48, 48%), Kupaysin × Namangan-77 (0.50, 50%), Namangan –77 × Kelajak (0.52, 52%) and 75007–11 × Kupaysin (0.53, 53%). Effect of genotypes and environment can be seen equal for variability of a raw cotton boll mass in $F_2$ hybrids. The environment appeared to mostly affect the size of bolls of Namangan-77 × 75007–11, UzFA-713 × Namangan-77 and Namangan-77 × UzFA-713 with the heritability estimates 0.18(18%), 0.21(21%) and 0.27(27%), respectively. Mean heritability estimates in other hybrid combinations by a cotton boll mass ranged from 0.30 to 0.47(from 30 to 30 to 47%). Thus, as it can be seen, a raw cotton mass in $F_2$ hybrids is affected by the environment factors more significantly than by the genetic ones. High heritable variability by the trait above was demonstrated in the hybrid swarms with higher genetic enrichment and adaptability to the environment. Reciprocal differences in the trait heritability estimates can be attributed to the origin of initial parent forms. As a whole, selection by a raw cotton boll mass is ineffective.

Thus, $F_2$ hybrids behavior is connected with the environmental effects on manifestation of a trait and with a response of polygenic system of the hybridized forms to specific conditions of cultivation. However, response of polygenic system to the environmental effects in various genotypes is inadequate. This can be confirmed by high typical heritable variability of a raw cotton boll mass in geographically separated hybrid swarms, where breeds of domestic selection and a breed of nondomestic selection served as the female parent.

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# STUDYING OF THE POLYMORPHISM OF ISOZYME SPECTRA OF ESTERASE IN SEEDS OF DIFFERENT WHEAT VARIETIES

**Abstract.** In the paper the data of study of electrophoretic structure of seed's esterase enzymes of different wheat varieties are submitted. Electrophoretic esterase's analysis of separate grains have shown, that electrophoretic spectrums of varieties Bezostaya-1, Intensivnaya, Sanzar-8 and Ulugbek-600 consist of two types of electrophoretic spectrums, varieties Skifianka, Marjon and Yenbosh – three types of electrophoretic spectrums, and variety Yuna – five types of electrophoretic spectrums appeared.

**Keywords:** wheat, esterase enzymes, polymorphism, Electrophoretic analysis, components.

**Introduction**

Modern intensive agricultural production requires wide application of the methods creating high productive varieties of the field crops in breeding based on the achievements of modern genetic and biotechnological science. Uzbekistan characterizes as a region with a sharp continental climate with different soil and climatic conditions and a complex peculiar relief. One of the moments that makes it possible to obtain stable yields with improved technological and baking qualities of the grain is the preservation of the genetic and breeding purity of the cultivated material.

For solving of this problem, certain results are obtained using the methods of biochemical genetics, allowing to assess the purity and quality of breeding and seed material on the genetic basis. The wide application of electrophoretic analysis of polymorphic proteins allowed at the qualitatively new level to develop method of genetic markers. For wheat, acceptable and convenient class of molecular-genetic markers were proteins and isoenzymes. Using of the electrophoretic analysis made it possible to reveal between variety polymorphism and intravariety heterogeneity of isoenzymes [1].

Esterases are buffer-soluble grain fractions representing of the polymorphic system. They can serve as an effective genetic markers in solving many problems of plant physiology, genetics, practical breeding, and biochemical systematics of plants. Esterous loci in wheat are controlled by genes localized in the chromosomes of the third and sixth homeological groups [1]. Plant esterases catalyze the conversion of carboxylic esters into bioactive acids and alcohols, thereby playing a key role in many biological processes. The absence of epistatic interactions and the codominant nature of the inheritance of esterase isoform make them relevant for a rapid and accessible

study of the processes of biochemical adaptation to changing environmental conditions. This type of markers is also convenient for solving practical problems of the breeding as a means that can accelerate and simplify the selection process of the significant breeding material [2].

In the present work, studies have been carried out to study the electrophoretic composition of the esterase enzymes of seeds of various wheat varieties.

**Materials and methods of research**

For the research, were used bread wheat varieties (Yuna, Bezostaya-1, Skifianka, Intensivnaya, Ulugbek-600, Sanzar-8, Yonbosh and Marjon) cultivated in various regions of the Republic of Uzbekistan.

Extraction of esterases from flour, obtained from grinding a grain was performed with Tris-glycine buffer (pH-8.9) for 30 minute. Electrophoretic analysis of the esterases of individual grains was carried out according to the method of V. I. Safonov and M. P. Safonova (1971) [5].

**Result and discussion**

The data on the isozyme spectra of the studied wheat varieties are shown in (Fig. 1 and tab. 1). Esterase components are divided into slow and fast migrating migratory groups, the first which consists of the indistinct bands, and the second – gives clear shaped bands. Relative electrophoretic mobility of the slowly migrating components consists from 0.21 to 0.42, and as fast migrating components from 0.83 to 0.93. Intravarietal differences in the majority of the studied varieties are observed as in the composition of the slowly migrating, and as part of fast migrating components.

Electrophoretic analysis of the esterase of individual grains showed that the Bezostaya-1, Intensivnaya, Sanzar-8 and Ulugbek-600 varieties consist of two types of electrophoretic spectra, Skifyanka, Marjon and Yonbosh varieties from three types of electrophoretic spectra, and the Yuna variety revealed five types of electrophoretic spectra of the Esterase. Among the identified electrophoretic spectra in different wheat varieties, variants with the same composition of slow-migrating and fast-migrating esterase components were not detected.

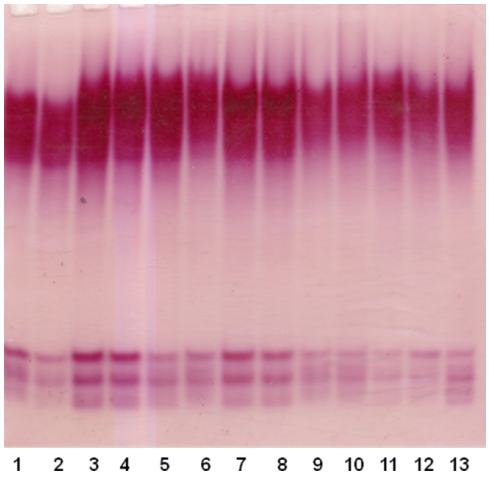


Figure 1. Isozyme spectra of the esterase of the individual bread wheat grains in the polyacrylamide gel pH –8.9. 1–2 Skifyanka, 3–4 Intensivnaya, 5–6 Ulugbek –600, 7–8 Marjon, 9–10 Sanzar-8, 11–12 Yuna, 13–Yonbosh

When studying the electrophoretic spectrum of gliadin in these varieties, it was shown that, according to this feature, most varieties are also polymorphic [3; 4]. For example, the varieties Yuna, Skifyanka consist five, and the variety Intensivnaya consists of the three electrophoretic variants [4].

Table 1.– Presence of electrophoretic components of esterase in some wheat varieties

| № | Presence of the components (ОЭП) | Wheat varieties | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Bez ostaya-1 | Skifyanka | Intensivnaya | Marjon | Yon-bosh | Yuna | Sanzar-8 | Ulugbek-600 |
| *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* | *9* | *10* |
| 1. | 0.21 | – | – | – | – | + | – | – | – |
| 2. | 0.22 | – | – | – | – | – | – | – | – |
| 3. | 0.24 | + | + | + | – | – | + | – | – |
| 4. | 0.27 | – | – | – | + | + | + | + | + |
| 5. | 0.29 | – | – | – | – | – | + | – | – |
| 6. | 0.31 | + | + | + | + | + | + | – | + |
| 7. | 0.33 | – | – | – | – | – | + | + | – |
| 8. | 0.35 | – | + | + | + | + | | + | + |
| 9. | 0.37 | – | – | – | – | – | + | – | – |
| 10. | 0.38 | + | – | – | + | + | – | – | – |
| 11. | 0.39 | – | – | – | + | + | – | – | – |
| 12. | 0.42 | – | – | – | – | – | – | + | – |

| *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* | *9* | *10* |
|---|---|---|---|---|---|---|---|---|---|
| 13. | 0.83 | + | + | + | + | + | + | + | + |
| 14. | 0.87 | – | + | + | + | + | + | + | + |
| 15. | 0.90 | – | – | + | + | + | + | + | + |
| 16. | 0.93 | – | – | – | – | – | – | + | + |

**Conclusion**

Thus, it was shown that, according to the isozyme spectrum of esterase, the varieties Bezostaya-1, Intensivnaya, Sanzar-8 and Ulugbek-600 consists of two types, Skifyanka, Marjon and Yonbosh three types, and variety Yuna consists five types of electrophoretic spectra.

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# TO DEFINE THE FLAVONOIDS HAVING ANTIOXIDANT PECULIARITIES IN CEREALS AND LEGUMINOUS PLANTS

**Abstract.** Quantity of flavonoids in cereals and leguminous plants was learned. Results showed, that the quantity of flavonoids in the cereals and leguminous plants are different in their variations and it depends their period of growth. The highest generalconcentration of flavonoidsin the cereals and leguminous plants in their period of growthis oats and it make up 37.4 mg/g on the fifth day of cultivation period. Research showed that the total amount of flavonoids in developed leguminous plants: soy and mung bean was lower than that found in wheat. It was defined that the total flavonoids in the developed soy bean on the fifth day was 21.2 mg/g and in mung bean was 17.2 mg/g.

**Keywords**: flavonoids, antioxidant, developed cereals and leguminous plants: oats, barley, wheat, soy and mung bean.

Flavonoids are not synthesized in organisms of animals, they are adopted in organism together with food. Flavonoids are wide spread in nature and they encounter almost in all high plants. Especially, Fabaceae, Asteraceae, Compostae, Apiaceae, Umbelliferae, Ranunculaceae, Rosaceae and other family members are rich to flavonoids. These group combinations will be as solution in cellular sap of all organs of plants. Flavonoids are more accumulated especially in flowering period of plants, then their quantity will be decreased [1; 7].

The amount of general flavonoids in various seasons for medicinal plants were defined [6]. Flavonoids are biologically active combinations, they influence as antioxidant, protecting the organism from free radicals and intensify tolerance against to an influence of external factors. Flavonoids can be used for correcting many diseases. Flavonoids especially decrease the fragility of blood vessel, can be used as the gall and urine extracting means [1; 2; 7].

Having antioxidant peculiarities in cereals and leguminous plants the amount of vitamin C has also been learned [4].

The main reason for our study to identify flavonoids that have antioxidant effects for wheat, barley, oats, soy and mung bean.

It was used over the 1% of triton X-100 with the solution of 96% spirts for determination flavonoids in plant materials. A reaction was based to complex arising with the stable color as a result of boron solution of lemon acid in the flavonoids that separated from plant tissues. The arisen color complex was measured in spectrometer-46 of 420 nm, the quantity of general flavonoids in medicinal plants was defined [5].

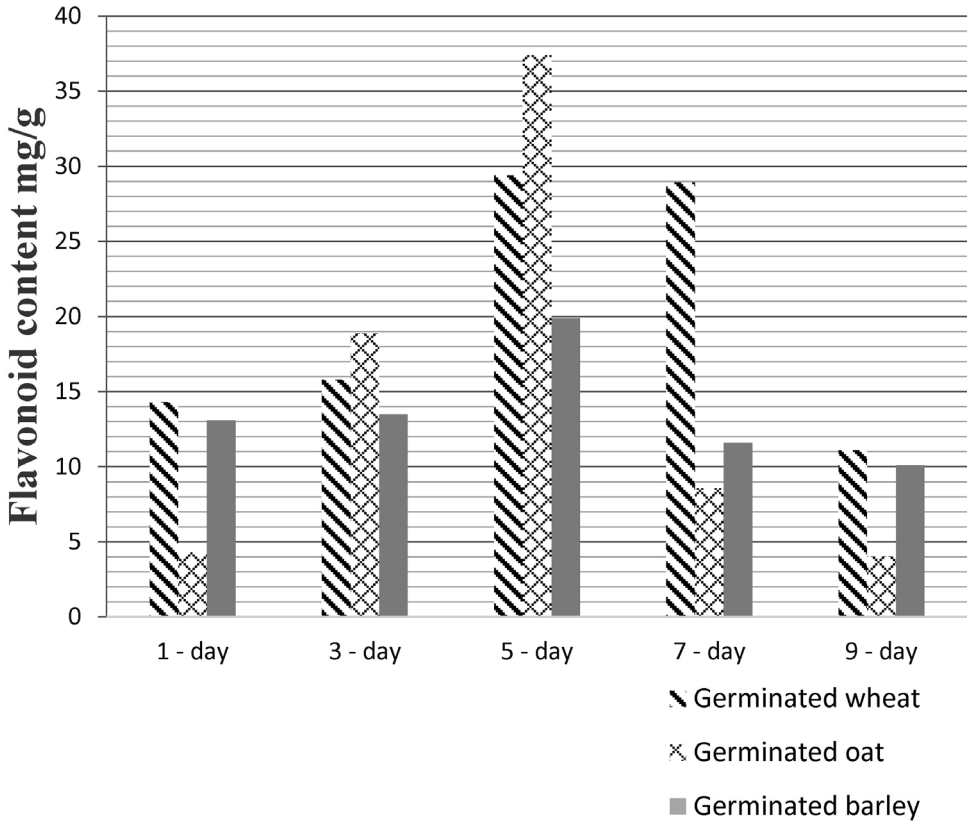


Figure 1. The content of flavonoids in germinated cereals

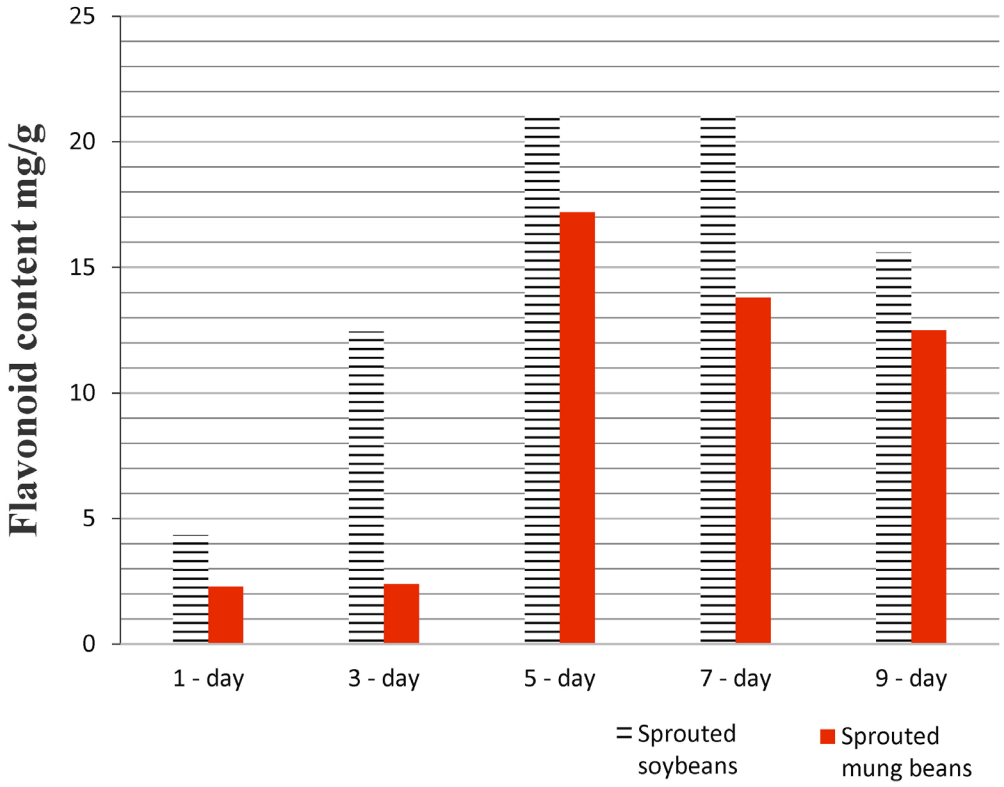


Figure 2. The content of flavonoids in sprouted legumes

The results show that the amount of flavonoids in the cereal and leguminous plants is different and depends on the period of their period of growth. The highest generalconcentration of flavonoidsin the cereals and leguminous plants in their period of growthis oats and it make up 37.4 mg/g. It was defined that during the remaining days of the cultivation periodit's amount was lower than wheat and barley. On the fifth day of cultivation period in wheat the amount of flavonoids waslower than oats and it made up 29.4 mg/g. The total amount of flavonoids on the first day of the growing period for wheat we found 14.3 mg/g, 15.8 mg/g on the third day, 28.95 mg/g on the seventh day, and 11.1 mg/g on the ninth day. In the cultivated barley, we observed that the total flavonoids was lower than wheat. On the fifth day of barley growing it's the highest concentration was 19.9 mg/g. On the first and third days of cultivating we defined that it was 13.3 mg/g, on the seventh day 11.6 mg/g and on the ninth day 10.1 mg/g.

Cultivated leguminous plants: the total amount of flavonoids in soy and mung bean was lower than that found in wheat. We haveidentified that the total flavonoids in soy bean on it's fifth day was 21.2 mg/g and inmung was 17.2 mg/g.

Thus, the flavonoids in the cultivation period of cereals and leguminous plants were different, and the highest concentration of flavonoids was observed on the fifth day of the oats.

The results showed, that the total flavonoids, which have antioxidant peculiarities, are found in cereals and leguminous plants – wheat, oats, barley, soy and mung bean, and the highest concentration was in oats of the fifth day cultivation period with 37.4 mg/g.

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# DEVELOPING OF UNIQUE FORMS WITH USE VICARIOUS COTTON SPECIES

**Abstract:** The results of research on studying of the morphobiologic and economically valuable traits of amphidiploids $F_1$ (cultivar "Kelajak" (*G.hirsutum subsp. euhirsutum*) × (*G.arboreum subsp. perenne* × *G.arboreum subsp. obtusifolium var. indicum)*) and $F_1$ (cultivar "Kelajak" (*G.hirsutum subsp. euhirsutum*) × (*G.arboreum subsp. obtusifolium var. indicum* × *G.herbaceum subsp. pseudoarboreum*)) obtained by use of vicarious cotton species.

**Keywords:** cotton, species, sympodial, monopodial, photoperiod, nectary, anther, petal, fiber length, weight of one boll, anthocyan, weight of 1000 seeds.

**Introduction**

The concept of the vicariate is sometimes interpreted very narrowly or very large. In a very large interpretation, it includes not only genetically related taxa replacing each other, but also life forms. In the narrow interpretation, the vicariate understands the phenomenon of the replacement of the plant and the animal species in the fauna and flora of various continents or of spatially significantly remote territories of the same continent.

Vicarious species are called closely related to the species of the plants and the animals that occupy different areas of the distribution (*geographical vicariate*) or are found within the same range, but in different environmental conditions (*ecological vicariate*). One of the main criteria by the presence or absence of the vicariate is judged the relative position of the geographic areas of closely related species.

It is known that the boundaries of the ranges are mobile and depend on a complex of factors, the most important of that: climatic, soil–ground, biotic and historical. Depending on the history of the settlement and the current range, the species are assigned to a specific arealogical group.

The vicariate in plants is associated with the issues of the historical transformation of the vegetation cover and the interpretation of the biological concept of "species". The phenomenon of the vicarism in the genus *Gossypium* L. is mainly the result of the rupture, which were never uniform, areas were divided into parts, isolated by indefinite geographic barriers (*sea spaces*) during the long geological periods.

This circumstance associated with the profound changes in ecological conditions explains that all island species, inhabiting islands of the continental origin are vicar in relation to the species of the neighboring continent [4].

L. V. Semenikhina, L. I. Gurevich, A. E. Egamberdiev [1] under the action of a 0.1% solution of colchicine on the growing point, actively growing shoots of the interspecific sterile hybrid *G.hirsutum* × *G.trilobum* with the number of hromosome $2n = 39$, hexaploid amphidiploid with chromosome number $2n = 78$ is induced.

In amphidiploid, the manifestation of 26 contrasting signs of the wild species *G.trilobum* and cultural *G.hirsutum* L. has been studied. Amphidiploid has polyploid capacity, fertility, natural leaf fall, disease resistance and can be used in breeding.

When studying hybrid progeny (*G.hirsutum* × ×*G.herbaceum*) × *G.harknessii*, H. Babamuratov [2] was able to identify individual genotypes with the high combinational value for the weight of one boll, yield and fiber length.

S. M. Rizayeva [5; 6; 7] obtained numerous unique amphidiploid and hexaploid forms with high economically valuable traits based on intergenomic hybridization of the remote cotton species.

Part of the germinated seeds of the triploid ($2n = 39$) $F_0$ hybrids with the well developed roots of 0.5 cm were picked and laid out in Petri dishes on filter paper moistened with a 1% aqueous solution of the colchicine with an exposure of 24 hours. Then the seedlings were rinsed several times with the running water to remove traces of colchicine.

After that, both control and colchicine seedlings were planted in earth–sand paper cups. In the period of 2–3 true leaves of the plant were transplanted into Wagner's vessels and grown in greenhouse conditions. Plant care, phenological observations and description of morphobiological and economically valuable traits were carried out according to the generally accepted methods [3].

**Materials and methods.** The initial material for the research was $F_1$ hybrids obtained by interspecific and intraspecific hybridization of the vicar species *G.herbaceum* L. and *G.arboreum* L.: *G.arboreum subsp. perenne* × *G.arboreum subsp. obtusifolium* var. *indicum*; *G.arboreum subsp. obtusifolium* var. *indicum* × *G.herbaceum subsp. pseudoarboreum,* as well as the regionalized variety Kelajak (*G.hirsutum subsp. euhirsutum*).

**Results**. Below is a brief description of the amphidiploids $F_1$ by morpho-biological and economically valuable traits, obtained as a result of the research conducted on the creation of valuable forms using the varieties of the cotton.

**$F_1$ (*G.arboreum subsp. perenne* × *G.arboreum subsp. obtusifolium* var. *indi–cum*).** Bush upright, compact, medium density. The height of the main stem is 50.0–55.0 cm, green; pubescence and anthocyan tan are average, the number of common nodes is 20–25 pcs. The branch is sympodial, the first sympodial branch is at 7–8 nodes, the number of monopodiae is 3–2 pcs., The number of sympodia is 13–17 pcs. The leaf is medium (9.5 × 9.0 cm), green, five to seven separate, slightly pubescent. Nectary is not available. The length of the leaf stalks is 7.0–8.0 cm, with a weakly anthocyanin tan. With the short pedicle, 0.5–0.6 cm. Petal medium, 5.0 × 4.5 cm, heart–shaped, with 8–10 teeth, with a light yellow color, with an anthocyanin stain at the base. Anthers and pollen are light yellow. The boll is small, cone–shaped with a sharp nose, with a non–smooth surface, the weight of one boll is 2.2–2.4 g, four–fold, with 5–6 seeds in each nest. The seeds are small, stony, the weight of 1000 seeds is 66.0–69.0 g. White fiber, short, 24.0–26.1 mm. Not photoperiodic, in the conditions of a short day, the first fertile branches are laid on 7–8 nodes. Symptodial branches of type I. Mid-season.

**$F_1$ (*G.arboreum subsp. obtusifolium* var. *indicum* × *G.herbaceum subsp. pseu–doarboreum*).** Bush compact, sredneopushenny, with a strong anthocyanin–tan. The branching is sympodial, the number of monopodia is 8–10, the sympodium is average. The height of the stem is 75.0–80.0 cm, the number of common nodes is 35–38 pcs. The leaf is light green, medium, 10.5 × 10.5 cm, 5–7 split, slightly pubescent. Nectary is not available. The length of leaf stalks is 7.0–7.5 cm, with medium anthocyan tan. The flower is medium, with a short pedicel, 3.5 cm. The petal is medium, 5.4 × 4.5 cm, heart-shaped, with 8–9 teeth, with a yellow color, with an anthocyanin stain at the base. Anthers and pollen are light yellow. The stigma protrudes 0.2 cm above the stamina. The boll is small, oval, with a sharp nose, with a smooth surface, the weight of one boll is 2.0–2.2 g, 3–4–fold, with 4–5 seeds each nest. Seeds are small, weight is 1000 seeds – 54.0–56.0 g. White fiber, short, 24.5–26.0 mm. Not photoperiodic, in conditions of a short day, the first fertile branches are laid on 12–14 nodes. Sympodial branches, I–II type. Mid–season.

**Cultivar "Kelajak" (*G.hirsutum subsp. euhirsutum*).** Spreading bush. The branch is sympodial, the number of monopodia is 1–2 pcs., The sympodium is short, weak. The height of the stem is 90–100 cm. The leaf is light green, medium, 11.0 × 10.0 cm, 3–5 – palmate, slightly pubescent. Nectary one. The length of the leaf stalks is 9.0–9.5 cm, with medium anthocyan tan. The flower is medium, with short pedicel, 1.5–2.0 cm. The petal is medium, 4.5 × 3.5 cm, heart–shaped, with 10–11 teeth, with a white color, there is no anthocyanin stain. Anthers and white pollen. The stigma protrudes 0.3 cm above the stamina. The boll is average, oval, the weight of one boll is 5.5–6.5 g, 4–5–fold, with 9–10 seeds in each nest. The seeds are small, the weight of 1000 seeds is 118.0–123.0 g. White fiber, short, 33.0–38.0 mm. Not photoperiodic, resistant to drought, salt and pests, the first fertile branches are laid on the 4–5 nodes. Simpodial branches of type II. Early.

**$F_1$ (cultivar "Kelajak" (*G.hirsutum subsp. euhirsutum*) x (*G.arboreum subsp. perenne* × *G.arboreum subsp. obtusifolium* var. *indicum*)).** Bush compact, slightly pubescent, with a medium anthocyanin tan. The branch is sympodial. There are no monopods, the sympodium is short, weak. The height of the stem is 55.0 cm, the number of common nodes is 20 pcs. The leaf is light green, medium, 10.0 × 13.0 cm, 3–5–finger–blade, slightly pubescent. Nectarnik– 3, oval, colorless. Leaf with medium anthocyanin tan. The flower is medium, with short pedicel, 0.5–1.0 cm. Petal is medium, 4.0 × 3.8 cm, heart–shaped, with 8–10 teeth, with a light yellow color, there is no anthocyanin stain. Anthers and pollen are light yellow. The stigma protrudes 0.1 cm above the stamina. The boll is average, ovoid, the weight of one boll is 2.3–7.3 g, 4–5–fold. Seeds are average, weight is 1000 seeds – 152.0 g. White fiber, 32.0–38.0 mm. Not photoperiodic, the first fertile branches are laid on the 7 $^{th}$ node. Simpodial branches of type II.

**$F_1$ (cultivar "Kelajak" (*G.hirsutum subsp. euhirsutum*) × (*G.arboreum subsp. obtusifolium* var. *indicum* × *G.herbaceum subsp. pseudoarboreum*))**. Bush compact, slightly pubescent, with an average anthocyanin tan. The branch is sympodial, there are no monopods, the sympodium is short, weak. The height of the stem is 60.0 cm, the number of common nodes is 13 pcs. The leaf is light–green, medium, 14.0 × 17.0 cm, palmate-lobed, slightly pubescent. Nectars– 3, oval, colorless. The color of the nerve node is red. Leaf petioles with medium anthocyanin tan. The flower is medium, with short pedicel, 0.7–1.0 cm, heart–shaped, 10–12 teeth. The boll is average, ovoid, the weight of one boll is 1.2–2.2 g, 4–5–folding. The seeds are small, the weight of 1000 seeds is 140.0 g. The fiber is light brown, medium, 30.0–37.0 mm. Not photoperiodic, the first fertile branches are laid on the 5th node. Simpodial branches of type II.

Thus, as a result of the research, unique forms of the cotton have been created using the vicar species of cotton *G.herbaceum* and *G.arboreum*, which have valuable economic characteristics that are recommended to be used in further research programs and the selection process as a initial material.

**Conclusions.** Consequently, the preservation, study, enrichment and efficiently use of the unique diversity of the genetic resources of the cotton genus *Gossypium* L. in the national economy is important. This valuable genetic fund is the basis of the basic and applied research, as well as the basis for the creation of new high–yielding and high–quality cotton varieties resistant to biotic and abiotic environmental factors that meet the needs of the national economy and are competitive in the global market.

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# STRUCTURE AND DISTRIBUTION OF ANIMALS IN THE BUKHARA REGION

**Abstract.** In Bukhara region, information on the types of animal species, their distribution in hunting farms, hunting, informal or poaching species, and the ecological features of hunting farms are provided.

**Keywords:** water basins, hunting farms, poaching, biodiversity.

Hunting farms are an important aspect of the use of the animal world and are of vital importance in the development of hunting tourism, biodiversity conservation, and rational use of nature. As a result of the study, officially 13 species of animals were identified in 5 hunting farms in Bukhara region in 2014–2017 (table). In the region, officially hunted species make up 8.2% of the vertebrate species (158 species) allowed for hunting in Uzbekistan.

Table 1.– The main types of hunting in the Bukhara region and their distribution in hunting farms (2014–2018)

| S/n | Species | Hunting farms | | | | |
|---|---|---|---|---|---|---|
| | | Korakir | Shurkul | Zikri | Karakul forestry farms | "Peshku Korakir fortress" LTD |
| 1. | Sus scrofa | + | – | – | + | + |
| 2. | Meles meles | + | – | + | – | + |
| 3. | Lepus capensis | + | + | + | + | + |
| 4. | Vulpes vulpes | + | + | + | + | + |
| 5. | Canis aureus | + | + | + | + | + |
| 6. | Anser anser | + | + | + | + | + |
| 7. | Netta rufina | + | + | + | + | + |
| 8. | Aythya ferina | + | + | + | + | + |
| 9. | Anas platyrhynchos | + | + | + | + | + |
| 10. | Anas crecca | + | + | + | + | + |
| 11. | Fulica atra | + | + | + | + | + |
| 12. | Phalacrocorax carbo | + | + | + | + | + |
| 13. | Pterocles orientalis | + | + | + | + | + |
| **Total** | | **13** | **11** | **12** | **12** | **13** |

On the basis of observations and surveys, 10 types of hunting (Canis lupus, Felis libyca, Ondatra zibethicus, Gazella subgutturoza, Phasianus colchicus, Columba livia, Merops superciliosus, Agrionemys horsfieldi, Varanus griseus, Eryx miliaris) were illegal or poaching. Thus, 23 species of vertebrate animals were identified in the region (figure 1).

Korakir and "Peshku avoid fortress" LTD hunting farms are located in the liveliest part of the Korakir lake for hunting, with all the main types of hunting in the region – 13 species of animals. There is very little vegetation cover for the animals around Shchurkul lake, so 11 species of animals are being hunted in the Shorkul hunting farm.

All hunting farms in the region are located in the coastal zone of water and reservoirs. Especially in the desert zone, biodiversity conservation is a clear indication of the importance of reservoirs in the collection of water and water birds, which form the basis of hunting facilities, where the distribution and density of the species grown are closely linked to complete water basins and existing ecological conditions. The diversity of hunting facilities in hunting farms serves as a unique bioindicator for evaluating the economic environment.

The analysis of scientific researches, reports and statistical data shows that the list of species in the country is not complete, that the reports submitted by hunting farms do not meet the requirements, and that the hunters do not have enough knowledge about the species being hunted. They include species that are not allowed to hunt in Uzbekistan or that are not practically hunted by hunters (Podiceps cristatus, Ardea cinerea, Streptopelia decaocto, Streptopelia turtur, Sturnus vulgaris etc.).

In 2014–2017, hunting farms studied the size of hunted animals. The average annual size are as high as the species such as Anatidae (Netta rufina, Aythya ferina, Anas platyrhynchos, Anas crecca) (6720), Fulica atra (1983) and Anser anser (1978). The average annual hunting capacity of Sus scrofa (7), Vulpes vulpes (6) and Canis aureus (7) is very low. There is a low share of mammals in the total number of species as 9,5%.

The average number of hunting farms in hunting farms is occupied by the highest number of hunting farms (6829; 48%), Karakul forestry is the lowest (447%, 3%) indicator.


Figure 1. Percentage of official and informal types of hunting species in Bukhara region

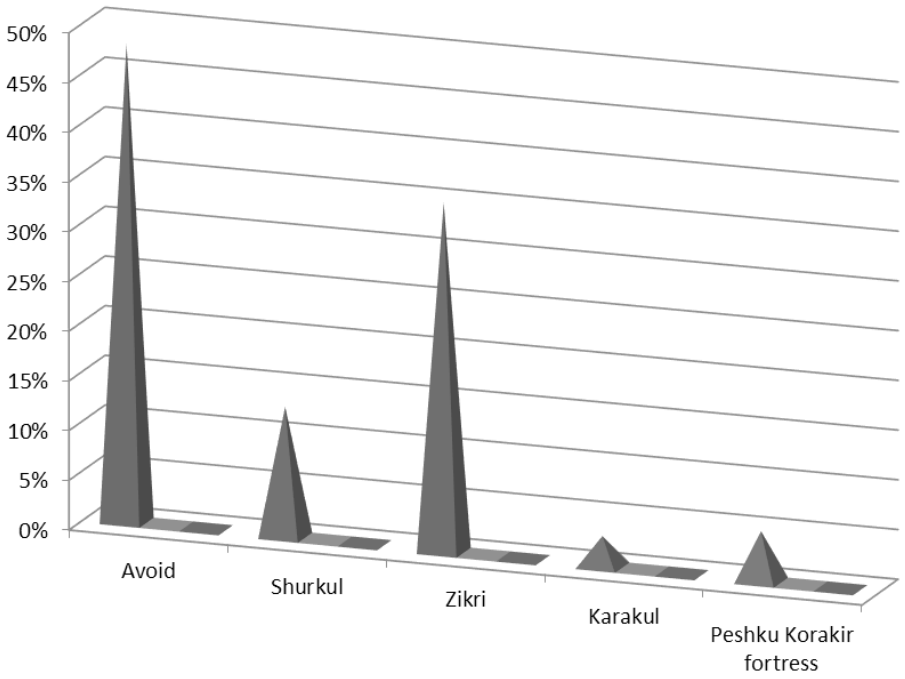


Figure 2. Average Annual Hunting in Hunting Farms (in percent)

Due to the end of industrial hunting and falling need for fur, the species such as Ondatra zibethicus, Canis lupus, Vulpes vulpes, are not very rarely hunted or never hunted in the country in 2014–2017. It has led to the loss of these species as an object of hunting.

According to the results of the study, excessive hunting of species such as Alectoris chukar, Lepus capensis in Uzbekistan has resulted in a decrease in the number of species such as Vulpes vulpes, Canis aureus, which resulted in their rarely hunting.

This can lead to the likelihood of further spread of diseases that may endanger nature and human health.

G. I. Ishunin (1984) notes that the decline or the loss of the number of livestock in Uzbekistan is associated with a natural disaster (adverse climate) that occurs in 8–20 years. In our opinion, it is possible to prevent the mass extermination of the species through adverse weather forecasting and appropriate biotech activities. However, due to inadequate biotech activities, hunting facilities are damaging to climate and nutritional deficiencies.

In summary, the efficiency of hunting farms in Bukhara region is related to the ecological conditions in the reservoirs, the organization of biotechnical activities, the negative anthropogenic factors, and the rate of hunting of hunting areas.

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# THE DISTRIBUTION AND NUMBER OF ACRIDOTHERES TRISTIS IN DIFFERENT HABITATS IN THE KYZYLKUM REGION

**Abstract.** Different habitats, i.e anthropogenic elements in natural landscapes, agrocenoses, distribution of A. tristis in settlements, average number and their ecological factors are studied.

**Keywords:** agrocenosis, anthropogenic element, local migration, household waste.

The Acridotheres tristis is a synanthropic species in Uzbekistan, which is one of the dominant species in the Kizilkum region ornithofauna. Many settlements in its populated areas were involved in various environmental pollution and competing with other species led to the use of firearms to control its number. However, the lack of adequate knowledge of the ecology, ethnology and significance of the jungle in local areas and the unilateral approach to solving the problem led to the inefficient conclusion of the event. In this regard, it is urgent to study the spread and the number of Acridotheres tristis in each ecosystem and to identify the factors that determine these indicators.

The following are the results of the study of the distribution of Acridotheres tristis, the number and the factors determining them in the case of the basic biotop in Kyzylkum.

1. Anthropogenic elements in the natural landscape. These elements include various structures of animal husbandry, forestry, hunting and water economy (buildings, wells, small woods, roads, bridges, pipes, electric drives). They have penetrated the natural landscape of the steppes and are located far away from settlements. The distribution of Acridotheres tristis in Kyzylkum is limited to anthropogenic elements. The main factor that ensures the appearance of Acridotheres tristis in such places is the existence of a network of premises and food sources.

An average annual number of Acridotheres tristis in anthropogenic elements of the natural landscape is 5.2(3–9) per 10 hectares (table). The highest indicator is in March-May (7–9), the lowest indicator falls in July-October (3–4) months. At the beginning of spring and early summer, the high number of abnormalities and abnormalities are explained by the increase in competition and the availability of adequate nutritional resources, while the number of other seasons can be explained by the availability of fruits that are easily accessible to agrocenosis. Climate-related seasonal shifts can result in small migrations.

2. Agrocenoses. In the Kyzylkum region, agrocenoses occupy a large area. Considering their biodiversity conservation and the growing demand for ecologically clean crops, it is one of the pressing issues to study the faunistic composition of this biocenosis and to consider it as an experimental area.

In 2000–2010, 4 night colonies of Acridotheres tristis were registered in local orchards in Bukhara Region, and these colonies were not registered in the newly built intensive orchards. The number of fencing was also lower in the intensive gardens than in the gardens.

In the study, the average annual number of A. tristis, in cotton, winter wheat, berries, fruit gardens and vineyards, was determined (Table 1). In spring and summer, the number of Acridotheres tristis grown in these agrocenoses is higher than the other seasons of the year. The average annual yield was higher for bedbugs (19.8 per cent), and the lowest in winter wheat (9.9). The average monthly high indicator also showed the death tolls (37 mph) and the low figure to the cotton field (February 2).

3. Population points. Due to the relative convenience of habitats for high competitive, environmentally friendly and ecologically vulnerable Acridotheres tristis, there is a large number of households, especially for household waste its number increases. Here, along with the seasonal fluctuation of seasonal variations, there is daily change in winter in cities. Such dynamic vibrations depend on environmental factors, quantities of nutritional resources, location, and life cycles of Acridotheres tristis. In the winter and early spring, resource depletion of A. tristis in the agrocenosis leads to an increase in the number of nutrition due to the fact that it is concentrated in settlements, industrial facilities and waste collection. During this time, they make "local migration" to comfortable living conditions. The total number of A. tristis in the waste dump has the highest average

monthly indication (1308, January) and an annual number (712) possesses high indicator (table 1).

To sum up, the distribution and number of A. tristis in various habitats determine the seasonal changes in quality and quantity of nutrient resources, availability of sleeping and sleeping places, seasonality of man's economic activity. The seasonal fluctuation of food resources will cause seasonal and daily "local migrations" of A. tristis. Local migrations can be seen as an important stage in the life cycle of the A. tristis. This migration plays an important role in the biotopic redistribution and distribution of A. tristis.

Table 1.– The average number of A. tristis in habitats and its annual dynamics (2012–2017)

| Habitat | Months, average number of hits (in 10 hectares) | | | | | | | | | | | | Average annual number (10 hectares) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | I | II | III | IV | V | VI | VII | VIII | IX | X | XI | XII | |
| Anthropogenic elements in the natural landscape | 5 | 6 | 8 | 7 | 9 | 6 | 3 | 3 | 4 | 3 | 5 | 4 | 5.2 |
| Agroocenoses: Field of cotton | 3 | 2 | 7 | 12 | 14 | 17 | 24 | 18 | 16 | 14 | 6 | 3 | 11.3 |
| The autumn wheat field | 5 | 3 | 4 | 6 | 11 | 22 | 15 | 12 | 14 | 12 | 8 | 7 | 9.9 |
| clover field | 7 | 11 | 16 | 28 | 37 | 32 | 29 | 24 | 18 | 15 | 12 | 9 | 19.8 |
| Fruit gardens and vineyards | 5 | 8 | 14 | 17 | 11 | 7 | 13 | 16 | 21 | 18 | 10 | 4 | 12.0 |
| Villages | 27 | 34 | 42 | 49 | 54 | 68 | 74 | 82 | 60 | 56 | 43 | 30 | 51.6 |
| Cities | 30 | 26 | 21 | 35 | 40 | 49 | 32 | 27 | 18 | 21 | 24 | 33 | 29.7 |
| Industrial production facilities | 96 | 114 | 82 | 73 | 58 | 64 | 68 | 80 | 97 | 80 | 86 | 92 | 82.5 |
| Floods | 1308 | 1140 | 980 | 824 | 562 | 371 | 246 | 289 | 360 | 491 | 705 | 1273 | 712.4 |
| Amusement parks and alleys | 17 | 24 | 32 | 37 | 40 | 47 | 44 | 39 | 36 | 34 | 28 | 20 | 33.2 |

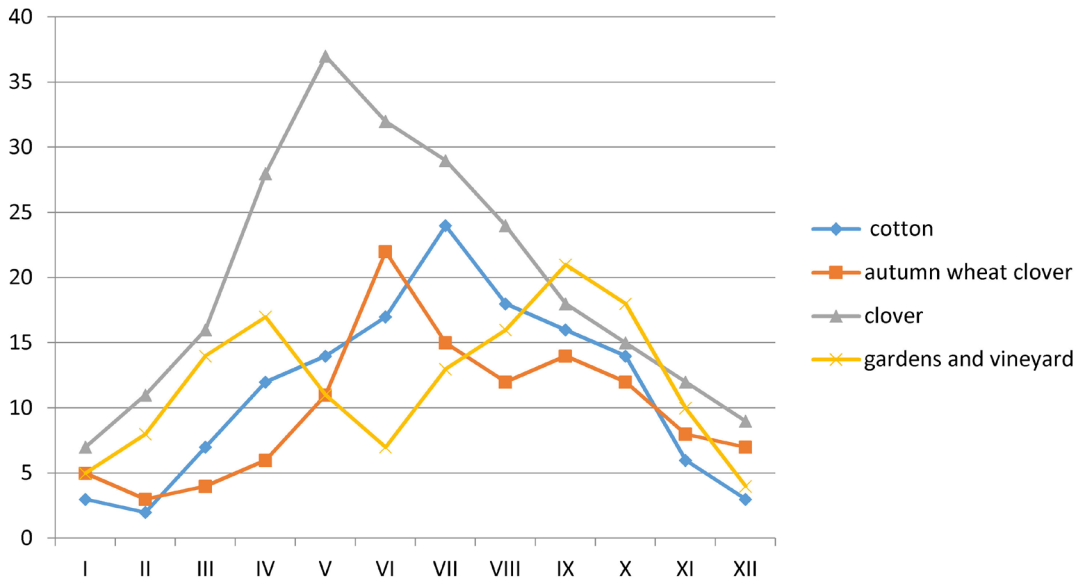


Figure 1. Average monthly dynamics of the number of A. tristis in agrocenosis

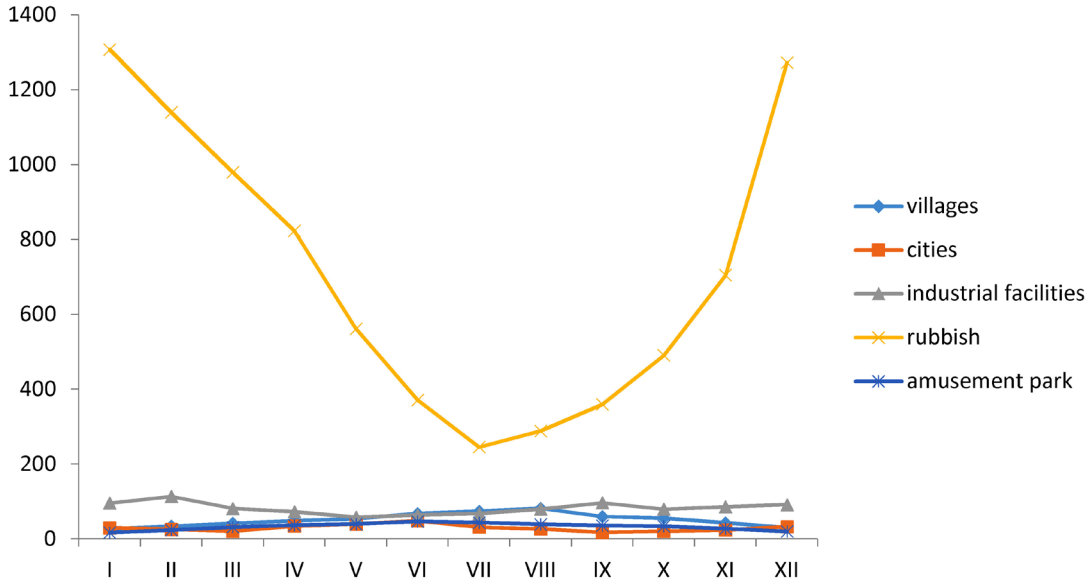


Figure 2. Average monthly dynamics of number of population in settlements

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# EFFICIENCY OF INOCULATION OF THE MUCORRHIZA FUNGI WITH SOYBEAN

**Abstract.** The influence of arbuscular mycorrhiza (AM) fungi inoculation on growth performance of *legume plants* was studied in a green house experiment. The results obtained indicated the dependence of *Soybeans* on mycorhizal symbiosis. Inoculation with arbuscular mycorrhiza significantly improved the growth performance of *Soybean*. The height growth increased significantly by 85% after only three months. Shoot production increased by 213% while root biomass increased by 241%. Inoculation with arbuscular mycorrhiza increased plant tissue phosphorus, nitrogen and potassium content. The better growth response of mycorrhizal plants was attributed to improvement in nutrient uptake, especially phosphorous, nitrogen and potassium. Arbuscular mycorrhiza inoculation has a high potential in agriculture as a biofertilizer.

**Keywords:** symbioses, AM fungi, Soybean.

**Introduction**

Mycorrhizae result from symbiotic associations between soil fungi and the roots of most plants. Mycorrhizae are considered to be classic examples of mutualistic symbioses. The basis for this mutualism relies on the supply of carbon to the fungus by the host plant and, in return, on the supply of mineral nutrients and water to the plant and on the plant's protection against soil-borne diseases by the fungus. Among mycorrhizal symbioses, arbuscular mycorrhizae (AM) are the most wide-spread. AM are recorded in 80% of land plants and are generated by the association of plant roots and fungal populations belonging to the Glomeromycota phylum, which includes around 160 species. AM are ancient; the first fossil evidence of this symbiosis dates back 400 million years. Several authors have proposed that AM have contributed to the colonization of early land plants. AM are generally assumed to be nonspecific associations, since Glomeromycota are able to colonize roots of several host plants and are themselves colonized by different AM fungal species. Despite this lack of host specificity, the diversity of AM fungi has been shown to affect the plant community composition under field conditions and the genetic structure of the AM fungal community was shown to differ significantly according to the plant species. The long, joint evolution of plants and AM fungi is expected not to have occurred independently of the resident bacterioflora [1].

**Materials and Methods**

The experiment was conducted in a green house. The experiment was design, with three replicates The soil was air dried, pulverized and passed through a 2mm sieve and was sterilized by avtoclav under 121 $^0$C for 30 minutes at 0.5 atmosphere. The soil had an initial pH of 5.0 were used pots with 20 cm clay, and for every pots were used of 4 plants. The mycorrhizal fungi inoculants consisting of spores, mycorrhizal root fragments and infected soil was collected from pot cultures of plants leguminous which had been grown for five months after being inoculated with mycorrhiza fungus species. The seeds were germinated in sterilized river sand. After the seedlings had developed two leaves each, four seedlings were transplanted to each clay pot containing the sterilized soil, with arbuscular mycorrhiza inoculum. To determine the effect of arbuscular mycorrhiza inoculation inoculated and non-inoculated legume plants were raised in a green house for three months. Height growth was measured after every 15 days, except during the first months. After 100 day, 50% of the plants were harvested. At the end of four month, some plants were harvested randomly per treatment and arbuscular mycorrhiza infection level was assessed. For the plant tissue nutrient content, above ground biomass was harvested and was oven dried at 70 °C. The plant tissues were then analyzed for total nitrogen. The numbers and length of primary roots per plants were assessed and determined. The measured plants parameters were analysed.

**Results and discussion**

The results obtained indicated the dependence of Soybean mycorrhiza symbiosis. The effect of arbuscular mycorrhiza inoculation on the height increment was obvious on visual comparison at the end of 90 days. The enhanced height increment in Soybean could be attributed to the arbuscular mycorrhiza colonization. Mycorrhiza inoculation is known to enhance plant growth by increasing nutrients uptake of nitrogen, phosphorus and potassium is limited by the rate of diffusion of each nutrient through the soil [2]. It seems likely that arbuscular mycorrhiza in this study increased nutrient uptake by shortening the distance nutrients diffused through the soil to the roots. During

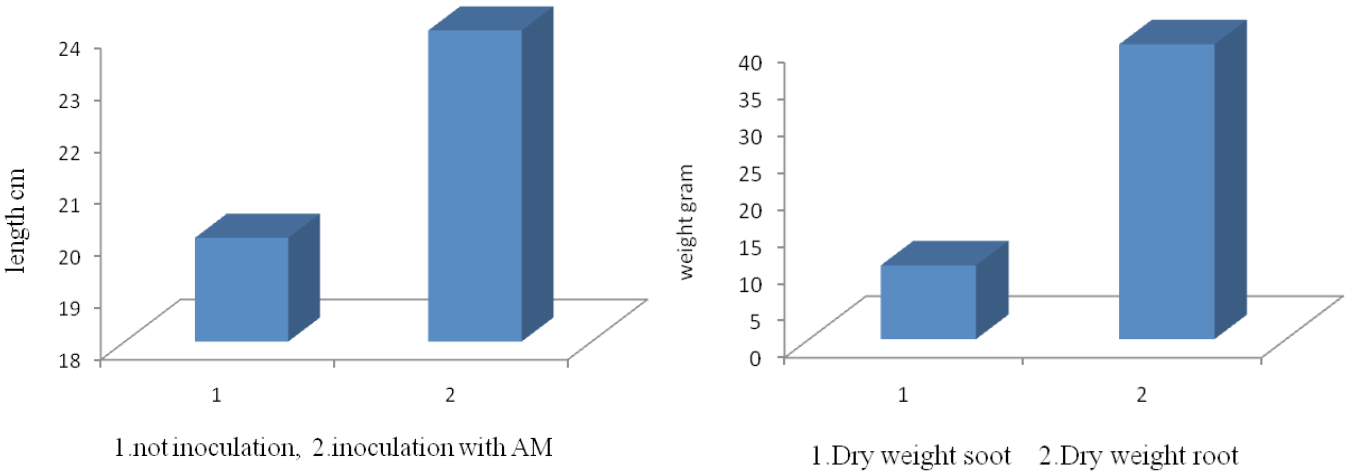
the first 45 days, there was small difference in height increment between inoculated and non inoculated plants, although the height increment in inoculated plants was higher. This could be due to the "lag phase" effect of mycorrhiza inoculation. Many studies have shown that there is a lag phase between mycorrhiza inoculation and the time period when its effect is manifested in the plant [3]. At the end of ninety days, height growth of inoculated Soybean was highly significant as compared to the non inoculated plants. The higher height increment registered with inoculated plants could be as a result of enhanced inorganic nutrient absorption and greater rates of photosynthesis [4]. Arbuscular mycorrhizas are known to affect both the uptake and accumulation of nutrients and therefore, act as important biological factors that contribute to efficiency of both nutrient uptake and use. Researchers have demonstrated that arbuscular mycorrhiza fungi, not only increases phosphorus uptake, but also plays an important role in the uptake of other plant nutrients and water inflows of phosphorus to mycorrhiza roots can be greater than inflows to comparable non-mycorrhiza roots by up to 2–5 times[5].

**Shoot Biomass**

Inoculating Soybean with arbuscular mycorrhizal fungi increased significantly the shoot biomass yield. The shoot biomass production increased by 213% and was highly significant. The highly significant shoot biomass production by the inoculated plants, could be attributed to enhanced inorganic nutrition absorption and greater rates of photosynthesis in inoculated plants [6]. Arbuscular mycorrhizal fungi are reported [7] to enhance plant growth rate through an increase in nutrient uptake, especially phosphorus which is relatively immobile in soils. Arbuscular mycorrhiza inoculation could have enhanced Soybean to absorb more nutrients via an increase in the absorbing surface area. Similar observation has been reported with another scientist [8].

**Root Biomass**

The movement of nutrients to plant roots and the rate of absorption of nutrients by roots, especially nitrogen, phosphorus and potassium, is known to be limited by the rate of diffusion of each nutrient through the soil and not by the ability of the root to absorb the nutrient from low concentration in the soil solutions [9]. In picture 1, A and B shown, inoculating Soybean with Arbuscular mycorrhiza significantly increased the soot length and root, soot biomass production. Arbuscular mycorrhiza infection has been reported to increase both the uptake of nutrients by the roots and the concentration of nutrients in the plant tissues [10]. An increase in nutrient uptake, especially phosphorus in the poor soil used, could have resulted in relief of nutrients stress and an increase in photosynthetic rate, which obviously could have given rise to an increase in plant growth. Research has shown that when root exploration is restricted, up to 80% of the plant phosphorus can be delivered by the external arbuscular mycorrhizal hyphae to the host plant over a distance of more than 10 cm from the root surface [11]. Inoculating Soybean with arbuscular mycorrhiza fungi significantly increased the root length. The inoculation with AM increased the root length by 25%. Mycorrhiza inoculation is known to enhance the plants absorption of more nutrients especially phosphorus via an increase in the absorbing surface area. This in turn could have enhanced a higher plant growth rate resulting to more roots per plant. Mycorrhiza colonization also protect the roots from the soil pathogens and, therefore could have lead to an increase in not only the root growth and nutrient acquisition of the host roots, but also the number of surviving roots [12].




A B

Figure 1. Effects of Mycorrhizal fungi inoculation with Soybean in the green house
MED (Minimal Essential Difference) test. $t = 0.86$, $t > 0.05$, $P = 0.01\%$

**Root to Shoot Ratio**

As shown in (Table 1), the difference between the root to shoot ratio of inoculated and non-inoculated Soybean, was not statistically significant at 5% level though the inoculated Soybean had a higher root to shoot ratio as compared to non inoculated plants. The higher root to shoot ratio of the inoculated plants could be attributed to the effect of mycorrhiza infection, which could have increased nutrients absorption, giving rise to a higher root and shoot biomass increment with a uniform growth.

**Plant Tissue Nutrients Concentration**

In the Soybean after 90 days of phosphorus, nitrogen and potassium concentration was much higher in the inoculated plants than non inoculated ones. The higher phosphorus concentration in the inoculated plants could be attributed to a higher nutrients absorption rate by mycorrhiza plants. Several authors have reported that mycorrhizal roots are able to absorb several times more phosphate than non inoculated roots from soils and from solutions [13]. Increased efficiency of phosphorus uptake by mycorrhizal plants could have led to higher concentrations of P in the plant tissues. The greater phosphate absorption by arbuscular mycorrhizae has been suggested to have arisen due to superior efficiency of uptake from labile forms of soil phosphate, which is not attributable to a capacity to mobilize phosphate sources unavailable to non mycorrhizal roots [14].

**Conclusion**

The current study had shown that inoculating Soybean with arbuscular mycorrhyza enhances growth performance. The inoculation resulted in an increment in height growth by 85% and root by 71% within three months. Shoot biomass increased significantly by 213% while root biomass increased by 241%.

Inoculated plants subequently produced more leaves per plant, which could have increased the rate of photosynthesis. Inoculated plants produced also more roots per plant which were longer than in the non inoculated plants. This improvement in plant growth could be attributed to the enhancement of the plant to absorb more nutrients, via an increase in the absorbing surface area. Arbuscular mycorrhiza colonization also protects roots from soil pathogens and thereby increase root growth and nutrients acquisition of the host plants.

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# STUDY OF WATER STRESS IN SOYBEAN PLANTS WITH JOINT INOCULATION WITH STRAINS BRADYRHIZOBIUM JAPONICUM AND RHIZOBIUM ESPARSETA

**Abstract.** Among the environmental stress factors the most widely limiting for crop production on a global basis is water. Water stress has been found to decrease productivity of most plant particularly soybean. The aims of the study of nodule bacteria of drought water treatment. The result indicated that nodule bacteria showed as *Rhizobium sp*. *Bradyrhizobium sp.* The investigation of drought water stress indicated that, there are significant difference on the treatment of 50 ml water/1000 g soil of drought water stress toward the growth i.e. plant hight, number of leaves and nodule formation on soybean plant.

**Keywords:** Nodule bacteria, *Rhizobium*, *Bradyrhizobium sp*., drought water stress, soybean.

**Introduction**

Soybean is a major source of vegetable protein for most people. The ability of *Rhizobium sp*. to survive at a low water potential in soil has been established by many studies in which viability was assessed by determining colony forming ability on agar plates with a high water potential. Very few studies have addressed either the efficiency of *Rhizobium* growth at low water potential or growth recovery after a rapid water potential increase brought about by a rewetting process [1]. It is unknown what impact a rapid water potential change might have on soil Rhizobium spreading both under free-living conditions and during the period of establishment of the symbiosis. Keeping in view numerous manifestations of a beneficial action of *Rhizobium* bacteria on plants, present investigation involves isolation and characterization of nodule bacteria *Bradyrhizobium japonicum* from soybean and *Rhizobium Esparseta* from roots of wild legume plants of Esparseta. This study was based on the hypothesis that these microbes *Rhizobium* which are nitrogen fixing and growth promoting exhibit the ability to survive and tolerate moisture stress, should they be implied in imparting tolerance to host plant. To achieve this goal, were conducted isolation of nodule bacteria from root of wild type legume plants Esparseta and characterization to drought water stress.

**Material and methods**

Research was conducted at the laboratory and greenhouse conditions. The laboratory research included isolation of nodule bacteria from root nodule from soybean and plants Esparseta by using manual of S. Long laboratory (http://cmqm.stanford.edu/biology/long.protocols.htm). Nodule was characterization of greenhouse treated of drought water stress. The nodules soybeans were collected from experimental station were grown where grown of soybean and from Esperseta planting on dry areas of Kisil Kum, Central Asia. The purification of the nodule bacteria were purified and maintained on yeast extract mannitol, YEM, [2]. Nodule bacteria that have been taken with a needle and entered into sterile (1,5 ml eppendorf tube), and then shaken using a vortex, pipetted 0.1 ml included in petri dish YEMA containing media, and leveled with a spatula, and then incubated at room temperature. Separate colony grows well selected and planted in the media YEMA slant in a test tube (as a pure culture). Characterization of nodule bacteria grown on selective media and studying by electrophoresis with methods T. Eckhardt [3]. Investigation of drought water stress on soybean plant in greenhouse was study uses soybean seed Genetik-1. Soybean seeds were planted in pots (size 20 cm), where each pots filled with 4 soybean seed. Soybean seeds soaked first into sterile distilled water for 2 hours before being planted into pots. After that, the seeds were stocked directly into pots; each pot filled 4 soybean seeds. After one week selected the best seed, while others deprived of pots. Nodule bacteria were identified as *Rhizobium* isolate, propagated in the medium of YEMA. Applications of *Bradyrhizobium japonicum* and *Rhizobium Esparseta* on soybean plant were done at 14 days after planting, by pouring the 2 holes near the rhizosphere. *Rhizobium* concentration used $10^5$ was cfu/ml by 5 ml each hole, where the inoculation is done only once. The investigation of drought water stress is conducted with five levels of water, namely: WSO = Water Stress 0 ml/1000 g soil; WS1 = Water Stress 25 ml/1000 g soil; WS2 = Water Stress 50 ml/1000 g soil; WS3 = Water Stress 75 ml/1000 g soil; WS4 = Water Stress 100 ml/1000 g soil, where each treatment was the provision of water once every day and performed at 17.00 pm. The investigation was repeated 4 times. The parameter of this investigation is plant height, the number of leaves and the number of nodule. The

observations were made in the afternoon every other day for 4 weeks.

Statistical Analysis for the investigation of drought water stress, ANOVA was also performed to determine the effects of plant height, the number of leaves and nodule formation. The percent data were arcsine-transformed before being subjected to ANOVA. When significant differences were detected, means were separated using Tukey's test at 5% probability level.

**Result and discussion**

Soil bacteria of the genera *Rhizobium*, *Azorhizobium* and *Bradyrhizobium* (collectively referred to as *rhizobia*) are involved in interaction with legume plants to form $N_2$-fixing nodules. *Rhizobia* have also been found to be capable of colonizing roots of non-legumes as efficiently as they colonize their legume hosts These organisms are characteristically able to invade the roots hairs of temperate-zone and dry- zone legume plants and incite production of nodules. *Rhizobia* have great potential to nitrogen fixers. They are rods, cocci, gram negative; colonies are circular, convex, semitranslucent, raised and mucilaginous, usually 2–4mm in diameter within 3–5 days on yeast mannitol-mineral salt agar media, Commonly pleomorphic under adverse conditions [4]. Cells contain plasmids, including large, naturally-occurring plasmids of 1500, 1000 kb [5]. The nitrogen-fixation (Nif) genes also appear to be plasmid-borne [6]. The present studies found that *Rhizobium Esparseta* grow less than 2 days. The genus *rhizobium* can be distinguished by the growth rate which the growth rate of the time needed to establish of a colony, there is growing quite fast, less than 3 days as *Rhizobium*, *Sinorhizobium*, and *Allorhizobiu*m [7]. There are currently classified as growing, between 4–5 days, such as *Mesorhizobium* and *Azorhizobium*, but there is also a relatively slow-growing bacteria, more than 6 days, such as *Bradyrhizobium*.

**Investigation of Drought Water Stress on Soybean Plant in Greenhouse**

The means of plant height of soybean at 50% treatment (WS2) showed statiscally significant difference with the treatment of control (WS0) or treatment with 25% (WS1), but did not show significant differences by treatment with 75% (WS3) and 100% (WS4) (Table 1).

Table 1. Means of plant height of soybean (cm)

| Treatment | Week After Treatment | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| WS0 | 33 | 32 | 6 | 6 |
| WS1 | 28 | 28 | 28 | 29 |
| WS2 | 43 | 43 | 43 | 44 |
| WS3 | 41 | 41 | 42 | 43 |
| WS4 | 43 | 45 | 46 | 46 |

*MED – Minimal Essential Difference; P = 0.05*

This indicates that simply by giving 50% of water from the minimum requirements with the use of Rhizobium isolate has been able to increase the growth of soybean plants after treatment with *Rhizobium* isolate. The growth of some strains of *Rhizobium* isolate greatly influenced by high salinity and low water potential conditions of the cropping land [8]. The developmental stage of a cultivated plant has its influence on multiplication of *Rhizobium*. Developmental stage of a cultivated plant determines, to a sufficient degree, the number of *Rhizobium* occurring in a crop [9]. Increased growth rate and metabolism of bacteria is probably related with the development of root system, photosynthetic activity and the amount of exudates associated with this and produced by plants [10].

Effect the number of leaves in the treatment of WS2 (50 ml/1000 soil) is always higher than the other treatments (Figure 1).

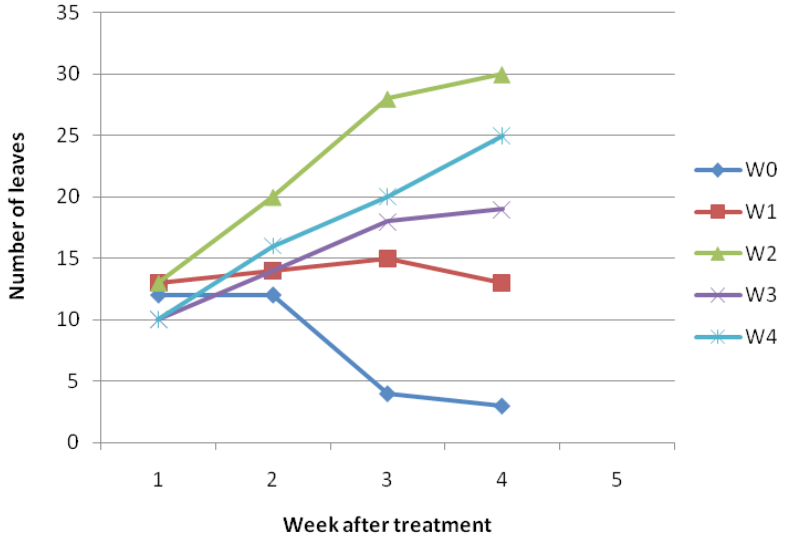


Figure 1. Number of leaves of soybean plant

Maximum leaves in the treatment of WS2 indicated that the optimum growth and development of soybean plant and may be attributed to the symbiotic relationship of *rhizobium* (bacteria) with the roots of leguminous crops, which fix the atmospheric nitrogen into the roots of soybeans and thus the number of leaves plant was increased.

Effect the number of nodule plant-1 in each treatment and control has no statistically different, while the level is low. The number of nodule plant1 in the treatment of WS2 (50 ml water/1000 soil) is higher than the other treatments, which 18 nodule plant1 (Table 2).

Table 2. Means of number of nodule plant

| Treatment | Number of nodule plant | |
|---|---|---|
| WS0 | 1 | Low |
| WS1 | 7 | Low |
| WS2 | 18 | Low |
| WS3 | 8 | Low |
| WS4 | 10 | Low |

The low number of nodule plant1showed that the root formation is not well developed. *Rhizobium* isolates require foods for photosynthesis of soybean plants as an energy source for the formation of root nodules. The water-stress effect have studied at different stages of $N_2$ fixation and verified the adaptive physiological response to stress. Was found a positive interaction between water stress and development stages of $N_2$ fixation. Water stress applied at the stage of 15–30 days gave the most negative interference, indicating it is possibly a critical period of water stress for cowpea. In our study, the water stress was applied from day 10 to day 30 of growth. The treatment of WS2 (50 ml water/1000 g soil), indicated of the role of *Rhizobium* isolate as a stimulus to grow of the soybean plant though not much. This is evidenced by the formation of the structure of pods on the plants treated by WS2 at 3 weeks of observation or five (5) weeks after planting. Basically the use of *Rhizobium* isolate is to increase crop yields, but in achieving optimum outcomes is influenced by several factors such as the number of microorganisms in the soil, pH, soil structure, content of certain chemical elements and temperature [11].

**Conclusions**

This study shows that there was a treatment of WS2 (50 ml water/1000 g soil) treated with *Rhizobium* isolate, the optrimum level for the growth of soybean plant i.e. plant hight, number of leaves and nodule formation on soybean plant.

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# THE STUDY OF THE BIOLOGICAL PROPERTIES OF POTATO VIRUS X IN COMMON ENVIRONMENTAL CONDITIONS OF UZBEKISTAN

**Abstract.** In recent years, PVX has been widely spread in Uzbekistan's climatic conditions, causing symptoms of the disease, like spotty mosaic and curling of potato leaves. The appearance of signs of this viral disease depending on environmental factors, especially temperature, contributes to the fact that it begins to meet in a latent state at a high temperature in the climatic conditions of Uzbekistan, remaining in the nodules of potatoes, causes a decrease in yields every year to 10–59%. Therefore, the extent of the spread of this virus in the climatic conditions of Uzbekistan, natural reserve reservoirs, have been studied by the highly sensitive ELISA method. Based on studies conducted in this direction it was found that the extent of the spread of this virus was initially 16.65%, and in subsequent studies it increased to 24.06%. At the same time, in the climatic conditions, reserve plants such as *Solanum nigrum L., Rumex crispus L., Datura stramonium L., Solanum melongena L., Convolvulus arvensis L., Althaea officinalis L., Malva neglesta Wall* were first established by the ELISA method.

**Keywords:** PVX, enzyme linked immunosorbent essays (ELISA), plant reservations, Tashkent, Uzbekistan.

**1. Introduction**

Over 20 species of viruses have been identified worldwide, causing potato diseases and each of them differs according to the pathological symptoms observed in the plant and economic damage [4]. A number of such pathogenic viruses can include the X-virus of potato, which, depending on potato varieties, environmental conditions and strains of the virus, reduces the yield to 10–59% [2; 4; 11; 15]. This virus is considered one of the dangerous viruses, seriously threatening potato yields worldwide and planting resistant varieties of potatoes that lead to a minimum harm from the influence of the virus [13]. PVX belongs to the genus Potexvirus and known strains such as PVX HB [10; 12] and the newly discovered PVX [4; 21] and PVX Tula [12; 19]. The virus is in many cases stored in nodules, reduces yields year after year and is distributed mechanically and with the help of carriers (vectors) – insects [5].

In many cases, it does not cause symptoms of the disease in plants and is latent, but can cause chlorosis, mosaic and a decrease in the size of the sheets. This virus is found with other viruses (PVY and PVA) and the disease can take a serious nature and this leads to a catastrophic decline in yields [4; 6; 17].

To combat such pathogenic viruses, the focus should be on their "natural foci" [6; 7]. Various diseased plants and the remnants of various organs of such plants in the soil layers can serve as "natural foci" of viral diseases [4; 6]. A. L. Ambrosov, I. T. Ergashev and a number of other authors have experimentally proved that such wild plants as *S. nigrum, D. stramonium, C. arvensis* [9], and in Uzbekistan N. N. Babrishev proved that *L. esculentum* and *C. annum* cultivated plants are hidden reservoirs of X, S and M (K) – potato viruses. The degree of their spread, as well as natural reserves differ from each other in the type of virus, carrier and environmental conditions [7; 8; 18].

Therefore, a study of the extent of spread and natural reserve plants PVX using a highly sensitive, rapid and reliable method (ELISA) is important in developing measures to control the virus and eliminate inaccurate results obtained with low-sensitivity methods. This article is aimed at studying this issue.

**2. Materials and Methods**

The main materials for the study – antibodies of potato viruses (AT (IgG)), conjugate (IgG + enzyme), polystyrene plates and chemical reagents were obtained from the organization "International Center of Potato".

To diagnose potato viruses using IFA, the following were used:

- a specific antiserum prepared on the X potato virus (IgG);
- Polystyrene boards;
- conjugate (IgG + enzyme);

– Buffers (phosphate buffer (composition for 1 liter of distilled water: 8 g NaCl, 0.2 g $KH_2PO_4$, 1.15 g $Na_2HPO_4$, 0.2 g KCI, 0.195 g $NaN_3$) twin phosphate buffer PBS-T), buffer for grinding sample (0.4 g PVP-40.000, 2.0 g egg albumin), conjugate buffer (4.0 g PVP-40.000, 0.04 g egg albumin), substrate buffer;

– clean dishes;

– polyethylene bags for samples;

To determine the viruses, the organs of plants (leaves, stem, root) with the primary signs of the disease were separately packed into polyethylene bags and with the addition of phosphate buffer (composition for 1 liter of NaCl, $KH_2PO_4$, $Na_2HPO_4$, KCl, $NaN_3$, pH-7.4) and a homogenate was prepared. Then, viral AT (IgG) was immobilized in polystyrene plates at 37 °C for 3–4 hours or at room temperature for 5–6 hours, excess of AT (20 drops (0.5 ml) were added to 1 liter of the prepared phosphate buffer) Tween PBS-T) is washed off with Tween phosphate buffer, homogenate is added from the organs of the plant under study (AG) and stored for 3–4 hours in a thermostat at 37 °C. After a certain time, the vegetable juice is washed using a specially designed for washing Tween phosphate buffer and after the conjugate is placed in the microplate of the poly styrene plates, the latter are placed polyethylene bags and stored for 3–4 hours at 37 °C or can be left for 5–6 hours at room temperature 25 °C). The excess conjugate (IgG + enzyme) is washed with Tween Phosphate Buffer (RVS-T) and 50 µl substrate (diethanoamine, 37% HCl), distilled water and substrate tablet (p-nitrophenyl phosphate) are poured into each well of polystyrene plates. When viruses are present in the plants under investigation for 30–60 min, they are detected by a change in the color of the reaction, and the results are taken into account.

**3. Results and discussion**

For investigation of PVX distribution level in Tashkent region samples (leaves) of potato plant were separately collected from Kibray, Parkent, Tashkent and Zangiota districts, for four in one district, from 15 village communities, checked by ELISA method in laboratory condition and obtained results given in the table (1 table).

Table 1.– Determination of sickness rate of potato sorts in Tashkent region by PVX virus with the help of ELISA method

| № | District | Names of farms | First assay | | | Second assay | | |
|---|---|---|---|---|---|---|---|---|
| | | | Potato kinds | Area, ha | Morbidity rate.,% | potato varieties | Area, ha | Morbidity rate,% |
| 1. | Kibray | Kibray agrocomplex | Ditta | 6.0 | 5.0 | Desire | 4.0 | 90.0 |
| 2. | | Jaydakbayev Edil | Desire | 3.5 | 0 | Desire | 1.0 | 70.4 |
| 3. | | Kibray | Mixed | 1.0 | 0 | Ditta | 8.0 | 5.4 |
| 4. | Parkent | Baykazam Jam-plus | Santé | 0.7 | 10.2 | Santé | 1.0 | 0 |
| 5. | | Baykazam Valid plus | Santé | 1.0 | 20.3 | Santé | 0.5 | 0 |
| 6. | | Baykazam tarnovi | Romano | 1.5 | 5.0 | Santé | 1.5 | 0 |
| 7. | | Oqul Orzu rivoji | Ditta | 1.0 | 35.0 | Ditta | 1.0 | 0 |
| 8. | Tashkent | Abdurakhmon | Foody | 1.5 | 15.5 | Marphona | 3.0 | 0 |
| 9. | | Gulnoza Fayz-baraka | Foody | 1.0 | 5.4 | Foody | 2.0 | 15.0 |
| 10. | | Murad agro-plus | Foody | 2.0 | 30.0 | Nevsky | 3.0 | 15.7 |
| 11. | | Batko agro-plus | Foody | 7.0 | 50.0 | Nevsky | 3.5 | 5.4 |
| 12. | Zangi-ota | Dustov Yuldash | Foody | 2.0 | 10.3 | Foody | 3.0 | 20.5 |
| 13. | | Yulchi Khamid | Romano | 1.0 | 0 | Foody | 4.0 | 20.3 |
| 14. | | Yunusov Bakhrom | Foody | 1.0 | 50.0 | Foody | 1.5 | 55.2 |
| 15. | | Okul Orzu rivoji | Foody | 1.5 | 30.6 | Nevsky | 1.5 | 25.0 |

*Note: "0" means absence of virus in the table*

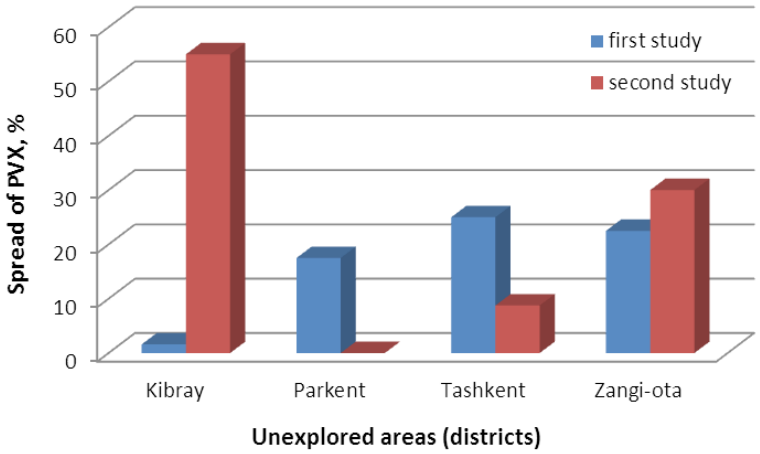
As a result of preliminary studies of samples obtained in Kibray district, the level of PVX distribution in the area was maximum 5%, and secondly, two years after repeated studies, it was found that the level of virus spread increased from 5 to 90%.

As a result of studies, conducted by the Parkent district, at first, the spread of the virus in this area was 5–20%; as a result of repeated studies, the virus was not detected.

In Tashkent district, in a preliminary check, the spread of the virus was 5–50%, after two years after repeated studies it was revealed that the level of spread of the virus decreased by 5–15%.

In the Zangi-Ota area, in both studies, it can be observed that the spread of the virus has not changed much; detailed information about this is given in the table (1-table). Based on the obtained results, the average level of virus spread in

the regions of the region was revealed and given in the form of a histogram (figure). The figure shows that in the Kibray region of the region, compared with the results of preliminary studies in subsequent studies, the spread of the virus increased dramatically, i.e. increased by 50%. According to a number of researchers who conducted research in this direction, the cultivation of potato-infected tubers for many years led to the wide spread of the virus in one field. The same situation is observed in this area, i.e. the re-cultivation of varieties such as ditta and desire for three years (table 1) led to the large-scale spread of the virus in these farms. In Parkent and Tashkent, areas where a decrease in the spread of the virus was observed, phytosanitary measures were carried out in a timely manner in potato fields and potato seeds were annually updated (figure). In the total area studied (31.7%) of Tashkent region, 50.4% of the field (16.1 ha) were sown with the local variety Tuyimli, and foreign varieties such as Ditta, Desiree and Ramona were grown for the remaining 40.6%.




Fifure 1. The prevalence of PVX in areas of Tashkent region

Natural reserves play an important role in the spread of viruses. A number of wild and cultivated plants can be attributed to natural reserves of phytoviruses and these plants occupy an important place in the spread of viruses [6; 9]. Therefore, in the following studies, the fields of rural farms with a high level of distribution and 27 species of wild and cultivated plants in the vicinity of these fields were studied using the ELISA method and the results are shown in the table (table 2).

Table 2.– Determination of PVX Reserve Plants by ELISA

| № | Plant names | | Reaction rate |
|---|---|---|---|
| | Species | Family | |
| *1* | *2* | *3* | *4* |
| 1. | *Cynodon dactylon* (L.) Pers. | *Gramineae* | – |
| 2. | *Cyperus rotundus* L. | *Cyperaceae* | – |
| 3. | *Cucumis sativus* L. | Cucurbiteceae | + + + + |
| 4. | *Atriplex micrantha* C. A. Mey. | *Chenopodiaceae* | – |
| 5. | *Sorghum halepense* L. | *Gramineae* | – |
| 6. | *Solanum nigrum* L. | *Solanaceae* | + |
| 7. | *Artemisia vulgaris* L. | *Compositae* | – |
| 8. | Chenopodium amaranticolor | Chenopodiaceae | + |
| 9. | *Rumex crispus* L. | *Poiygonaceae* | + + + |
| 10. | *Datura stramonium* L. | *Solanaceae* | ++ |
| 11. | *Solanum melongena* L. | *Solanaceae* | + + |
| 12. | *Capsicum annuum* L. | *Solanaceae* | – |
| 13. | *Brassica juncea* Czern | Cruciferae | + |
| 14. | *Mentha asiatica* Boriss | *Labiatae* | + |
| 15. | *Solanum tuberosum* L. | *Solanaceae* (Diyora kind) | + |
| 16. | *Solanum tuberosum* L. | *Solanaceae* (Umid kind) | + + + |

| *1* | *2* | *3* | *4* |
|---|---|---|---|
| 17. | *Solanum tuberosum* L. | *Solanaceae* (Aqrab kind) | + + + + |
| 18. | *Chenopodium quinoa* L. | *Chenopodiaceae* | – |
| 19. | *Convolvulus arvensis* L. | *Convolvulaceae* | + + + |
| 20. | *Ocimum basilicum* L. | *Labiatae* | – |
| 21. | *Amaranthus retroflexus* L. | *Amaranthaceae* | + |
| 22. | *Sinapsis arvensis* L. | *Cruciferae* | + |
| 23. | *Althaea officinalis* L. | *Malvaceae* | + + + + |
| 24. | *Lycopersicum esculentum* Mill. | Solanaceae | + + + + |
| 25. | Alhagi adans | *Leguminosae* | – |
| 26. | *Malva neglecta* Wall. | *Malvaceae* | + + + |
| 27. | *Artemisia vulgaris* L. | *Composita* | – |

*Note: in the table means "–" – the reaction is absent, "+" – the reaction is weak, "++" – the average reaction and "+++" – the strong and "++++" – the very strong reaction.*

As can be seen from the table, the X virus can exist in addition to potatoes in plants such as Cucumis sativus L., Solanum nigrum L., Rumex crispus L., Datura stramonium L., Solanum melongena L., Petunia hybrida, Convolvulus arvensis Althaea officinalis L., Lycopersicum esculentum Mill., Malva neglesta Wall and these plants have a very high virus content (3+ and 4+). In addition, the virus can multiply in plants such as *Solanum nigrum L, Ch. amaranticolor, Brassica juncea Czern., Mentha asiatica Boriss*, but in small quantities. In *Cynodon dastylon (L.) Pers., Xanthium strumarium L., Sorghum halepense L., Capsicum annuum L., Ocimum basilicum L., Artemisia vulgaris L. In Artemisia vulgaris L.*, the virus was not detected (Table 2).

Based on the above data, under the climatic conditions of Uzbekistan, PVX infects single and perennial plants of the families Solanaceae, Malvaceous (Malvaceae), cruciferous (Cruciferae), amaranth (Amaranthaceae), complex flowers (Compositae) and accumulates in large quantities. This means that these plants undoubtedly serve as PVX reserve plants.

In general, potato viral diseases have been studied since 1916 in England, Holland, USA, Germany, Russia, Estonia by such scientists as Quiner, Boties, Schulz, Folsom, Cassanis, Martin, Yora, Morel and Ambros [4; 2; 3; 8], but studies conducted in the conditions of Uzbekistan were carried out only at the level of the plant-indicator, by the drop method and on the sensitivity of the ABC test (0.2 μg / ml). Many reserve plants and a small amount of viruses in potato varieties remained outside the sensitivity level of the method. In this work, highly specific titrated antiserum was used [3], the sensitivity level of which is 0.01–1 ng and prepared only for this virus.

Many plants are asymptomatic and analyzed for the first time. For example, the plants first analyzed are *Cucumis sativus L., Rumex crispus L., Brassica juncea (L.) Czern., Althaea officinalis L., Malva neglesta Wall* and their PVX content is high. It means, undoubtedly, these plants are introduced into a number of plants-reservers for PVX for the first time in phytovirusology in the climatic conditions of Uzbekistan.

On the basis of the identification of these plant-reserve plants, the regularity of the PVX-Uz cycle in nature and the type of "natural focus" were revealed. According to the theory of E. N. Pavlovsky on "Natural foci of vector-borne diseases" [22] the natural focal type of this virus belongs to the second type, i.e. to the type of "naturally focal diseases with a stable circulation within cultivated plants." Despite the existence of a number of plants that reserve the virus in nature, they are transmitted through nodules from generation to generation and there remains a strong link between the pathogen (virus) and the cultivated plant (potato).

**4. Conclusions**

Thus, in the climatic conditions of Uzbekistan, the presence of a number of natural plant-reserving agents, such as *Cucumis sativus L., Rumex crispus L., Brassica juncea Czern., Althaea officinalis L., Malva neglesta Wall, D. stramonium L., D. metel L* and with the fact that the virus belonged to natural foci, it was found that they belong to the type of "natural circulation within cultivated plants".

At the same time, the distribution of PXV in the Tashkent region was studied by ELISA, one of the most sensitive methods. According to the results of the study, the spread of the virus in the Kibray district of the Tashkent region increased to 50% compared with initial surveys, while in the Parkent region there was a noticeable decrease in the number of viruses.

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# EFFECT OF ESCIN ON THE VOLUME REGULATION OF RAT THYMOCYTES

**Abstract.** It was demonstrated that a horse chestnut saponin, escin, stimulates the cell volume regulation system of thymocytes under hypoosmotic stress. However, this effect could be detected only at relatively low concentrations (1–5 μM), whereas at higher doses (10–100 μM) we observed multy-phase changes in the cellular volume and sustained swelling.

**Keywords:** escin, hypoosmotic stress, thymocytes, Donnan equilibrium, regulatory volume decrease.

**Introduction**

Escin (polyhydroxyolean-12-ene 3-O-monodesmosides) is a natural mixture of pentacyclic triterpenoid saponins derived from the seeds of the horse chestnut (Aesculus hippocastanum) [1; 2]. It exerts remarkable anti-inflammatory, anti-oedematous and vasoprotective properties. Recently, escin was found to induce apoptosis in cancer cells of various origins, reduce the tumor size in vivo and is considered as a perspective anti-cancer drug [1]. However, despite an increasing significance of escin in medicine, its molecular mechanism of action and influence on the cellular membrane remains unclear. In our previous study, we have demonstrated that escin induced human red blood cell lysis by forming very large pores with a radius of app. 2.6 nm, which is comparable to the size of hemoglobin [3]. In the present study, we show that escin greatly modulates the cell volume regulation of thymocyte under hypoosmotic stress condition.

**Materials and methods**

1. The normal Ringer solution contained (mM): 135 NaCl, 5 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 11 HEPES, 5 glucose (pH 7.4, 290 mOsm/kg-$H_2O$). The H-buffer contained (mM): 5 KCl, 10 HEPES, 2 $CaCl_2$, 1 $MgCl_2$, 5 glucose, pH 7.4 (40 mOsm/kg-$H_2O$). Hypotonic solution was prepared by mixing the normal Ringer solution with H-buffer in a ratio of 3:4 (vol/vol). Cell isolation was performed as described previously [4–8]. All animal experiments were conducted in accordance with the ARRIVE guidelines and approved by the Bioethics Committee of the Institute of Biophysics and Biochemistry. Briefly, the 6–8 weeks old rats, kept in a vivarium on an average diet, were anaesthetized with halothane or diethyl ether and painlessly euthanized by cervical dislocation. The thymi were dissected and carefully washed with an ice-cold normal Ringer solution. The thymi were then minced using fine forceps and passed through a 100 μm-nylon mesh. The suspension was centrifuged at 1000 g for 5 min, the pellet was washed two times with the normal Ringer solution and resuspended in this medium at a cell density of $100 \times 10^6$ cells/ml. The cell suspension was kept on ice for ≤5 h and contained no more than 5% of damaged cells as assayed by trypan blue exclusion. Cell volume changes under

non-isoosmotic conditions were recorded by light transmittance measurement as described previously [4–7, 9]. Briefly, 900 µl of the normal Ringer, or hypotonic solutions was added to the 1.5 $cm^3$ glass cuvette thermo stated with a water jacket and equilibrated for 10 min. Escin (Sigma Cat No. E1378) was added from a stock solution in DMSO. The final solvent content never exceeded 0.1%, and at this dose it did not affect the measured parameters. An aliquot (100 µl) of cell suspension was added to this medium to yield the final cell density of $10 \times 10^6$ cells/ml. The light transmittance was measured at 610 nm (band-pass filter) using a photometer MKMF-01 (Russia). The output signal was amplified by U5–11 amplifier (Russia), digitized at 100 Hz using a USB sensor interface GO! Link and recorded by Logger Lite software (Vernier, Beaverton, OR). The parameter RVD (Regulatory Volume Decrease) was calculated using the following equation:

$$RVD = (T_{max} - T_{15})/(T_{max} - T_0)*100\% \quad (1)$$

where $T_0$ and $T_{max}$ are the initial and maximal light transmittances, and $T_{15}$ is the light transmittance measured 15 minutes after the onset of hypotonic stress. The *RVD* = 100 for complete recovery of the cell volume to the initial level, and *RVD* = = 0 when volume regulation is fully suppressed. Under control conditions, *RVD* usually had values of 60–90% depending on the cells condition, osmotic gradient, temperature and other experimental conditions.

**Results and Discussion**

In our research, we examined the influence different concentrations of escin on the cell volume regulation in rat thymocyte. In the isotonic medium (normal Ringer's solution), the volume of thymocytes remained unchanged for 15–20 minutes. When the thymocytes were placed in the hypotonic medium, they rapidly swelled (a passive response) and then started actively restore their initial volume (Fig. 1 A). In the control group, the parameter *RVD* averaged at 70.3 ± 4.5% ($n = 5$).

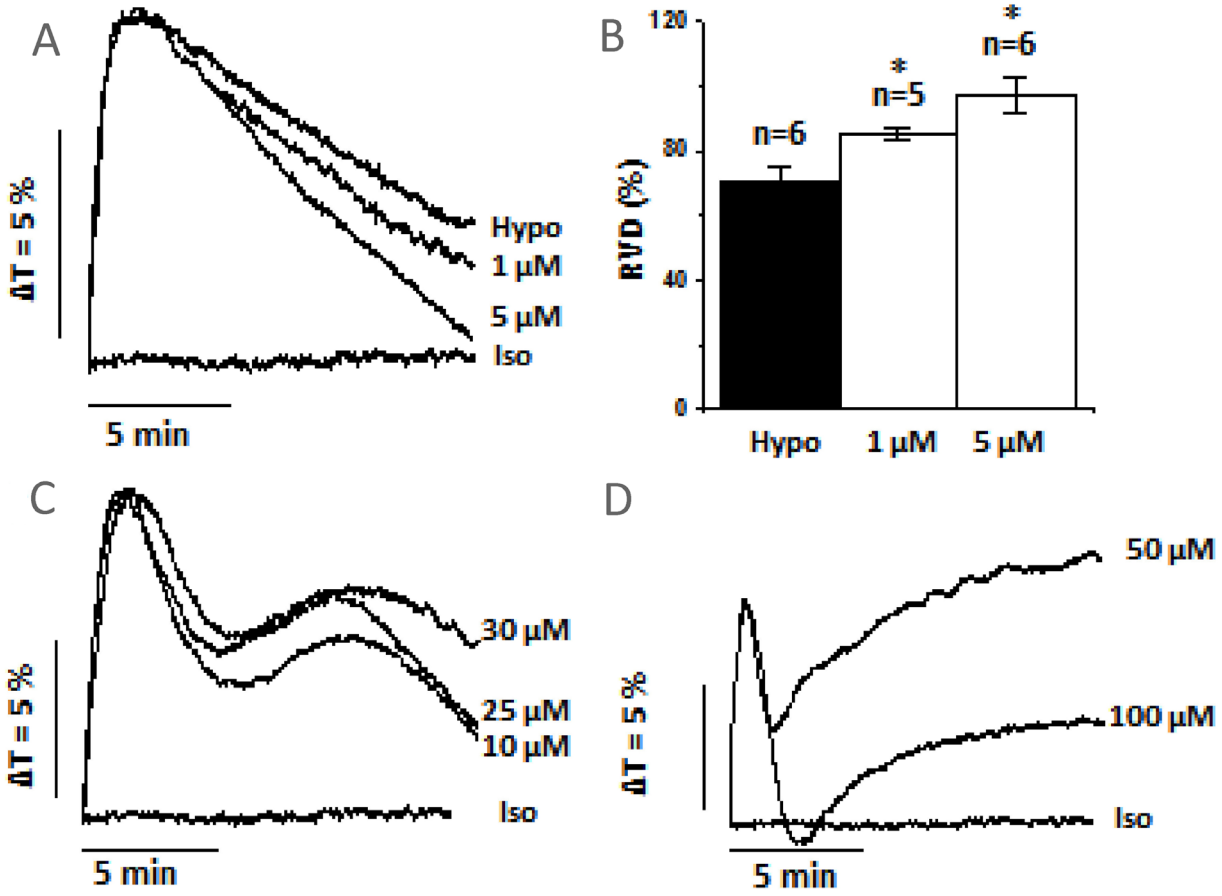


Figure 1. The effect of escin on regulation of thymocytes volume under hypoosmotic stress

Original recordings of the light transmittance change of the cell suspension (an indicator of the cell volume change, see Experimental section) of thymocytes in isotonic medium (Iso) and under hypoosmotic stress in Control hypotonic conditions (Hypo) and in the presence of escin at indicated concentrations (A, C, D) and respective mean values of the parameter RVD at 1 µM and 5 µM (B). Significantly different from the control values at $P < 0.05$, n is number of experiments

When escin was added to the hypoosmotic medium at a concentration of 1 μM, we observed an up-regulation of the ability of cells to restore their volume, and parameter RVD was 85.3 ± 1.8% (n = 6). This effect was even more pronounced at a concentration of 5 μM, at which RVD = 97.3 ± 5 (n = 6) (Fig. 1 A, B). The observed enhancement of the volume regulation is unusual and could be explained by the pore-forming properties of escin. We suppose that intracellular osmolytes exit the cells through the escin-formed pores thereby facilitating a decrease in the intracellular osmotic pressure.

When escin was applied at higher doses of 10–30 μM, the time course of cell volume changes had a complex shape (Fig. 1 C). First, cells swelled and then started to decrease their volume. However, after app. 5 min cells again swelled to the volume which was lower than maximal level. Then, after app. 10 min from the beginning of osmotic stimulation, a second phase of volume decrease was recorded. Explanation of such a complex kinetics is difficult. We believe that, as the amount of substance increases, the number of escin-formed pores in the plasma membrane also increases. Since the size of the escin pore is very large [3], the system turns from a double-Donnan equilibrium to a simple Donnan system resulting in the cellular swelling. The late phase of the light transmittance recordings could reflect cell lysis.

When we increased the dose of escin to 50 and 100 μM, the shape of the time course was distorted even more (Fig. 1 D). We believe that recorded kinetics could largely reflect micelle formation process by the saponin, although initial swelling phase, regulatory volume decrease and secondary swelling we still observable.

In conclusion, we found a prominent stimulating effect of low doses of escin on the cell volume regulation of rat thymocytes, Since volume regulation machinery is deeply involved in the first phase of apoptosis – apoptotic volume decrease [10], we suppose that the effects of escin observed in our experiments are related to the recently explored anti-cancer properties of this drug.

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# INVESTIGATION OF THE GENETIC BASIS OF SALT TOLERANCE IN COTTON

**Abstract.** Based on the analysis of the $F_1$ and $F_2$ hybrids derived from the crossing of 3 salt-tolerant forms of cotton with a susceptible tester line, it has been revealed that the variety An-Bayaut-2 has one salt tolerance gene with no dominant effect. Navbahor-2 has one dominant resistance gene with complete dominance and Gulbahor-2 has three dominant salt tolerance genes.

**Keywords:** salt tolerance, lamina, small cells, chloroplast, motor cells, xylem, seedling, photosynthesis.

**1. Introduction**

Soil salinization is one of the extreme factors prevalent in very large areas both in our country and around the world. For all cultivated species, this factor has a negative effect, the degree of which is the greater, the higher the level of salinity. The negative effect of salinization is manifested in the deterioration of many properties and functions of plants and eventually leads to a decrease in their productivity [4].

It is known that the main method to control soil salinization is the use of soil reclamation and agrotechnical measures. However, along with them, the development of methods for increasing the salt tolerance of plants is of great practical importance in combating salinization.

The study of this problem is conducted mainly in two directions. First, the study of the physiological mechanisms of salt tolerance and changes occurring in a plant under the influence of salinity. Second, the investigation of the genetic basis of salt tolerance.

**2. Materials and methods**

Laboratory method for assessing salt tolerance of seeds: Determination of seed germination (in rolls). Assessment of the salt tolerance of samples is based on the germination rates of seeds and seed sprouting in salt solution, compared with sprouting in water (control):

$$P = \frac{n1 * 100\%}{n}$$

Where, P is the salt tolerance of the sample:

$n$ – is the number of seedlings in control;

$n1$ – is the number of seedlings in the salt solution.

**3. Results of the study**

The genetic aspects of salt tolerance in cotton plants remain poorly studied. The salt tolerance of cotton, like all other traits, is genetically determined. This is evidenced by the facts of transmission through distant hybridization of salinity resistance to a number of varieties and forms of cotton [1].

Three salt-tolerant varieties (Gulbahor-2, Navbahor-2, AN-Bayaut-2, susceptible variety Tashkent-6) and six hybrids derived from crosses with the involvement of these varieties served as the research material in our experiment. The relative length of the seedlings was used as a salt tolerance criterion.

The findings indicate that in the absence of salinity there were no statistically significant differences in length of the seedlings of the samples selected for investigation.

This observation suggests that in hybrid plants the differences in the length of the seedlings when grown on a saline background will be only due to salt tolerance genes.

Under the conditions of salinity, the salt tolerance of $F_1$ hybrids in two combinations of salt-tolerant samples with a susceptible tester was close to the salt tolerant parent (Gulbahor-2 × Tashkent-6, AN-Bayaut-2 × Gulbahor-2). The crossing of a saline-resistant tester with salt tolerant samples did not show significant differences in resistance rates. The dominant trait of salt tolerant parents showed hybrid combinations Gulbahor-2 × Tashkent-6, Gulbahor-2 × AN-Bayaut-2) (Table 1). Dominance was practically absent in two hybrids (Tashkent-6 × Gulbahor-2, AN-Bayaut-2 × Gulbahor-2).

An analysis of $F_1$ from crossing of resistant samples with a susceptible tester Tashkent-6 variety showed a different dominance pattern of resistance genes. $F_1$ samples (Gulbahor-2 × Tashkent-6), $F_1$ (Gulbahor-2 × AN-Bayaut-2) have almost complete dominance of the salt tolerance gene. Samples $F_1$ (Tashkent-6 × Gulbahor-2), $F_1$ (AN-Bayaut-2 × Gulbahor-2) and $F_1$ (Navbahor-2 × Gulbahor-2) lack the dominance of the salt tolerance gene, which suggests that they are not identical. At the same time, based on this analysis, the hypothesis of their possible allelicism cannot be excluded.

In $F_2$ generation, from the crossing of the cultivar Gulbahor-2 with a susceptible form a following segregation by seedlings length has been found: 236 plants with a length of 17.5–20.2 cm and 7 plants with a length of 9.1–10.2 cm.

Table 1.– Characteristics of $F_1$ hybrids derived from crossing salt-resistant samples with susceptible testers by the seedlings length under the salt conditions (NaCl, 0.7 MPa)

| № | Varieties and hybrids | Seedlings length, NaCl, 0,3% | | *hp* |
|---|---|---|---|---|
| | | $x \pm S_x$ | *Cv*,% | |
| 1. | Tashkent-6 | 1.56 ± 0.18 | 40.27 | |
| 2. | AN-Bayaut-2 | 3.50 ± 0.25 | 25.56 | |
| 3. | Gulbahor-2 | 4.30 ± 0.27 | 22.31 | |
| 4. | Navbahor-2 | 2.82 ± 0.22 | 27.86 | |
| 5. | Tashkent-6 × Gulbahor-2 | 1.66 ± 0.20 | 43.17 | –0.48 |
| 6. | Gulbahor-2 × Tashkent-6 | 3.49 ± 0.28 | 27.98 | 1.01 |
| 7. | AN-Bayaut-2 × Gulbahor-2 | 3.58 ± 0.24 | 23.88 | –0.8 |
| 8. | Gulbahor-2 × AN-Bayaut-2 | 4.32 ± 0.25 | 20.02 | 1.05 |
| 9. | Navbahor-2 × Gulbahor-2 | 2.94 ± 0.23 | 27.32 | –0.84 |
| 10. | Gulbahor-2 × Navbahor-2 | 4.16 ± 0.28 | 23.68 | 0.81 |

This segregation does not correspond to the theoretically expected with mono – or digenic control of salt tolerance, but does not contradict the hypothesis of salt tolerance control by three independent genes: ($\chi^2$= 2.75; 0.05 < P < 0.1).

In $F_2$ from crossing An-Bayaut-2 variety with a susceptible tester (Tashkent-6 variety), three groups of plants with seedlings length 17.4–18.9; 12.8–14.8 и 7.2–9.9 cm were clearly distinguished. The actual distribution by groups was 67:111. Taking into account the lack of dominance of salt tolerance trait in this sample, this findings can be considered as supporting the hypothesis of monogenic control of salt tolerance ($\chi^2$ = 2.84; 0.10 < *P* < 0.25). In F2, from the crossing of Navbahor-2 with the susceptible tester Tashkent-6 the ratio of long to short seedlings was 127: 39, which corresponds to the theoretical calculation with one dominant resistance gene in Navbahor-2 ($\chi^2$= 0.20, 0.50 < P < 0.75).

Thus, based on the analysis of $F_1$ and $F_2$ hybrids derived from crossing of 3 salt-tolerant forms of cotton with a susceptible tester, it was found that AN-Bayavut-2 has one salt tolerance gene without a dominant effect, Navbakhor-2 has one dominant resistance gene with complete dominance and Gulbahor-2 has three dominant salt tolerance genes.

The complex picture of salt tolerance inheritance is probably determined by the presence of numerous factors controlling this trait.

**4. Conclusion**

Based on the analysis of the $F_1$ and $F_2$ hybrids derived from crossing of 3 salt-tolerant forms of cotton with a susceptible tester, it was found that AN-Bayavut-2 has one salt tolerance gene without a dominance effect, Navbahor-2 has one dominant resistance gene with complete dominance and Gulbakhor- 2 has three dominant salt tolerance genes.

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# VSOR CHANNEL PROPERTIES IN MELANOMA CELLS CULTURED IN DIFFERENT MEDIUMS

**Abstract.** Effect of DMEM and RPMI-1640 mediums on VSOR anion channel properties in a melanoma cell line (KML) was studied. Selectivity and single channel amplitude exhibited significant differences in KML cells cultured under different conditions.

**Keywords:** Melanoma, B16, ion channel, VSOR, VRAC.

**Introduction**

Malignant melanoma is one of the most aggressive skin cancers. The percentage of the illness in Caucasian populations has extremely increased comparing to other tumors over the last 30 years [1]. Mortality risks in malignant melanomas are higher due to its resistance to conventional treatment [2]. Ion channels may emerge as new targets for melanoma treatment. Volume-sensitive outwardly rectifying (VSOR) anion channel plays a major role in cell volume regulation system, also involved in different physiological and pathophysiological processes [3]. However, the role of VSOR channel in malignant melanoma tumorigenesis and melanogenesis remains poorly understood. B16 mouse melanoma cell line is widely used as an appropriate model for metastasis, melanogenesis and tumor formation studies. Modification of B16 cells culture conditions are known to induce morphological changes (differentiation), as well as alterations in malignancy, melanogenesis and unusual metastasis locations [4; 5]. In the present study, we found that cell culture conditions significantly affect the biophysical properties (selectivity and single-channel amplitude) of the VSOR anion channel in KML melanoma cells.

**Materials and methods.** KML melanoma cell line (patent UZ IAP 02729) was originally generated by continuous culturing of excised primary lung tumors from mice intravenously injected with B16 melanoma. KML were cultured in RPMI-1640 (HiMEDIA, India) or in DMEM (GIBCO, Japan) supplemented with 100 U/ml penicillin plus 100 μg/ml streptomycin as well as with 10% fetal bovine serum. Cells were kept at 37 °C at 5% $CO_2$. For patch-clamp experiments, cells were cultured in suspension under gentle stirring during 4–5 hours.

Standard Ringer solution contained (in mM): 135 NaCl, 5 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 11 HEPES, and 5 glucose (pH 7.4 adjusted with NaOH, 290 mosmol/kg-$H_2O$). The standard pipette solution for whole-cell experiments contained (in mM): 125 CsCl, 2 $CaCl_2$, 1 $MgCl_2$, 3 $Na_2ATP$, 5 HEPES (pH 7.4 adjusted with CsOH), 10 EGTA, and 50 mannitol (pCa 7.65; 320 mosmol/kg-$H_2O$). For measurements of glutamate permeability, the low-Cl bath solution was prepared by replacing 135 mM NaCl in standard Ringer solution with 135 mM Na-glutamate. Hypotonic solution for single-channel measurements contained (in mM): 100 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 10 HEPES (220 mosmol/kg-$H_2O$, pH-7.4, adjusted with KOH). Pipette solution for on-cell experiments contained (in mM): 100 CsCl, 2 $CaCl_2$, 1 $MgCl_2$, 5 HEPES (210 mosmol/kg-$H_2O$, pH-7.4, adjusted with CsOH). Osmolality of experimental solutions was measured with a vapor pressure osmometer VAPOR5600 (WESCOR, South Logan, UT).

Patch electrodes were fabricated from borosilicate glass capillaries (outer diameter 1.4 mm, inner diameter 1.0 mm) with a micropipette puller (model PP-830; Narishige, Japan) and had a tip resistance of 2–5 MΩ when filled with pipette solutions. Fast and slow capacitative transients were routinely compensated for. For whole-cell recordings, the access resistance did not exceed 6 MΩ and was always compensated

for by 70–80%. Membrane currents were measured with an EPC-9 patch-clamp system (Heka-Electronics, Lambrecht/Pfalz, Germany). Data acquisition and analysis were done using Pulse+PulseFit (Heka-Electronics). Currents were filtered at 1 kHz and sampled at 5–10 kHz. When appropriate, off-line correction was made for changes in liquid junction potentials calculated using pCLAMP 8.1 (Axon Instruments, Foster, CA) algorithms. Whenever the bath $Cl^-$ concentration was altered, a salt bridge containing 3 M KCl in 2% agarose was used to minimize variations of the bath electrode potential. All experiments were performed at room temperature (23–25 °C).

Data were analyzed by OriginPro 8 (MicroCal Software, Northampton, MA). Pooled data are given as means ± SEM of *n* observations. Statistical differences of the data were evaluated by the unpaired Student's *t* test and considered significant at $P < 0.05$.

**Results and Discussion.** Under whole-cell patch-clamp configuration, hypertonic pipette solution (osmolality 320) induced visual swelling of the KML cells, which was accompanied by an increase of whole-cell current (Figure 1. A, B). Time of half- activation of swelling-activated conductance was app. 9.5 min (Figure 2. A). The activated current exhibited outward rectification and time-dependent inactivation at large positive potentials higher than +80mV. The macroscopic current density at +100 mV was app. 240 pA/pF. The current asymmetry (ratio of the outward to inward current) was around 6.5 (Figure 2. B). The activation time, current density and asymmetry did not show any significant difference in KML cells for both culturing mediums.

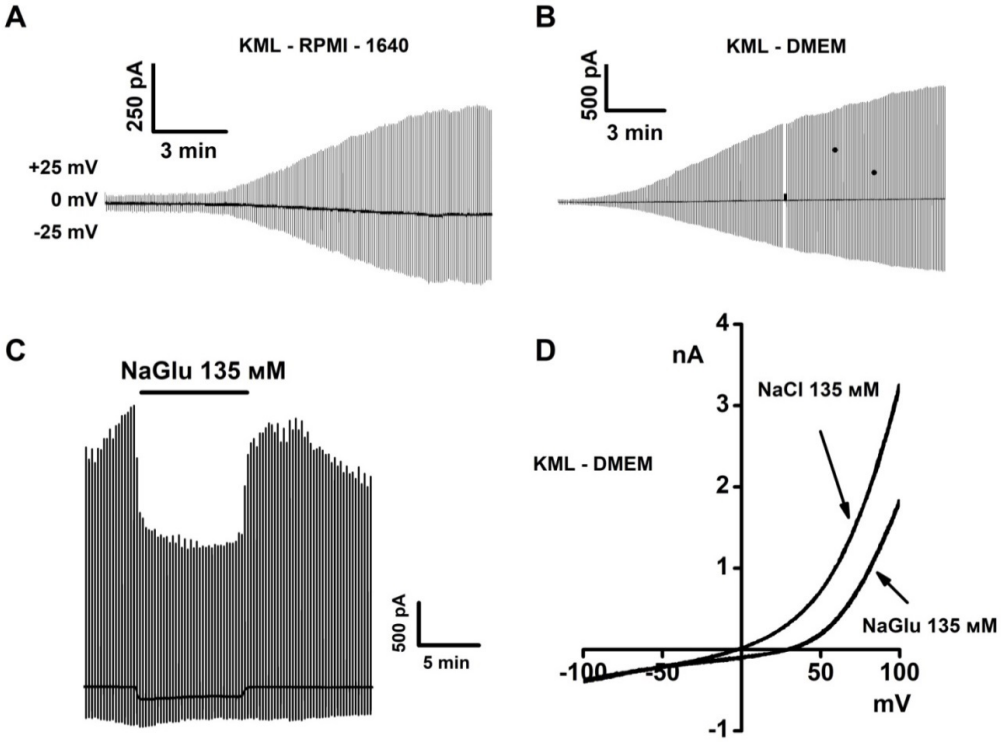


Figure 1. Activation and selectivity of the VSOR channel in melanoma cells cultured in RPMI-1640 and DMEM: (A) Activation of the VSOR currents in KML/RPMI-1640 at ± 25 mV upon osmotic swelling. (B) Activation of the VSOR currents in KML/DMEM at ± 25 mV upon osmotic swelling. (C) Demonstration of the VSOR channel selectivity measurements in KML/DMEM. Ramp pulses ±100 mV were applied every 10 s to the pre-swollen cell to elucidate the currents. (D) Voltage-current relationship of the macroscopic current in standard Ringer solution (146 mM $Cl^-$; $E_{rev}$ = –3,1 mV), and low $Cl^-$ solution (135 mM glutamate+11 mM $Cl^-$; $E_{rev}$ = 29.4 mV) in KML/DMEM

In order to elucidate changes in the selectivity properties of VSOR in KML cells, which were influenced by alteration of culture medium, the low-chloride bath solution was used. When activated current reached the steady state level, the standard Ringer solution (146 mM $Cl^-$) was replaced by Na-glutamate solution (135 mM glutamate + 11 mM $Cl^-$) (Figure 1. C, D). As illustrated in Figure 1C, this maneuver resulted in a decrease of the whole-cell current and shift of the reversal potential (Fig. 1D) for KML/DMEM to $E_{rev}$ = 30.6 ± 0.9 mV ($n$ = 9) and for KML/ RPMI-1640 to $E_{rev}$ = 36.9 ± 2.6 mV ($n$ = 6) (Figure 2. D). The shift of the reversal potentials to positive (more depolarized) values confirmed anion selectivity of the recorded currents. As shown in (Figure 2. D), comparison of the mean values of the reversal potentials in KML cells cultured in different mediums showed that the differences were subtle but significant. Permeability ratio $P_{Glu}/P_{Cl}$ was 0.213 ±

0.01 ($n$ = 9) and 0.17 ± 0.03 ($n$ = 6) for KML/DMEM and KML/RPMI-1640 conditions, respectively (Figure 2. E).

For single-channel experiments, bath hypotonic solution with high [$K^+$] was used. High [$K^+$] in bath and presence of $Cs^+$ ions in pipette nullified potassium potential on the membrane and decreased cationic $K^+$ – flux through the membrane. Before forming a gigaseal contact, cells were incubated for 5–10 min in hypotonic solution to induce sustained swelling. Single channel events were recorded in on-cell mode at +140 mV. The mean single-channel amplitude was 3.6±0.1 pA ($n$ = 87 from 9 patches) for KML/DMEM and 4.5 ± 0.9 pA for KML/RPMI-1640 ($n$ = 113 from 9 patches). As shown in (Figure 2. C), the difference in single-channel amplitude was statistically significant for KML/DMEM vs KML/RPMI-1640.

**In conclusion,** culturing the KML melanoma cells in different culture mediums causes significant changes in VSOR anion channel biophysical properties, such as selectivity and single channel conductance.

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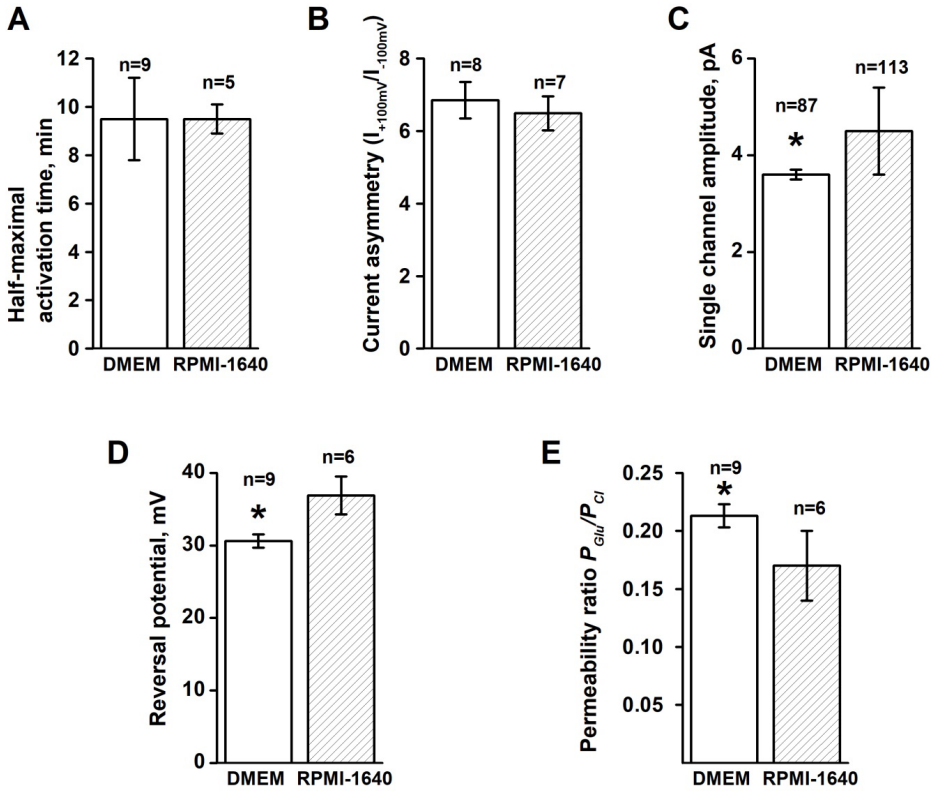


Figure 2. The summary graphs representing half-maximal activation time (A), current asymmetry determined as a ratio of the whole-cell current at +100 mV to that at –100 mV (B), mean single-channel amplitudes at +140 mV (C), reversal potential in the presence of Na-glutamate bath solution (D), and permeability ratio of glutamate over chloride calculated using Goldman-Hodgkin-Katz equation (E). * $P < 0.05$ DMEM vs. RPMI-1640

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# EFFECT OF UV IRRADIATION OF PGPR BACTERIA ON SEEDS GERMINATION AND PLANT GROWTH OF MUNG BEAN (*VIGNA RADIATA*)

**Abstract.** Plant growth promoting rhizobacteria (PGPR) are beneficial bacteria that colonize plant roots and enhance plant growth. The strains of *Pseudomonas putida 4/1, Azotobacter chroococcum P-29* and *Bacillus subtilis* were allowed for UV irradiation for different time intervals to cause mutation and observed for their consequent action on the seeds germination and plant growth of mung bean *(Vigna radiata)*. The 1% survival of bacterial isolates was resulted in the samples, treated with UV irradiation for 60 min. The mutant strains of *Pseudomonas putida M-1, Azotobacter chroococcum M-1* and *Bacillus subtilis M-1* were found effective to enhance the germination energy of mung bean seeds compared to parent strains. Moreover, treatment of the mung bean seeds with mutant strain of *Bacillus subtilis M-1* had a significant stimulation effect on plant growth. The length of the stems and roots of mung bean treated with *Bacillus subtilis M-1* increased significantly in comparison with parent strain in 2, 3 and 1, 3 times, respectively.

**Keywords:** PGPR bacteria, Mutagenesis, Nitrogen fixation, *Vigna radiate.*

**Introduction**

The increasing demand for crop production with a significant reduction of synthetic chemical fertilizers and pesticides use is a big challenge nowadays. The use of PGPR has been proven to be an environmentally sound way of increasing crop yields by facilitating plant growth. Plant growth promoting rhizobacteria (PGPR) are beneficial bacteria that colonize plant roots and enhance plant growth [1]. The use of PGPR could increase the yield of agricultural crops and that is an environmentally friendly step. They help in increasing nitrogen fixation (legumes); promoting free-living nitrogen-fixing bacteria; supply of macronutrients; production of plant hormones. They also enhance the growth of other beneficial microbes and control the other biotic stress causing agents [2]. PGPR could regulate growth hormone and nutritional balance, induce the immune system of plants, antagonist with phytopatogen and dissolve the nutrients to be easily absorbed by plants [3]. For decades, varieties of PGPR have been studied and some of them have been commercialized, including the species of *Pseudomonas, Bacillus, Enterobacter, Klebsiella, Azobacter,* and *Serratia* [4].

Strain improvement is an essential part of process development. Induced mutagenesis is widely used for selection of microorganisms producing biologically active substances and further improving of their activities. Strain improvement is usually done by classical mutagenesis which involves exposing the microbes to physical mutagens such as ultraviolet rays. Induced mutagenesis by using UV rays for selection of microorganisms to produce biologically active substances and

improvement of their activities have been known effective [5]. The present study was focused on strain improvement of bacterial strain through mutation and to assess the enhancement or reduction of mung bean (*Vigna radiata*) growth.

**Materials and Methods.** The objects of the study were bacterial strains of *Pseudomonas putida 4/1, Azotobacter chroococcum P-29* and *Bacillus subtilis* from the own collection of microorganisms. The cultures were maintained on King B agar (*Pseudomonas putida 4/1*), pea agar (*Azotobacter chroococcum P-29*), meat-peptone agar (*Bacillus subtilis*) and stored at 4 °C. All bacterial strains were subjected to UV mutagenesis at the range of 260 nm. 4 mL of bacterial suspension were poured aseptically into a sterile Petri dish. The exposure to UV rays was conducted in a dark chamber with UV lamp. The distance from the UV lamp to Petri dish was around ± 60 cm with a treatment time of 30, 45 and 60 min. During the exposure, petri dish cap was opened and all the other sources of light were cut off. After that, suspension was transferred into sterile test tubes covered with a black paper and kept in the refrigerator overnight to avoid photo reactivation. Next day, suspension of each treatment was serially diluted with sterile distilled water, plated on to nutrient agar medium and incubated for 24 h at 28 °C. The number of colonies in each plate was calculated [6].

The effect of the obtained PGPR mutant strains on the seeds germination and plant growth of mung beans was studied according to GOST [7]. The seeds germination and plant growth of mung bean was observed by placing the mung bean seeds on rhizosphere soil in seed trays. Germinated seeds were soaked in 3 ml mutant bacterial strains for 15 minutes. Growth of the germinated seeds was observed at regular intervals.

All the analyses were performed in triplicate, and the results were expressed as mean SD values of the three sets of observations [8].

**Results and Discussion.** The effect of the obtained mutant strains of PGPR bacteria on the germination and energy of germination of the mung bean seeds was studied. The energy of germination of mung bean seeds was determined on the 4$^{th}$ day after seeds treatment with culture liquid as well as the germination of the mung bean seeds was determined on the 7$^{th}$ day. The obtained data are presented in (Table1).

Table 1.– Effect of mutant PGPR strains on germination energy and germination of mung bean *(Vigna radiata)* seeds before and after UV irradiation

| PGPR strains | | 100 seeds | | Length, cm | |
|---|---|---|---|---|---|
| | | germination energy,% (after 4 days) | germination,% (after 7 days) | root | stem |
| mutant | Control (water) | 62 | 80 | 3.7 ± 0.3 | 7.8 ± 0.2 |
| | *P. putida M-1* | 91 | 100 | 16.5 ± 0.2 | 11.4 ± 0.3 |
| | *A. chroococcum M-1* | 100 | 100 | 5.3 ± 0.2 | 9.2 ± 0.3 |
| | *B. subtilis M-1* | 100 | 100 | 5.4 ± 0.2 | 22.7 ± 0.3 |
| parent | *P. putida 4/1* | 82 | 100 | 6.9 ± 0.2 | 12.9 ± 0.3 |
| | *A. chroococcum P-29* | 89 | 100 | 3.1 ± 0.2 | 7.6 ± 0.2 |
| | *B. subtilis* | 72 | 100 | 4.1 ± 0.1 | 9.5 ± 0.1 |

As can be seen from the data presented in (Table 1), treatment of the mung bean seeds with the mutant strains of *P. putida M-1, A. chroococcum M-1* and *B. subtilis M-1* with 1:1 concentration had a positive effect on germination energy of seeds compared to the parent strains. Moreover, it was found that *Bacillus subtilis M-1* mutant strain had a significant stimulation effect on plant growth. The length of the stems and roots of mung bean plants treated with *B. subtilis M-1* increased in comparison with parent strain in 2, 3 and 1, 3 times, respectively.

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# INTRAPOPULATION VARIABILITY OF COTTON CULTIVARS

**Abstract.** Cotton, being facultative self-pollinator, in each generation can reproduce the modified plants. In researches it is revealed, that in population of cultivars on the studied traits gradually increased variability on years observed. It affects change of intrapopulation variability which leads to cultivar deterioration of economic traits of the given cultivar.

**Keywords:** Cotton, cultivar, variability definition, population, the adaptation, weight of a raw, cultivar deterioration, breeding.

In the course of growth and development a number of the mechanisms providing the adaptation of an organism to environment are created. According to many scientists, everyones change phenotypical homogeneous and high-quality cleanliness lead to change at cellular level, to infringement population homeostasis, i.e. a constancy of the internal environment of a genotype [2, 432].

As a whole high-quality population of plants is characterisedby the inheritance fixed variability on a complex of signs. Inherently, cotton cultivars is facultativelyrecrosspollinated, partially heterogeneous populations which keeping characteristic high-quality morphology, have the latent hereditary and paratypical variability which is shown in separate atypical years.

The durability of a cultivar, its long preservation in manufacture, and also adaptive properties and stability to illnesses depend on structure population. Cotton cultivars should be not only productive, have a positive complex of economic-valuable signs, but also should be homogeneous enough, keep valuable properties of cultivar in the course of reproduction. In preliminary reproduction new cultivars of cotton are finished on high-quality cleanliness with preservation of initial economic-valuable qualities. However, many new cultivars after their transfer in State test enoughquickly removed from reproduction, as their economic-valuable properties worsen and occurs "scattering" of morphological signs. As a rule, it occurs because of not finished new cultivars, their raised heterozygosis and finally, splitting and gradual accumulation of the separate genotypes different from initial population [5, 18; 6, 11].

Usually high-quality cleanliness of a selection line in the course of breeding-seed-growing completion is defined eyes – on morphological signs. In this case, the selection line homogeneous to approved signs can be actually non-uniform to economic-valuable signs.

Loss by a non-uniform cultivar of its valuable initial qualities can be aggravated with wrong selection, at the same time because of presence of negative genetic correlations unilateral selection inevitably leads to strengthening variety of population biotypes.

Also more reliable revealing of the best genotypes in initial hybrid population or a selection line is actual that substantially causes its further selection perspectivity in process creation of a new cultivar.

Meaning that population of cultivars consists from genotypic variousplants, possibility of increase of variability in population of cultivars is very high. It is possible to lean on some factors to keep uniformity and positivity of economic significant signs. For example, correct zone placing of cultivars of cotton – to grow up those places where they are adapted and gives a high-quality stable crop, strict control of works of elite economy, application of optimum ways of care by crops and agroprocessing methods. In the course of adaptation to new condition of cultivar change a little. Variability such can lower genetic efficiency and a homeostasis of population and there is a deviation of a cultivar from the original descriptions.

Cotton, being a facultative self-pollinator, in each generation can reproduce the hybrids, supervised by active genes. Under D. J. Byubeykera's statement, "environment serves as a trigger for action of many genes" [3, 167].

Decrease in degree of uniformity of cultivars sometimes occurs and in elite farms. In a stage of primary reproduction and manufacture of elite seeds of cultivars of cotton always and continuously – before removal of this cultivar from manufacture, proceeds selections on a complex of signs. The individuals having an identical phenotype, but developing in various agroecological conditions of year and an area appear various in ontogenesis.

We have conducted researches by definition of degree of variability of some economic signs in population of some cultivars which are sowed different growing regions of our Republic. As object of researches cultivars of Omad, Akkurgan-2, Bukhara 6 and Bukhara 102 concerning kind G.hirsutum L. served. Each cultivar sowed in four allotments, till 20–25 plants. Analyses spent on the boxes collected from each cultivar on 80–100 pieces. In posterity of cultivars studied a variability range to some economic signs without breeding. The

studied cultivars had typical morphobiological phenotype, however judging by changes in growth and development in cultivars were shown hidden genotypic distinctions which were observed in the form of different individuals.

Studying of any line or cultivar which is, as a matter of fact, population, always begins with it phenetics, i.e. characteristics phenotipicalfeatures of individuals (genotypes) entering into it, their distribution in population, an establishment of parametersphenotypic variability to quantitative signs. The decision of these questions inevitably should lead to genetic research of population as such approach gives the chance to establish genetic structure of population, to reveal parities between the separate components characterizing population and further to pass to studying of action of factors defining its variability.

The weight of a raw of one box is more stable sign. The weight of raw of one box is an important structural component of productivity – the more largely a box, will be also an efficiency of plants more. For this sign polygene control, low factor genotypical, phenotipical and paratypical variability is characteristic. In our experiences the average index on plants of one cultivar is defined.

Three-year supervision in control group (without breeding), have shown, that weight of raw of one box slightly differ on years. In particular, in the first year at cultivar of Omad weight of raw of one box varied within 5.6–6.6 g (an average 6.0). Degree of variability of sign was made by 4.2%. By next year these indicators made 5.4–6.5 g, 6.0 g and 5.4% accordingly. From this it is visible, that, by second year of sowing in region in cultivar population on another it was shown variability degree – though homeostasis change was to lesser degree observed. By third year limit indicators equaled 5.5–6.5 g, and, thus amplitude of variability made 5.5%, and average indicator weight of raw of one box of 5.9. It is visible, that, absolute value has not changed almost rather by first year (difference-0.10). But, raised degree of variability and it is possible to explainë on sharp divergence of limit values on the smaller and the greatest. Increase of degree of variability of sign in cultivar population despite not changes of absolute values was observed.

In population of cultivar of Akkurgan 2 the same was marked position. But in this case change of indicators since the first year of supervision occurred more strongly than a cultivar of Omad. By third year it was marked high variability on 2.6% – rather by first year.

Above noted position shows that on grade population at which it is not conducted selections, in population degree популяционного a homeostasis gradually changes (decreases).

The cultivar Bukhara 6 has largely box. In our experiences the крупность boxes of plants of cultivarследущем to values: in the first year 6.3 g, by second year 6.1 g and by third year of 6.2. Variability degree equaled on 2.7, 2.3 and 3.1% accordingly. Variability degree on initial and next years differ on 0.4%. At cultivar Bukhara 102 though there is variability, but sharp distinction on years was not observed. And it shows most stability of cultivar on population level.

The important role in formation of structure of population belongs to selection process. There is an indisputable dependence between results of selection on a phenotype and size of heritability of sign. Selection of the best on phenotypes and high heritability gives to signs of genotypes shift of its values at posterity. Therefore, studying of change of indicator of heritability in the course of selection and possibility of the forecast of efficiency of selection to quantitative signs is of great importance for planning of selection process.

From references it is known that the most important component of productivity is the number of boxes on one plant. Hence, the increase in quantity of boxes at plant promotes productivityincrease. So, by many scientists it is proved, what not крупность boxes, and their quantity defines the general productivityof plants [1, 54; 5, 6–8; 4, 110].

Among the studied cultivars the most productivity in comparison with others had appeared cultivars of series Bukhara. Degree of variability of sign at cultivar Bukhara 6 on initial and next years differ on 0.8%. At cultivar Bukhara 102 the variability it is equal on 1.0%. And once again stability of cultivar proves to be true most. At cultivar of Omad a difference of variability of 2.6%, and at cultivar of Akkurgan-2 variability has raised on 2.1%. Practically these indicators of variability it is not felt. But in population level it to lead to serious changes of homeostasis of cultivar. Вообщем productivity change on years accordingly to changes at the previous sign.

Table 1.– Variability of weight of raw of one box

| № | Cultivars | n | 2009 y. | | | 2010 y. | | | 2012 y. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | X ± Sx | Lim. | $V_{\%}$ | X ± Sx | Lim | $V_{\%}$ | X ± Sx | Lim. | $V_{\%}$ |
| 1. | Омад | 40 | 6.0 ± 0.04 | 5.6–6.6 | 4.2 | 6.0 ± 0.4 | 5.4–6.5 | 5.4 | 5.9 ± 0.3 | 5.5–6.5 | 5.5 |
| 2. | Akkurgan 2 | 40 | 5.2 ± 0.08 | 4.9–5.7 | 6.1 | 5.0 ± 0.7 | 4.7–5.6 | 8.2 | 5.0 ± 0.2 | 4.6–5.6 | 8.7 |
| 3. | Bukhara-6 | 40 | 6.3 ± 0.03 | 6.0–6.5 | 2.7 | 6.1 ± 0.1 | 5.9–6.3 | 2.3 | 6.2 ± 0.3 | 6.0–6.3 | 3.1 |
| 4. | Bukhara 102 | 40 | 5.9 ± 0.02 | 5.6–6.2 | 3.2 | 5.9 ± 0.2 | 5.6–6.2 | 3.3 | 5.8 ± 0.5 | 5.6–6.0 | 3.0 |

Variability degree of cultivars studied in our experiences was miscellaneous. And it depended from places of creation and primary test of the given cultivars. Gradual change of homeostasis of cultivars which are created on an agroclimate of the most northern part of republic was observed and we studied on other zone. It affects change intrapopulation variability which lead to gradual deterioration of economic indicators of the given cultivars.

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# PROTEIN MARKERS IN COTTON SPECIES *G.HIRSUTUM* L., *G.BARBADENSE* L. AND THEIR CORRELATION WITH VARIOUS CHARACTERS

**Abstract.** The data on the study of protein markers of cotton seeds of the species *G.hirsutum* L. and *G.barbadense* L. are presented. It is shown that the studied cotton species differ in the content of water soluble protein markers, designated according to their electrophoretic mobility by the symbols H-0.13 and B-0.18 and the buffer fraction, denoted by the characters AU and BD. Inheritance of protein markers H-0.13 and B-0.18 corresponds to monohybrid co-dominant cleavage. The loci of protein markers H-0.13 and B-0.18 are interconnected with a number of biochemical and morphological characters. Protein markers H-0.13 and B-0.18 turned out to be convenient when studying the genealogy of *G.hirsutum* L. and *G.barbadense* L. species. In diploid cotton species of the genomic group D, protein H-0.13 was found in seeds of the species G. trilobum, and protein B-0.18 – in the species G. thurberi, which suggests that these cotton species participated in the formation of the amphidiploid species *G.hirsutum* L. and *G.barbadense* L. The cotton species studied also differ in the composition of protein markers buffer fraction. The species of cotton *G.hirsutum* L. contains protein markers designated by the symbols AC, BD, and BCD, whereas in the species *G.barbadense* L. there are only protein markers AC. The cleavage of protein markers AC and BD in generations of interspecific hybrids depends on the combination of hybrids. In some $F_2$ hybrids, the proteins AC and BD are inherited linked and correspond to monohybrid codominant cleavage, while in other $F_2$ hybrids various combinations of these markers are formed.

**Keywords:** cotton, water-soluble proteins, buffer-soluble proteins, protein markers, *G.hirsutum* L., *G.barbadense* L., linkage group.

**Introduction**

Genetic markers identified on the basis of hereditary polymorphism of proteins, enzymes and DNA fragments proved to be powerful tools for identifying

the range of population and species variability, studying phylogenesis, and the degree of genetic similarity of various species. The development of these works led to the formation of a new direction in the field of fundamental and applied plant for studying genetic diversity, analyzing the genetic structure of the source genetics,

which was called marker-associated selection. With the introduction of molecular genetic methods in the selection process, new opportunities are opened material, identifying and controlling the genetic purity of genotypes. One of the ways to assess genotypes at the molecular level is the protein marker method based on the biological specificity of proteins detected by electrophoresis. The use of electrophoretic analysis of storage proteins makes it possible to evaluate genotypes by their genetic purity.

**Materials and methods of research**

Seeds of various cotton varieties of the medium fiber species *G.hirsutum* L. and the fine fiber species *G.barbadense* L. of the Institute of Genetics and Experimental Plant Biology of the Academy of Sciences of the Republic of Uzbekistan were used as material for the study. Seed preparation for protein isolation and electrophoretic analysis was performed according to the methods described earlier by Yunuskhanov Sh. [1].

**Result and discussion**

Types of cotton *G.hirsutum* L. and *G.barbadense* L. have species-specific protein markers designated by symbols in the medium-fibrous species *G.hirsutum* L.– H-0.13 and in fine-grained *G.barbadense* L. species – B-0.18, detectable in the electrophoretic composition of proteins of the water-soluble fraction of defatted seeds [2–4]. Different grades of these cotton species, with the exception of these protein markers, are almost identical in the main components of the electrophoretic spectrum of the water-soluble fraction. Molecular masses of protein markers H-0.13 and B-0.18, established by the method of sedimentation analysis, are 120 and 112 KD, respectively [5]. Inheritance of protein markers H-0.13 and B-0.18 in generations of interspecific hybrids corresponds to monohybrid codominant cleavage. However, in the study of the interspecific reciprocal hybrid of *G. hirsutum* L. and *G. barbadense* L. cotton obtained by crossing, where the species *G. hirsutum* L. was represented by dwarf plants obtained as a result of the mutation induced earlier by gamma irradiation [6], and the species *G. barbadense* L.– C-6037 strain an anomalous pattern was observed [7]. A radiomutant form characterized by dwarfism was isolated among the hybrids of cotton $M_2$ obtained by pollination of flowers of plants of grade C-4727 with pollen of plants of Tashkent-3 type of medium-fibrous species *G.hirsutum* L. irradiated with Co60 gamma rays at a dose of 1.0 kR [8]. The sign of dwarfism has been consistently split into normal plants: dwarf plants 1: 2. To study the relationship between the inheritance of species-specific marker proteins H-0.13 and B-0.18 with the sign of dwarfism of cotton plants, we obtained reciprocal hybrids between the radiomutant dwarf form of the medium fibrous species *G.hirsutum* L. and with the Izhod strain of the fine-fibered species *G.barbadense* L. However, neither the F1 plants nor the $F_2$ hybrids showed a dwarfism sign, although the hybrid obtained with the participation of the Red-leaved Akala of the species *G.hirsutum* L. has a split ratio of 2: 1 (dwarf: tall plants). A similar picture was observed in the combination of the reciprocal hybrid, where one of the parents used the tall fine-fibrous variety C-6037 for crossing. Dwarf plants did not appear in the $F_1$ and $F_2$ populations of reciprocal hybrids. The hybrid obtained by crossing a dwarf form with the variety C-6037 of a thin-fibrous species of *G. barbadense* L. has been studied in various generations. The hybrid obtained by crossing a dwarf form with the variety C-6037 of a thin-fibrous species of *G. barbadense* L. has been studied in various generations. Plants of the dwarf form of the species *G. hirsutum* had a protein marker H-0.13, and in plants of the species *G.barbadense* L. the homologous marker was represented by protein B-0.18.

Plants of the species *G. hirsutum* had a protein marker H-0,13, and in plants of the type *G.barbadense* L. the homologous marker was represented by protein B-0.18. When analyzing phenotypic class relationships among generations of interspecies hybrids, including $F_2$, $F_9$ and $F_{10}$, plants containing only one type of protein (H-0.13 or B-0.18) were considered as homozygotes for the corresponding gene, and plants containing both proteins (H-0.13 and B-0.18), as heterozygotes. A number of polymorphic progeny polymorphs showed a significant change in the ratio of the phenotypic classes, which manifested itself as a shift towards an increase or decrease in the proportion of a homozygous phenotypic class, or as a significant increase or decrease in the proportion of the heterozygous class. The electrophoretic composition of the seed proteins of the cotton samples under study remained unchanged up to the ninth generation of hybrids, but in the tenth generation some heterozygous plants produced offspring, in the seeds of which there was no protein with an electrophoretic mobility of 0.70. Such plants belonged to the homozygous phenotypic class, in which the marker H-0.13 is detected. In the work of M. A. Abzalov et al. [9], using this dwarf line in his studies on the relationship of traits, they came to the conclusion that this line contains the lethal $Let^{dw}$ gene, the heterozygous state of which determines the sign of dwarfism of plants, and the homozygous forms die in the early stages of seedling development. Consequently, the

data obtained by us on anomalous splitting can be explained, apparently, by the presence of a lethal gene in the mutant dwarf line of cotton. Investigation of seed proteins of various interspecific hybrids has shown that the inheritance of protein markers H-0.13 and B-0,18 corresponds to monohybrid splitting and is interrelated with a number of economically valuable traits [4, 10–12]. Below are the clutch groups between protein markers H-0.13 and B-0.18 with a number of biochemical and morphological features of cotton:

$Pr^{H\text{-}0,13} – Pr^{H\text{-}0,70} – F^{ch} – Pr^{H\text{-}0,23} – Per^{0,33} – Peel^{W} – F^{quality} – F^{length} – S^{weight} – Plant^{height} – Boll^{quantity}$;

$Pr^{B\text{-}0,18} – Pr^{B\text{-}0,70} – F^{cb} – Pr^{B\text{-}0,15} – Per^{0,33} – Peel^{W} – F^{quality} – Fl^{ength} – S^{weight} – Plant^{height} – Boll^{quantity}$,

where with dashes marked closely linked loci and without dashes – recombined loci;

Pr – Protein, the figure in the index is the electrophoretic mobility;

$F_c^h$ and $F_c^b$ – loci encoding fuzz on the chalazal part of seeds *G.hirsutum* L. and *G.barbadense* L.;

$Per^{0.33}$ – Peroxidase – (peroxidase);

$Peel^{W}$ – Peel weight – (skin weight);

$F^{quality}$ – fiber quality;

$F^{length}$ – fiber length;

$S^{weight}$ – seed weight;

Plant $^{height}$ – plant height;

Boll $^{quantity}$ – the number of boxes.

Protein markers H-0.13 and B-0.18 were also useful in studying the origin of amphidiploids *G.hirsutum* L., and *G.barbadense* L. [4]. It is assumed that cotton amphidiploids were formed by the fusion of the genomes of diploid species of the genomic group A (*G.herbaceum*) and the genomic group D (*G.raimondii*). When studying the protein spectrum of these groups of cotton, it turned out that representatives of cotton genomic group A do not contain protein markers H-0.13 and B-0.18, and representatives of cotton genome group D are divided by this trait into different groups. The type of cotton *G.raimondii* contains a protein with an electrophoretic mobility close to H-0.13, but differs from it in other parameters. Protein protein marker H-0.13 was found in the species *G.trilobum*, in species *G.thurberi* – B-0.18, other species of this genomic group simultaneously contain proteins identical in electrophoretic spectrum to proteins H-0.13 and B-0.18. Protein H-0.13 as in the species *G.hirsutum* L. and the species *G.trilobum* undergoes changes during their long-term storage. The electrophoretic mobility of the protein marker H-0.13 in long-stored seeds becomes identical with the protein B-0.18. Based on the data obtained, it can be assumed that the type of cotton *G.trilobum* from the genomic group D also participated in the formation of *G.hirsutum* L. and the type of *G.thurberi* in the formation of *G.barbadense* L.

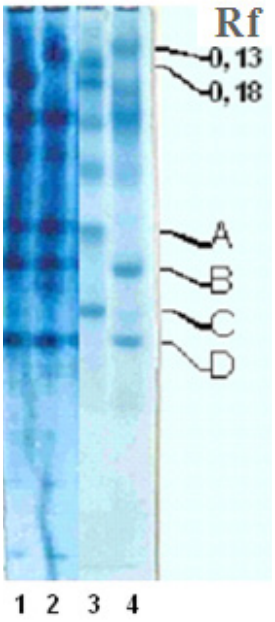


Figure 1. Electrophoregrams of water-soluble (1 and 2) and buffered soluble (3 and 4) proteins of defatted cotton seed flour. (1 and 3 – *G. barbadense* L., 2 and 4 – *G.hirsutum* L.)

The second group of protein markers was found in the composition of the buffer-soluble fraction of proteins of defatted seeds after removal of the water-soluble fraction [13]. This group of markers consists of two electrophoretic components, both *in G.hirsutum L.* species and in varieties of *G.barbadense* L. and according to their electrophoretic mobility are designated by the symbols A, B, C and D. Protein markers H-0.13 and B-0.18 are detected both in the water-soluble fraction of defatted seeds and in the buffer-soluble fraction, however, proteins A, B, C and D – only in the buffer-soluble fraction (Fig. 1). The study of the buffer-soluble proteins of various varieties of cotton showed that *G.hirsutum* L. varieties in the content of components A, B, C and D are polymorphic and are divided into groups containing AC, BD and BD + C, while *G.barbadense* L. contain only one group of proteins – AC. AC proteins in *G.hirsutum* L. species are found in Akala varieties and in varieties derived from them, as well as in the wild type cotton *G.hirsutum L., ssp.mexicanum var. nervosum*. The splitting of these proteins in generations of interspecies cotton hybrids depends on the combination of hybrids. There are combinations of hybrids in which the cleavage of the proteins AC and BD corresponds to normal monohybrid cleavage [13], with the loci encoding the proteins A and C on the one hand and B and D on the other are concatenated:

$$F_2 (AC \times BD) = AC + 2(AC+BD) + BD$$

In a number of combinations of hybrids in $F_2$, an anomalous cleavage occurs, up to the formation of various combinations:

$F_2(AC \times BD) = AC + (AC+BD) + BD + AD + AB + BC + A + + B + C + D$

The *G.hirsutum* L. cotton varieties derived from hybridization between *G.hirsutum* L. and *G.barbadense* L. show only protein AC markers.

The absence of protein markers of BD in the varieties of fine-grained *G.barbadense* L. seems to indicate the incompatibility of loci of protein markers B-0.18 and protein markers BD:


Figure 2. The interrelation of protein markers H-0,13, B-0,18 and buffer-soluble proteins A, B, C and D

**Conclusion**

The identified protein markers are promising for the biotechnological characteristics of the cotton gene pool and its use in solving problems of plant breeding and seed production.

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# Section 2. Medical science

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## CLINICAL-FUNCTIONAL FEATURES OF DILATED CARDIOMYOPATHY IN CHILDREN IN DEPENDENCE ON MEDICAL-BIOLOGICAL FACTORS OF DEVELOPMENT

**Abstract.** There have been studied clinical and functional characteristics of dilated cardiomyopathy in 42 children at the age of 2 months to 18 years, hospitalized into the cardiorheumatologic department of the Republican specialized scientific-practical medical center of pediatrics. With regard to predominant localization of the lesion in the myocardium according to echocardiographic criteria in children there were defined six variants of dilated cardiomyopathy with prevalence of variants with damage of the left atrium and left ventricle (33.3%) and with isolated damage of the left ventricle (23.8%). For favorable outcome of these diseases there is required early diagnosis and timely onset of therapy.

**Keywords:** dilated cardiomyopathy, clinical features, functional changes, children.

According to the current notions the dilatational cardiomyopathy is considered as cardiac muscle disease of unknown or unclear etiology, characterizing by cardiomegaly due to dilatation of the heart cavities, particularly cavity of the left ventricle, progressing attenuating of the myocardium contractility, suddenly developing and progressing heart insufficiency, arrhythmic and thromboembolic syndromes with ending frequently by sudden death [1]. Dilatational cardiomyopathy is characterized by continuously progressing development, occupies leading positions in the structure of disability and mortality of children, appeared to be main cause of the formation of chronic cardiac insufficiency at the childhood [2]. The prevalence of dilatation cardiomyopathy varied from 40 cases per 100000 a year in Europe. This disease is met more frequently in boys than in girls. The specific weight of dilatational cardiomyopathy among the other cardiomyopathies accounts for 60% [3]. The frequency of sudden mortality among children with dilatational cardiomyopathy accounts from 1.5% to 4%, in the majority of cases the cause of lethal outcome is arrhythmia. The cardiac rhythm disorders have both bradycardia (atrioventricular blockade) and tachycardia character (unstable ventricular tachycardia). Polymorphic gastric extrasystole is related to the risk factors of the sudden death. At the same time the disorders of the heart rhythm are not independent risk factors of the sudden death, because they closely connected with left ventricle dysfunction. In case of sudden death there is noted high frequency of ventricle fibrillation, its appearance connects with sharp disorder of the left ventricle pumping function and pressure arising in its cavity [4]. The wide introduction of the high informative instrumental methods for heart investigation, first of all, echodopplercardiography allows putting in good order the knowledge about cardiomyopathy as nosological notion [3]. Diagnostic criteria of DCMP, by opinion of European experts, are [4] left ventricular (V) ejection fraction less than 45%

(by echocardiography) or fraction shortening of the anteroposterior size of the left ventricle less than 25%. According to the results of genetic investigations of a number of scientists, in the development of idiopathic DCMP there was established family predisposition, predominantly by autosomal-dominant inheritance. There were also met autosomal-recessive Z-linked and mitochondrial forms of disease. In the development of DCMP the acute previous myocarditis also plays a role, when firstly myocardium impairs, and then chronic inflammation occurred, which, in its turn, results in remodeling of heart and its dysfunction (postinflammatory DCMD) [5]. It should be noted that in the dominant majority of the family forms of DCMP the genetic disorders associated with autoimmune ones, and the viruses can act as a starting factor for development of DCMP in people with genetic predisposition. On the whole DCMP etiology remains to be unclear to the present time.

It should be noted that for making diagnosis of idiopathic DCMP it is necessary to take into account its secondary etiology on the basis of systemic blood diseases, kidney pathology (uremic cardiomyopathy), on the basis of malformations of heart development and large vessels (syndrome of Gerland Blount White) and inflammatory diseases of great vessels, mitochondrial diseases, that requires performance of the additional methods of investigation.

The right and timely making diagnosis of DCMP remains to be not simple task. The determination of diagnosis should be performed on the basis of all methods, beginning from anamnesis collection, clinical examination of patient and ending with results of non-invasive and invasive methods of study.

Clinical picture of DCMP is variable and is determined, first of all, by severity of blood circulation disorders. Hemodynamic disturbance is the consequence of the significant reduction of myocardium contractility and cardiac pump function, and first of all of the left ventricle, which is accompanied by increase in pressure in the heart chambers, their dilatation with following development of congestive evidences in the pulmonary and systemic circulation.

At the early stages, unfortunately, the disease progresses little or without symptoms. Sometimes heart impairment is found during ECG performance or in roentgen logical investigation due to pathology of bronchopulmonary system.

The first clinical sign of disease may be disorders of heart rhythm and thromboembolic syndrome (thromboembolism of the pulmonary artery and embolism in the artery of the systemic circuit of circulation, acute disorder of the cerebral circulation with evidences of stroke and myocardial infarction) [3; 6].

The clinical picture of heart insufficiency depends on the severity degree of congestive evidences in the pulmonary and systemic circulation, at the early stages of disease there are mainly signs of impair of the left departments of the heart with progressing left ventricle insufficiency (with clinical picture before edema and edema of the lungs), during progressing of severity degree of heart the right ventricular insufficiency is added (appearance hepatomegaly, edema syndrome).

Taking into account severity degree of clinical symptom, progressing of clinical signs in dynamic of disease and hazardous complications, which frequently resulted in lethal outcome, the early diagnosis and differential diagnosis of DCMP in children is the actual problem of clinical pediatrics on a whole and children's cardiology.

On the basis of above presented **the purpose of this research** is determination of clinical, functional peculiarities of dilatational cardiomyopathy in children.

**Materials and methods**

We have studied 42 children with DCMP at the age of 2 to 18 years, admitted to the cardiorheumatological department of the Republican Specialized Research-practical Medical Center of Pediatrics of the Ministry of Health of the Republic of Uzbekistan. Control group included 30 practically healthy children.

Analysis of anamnesis and objective data showed that durability of DCMP in children, on the average, accounted 16.6 ± 3.4 months. Diagnosis was made on the basis of complaints, data of anamnesis (obstetrical mother anamnesis, anamnesis of life and child's disease, previous diseases, character of progressing and durability of disease). Clinical-functional (ECG, Holter monitoring, ECG), laboratory (general hematological analysis, biochemical blood analysis with determination of cardio specific markers of creatine kinase, lactatdehydrogenase) and instrumental (roentgenography of the chest, multispiral computed tomogram of the chest) methods of examination.

At the moment of investigation there were taking into account age, gender, height and mass of child body. On the basis of indicators of the body length/height and body mass there were calculated body surface area (BSA, $m^2$) and body mass index (BMI). BSA was calculated by formulae Du Bois: BSA = M0.425 × P0.725 × 71.84 × 10–4, where M – body mass (kg), P-body length/height (cm); BMI – by formulae: BMI = M/P2(($kg/m^2$). ECG was performed in patients according to plan order in every hospitalization in the department of cardiorheumatology, both in primary examination, and in repeated hospitalization in the department on the ultrasound apparatus Aplio-500 ("Toshiba", Japan) with sector sensors 3.0–6.5 MHz. EchoCG was made by standard methods with regard to native and foreign manual books and recommendations. There was used two-steps echocardiography with determination of echo metric parameters. The left ventricular myocardium contractility was evaluated by ejection fraction (EF) with method Teykholt or Simpson and fraction of the left ventricular myocardium shortening (FS) [7].

**Results and their discussion**

During investigations we studied medical-biological factors in development of DCMP in children.

The study of biological factors showed that disease develops more often in boys (59.5%). Development of DCMP more prevailed in children, age of mothers, which at the moment of this child birth was above 35 years (52%). In 19% of children the parents were closed relatives (Figure 1).

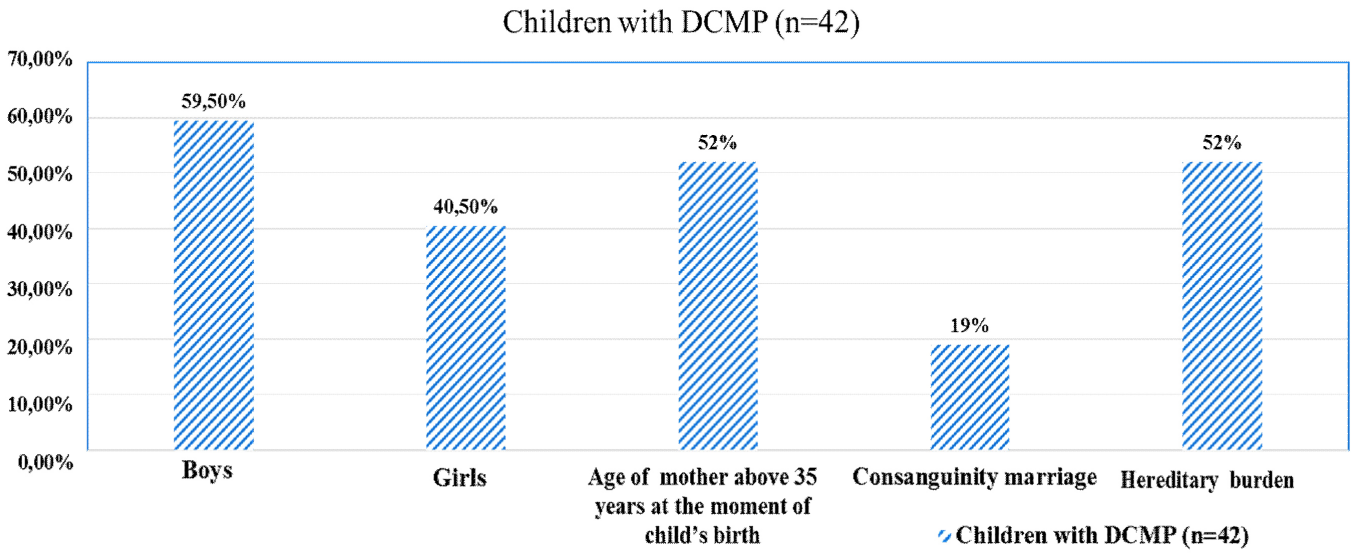



Figure 1. Evaluation of medical-biological factors in children with DCMP

As it is known the birth of children with various diseases and congenital anomalies, as well as the following their development and health state dependent on development of pregnancy, character of labors and health state of their mothers.

It should be noted that analysis of the obstetric anamnesis showed that mothers of children with DCMP in 88.2% of cases during pregnancy had ARVI, in 50% there were revealed TORCH-infections (cytomegalovirus, herpes virus), events of toxicosis in the second half of pregnancy: with preeclampsia of stage 1 in 28.5%, with preeclampsia of stage II – in 19.0%, preterm deliveries – in 28.5% of mothers, as well as in 19% of mothers the cases of stillborn in the previous pregnancies, in 30.9% of mothers the miss-carried fetus in the first and second trimester.

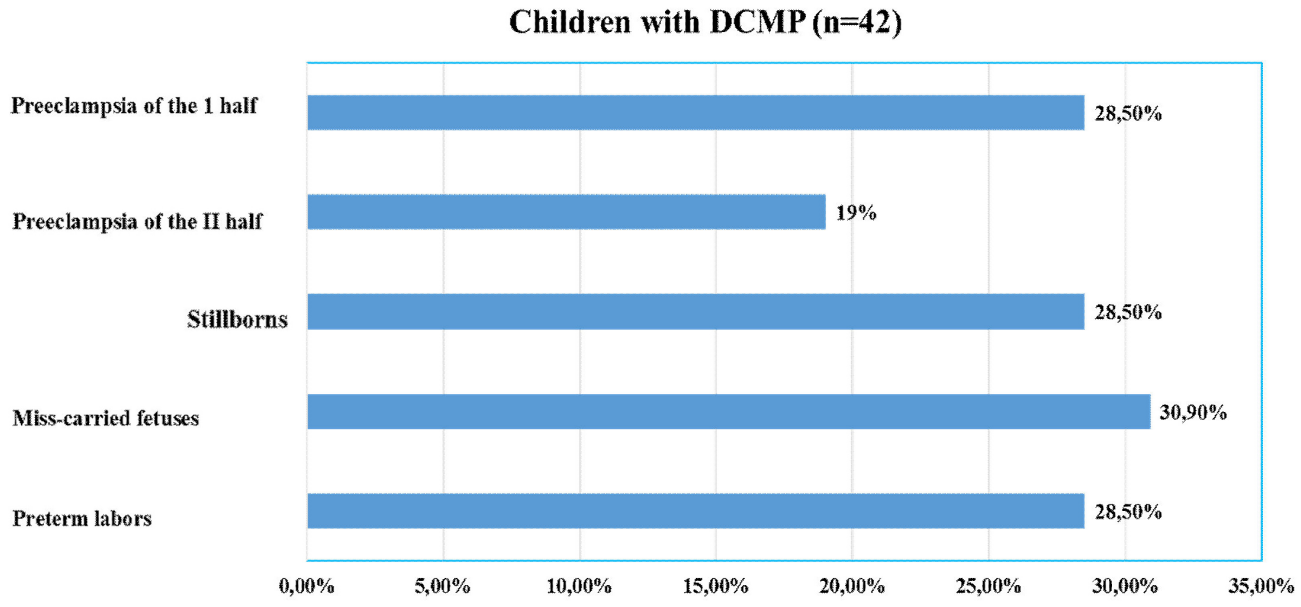



Figure 2. Evidences of the obstetric anamnesis of mothers of children with DCMP

Table 1.

| Previous diseases in children with DCMP | Children with DCMP (n=42), Abs/% |
|---|---|
| ARVI | 42(100%) |
| Chickenpok | 20(47.6%) |
| Bronchopneumonia | 11(26.2%) |
| Acute intestinal infections | 6(14.3%) |
| Septic angina | 5(11.9%) |
| Pyelonephritis | 4(9.5%) |

Table 1 shows that in anamnesis of children with DCMP cases of ARVI are frequent and in significant part of patients – chickenpox. The following positions of the previous diseases in group of children with DCMP were occupied by bronchopneumonia, acute intestinal infections, angina and pyelonephritis.

The symptoms of congestive heart disease were one of the most typical sign at admission. In 25(59.5%) children with DCMP there were features of left ventricular insufficiency, in 17(%) – of total heart failure (of 3–4-functional class by NYHA).

In 3 children admitted into gastroenterological department with dyspeptic syndrome: with vomiting, loose stool and edemas in the lower extremities the diagnosis of DCMP was made by chance, in plan EchoKG investigations, in which there was found significant reduction of myocardium contractility – with reduced ejection fraction to 25%. In 6 children (14.3%) the first sign of DCMP was sudden death during the first 6 hours from the moment of appearance of the events of heart insufficiency in spite of performance of therapeutic measures, in 4 children (9.5%) by syncopal state in physical loading.

The diagnosis of postinflammatory DCMP was established in 14 children (31.8%). In this case from the onset of myocarditis to establishment diagnosis of DCMP the period about one year passed. The complete recovery in postmyocardial DCMP was registered in one child.

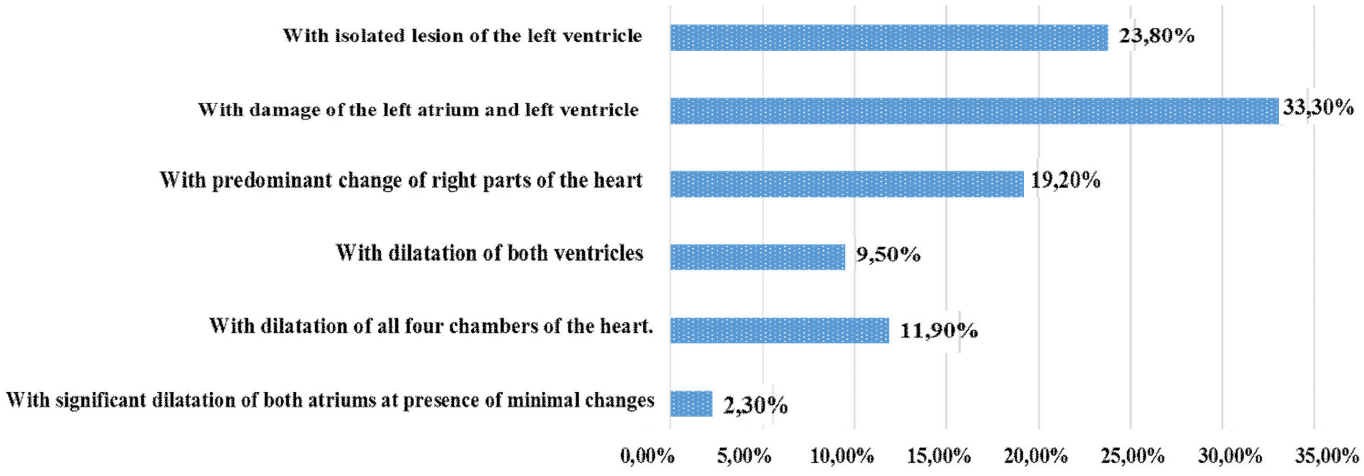
The roentgen logical investigation showed increase in heart sizes predominantly in the left parts in 57.1% o children, total enlargement was noted in 11.9% of children, cardiothoracic index accounted for, on the average, 63.3 ± 0.5%.

On ECG in children there was prevailed rigidity of sinus rhythm with tendency to tachycardia in 30(71.4%) children, disorders of cardiac rhythm looking like extrasystole in 12 (28.5%) children, supraventricular tachycardia in 20(47.6%) children, disturbance of conductivity in form of blockade of the bundle of His, more often in the left anterosuperior branch in 36(85.7%) children, that was accompanied by sharp deviation of the electric axis to the left (EOS), as well as signs of hypertrophy of the left ventricle in 42(100%) children, and both ventricles in 10(23.8%) children.

With use of EchoCG in children with DCMP there was revealed dilation of the heart chambers, systolic dysfunction with reduction of the ejection fraction from 40% to 16%, regurgitation on the mitral valve and tricuspid valve. Echocardiographic signs in studied children are presented in (Table 2).

Table 2. – Echocardiographic signs in children with DCMP

| Echocardiographic signs | Children with DCMP n=42 (%) |
|---|---|
| Valve regurgitation (MV and TV) | 42(100%) |
| Systolic dysfunction | 42(100%) |
| Cardiac output reduction to 40% | 42(100%) |
| LV hypokinetic wall motion | 42(100%) |
| Interventricular septum paradoxical motions | 20(47.6%) |
| Hypertrophy with dilatation | 5(11.9%) |



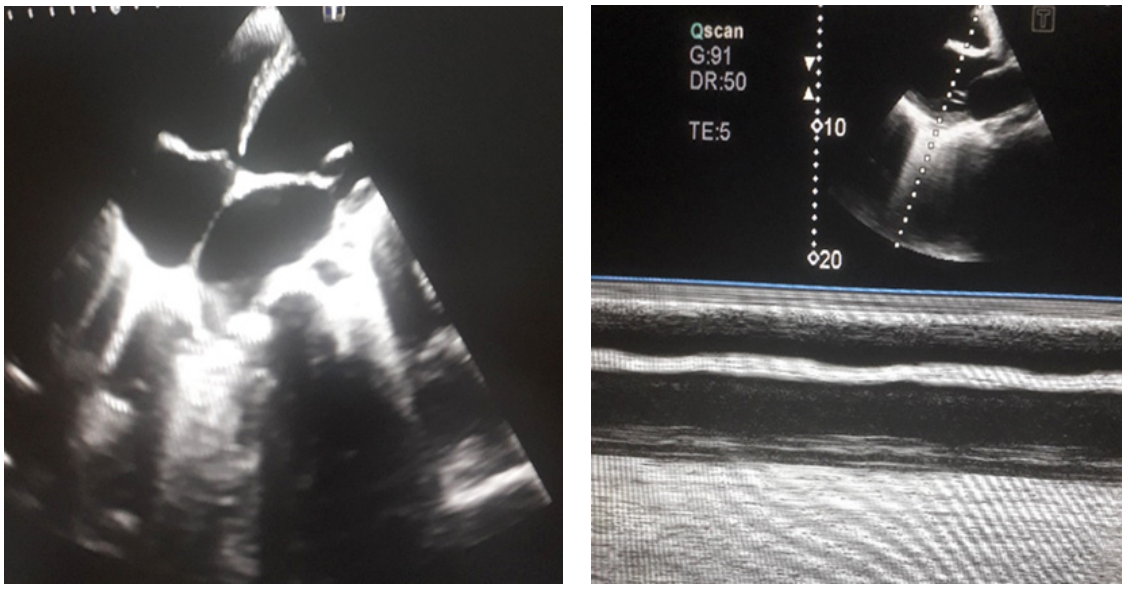

Figyre 3. Distribution of children with DCMP in relation to echocardiographic variants

In all children with DCMP there was noted systolic dysfunction, reduction of ejection fraction lower than 40%, hyperkinesia of the walls of left ventricle. Paradoxical motions on the interventricular septum were noted in 20 (47.6%) children with DCMP.

The results of echocardiographic investigations showed that in children with DCMP the end-diastolic volume of the left ventricle achieved from 94 ml to 206 ml, that was connected with arising its pressure of filling and marked dilatation of the left ventricle which was accompanied with various degree of progressing of relatively insufficiency of mitral in a part of cases and in the tricuspid valves. On the basis of our data the increase in end-diastolic pressure in the left ventricle higher 12 mm Hg was observed in 57.1% of children, and systolic and diastolic pressure in the pulmonary artery, respectively, more than 30 and 12 mm Hg – in 42.9% of children. This was accompanied by increase in pressure of filling of the tight ventricle higher than 6 mm Hg. Dilatation of the right heart parts in 42.9% of children was accompanied by dilatation of vena cava and hepatic veins, that was characteristic for blood congestion in the pulmonary circle of blood circulation.

With regard to predominant localization of lesion in the myocardium according to echocardiographic criteria the children were subdivided into six variants of DCMP:

The distribution of children with DCMP in relation to echocardiographic variants is presented on fig.3. It may be seen that with regard to predominant localization of the lesion in the myocardium according to the echocardiographic criteria the children are subdivided into six variants of DCMP: 10 (23,8%) children with variant 1 – with isolated lesion of the left ventricle; 14(33.3%) children with variant 2 – with damage of the left atrium and left ventricle; 8(19%) children with variant 3 – with predominant change of the right heart parts; 4(9.5%) children with variant 4 – with dilatation of the both ventricles; 5(11.9%) children with variant 5 – with dilatation of all 4 chambers of the heart; 1 child (2.4%) with variant 6 – with significant dilatation of the both atriums in presence of minimum changes of the morphofunctional state of the heart ventricles. In children with 3 echocardiographic variants of DCMP there was performed differentiation with arhythmogenic dysplasia of the right ventricle. Among the variants of echocardiography the variant 1 and variant 2 were most often noted (57.1% of children), which manifest by dilatation of the left ventricle and left atrium. In these children there was performed differentiation of DCMP with nonrheumatic myocarditis. Of them in 23,8% of children on the basis of adequate complex therapy the positive dynamics with improvement of functional parameters, particularly – improvement of contractility of myocardium, increase in ejection fraction (in dynamics to 45%), decrease of end-diastolic volume of the left ventricle (LVEDV). In one child there was observed liquidation of the signs of the cardiac insufficiency with restoration of pump function of heart (EF 40%, in dynamics 60%). That is the reason for change of primary diagnosis of DCMP to nonrheumatic myocarditis in the following time. In 5(11.9) children there was noted lethal outcome in spite of performed complex therapy due to growing heart insufficiency and arrhythmic syndrome, that is one of the hazardous complications of DCMP. In the children of this group on the EchoCG dilatation is visualized in all four chambers of the heart (5 variant of the DCMP).




A B

Figure 4. Echocardiogram of patient A., of 2-year-old with DCMP: a) total hypokinesia of the LV walls; b) dilatation of all chambers of the heart in the four-chamber position

Echocardiographic parameters of variant 1 and 2 of DCMP have likeness with signs of acute myocarditis particularly in children of young age. The specific features in children with DCMP are progressing development of cardiac insufficiency and refractory of performed anti-inflammatory therapy, that is, progressing reduction of the myocardium contractility, lesions and other heart chambers to total broadening of all heart chambers.

**Conclusions:**

1. For development of children with dilatational cardiomyopathy the following factors have effect: on medico-biological factors – age of mother above 35 years, previously diseases in mother during pregnancy (predominantly of viral etiology), complicated pregnancy (eclampsia, abortion), preterm labor, hereditary predisposition to cardiomyopathy and closely related (congeneric) marriage;

2. For DCMP in children there are characteristic peculiarities in the functional parameters of the cardiovascular system: disorders of echocardiographic parameters such as systolic dysfunction, reduction of the ejaculation fraction lower than 45%, hypokinesia of the left ventricle wall. For children with DCMP (in 47.6% of cases) there were also characteristic paradoxal movements on the interventricular septum.

3. According to predominant localization of lesion in the myocardium and on the basis of echocardiographic criteria there are identified six variants of DCMP in children with prevalence of variants with lesion of the left atrium and left ventricle (33.3%) with isolated damage of the left ventricle (23.8%).

Thus, dilated cardiomyopathies are severe pathology of the childhood, for identification of which there is required careful study at early stages medico-biological factors, clinical evidences and data of the current methods of the functional diagnosis (ECG, EchoCG).In order to prevent development of DCMP in children it is necessary to make preventive methods for prevention of delayed labors, providing safe pregnancy and deliveries, prophylaxis and effective treatment of the diseases of viral etiology in mothers and children, and for favorable outcome of these diseases there is required early diagnosis and timely onset of therapy.

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# CURRENT APPROACHES TO EARLY DIAGNOSTICS OF CHRONIC KIDNEY DISEASE AND EVALUATED RISK FACTORS

**Abstract.** Chronic kidney disease (CKD) in adults is a common condition and a major public health issue worldwide. Given the increasing incidence of CKD and the availability of effective therapeutic measures, is of vital importance perform early detection of risk factors (RF), in order to delay or prevent progression to ESRD. The optimal cost-effective strategy seems to be an investigation aimed at patients with one or more risk factors for CKD. In order to detect early indicators of CKD and associated risk factors, we conducted a study in an adult population.

**Keywords**: adult, albuminuria. chronic kidney disease; early detection of risk factors for CKD.

The prevalence of diseases in which chronic kidney disease (CKD) develops is significant and currently continues to increase. Chronic kidney disease is a serious public health problem, characterized by a higher incidence and progression [3].

An important aspect of the study of chronic kidney disease in the population is the early detection of the disease and appropriate treatment. If we take into account the fact that this pathology still does not have a tendency to decrease among persons of different ages, then the determination of factors contributing to the formation and development of this pathology is relevant [1; 6].

It is known that the number of factors contributing to the formation and development of CKD is many, but the level of their influence on the development of this disease is varied [5].

The prevalence of chronic kidney disease (CKD) is comparable to such socially significant diseases as hypertension and diabetes, as well as obesity and metabolic syndrome. Signs of kidney damage and / or a decrease in glomerular filtration rate are detected, at least, in every tenth representative of the general population. At the same time, comparable figures were obtained both in industrialized countries with a high standard of living, and in developing countries with medium and low incomes of the population [4; 6].

The problem of screening for CKD is very serious. Its solution is possible only with close cooperation of doctors of different specialties. On the other hand, it is necessary to integrate nephrology and primary health care, as well as other specialties in order to carry out extensive preventive measures, early diagnosis of CKD, ensuring continuity of treatment and effective use of available resources. There are several ways to identify CKD, among which is the determination of CKD markers in patients undergoing screening for various diseases. One of the important ways to identify CKD is to examine a conditionally healthy population in which they have risk factors for the development of CKD [2; 7].

Given this fact, the determination of the degree of influence of each factor contributing to the formation and development of the disease and the so-called "risk factors" still remains in demand in modern nephrology.

When conducting research at this stage of work, it was taken into account that the effect of risk factors on the human body is individual and the likelihood of developing CKD depends on the compensatory-adaptive capabilities of this organism. The intensity of risk factors in prenosological diagnostics was investigated in relation to the various functional states of the patients.

Therefore, the purpose of this stage of work was to identify and assess the risk factors associated with albuminuria affecting the development of CKD. Based on the interpretation of the data, a methodical approach was used by a number of researchers who used it to evaluate various factors. In this case, 21 factors were selected for analysis, which occupied a definite place in the onset and development of CKD. These included: the age of the patient over 60 years of age, overweight; obesity, arterial hypertension; coronary heart disease; diabetes; rheumatic diseases; hyperlipidemia; pathology of the urinary tract; ischemic heart disease in straight line relatives; hypertension in relatives of the direct line; diabetes in direct line relatives; nephropathy in pregnant women with a history of women; hypertension in pregnant women with a history of women; a history of proteinuria; a dysuria of not clear etiology in the anamnesis; bad habits, smoking and drinking alcohol; abuse of drugs like NSAIDs and antibiotics; the presence of a chronic infection; history of acute allergic reactions; a history of acute bleeding and/or hypovolemic shock;

In this regard, all patients were divided into two groups according to the level of microalbuminuria and the functional state of the kidneys. The group of patients was distributed in such a way, since in the previous chapter we established the diagnostic value of these parameters.

All selected 317 patients were divided into the following groups:

Group 1 – examined with MAU > 30g/ml (above the normal limit) with impaired renal filtration function (GFR < 90 ml/min/1.73 $m^2$) n = 91. This group includes the parameters of microalbuminuria 30–80 mg/l (medium increase) and 80–150 mg (high level).

2 – group – examined with MAU > 30g/ml (above the normal limit) with preservation of the filtration function of the kidneys (GFR ≥ 120 ml/min/1.73 $m^2$)*n* = 226. This group includes the parameters of microalbuminuria 30–80 mg/l (medium increase) and 80–150 mg (high level). In addition, this group also included the examined microalbuminuria indicators in the border of the norm (MAU = 10 mg/l), but albumin / creatinine ratio (ACR) with pathological deviation (Abnormal – pathology and Highabnormal – pronounced pathology), which has a diagnostic value in early CKD determination.

The results of the study show that the number of the most significant risk factors increases in the examined 1 – group and reaches 8 factors: a history of proteinuria (48.35 ± 4.99, *n* = 44); drug abuse as NSAIDs and antibiotics (50.55 ± 4.99, *n* = 46); overweight (53.84 ± 4.98, *n* = 49); a dysuria of unclear etiology in the anamnesis (52.75 ± 4.99, *n* = 48); hyperlipidemia (69.23 ± 4.61, *n* = 63); hypertension in a straight line relative (69.23 ± 4.61, *n* = 63); arterial hypertension (79.12 ± 4.06, *n* = 72); the presence of chronic foci of infection, such as chronic tonsillitis, caries, chronic otitis media (90.11 ± 2.98, *n* = 82).

In group 2, the picture is somewhat different, since the most significant factors were 6 and they are the following overweight (53.98 ± 4.98, *n* = 122) hyperlipidemia (57.52 ± ± 4.94, *n* = 130); arterial hypertension (58.41 ± 4.92, *n* = 132); abuse of drugs like NSAIDs and antibiotics (58.85 ± 4.92, *n* = 133); the presence of chronic foci of infection, such as chronic tonsillitis, caries, chronic otitis media (92.04 ± 2.7, *n* = 208).

Between 1 and 2 groups of coincidence or recurrence of the most significant risk factors were the following parameters: arterial hypertension, hyperlipidemia, overweight, abuse of drugs like NSAIDs and antibiotics; presence of chronic foci of infection.

On the basis of these data, a mathematical model has been developed that allows calculating the risk index (IR) for the development of CKD.

Given the natural separation of the studied, according to the studied risk factors, we calculated the risk ranges. For this weight, the risk range was divided into three subranges and the boundaries of the patients with a risk of development were determined (tab. 1).

Table 1.– Evaluation of CKD risk index (in points)

| Risk Index | Risk Limits | Risk Group |
|---|---|---|
| Moderate | 5.99–4.1 | favorable forecast" |
| Average | 7.89–6.0 | "Warning" |
| High | 7.9–9.6 | "Unfavorable forecast" |

It was established that among the examined patients with a moderate CKD development index was 38.9 ± 4.87%(*n* = = 88), with an average risk with a "Warning" of 46.5 ± 4.98% (n = 105) and with a high risk and "unfavorable prognosis" 14.6 ± 3.53% (n = 33).

MAU ≤ 150g/l among the surveyed risk groups were not found. MAU ≤ 10g/l – a low level of microalbuminuria with a pathological albumin/creatinine ratio in the urine (abnormal ACR).

The most numerous was the group surveyed with an average risk index. The main identified risk factors for CKD in this group were arterial hypertension, coronary heart disease, overweight, diabetes, drug abuse (NSAIDs and antibiotics). Among women in this group, proteinuria was more common in the history (nephropathy of pregnant women).

Taking into account the position of screening the population to identify CKD, as well as the high cost and laboriousness of conducting laboratory tests when conducting mass surveys in population groups, it is proposed to conduct an interview to identify prognostically significant risk factors with the subsequent calculation of the risk index for CKD.

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# EFFICACY OF MINIMALLY INVASIVE PROCEDURES IN THE TREATMENT OF LOWER EXTREMITIES DIABETIC GANGRENE

**Abstract.** The results of the study and inpatient treatment of 311 patients were analyzed with purulent-necrotic complications of VTS in the Republican Center of purulent surgery and surgical complications of diabetes at the 2nd clinic of the Tashkent Medical Academy. All patients suffered from type 2 diabetes. Thus, minimally invasive endovascular interventions are most effective in treating diabetic gangrene of the lower extremities. Conducting intra-arterial catheter therapy with the administration of drugs after balloon angioplasty with improved blood circulation in patients with foot purulent-necrotic lesions against the background of critical ischemia increases the chances of preserving the musculoskeletal function of the lower extremities to 88.3%.

**Keywords:** Diabetic foot syndrome, transluminal balloon angioplasty, surgical complications of diabetes.

**Introduction**

Diabetic foot syndrome (DFS) is defined as an infection, an ulcer and/or destruction of deep tissues associated with neurological disorders and/or a decrease in the main blood flow in the arteries of the lower extremities of varying severity. Despite the new methods of diagnosing and treating diabetic gangrene, the frequency of limb amputations on the background of diabetes mellitus remains high [1].

Currently, a number of classifications of DFS have been proposed, based on ideas about the main pathogenetic mechanisms for the development of this diabetic complication, which takes into account the severity of damage to the peripheral nervous system, the peripheral arterial bed, the size of the wound defect and the severity of the infection process [2; 5].

Diabetic gangrene of the lower extremity is a serious complication of diabetic foot syndrome on the background of diabetes mellitus. The severity of this complication is determined not only by the mental trauma caused by the understanding of leg loss and disability, but also by the real danger of the death of the patient. Mortality after limb amputation is currently 20–33% [1; 3; 5]. Amputations performed below the knee joint are accompanied by reamputations in almost 40% of patients. Complications and defects of the stump in one form or another occur in 30–35% of operated patients [2; 7; 8].

The lesion of the peripheral arterial bed in patients with diabetes is most closely associated with bilateral amputation [4; 6]. Literature data showed that large amputations range from 48.9 to 60%, while according to cohort studies this number is 24% [5].

Historically, the gold standard for the treatment of critical lower limb ischemia (CLLI) is surgical revascularization (endovascular treatment), but this method can only be used in patients with a good distal recipient vessel without severe concomitant pathology. The prospects of balloon angioplasty are determined by the following factors: the achievement of adequate results at lower costs, a low rate of complications, the possibility of repeated interventions and insignificant mortality. All this opens up great opportunities in the application of this method in the treatment of CLLI [8].

Despite the long history of amputation, a large number of scientific studies, the treatment of patients with gangrene of the limb on the background of diabetes is an unsolved extremely urgent, not only medical, but also a social problem [9; 10].

In this regard, the purpose of this study was to assess the effectiveness of minimally invasive methods in the treatment of patients with gangrene of the lower extremities against the background of diabetes mellitus.

**Material and methods**

The results of the study and inpatient treatment of 311 patients for 2012–2018 were analyzed with purulent-necrotic complications of VTS in the Republican Center of purulent surgery and surgical complications of diabetes at the 2nd clinic of the Tashkent Medical Academy. All patients suffered from type 2 diabetes. In 63% of cases (203) patients for the correction of blood sugar received insulin.

The average duration of diabetes was 14.7 ± 5.2 years. The age of patients ranged from 47 to 81 years (on average, 62.3 ± ± 6.8 years). Among male patients, there were 217 (69.7%) and 94(30.3%) women. The neuroischemic form of diabetic

foot syndrome was diagnosed in 262(84.2%) patients, ischemic form – in 49(15.8%).

The main instrumental method of assessing the state of macrocirculation was duplex scanning of the lower extremities, performed on the Acuson-128 XP/10 ultrasonic duplex system (Acuson, USA) by a standard technique using a linear sensor with a frequency of 7–15 MHz and multispiral computed tomography of the lower limb arteries (MSCT). After checking renal activity and normalizing renal tests (urea, creatinine), all patients underwent MSCT, which determined the level of stenosis and occlusion of peripheral arteries, the degree of artery narrowing, the extent of the lesion and the exact location of atherosclerotic plaques.

After the establishment of the affected segment (occlusion and/or stenosis) of the segment, transluminal balloon angioplasty (TLBAP) of the lower limb arteries was performed in all patients. Balloon angioplasty was carried out strictly according to the angiosomal structure of the foot and lower leg, and these patients were conditionally divided into 2 groups. In the first group, 252(81%) patients received only BAP. Of the 323 patients after balloon angioplasty, 59(19%) patients of group 2, in connection with severe purulent-necrotic process of the foot and critical ischemia, prolonged intra-arterial catheter therapy (PIACT) was done with catheterization of the external iliac artery on the affected side. The duration of PIACT was from 3 to 5 days with continuous administration of drugs. After improving blood circulation, small surgical interventions were performed on the foot.

**Results and discussion**

When analyzing the affected segments of the peripheral arterial bed, patients often had a lesion of two arteries of the lower leg – anterior and posterior tibial (ATA and PTA) – 22.2%. An isolated lesion of the superficial femoral artery (SFA) was observed in 50 (20.6%) patients and, together with isolated occlusion of the ATP, was distinguished by a malignant course. In these patients, high limb amputations were often performed (half of all amputations) (Table 1).

Table 1.– Analysis of the results of treatment in patients performed TLBAP (n=252)

| № | Lesion segment | Number of patients | Amputation of fingers | Necroectomy | Amputation by Sharpe | Amputation of the leg | Hip amputation | Mortality |
|---|---|---|---|---|---|---|---|---|
| 1. | External iliac artery | 3(1.2) | 1(33.3) | 1(33.3) | – | – | – | – |
| 2. | superficial femoral artery | 52(20.6) | 27(52.0) | 16(30.7) | 7(13.4) | 8(15.3) | 4(7.7) | 3(5.7) |
| 3. | popliteal artery | 31(12.3) | 8(25.8) | 15(48.4) | 4(13.0) | 1(3.2) | 1(3.2) | 1(3.2) |
| 4. | posterior tibial artery | 25(9.9) | 6(24) | 11(44.0) | – | 4(16.0) | 1(4.0) | 4(16.0) |
| 5. | anterior tibial artery | 31(12.3) | 11(35.4) | 14(45.1) | 6(19.3) | 3(9.6) | – | 2(6.4) |
| 6. | fibular artery | 4(1.6) | 2(50.0) | – | – | – | – | – |
| 7. | anterior and posterior tibial arteries | 62(24.6) | 31(50.0) | 17(27.4) | 9(14.5) | 5(8.0) | 2(3.2) | 3(1.6) |
| 8. | Two different segments | 44(17.4) | 7(16.0) | 11(25.0) | 4(9.1) | 3(8.0) | 1(1.6) | 2(3.2) |
| Total | | 252(100) | 93(36.9) | 85(33.7) | 30(12) | 24(9.5) | 9(3.5) | 15(6.0) |

With a lesion of the popliteal artery (PA) after balloon angioplasty, staged necrotomy was most often performed (48.4%). This indicates the great role of the popliteal arterial network in compensating for the circulation of the foot ("rete genu").

In the long term (72 months) after performing balloon angioplasty of the lower limb arteries, 15(6.0%) cases were fatal. Half (8) of the patients had a fatal outcome from acute myocardial infarction and coronary syndrome (AMI and ACS), in 4(33.3%) cases there was an acute cerebrovascular accident (ACVA), one patient died from uremic coma and 2(13.3%) the cause of death has not been established.

59(18.9%) patients with severe purulent-necrotic lesion and critical ischemia of the lower limb the next day or two days after the TLBAP, a catheter (F5) was installed in the femoral artery on the affected side for intensive intraarterial drug administration using a dosimeter. This procedure lasted from 3 to 5 days.

It should be noted that in the patients who received PIACT, in most cases, isolated PAB lesion was observed (33.9%) and two lower leg arteries – 23.6% (PBBA and ASFA) (Table 2). Staged necrotomies (32.2%) were performed in the most frequent patients who received PIACT.

These data in turn shows that, against the background of PIACT with the introduction of antibiotics, angioprotectors and anticoagulants, can lead to rapid relief of purulent-inflammatory process and improve local blood circulation,

thereby accelerating the appearance of the demarcation line in the lesion.

Minor surgeries on the foot are often performed in patients with lesions of the arteries of the lower leg (78.5%). With the defeat of two or more arterial segments, these surgeries were performed in all cases (Table 2).

As can be seen in (Table 2) patients who received PIACT managed to maintain the support function of the limbs in 83% of cases, only 5(8.4%) patients had to perform amputation of the limb due to the progression of the purulent-necrotic process. Amputation above the knee of the hip in one patient due to total occlusion of the SFA.

Table 2. – Analysis of the results of treatment in patients undergoing PIACT after TLBAP ($n$ = 62)

| № | Lesion segment | Number of patients | Amputation of fingers | Necrectomy | Amputation by Sharpe | Leg's amputation | Hip amputation | Mortality |
|---|---|---|---|---|---|---|---|---|
| 1. | superficial femoral artery | 20(33.9) | 3(14.2) | 6(28.5) | 7(33.3) | 2(9.5) | 1(4.7) | 1(4.7) |
| 2. | popliteal artery | 4(6.7) | 2(50.0) | 1(25.0) | – | – | – | – |
| 3. | posterior tibial artery | 3(5.0) | 1(33.3) | 1(33.3) | – | | – | – |
| 4. | anterior tibial artery | 11(18.6) | 4(36.3) | 2(18.1) | 3(27.2) | – | – | – |
| 5. | anterior and posterior tibial arteries | 15(25.4) | 6(40.0) | 5(33.3) | 4(26.6) | 2(13.3) | – | 1(6.7) |
| 6. | Two different segments | 6(10.1) | 1(16.7) | 4(66.7) | 1(16.7) | – | – | – |
| Total | | 59(100) | 17(28.8) | 19(32.2) | 15(25.4) | 4(6.7) | 1(1.7) | 2(3.3) |

Amputation at the level of the leg was performed in 4(6.7%) cases. Fatal outcome was observed in 2 patients (3.3%). One patient died after hip amputation, in the second patient with a total occlusion of all the arteries of the lower leg, died of acute myocardial infarction.

Thus, an analysis of the dependence of the risk of amputations on the nature and localization of purulent-necrotic lesions showed that with isolated balloon angioplasty in patients with diabetic gangrene of lower extremities (DGLE) the number of amputations (above and below the knee joint) is 13%.

The most aggressive course of purulent-necrotic lesions of the feet was observed in patients with occlusive-stenotic lesions of PTA and SFA. A segmental or total lesion of the PTA led to limb amputations in 20% of cases and in 4 (16%) deaths were observed.

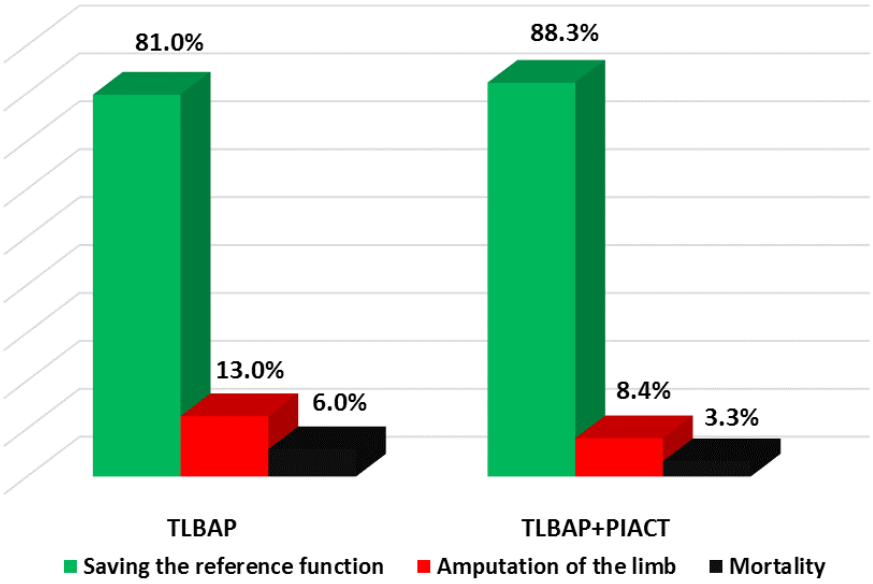


Figure 1. Comparative analysis of the results of treatment of patients

The performance of an adequate isolated revascularization of the peripheral arteries of the extremities and the complex of therapeutic measures carried out in 81.0% of cases led to the preservation of the support function of the limb. The

catheterization of the NLA with the conduct of PIACT improved the result by 7.3% and this shows the effectiveness of the integrated use of minimally invasive treatment methods for gangrene of the lower extremities against the background of diabetes mellitus.

**Discussion**

A comparative analysis of the results of patients who received intra-arterial catheter therapy showed that these patients most often from minor surgeries on the foot were performed stepwise necrotomy (32.2%), due to the appearance of a demarcation line in the lesion for a short time and a sharp decrease in purulent inflammatory process. Despite the conducted medical procedures, amputation of the limb was performed in 5(8.4%) cases.

Thus, minimally invasive endovascular interventions are most effective in treating diabetic gangrene of the lower extremities. Conducting intra-arterial catheter therapy with the administration of drugs after balloon angioplasty with improved blood circulation in patients with foot purulent-necrotic lesions against the background of critical ischemia increases the chances of preserving the musculoskeletal function of the lower extremities to 88.3%.

**Findings**

1. Revascularization of the lower limb arteries is a highly effective method of treatment in the rescue of the limb in patients with diabetic gangrene of the lower extremities and, in the presence of purulent-necrotic processes against the background of critical ischemia of the foot, in 81.0% of cases it will be possible to save the limb.

2. After the restoration of the blood flow of the peripheral arterial bed of the lower extremities, the introduction of drugs using intra-arterial catheters increases the chances of maintaining the support function of the limb to 88.3% and reduces mortality by 3.3%.

3. Conducting comprehensive minimally invasive treatment methods, allowing us to achieve the expected result even in patients with a critical situation and thereby improve their quality of life.

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# FEATURES OF CLINICAL MANIFESTATIONS AND TREATMENT OF ALLERGIC LESIONS OF THE EYE IN UZBEKISTAN

**Abstract.** Has been studied the clinical course of allergic eye diseases in the Bukhara region and a new treatment method of 68 patients, that prevents severe disease has been developed.

According to the research results in 50% of the examined patients experienced acute allergic edema of the conjunctiva (34 patients), which is the most common form of eye damage in allergic diseases in the Bukhara region, 16 (23.6%) patients had follicular conjunctivitis, 9 (13.2%) – blepharoconjunctivitis and 9 (13.2%) – papillary. Due to the long period of allergization, according to the flowering of herbs in the region, allergic conjunctivitis has a long course (february-november).

Treatment of patients with allergic diseases of the eye with the drug cromoviz gives a pronounced therapeutic effect in 87% of cases.

**Keywords:** allergic conjunctivitis, Bukhara region, cromoviz, acute allergic edema of the conjunctiva.

**Relevance.** The global experience of recent years shows not only the widespread prevalence of allergic diseases, but also a steady upward trend. Every year, about 35% of the world's population seek for medical care with the clinical manifestations of allergy. One of the main reasons for the increase in the incidence of this pathology is the living conditions of the modern person, which change the reactivity of the organism. These conditions usually include: environmental pollution, the widespread use of chemicals in everyday life and others. The main sources of air pollution in the city are motor vehicles and industrial enterprises [1; 2; 4; 8; 9; 10].

In addition, almost 50% of patients with systemic allergies (after 2–3 years of transformation of the allergophon due to the underlying disease) inevitably develop allergic conjunctivitis as a concomitant pathology [7; 12; 13; 14].

In modern conditions, the active relationship between human and the environment leads to its significant change and complication. Complexes of natural and social factors acquire new qualities that affect on the health of the population. Everywhere registered changes in the structure, dynamics and nature of human pathology are determined not so much by geographical, climatic, natural focal features, as global technological transformations, somehow causing environmental pollution [1; 2; 11].

The presence in the Republic of Uzbekistan of enterprises of the chemical, electrical industry, construction industry, mechanical engineering and metalworking causes the presence in the atmosphere at elevated concentrations of various specific pollutants [2].

According to expert estimates, the entire territory of the Bukhara region falls into a zone of very high environmental pressure, that so-called "uncomfortable". Annually, from 200 to 700 kilograms of the total flow of dust and salts fall on the territory of the region, negatively affecting on state of atmospheric air and causing enormous damage to water, soil, animal and plant life. All because of the ecological crisis of the Aral Sea region. Sand and salt from the dried part of the once one of the largest seas on the planet extends up to 500 kilometers from

the epicenter. Bukhara region is a transboundary region: on the one hand, emissions from industrial enterprises of Navoi and Kashkadarya regions, on the other hand, harmful, carcinogenic substances of industrial enterprises of the neighboring Republic of Turkmenistan. Another transboundary problem is the pollution of the Zarafshan River by the waste and drainage waters of the Samarkand and Navoi regions.

In modern conditions, research aimed at studying and timely diagnosing of the state of the environment and the incidence of the population is largely dependent on the creation and functioning of environmental-medical monitoring. Until recently, issues of organizing and improving allergic care to the population were solved in isolation from a comprehensive analysis of environmental, social, hygienic and other factors leading to the development of allergic diseases [3; 5; 6]. Uzbekistan is characterized by an abundance of vegetation; the period of flowering of plants covers a rather wide range (February-November). All this undoubtedly contributes to the development of sensitization and the emergence of allergic conjunctivitis.

In this regard, **the purpose** of this study was to study the characteristics of the clinical manifestation of allergic eye diseases in the Bukhara region, and the development of new methods of treatment that prevent severe disease.

**Materials and research methods.** Under our supervision, there were examined 68 patients with allergic conjunctivitis aged 18 to 60 years with a disease duration from 2 months to 8 years. Among the surveyed men prevailed – 48 patients, 20 patients were women.

For their examination, general ophthalmological and special methods of research were used, including the determination of allergic and immunological status.

Research results indicate the presence of clear seasonality of manifestations of clinical symptoms in 57 patients (86.2%). According to our data, weed pollen was the most common cause of eye lesions – 18 patients (26.7%), 26 patients (39.3%) were allergic to edge pollen allergens (almonds, Chinara, etc.), 13 patients (19.6%) – to meadow grass pollen. Polyallergy occurred in 35.5% of cases.

The clinical picture is due to allergic inflammation of the conjunctiva, nose, nasopharynx, trachea and bronchi, less often the skin and nervous system.

The most common clinical manifestations of allergic lesions are the combination of allergic rhinosinusitis and conjunctivitis.

According to research results, 50% of the examined patients experienced acute allergic edema of the conjunctiva (34 patients), which is the most common form of eye damage in allergic diseases in the Bukhara region, in 16 (23.6%) patients – follicular conjunctivitis, in 9 (13.2%) – blepharoconjunctivitis and 9 (13.2%) – papillary conjunctivitis.

In the Bukhara region, in conditions of a dry and hot climate, allergic eye lesions had a rather severe course. This is an acute sudden onset, accompanied by severe itching and burning in the eyes.

Acute allergic edema of the conjunctiva was characterized by a marked conjunctiva chemosis of the eyelids and eyeball, and abundant mucous discharge.

Follicular conjunctivitis manifested lesion of the mucous membrane of the eyeball, eyelids and limbus. The follicles initially appeared on the conjunctiva of the upper transitional fold, then passed to the lower one.

The clinical picture of patients with blepharoconjunctivitis was characterized by changes in the conjunctiva of the eyeball with damage of the eyelashes edges and eyelids skin.

The group of patients constituting papillary conjunctivitis resembled spring catarrh. In the area of the upper cartilage of the eyelids, diffuse papillary infiltration was observed against the background of the pale conjunctiva.

The effectiveness of the treatment of allergic eye lesions depends primarily on the timely identification of the allergen and its elimination.

However, antiallergic drugs and drugs of symptomatic therapy occupy an important place in the treatment of allergic blepharoconjunctivitis.

The classical method of prophylactic specific immunization is the most effective in the treatment of allergic conjunctivitis during the period of allergies. The method is available and is widely used in allergology in the remission of the disease, before the flowering season of plants, at certain time intervals, extracts of the corresponding pollen allergens are given subcutaneously in increasing doses. Treatment begins with the lowest dose in the autumn-winter period in the absence of signs of allergy and other intercurrent diseases.

Depending on the treatment, the patients were divided into 2 homogeneous groups. In the control group, patients were used "EYECROL" eye drops 4%, World Medicine Ophthalmics, UK, per 2 drops in the conjunctival sac of the affected eye 4 times for 7 days, amid desensitization therapy. In the main group, the drug Cromoviz ophthalmic drops 4% (manufactured by ASEPTICA LLC, Uzbekistan) was used in a similar pattern. Cromoviz is a domestic antiallergic drug that contains cromoglycic acid disodium salt. The therapeutic effect is the membrane stabilizing action of cromoglycic acid, which prevents mast cell degranulation and the release of histamine, bradykinin, leukotrienes (including anaphylaxis), prostaglandins and other biologically active substances from them. According to the results of our clinical studies, the drug is approved by the Pharmacological Committee of Uzbekistan for use in the ophthalmic practice of the republic.

Prior to the study, the leading complaint of patients in both groups was significant irritation of the conjunctiva in 56.7% of cases, tearing was less pronounced and accounted for 38.8% and 40%, respectively, itchy eyes were observed in 43.7% and 42% of cases, respectively in the main and control groups. Re-examination of patients marked positive dynamics in all parameters of subjective complaints. After treatment, all observed patients showed a significant positive trend. The effectiveness of the treatment was 96.7% in the main group and 98% in the control group. The drug was well tolerated by patients with local instillation and contributed to a favorable outcome of the disease. In the control group of patients, the results of treatment were comparable in all parameters.

Thus, the examination of patients with allergic eye lesions at the present level of allergological knowledge will help in a timely manner to identify the cause of the disease and prescribe an effective treatment, which will reduce the number of complications.

**Conclusions:** 1. Due to the long period of allergization, because of the flowering of herbs (February-November) in the region, allergic conjunctivitis has a long course.

2. Allergic eye lesions in the region are manifested in the following clinical forms: acute allergic conjunctival edema, follicular conjunctivitis, papillary conjunctivitis, and blepharoconjunitis.

3. Treatment of patients with allergic diseases of the eye with the drug cromoviz gives a pronounced therapeutic effect in 87% of cases.

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# CHARACTERISTICS OF THE DYNAMICS OF INDICATORS OF THE CENTRAL NERVOUS SYSTEM AND FUNCTIONS OF ATTENTION OF THE WORKERS OF SHOE PRODUCTION

**Abstract.** The indicators of the functional state of the central nervous system were assessed by determining the speed of visual and auditory-motor reactions, the stability of the attention function among workers of shoe production. The results of research have shown the development of inhibitory processes in the central nervous system, leading to an increase in errors in differentiation, and at elevated air temperatures at workplaces, changes in simple and complex visual-motor response are more pronounced and significantly exceed the maximum permissible values of physiological changes. They also revealed the development of inhibitory processes in terms of simple and complex auditory-motor response, with more pronounced changes observed in those occupational groups where higher levels of noise at workplaces are recorded. When studying attention functions among working women, it has been established that the number of errors made increases, the actual performance decreases, the time spent on completing the assignment during the summer period of observations increases, where the quality of the corrective test deteriorates and the level of performance decreases, indicating a more pronounced production fatigue.

**Keywords:** workers, shoe production, women, central nervous system, intensity of the labor process, visual-motor reaction, auditory-motor reaction, correction test.

**Relevance.** The shoe industry is one of the largest branches of light industry. The main task of the shoe industry is to satisfy the need of people for high-quality footwear and a diverse range. The modern footwear industry, which produces shoes of mass production, characterized by a fairly high level of introduction of new technologies, the pace of technological processes requires a constant concentration of central nervous system functions [1; 2].

Thus, significant neuro-emotional stress in the activities of various professions of shoe manufacturing, combined with physical labor and production factors, create large loads on the central nervous system [3; 4]. Materials on the study of health among workers of shoe production showed a high increase in the incidence associated with the impact of psycho-emotional stress present during the 8-hour working day while performing the basic functional duties [5; 6; 7].

Scientific studies have shown that, for assessing the functional status of the central nervous system in certain professional groups, a number of different specially developed methods are determined, taking into account the indicators of the intensity of the labor process [8; 9]. In the manufacture of shoes, workers have increased eyestrain and attention, as well as the monotony of the movements of the hands and fingers, especially when using conveyors with a strictly defined work rhythm [10].

**Purpose.** The study of changes in the indicators of the functional state of the central nervous system, by determining the speed of visual and auditory-motor reactions, the stability of the attention function occurring in the dynamics of the working day.

**Materials and methods**

Taking into account the specifics of the work of the main professional groups of shoe production, where women make up the bulk, to assess changes in the central nervous system, the speed of visual and auditory-motor reactions and the stability of attention were determined using correction tables. The determination of the speed of visual and auditory-motor reactions was carried out on a universal chronoreflexometer. A widely used technique for studying the conditioned-motor reaction of Ivanov-Smolensky with preliminary verbal instruction was used. The speed of a simple and consistent visual – and auditory-motor reactions was recorded; red and white light, a low and loud sound were used as a signal; differentiation to stimuli was developed by warning not to respond by pressing a button on white light and a loud sound. The studies were conducted according to the scheme:

10–12 positive signals were fed, 5 – complex, 5 – differentiating. The reaction rate (time from the moment when the conditioned stimulus was applied to the response) was noted in hundredths of a second (mln), taking into account both the correctness of the response to the differentiation signal and the speed of the visual and auditory-motor responses to the positive stimulus following differentiation.

The attention function was studied by using proof samples. Used tables with settled text. The subject was asked to cross out a certain letter, while taking into account the time of the assignment, the number of errors, and the actual performance was calculated using the Whipple formula.

**Results**

Conducted research among women shoe production showed results that differed significantly in the spring and summer periods in the tables below – 1, 2, 3, 4, 5, 6.

Table 1 presents the materials obtained during the survey of harvesters in the spring and summer periods of observations. From the table it can be seen that in the spring period, the background to the operating speed of a simple visual-motor reaction corresponded to 307.1 ± 0.12 mlc, during the working day the reaction time increased to 328.5 ± ± 0.15 mlc ($p < 0.001$), which indicates a decrease in the rate of simple visual-motor reaction. In the summer period of observations, the nature of changes in the indices of a simple visual-motor reaction was similar to the data of the spring period of observations, however, the intensity of the changes was more significant. If air temperature of workplaces, at the optimum spring the time of a simple visual-motor reaction had increased on average by 6.8%, then at elevated temperatures the decrease in the reaction rate had corresponded to 35.7% (from 248.1 ± 0.12 to 336.8 ± 0.11 mlc).

According to the obtained materials, it was revealed that the time of the visual-motor reaction to a positive signal following the differentiation signal (a complex or sequential visual-motor reaction) increased in the spring period at the beginning of work by 18.9 mlc, by the end – by 8.3 mlc, in the summer period – by 113.9 and 149.3 mlc, respectively. This indicates the development of consistent braking due to production fatigue.

Table 1. – Changes in visual-motor response for harvesters in the spring and summer periods of observations, mlc

| No. | Indicators of the visual-motor reaction (mlc) | At the beginning work | | Before lunch break | | In the end work | | Credibility |
|---|---|---|---|---|---|---|---|---|
| | | n | M ± m | n | M ± m | n | M ± m | $P<_{3-7}$ |
| **spring period** | | | | | | | | |
| 1. | simple | 400 | 307.1 ± 0.12 | 400 | 322.5 ± 0.14 | 400 | 328.5 ± 0.15 | 0.001 |
| 2. | complex | 200 | 326.0 ± 0.11 | 200 | 369.7 ± 0.18 | 200 | 427.1 ± 0.13 | 0.001 |
| 3. | errors (number) | 200 | 0.09 ± 0.02 | 200 | 0.22 ± 0.02 | 200 | 0.43 ± 0.03 | 0.001 |
| **summer period** | | | | | | | | |
| 1. | simple | 400 | 248.1 ± 0.12 | 400 | 289.6 ± 0.13 | 400 | 336.8 ± 0.11 | 0.001 |
| 2. | complex | 200 | 362.2 ± 0.13 | 200 | 376.2 ± 0.11 | 200 | 486.1 ± 0.11 | 0.001 |
| 3. | errors (number) | 200 | 0.03 ± 0.01 | 200 | 0.24 ± 0.03 | 200 | 0.46 ± 0.03 | 0.001 |

In addition, from the beginning to the end of the shift, erroneous reactions to the differentiating stimulus increase: in spring, from 0.09 ± 0.02 to 0.43 ± 0.03, and in summer, from 0.03 ± 0.01 to 0.46 ± 0.03.

Consequently, the working conditions and the nature of the labor of the procurers cause certain changes in the state of the central nervous system, which manifest themselves in lengthening time, reducing the speed of a simple visual-motor reaction, which indicates the development of inhibitory processes in the central nervous system, increasing the erroneous reactions to the differentiation irritant and in the development of consistent inhibition.

It is noted that in the summer period, the severity of shifts increases, which is likely due to a more pronounced manifestation of production fatigue. Table 2 presents the results of studying the visual-motor reaction in a seamstress. In this professional group, the nature of the changes in the visual-motor reaction in the dynamics of the working day is the same as that of the harvesters. At the beginning of work, the time of a simple visual-motor reaction was on average equal to 278.9 ± 0.12 mln, to the lunch break it increased to 285.9 ± ± 0.9 mlr, and by the end of the shift – to 293.0 ± 0.2 mlc, that is, 5% compared with background indicators. n the summer period of observations in the dynamics of work, the reaction time increased by 14.2%. The time of the successive visual-motor reaction in the dynamics of the shift also increased in the spring period by 5.5%, in the summer period by 8.5%. In addition, there is an increase in the erroneous reactions to the differentiating stimulus in the spring period by 45%, in the summer – by 58%.

Table 2.– Changes in the visual-motor reaction indices of a seamstress in the spring and summer periods of observations, mlc

| No. | Indicators of the visual-motor reaction (mlc) | At the beginning work | | Before lunch break | | In the end work | | Credibility |
|---|---|---|---|---|---|---|---|---|
| | | n | M ± m | n | M ± m | n | M ± m | $P<_{3-7}$ |
| **spring period** | | | | | | | | |
| 1. | simple | 400 | 278.9 ± 0.12 | 400 | 285.9 ± 0.13 | 400 | 293.0 ± 0.12 | 0.001 |
| 2. | complex | 200 | 321.9 ± 0.1 | 200 | 327.8 ± 0.2 | 200 | 339.8 ± 0.2 | 0.001 |
| 3. | errors (number) | 200 | 0.11 ± 0.02 | 200 | 0.26 ± 0.03 | 200 | 0.38 ± 0.03 | 0.001 |
| **summer period** | | | | | | | | |
| 1. | simple | 400 | 259.1 ± 0.9 | 400 | 288.8 ± 0.12 | 400 | 295.9 ± 0.07 | 0.001 |
| 2. | complex | 200 | 348.0 ± 0.1 | 200 | 367.1 ± 0.06 | 200 | 377.9 ± 0.1 | 0.001 |
| 3. | errors (number) | 200 | 0.19 ± 0.02 | 200 | 0.22 ± 0.02 | 200 | 0.47 ± 0.03 | 0.001 |

Table 3 presents the results of the examination of the visual-motor reaction of the preparators and pickers. In the dynamics of the change, the time of the visual-motor reaction increased from 325.8 to 345.6 mln (6.7%) in the spring period of observations and from 296.1 to 331.8 mln (12.5%) in the summer period. At the same time, the time of consistent visual-motor reaction increases from 339.8 to 448.9 mln (by 32.1%) in spring and from 347.8 to 430.6 mln (by 45.4%) in summer, in addition in the spring period, the number of erroneous reactions to the differentiating stimulus increased from 0.07 to 0.51, and in summer, from 0.07 to 0.55.

Table 3.– Changes in visual-motor response at the preparatory and collectors in the spring and summer periods of observations, mlc

| No. | Indicators of the visual-motor reaction (mlc) | At the beginning work | | Before lunch break | | In the end work | | Credibility |
|---|---|---|---|---|---|---|---|---|
| | | n | M ± m | n | M ± m | n | M ± m | $P<_{3-7}$ |
| **spring period** | | | | | | | | |
| 1. | simple | 400 | 325.8 ± 0.16 | 400 | 337.5 ± 0.14 | 400 | 345.6 ± 0.15 | 0.001 |
| 2. | complex | 200 | 339.8 ± 0.27 | 200 | 369.6 ± 0.17 | 200 | 448.9 ± 0.21 | 0.001 |
| 3. | errors (number) | 200 | 0.07 ± 0.01 | 200 | 0.23 ± 0.03 | 200 | 0.51 ± 0.03 | 0.001 |
| **summer period** | | | | | | | | |
| 1. | simple | 400 | 296.1 ± 0.13 | 400 | 320.3 ± 0.12 | 400 | 331.8 ± 0.28 | 0.001 |
| 2. | complex | 200 | 347.8 ± 0.27 | 200 | 336.8 ± 0.17 | 200 | 430.6 ± 0.31 | 0.001 |
| 3. | errors (number) | 200 | 0.07 ± 0.01 | 200 | 0.31 ± 0.03 | 200 | 0.55 ± 0.03 | 0.001 |

Consequently, the nature of the labor processes of harvesters, seamstresses, shoemakers, who require eye strain and attention from workers, causes considerable fatigue among working women, which is manifested in the development of the predominance of inhibitory processes in the central nervous system, sequential inhibition and an increase in differentiation errors, moreover, at elevated air temperatures at workplaces, in the summer period of observations, the change in indicators is more pronounced.

Considering that noise is one of the leading adverse factors in production of footwear, in the dynamics of the working day, the rates of the auditory-motor response of women from the main occupational groups were studied. The obtained data are presented in tables 4, 5, 6.

Table 4.– Changes in hearing-motor response at harvesters in spring and summer periods of observations

| No. | Indicators of the visual-motor reaction (mlc) | At the beginning work | | Before lunch break | | In the end work | | Credibility |
|---|---|---|---|---|---|---|---|---|
| | | n | M ± m | n | M ± m | n | M ± m | $P<_{3-7}$ |
| ***1*** | ***2*** | ***3*** | ***4*** | ***5*** | ***6*** | ***7*** | ***8*** | ***9*** |
| **spring period** | | | | | | | | |
| 1. | simple | 400 | 261.0 ± 0.19 | 400 | 272.5 ± 0.31 | 400 | 277.5 ± 0.21 | 0.001 |

| *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* | *9* |
|---|---|---|---|---|---|---|---|---|
| 2. | complex | 200 | 272.1 ± 0.13 | 200 | 309.6 ± 0.45 | 200 | 377.5 ± 0.22 | 0.001 |
| 3. | errors (number) | 200 | 0.07 ± 0.001 | 200 | 0.22 ± 0.03 | 200 | 0.43 ± 0.03 | 0.001 |
| **summer period** | | | | | | | | |
| 1. | simple | 400 | 196.3 ± 0.15 | 400 | 238.3 ± 0.18 | 400 | 290.0 ± 0.21 | 0.001 |
| 2. | complex | 200 | 307.2 ± 0.19 | 200 | 331.9 ± 0.15 | 200 | 438.1 ± 0.53 | 0.001 |
| 3. | errors (number) | 200 | 0.08 ± 0.01 | 200 | 0.35 ± 0.03 | 200 | 0.53 ± 0.03 | 0.001 |

Table 5. – Changes in the acoustic-motor reaction in a seamstress in the spring and summer periods of observations

| No. | Indicators of the visual-motor reaction (mlc) | At the beginning work | | Before lunch break | | In the end work | | Credibility |
|---|---|---|---|---|---|---|---|---|
| | | n | M ± m | n | M ± m | n | M ± m | $P<_{3-7}$ |
| **spring period** | | | | | | | | |
| 1. | simple | 400 | 237.1 ± 0.15 | 400 | 241.9 ± 0.18 | 400 | 245.4 ± 0.14 | 0.001 |
| 2. | complex | 200 | 321.9 ± 0.1 | 200 | 327.8 ± 0.3 | 200 | 339.8 ± 0.2 | 0.001 |
| 3. | errors (number) | 200 | 0.11 ± 0.02 | 200 | 0.26 ± 0.03 | 200 | 0.41 ± 0.03 | 0.001 |
| **summer period** | | | | | | | | |
| 1. | simple | 400 | 209.5 ± 0.27 | 400 | 238.5 ± 0.17 | 400 | 240.6 ± 0.16 | 0.001 |
| 2. | complex | 200 | 320.3 ± 0.18 | 200 | 320.6 ± 0.18 | 200 | 347.4 ± 0.28 | 0.001 |
| 3. | errors (number) | 200 | 0.08 ± 0.01 | 200 | 0.35 ± 0.03 | 200 | 0.53 ± 0.03 | 0.001 |

Table 6. – Changes in the parameters of the auditory-motor reaction in preparators and collectors in spring and summer periods of observations

| No. | Indicators of the visual-motor reaction (mlc) | At the beginning work | | Before lunch break | | In the end work | | Credibility |
|---|---|---|---|---|---|---|---|---|
| | | n | M ± m | n | M ± m | n | M ± m | $p<_{3-7}$ |
| **spring period** | | | | | | | | |
| 1. | simple | 400 | 277.9 ± 0.15 | 400 | 287.8 ± 0.16 | 400 | 291.3 ± 0.15 | 0.001 |
| 2. | complex | 200 | 295.8 ± 0.28 | 200 | 291.0 ± 0.18 | 200 | 382.5 ± 0.31 | 0.001 |
| 3. | errors (number) | 200 | 0.07 ± 0.01 | 200 | 0.31 ± 0.03 | 200 | 0.38 ± 0.03 | 0.001 |
| **summer period** | | | | | | | | |
| 1. | simple | 400 | 246.8 ± 0.19 | 400 | 273.7 ± 0.14 | 400 | 282.7 ± 0.16 | 0.001 |
| 2. | complex | 200 | 310.8 ± 0.29 | 200 | 319.9 ± 0.27 | 200 | 397.2 ± 0.22 | 0.001 |
| 3. | errors (number) | 200 | 0.08 ± 0.01 | 200 | 0.36 ± 0.03 | 200 | 0.54 ± 0.03 | 0.001 |

Research results show that in all professional groups from the beginning to the end of the shift, an increase in the time of both simple and complex hearing-motor response is observed. If at the beginning of work, the time of a simple auditory-motor reaction ranged from 237 to 277 mls on average, by the lunch break it increased to 241–287 mls, and by the end of the work – to 245–291 mls, that is, the speed of a simple hearing-motor reaction in the dynamics of work significantly ($p < 0.001$) decreased in all professional groups. It is noteworthy that if at the time of the seamstresses and the preparators, the simple hearing and motor response increased by the end of work by 3 and by 4.8%, respectively, then for the harvester workers by 6%, which is probably due to the fact that the harvesters are subjected to higher noise levels (up to 104 dB), which is manifested by an adequate response of the body – a more pronounced predominance of inhibition on a sound stimulus, as a sign of production fatigue.

In addition, in the dynamics of work in women of all surveyed occupational groups, the rate of complex auditory-motor response decreased, and the number of errors per differentiating stimulus increased, which was a manifestation of developing sequential inhibition and deterioration of differentiation.

In the summer period of observations, the background pre-work time indices of both simple and complex hearing-motor response were lower than in spring, which is probably due to

the fact that high both external and internal air temperatures increase the mobility of the nervous processes in the central nervous system. In the dynamics of work, the time of a simple auditory-motor reaction increased on average for harvesters from 196.3 to 290.9 mls, for a seamstress – from 209.5 to 240.6 mls, for female workers and pickers from 246.8 to 282.7 mls.

Moreover, if, for seamstresses, preparers and pickers, a change in the rate of a simple auditory-motor reaction is 14%, then in stockpiles – 48%, which can be attributed to the effect of a higher noise level.

More pronounced shifts were established in terms of the complex auditory-motor response. In the dynamics of work of the harvesters at elevated air temperatures, the reaction time increased from 307.2 to 438.1 mls (42%), in a seamstress – from 320.3 to 347.4 mls (8.4%), in preparators and collectors – from 310.8 to 397.2 mls (27%).

In addition, in all professional groups, the number of errors per differentiating stimulus increased. If at the beginning of the working day this indicator in various professional groups was on average equal to 0.08, by the lunch break it was 0.35–0.36, by the end of the shift it was 0.53–0.54, which indicates a deterioration in differentiation those. reduced attention. The obtained data are confirmed by the results of testing working on the correction test (taking into account the unidirectionality of changes in the visual-motor reaction and the auditory-motor reaction in women of the main occupational groups, the data on the corrective test are presented on average for all examined, without a breakdown into professional groups).

The results of the research are presented in Table 7. The materials show that in the spring, the task execution time on the proofreading test significantly increased from 62.3 to 69.1 s, while at the beginning of the work 1.1 ± 0.1 errors were made on average, for the lunch break – 1.6 ± 0.2, and by the end of the work – 2 ± 0.1. The increase in the number of errors was accompanied by a decrease in the actual performance calculated by the Whipple formula: if at the beginning of work it was equal to 430 ± 1.7 conventional units, then at the end it decreased to 421 ± 2.1 ($p < 0.01$). The number of deleted characters in the dynamics of the change has not changed significantly. The increase in errors and the decrease in actual performance can be regarded as a deterioration in the quality of work and a decrease in the level of efficiency associated with developing production fatigue.

Table 7. – Changes in the indicators of the correctional test of workers in shoe production during spring and summer observations periods

| Indicators of the proof test | At the beginning work | | Before lunch break | | In the end work | | Credibility |
|---|---|---|---|---|---|---|---|
| | n | M ± m | n | M ± m | n | M ± m | $P<_{3-7}$ |
| **spring period** | | | | | | | |
| task time. s | 75 | 62.3 ± 1.2 | 75 | 65.1 ± 1.1 | 75 | 69.1 ± 1.3 | 0.001 |
| number of crossed out characters | 75 | 55.4 ± 1.7 | 75 | 53.6 ± 1.6 | 75 | 52.5 ± 0.7 | – |
| number of mistakes | 75 | 1.1 ± 0.1 | 75 | 1.6 ± 0.2 | 75 | 2.0 ± 0.1 | 0.001 |
| actual performance | 75 | 430 ± 1.6 | 75 | 428 ± 1.1 | 75 | 421 ± 2.1 | 0.01 |
| **summer period** | | | | | | | |
| task time. s | 75 | 68.8 ± 0.9 | 75 | 69.5 ± 0.5 | 75 | 71.8 ± 1.0 | 0.05 |
| number of crossed out characters | 75 | 51.9 ± 1.5 | 75 | 53.9 ± 1.1 | 75 | 54.6 ± 1.1 | – |
| number of mistakes | 75 | 1.1 ± 0.03 | 75 | 1.6 ± 0.1 | 75 | 2.6 ± 0.1 | 0.001 |
| actual performance | 75 | 433 ± 1.6 | 75 | 427 ± 1.3 | 75 | 406 ± 1.1 | 0.01 |

In the summer observations period, at elevated air temperatures, the direction of change in the indices of the correction test was similar to that described above. However, attention is drawn to the fact that in the summer before work on the execution of the sample took more time than in the spring. In addition, by the end of the work, a greater number of errors were allowed, and the actual productivity more significantly, i.e. in summer, the quality of work was worse than in spring, and the level of efficiency was lower, indicating a more pronounced production fatigue.

Consequently, at elevated air temperature and in terms of the correction test, the examined workers of the main professional groups revealed a disturbance in the relationship between the excitatory and inhibitory processes, the predominance of inhibition processes in the central nervous system, and weakening of differentiation. The described shifts in the correction test indicators are associated with a negative impact on the working temperature factor.

**Conclusions:**

1. Working conditions and the nature of work processes in workers causes the development of the predominance of inhibitory processes in the central nervous system, sequential inhibition and an increase in differentiation errors, and at elevated air temperatures at workplaces, changes in simple

and complex visual-motor response are more pronounced and significantly exceed maximum permissible values of physiological changes.

2. The dynamics of the working day also revealed the development of inhibitory processes in terms of simple and complex hearing-motor response, with more pronounced shifts observed in those occupational groups where higher levels of noise at workplaces are registered (procurers), as well as at higher temperatures the environment.

3. It was found that in the dynamics of work indicators characterizing the attention function of working women are deteriorating: the number of errors increases, actual performance decreases, the time spent on the assignment increases; more pronounced production fatigue.

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# NON-PALPABLE BREAST TUMORS AND FEATURES IN MORPHOLOGICAL APPROACHES TO DIAGNOSIS

**Abstract.** This review article presents the types of non-palpable breast tumors. All types of diagnostic studies of the mammary gland, and features in the morphological approaches to the diagnosis of intraductal formations of the mammary gland are given.

**Keywords:** Breast, tumor, diagnosis.

Breast cancer occupies the first place in the structure of the cancer incidence of the female population, its frequency continues to grow, especially in old age. Mortality from breast cancer remains high, despite advances in treatment and improving the quality of diagnosis of this pathology [3; 5; 10].

Early diagnosis of breast cancer improves the quality of treatment and improves the prognosis of the disease. In this regard, intracystic breast cancer is of undoubted interest [4; 8]. On the morphological basis, it is papillary, and belongs to rare forms of cancer. For the first time, papillary cancer was isolated as "independent" in 1959. Its frequency, according to a number of authors [2; 6; 7] ranges from 0.3–2.2% of all breast cancer cases.

Diagnosis of intracystic breast cancer is difficult, a reliable diagnosis in a clinical examination is impossible. Differential diagnosis of intracystic cancer with intracystic papillary growths is difficult and often impossible without a combination of several diagnostic methods. According to various authors, the age of patients with papillary cancer ranges from 55 years to patients older than 60 years.

Intra cystic cancer is characterized by a slow rate of tumor growth [7], which affects the degree of aggressiveness of the disease. According to the type of tumor growth, intracystic cancer belongs to the nodular form. Metastasis to regional lymph nodes, according to domestic and foreign literature, is observed in 6.2–26% [6]. These features characteristic of intracystic cancer can affect the choice of surgical treatment in the direction of organ-preserving operations.

Traditionally, intraductal proliferation is divided into simple ductal hyperplasia, atypical ductal hyperplasia and cancer in situ. Population mammology screening requires the identification of pathological conditions that are extremely high risk of developing invasive breast cancer. The results of further clinical studies have shown that various intraductal proliferations with different frequencies pass into cancer in situ and invasive cancer. Thus, the risk of developing vasic breast cancer from simple ductal hyperplasia is 1.5%, from atypical ductal hyperplasia 4–5% and cancer in situ 8–10% [1].

Simple (ordinary) ductal hyperplasia often occurs against the background of mastopathy and looks like the proliferation of the epithelium with signs of some polymorphism inside the ducts. The ducts are unevenly sized. Characterized by a change in the normal structure of the ducts, the formation of dilated, regular shape of the ducts around the lobules of normal structure. Ducts branch in the form of streams from the center of

the site of hyperplasia to the periphery. Cell proliferates can form solid areas, cribrosa structures, bridges [1; 5].

Cellular composition of proliferates polymorphic. Moreover, it should be noted that cell polymorphism is tumor. The epithelium of the ducts, despite the different size of the nuclei and different expressions of the cytoplasm, has a mature appearance. Cell polymorphism is formed by the presence of the epithelium, which is in a functional of a different state. In one duct, cells with marked signs of secretion (often the cells are located in the center of the duct), as well as signs of proliferation (usually near the basement membrane) can be marked. Epithelial cells can form 2–4 layers. The presence of microcalcifications and necrosis is not excluded. In cases where there is no true atypia of the cells, these signs should not bend the pathologist towards the diagnosis for "atypical hyperplasia" or "cancer in situ". It should be noted that necrosis and microcalcinates often imitate cancer in situ [2; 6].

**Criteria for simple ductal hyperplasia. Cytological.** Variability of nucleus forms with hyperchromic round and oval nucleoli, asymmetric nucleoli.

**Histological.** Epithelial cells tend to be irregularly located in the ducts, the variability of the distance between the nuclei is noted, the orientation of the cells is disturbed, their cytoplasm is not clearly delineated, and secretion is often detected [3]. Intercellular distances differ in size and shape, often gap-like structures are noted. An immunohistochemical study confirms the mosaic pattern of various cell patterns. Some cells express high molecular weight cytokeratin (HMW SC), such as CK 5/10/14. There is a high expression of E-cadherin. The number of cells with an estrogen receptor is higher than in normal breast tissue. Cyclin D1 was detected in 11–19% of cases of simple ductal hyperplasia [1; 4; 6].

The risk of developing invasive cancer from simple ductal hyperplasia is 2.6% over the observation period of about 14 years. It should be noted that this percentage of invasive cancer on the background of atypical ductal hyperplasia is formed in 8.3 years [7; 8]. Ordinary ductal hyperplasia is one of the morphological manifestations of hormonal changes in a woman's body.

Morphological and functional changes that occur during different periods of the menstrual cycle and pregnancy can simulate normal ductal hyperplasia, so the pathologist must have information about the condition of the woman, her age, the presence of endocrine and gynecological diseases. Be sure to meet the timing of taking a biopsy or an operation in accordance with the menstrual cycle [3; 9].

**Ductal neoplasia with mild atypia.** In this variant of ductal neoplasia, proliferation of the epithelium is more pronounced compared to the previous one, the cells form in the duct from 1 to 3–5 rows, more significantly the manifestation of cell atypia. Papillary, cribrous, solid proliferates are absent.

The morphological picture in this pathology corresponds to Grade 1A ductal intraepithelial neoplasia. The risk of developing invasive cancer against the background of simple ductal atypia is higher than against the background of simple ductal hyperplasia [3].

**Atypical ductal hyperplasia.** This disease is characterized by a more pronounced proliferation of the epithelium, increased sign of accurate polymorphism and the appearance of atypia of varying severity. The disease is characterized by a moderate risk of developing invasive breast cancer.

The morphological picture corresponds to Grade 1B ductal intraepithelial neoplasia, in some places the ducts resemble cancer in situ G1. For atypical ductal hyperplasia, areas of simple ductal hyperplasia are required. The most important feature of any form of ductal intraepithelial neoplasia is the presence of a continuous basement membrane and a layer of myoepithelial cells. Depending on the degree of the duct of intraepithelial neoplasia, the number of epithelial cells is different [3; 9].

**Intraductal papilloma.** These formations are possible anywhere within the duct system from the nipple to the terminal lobular ductal unit. There are benign variants (intraductal papilloma), atypical (atypical papilloma) and malignant (intraductal papillary cancer) [2; 5; 7].

Central and peripheral variants are distinguished from intraductal papillomas, depending on localization. Central intraductal papilloma is a solitary formation, which is located, as a rule, in the subareolar zone, often in the cystic extended duct. Peripheral intraductal papillomas often multiple. Most researchers believe that single intraductal papillomas do not have a tendency to malignancy. Multiple papillomas, especially in the peripheral parts of the lobular duct system, are prone to malignancy. Great difficulties arise in the diagnosis of central intraductal papillomas, since they can be clinically accompanied by bloody nipple discharge [1; 5].

Diagnosis of papillomas includes necessarily mammography, ultrasound (US), as well as cytological examination of nipple discharge [10]. All intraductal papillomas have a common morphological code in the International Classification of Oncological Diseases – 8503/0.

**Central intraductal papilloma.** It is 10% of all benign lesions of the breast. More often detected in women of middle age (40–50 years). Palpable lesions are rounded formations with well-defined contours; there is a connection with the dilated large duct. Puncture biopsy allows to obtain serous contents. The size is usually large, from 3–4 mm to several centimeters.

The histological structure of the central and peripheral intraductal papilloma is the same. However, given the large size of the central papilloma in it can be noted areas of two types:

ductal and papillary. Papillary formations are represented by a fibrovascular pedicle covered with two epithelium. The ductal component has the structure of the ductal hyperplasia described above. Tumors dominated by ductal component and sclerosis are commonly referred to as "sclerosing papilloma" [2; 5].

**Peripheral intraductal papilloma.** Unlike the central intraductal papilloma, this tumor develops in younger women. The clinical course often proceeds hidden. Large papilloma sizes can be palpated. Mammography often reveals multiple nodules with clear contours, and microcalcifications are possible [5].

**Atypical intraductal papilloma.** This form of intraductal papilloma is highlighted by its important prognostic value, because, however, against the background of atypical intraductal papi, invasive carcinomas are more common [5; 6].

Intraductal papillary carcinoma is deprived (almost all over) of the myoepithelial cell layer and is characterized by the proliferation of atypical epithelium. Often there is a multicenter growth [2; 3].

This tumor has its own morphological code in the International Classification of Oncological Diseases –8503/2.

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# CHARACTERISTICS OF MORPHOMETRIC PARAMETERS OF THE MAXILLO-FACIAL REGION OF PATIENTS WITH GNATIC FORMS OF OCCLUSION ABNORMALITIES

**Abstract.** The data from the archives of the 38 patients (ethnic Uzbeks) with the gnathic forms of occlusion anomalies, who have a treatment at the Clinic of Tashkent State Dental Institute was analyzed. And the criteria of normal range for the ethnic Uzbeks were determined by the cephalometric evaluation during the treatment of the patients with the dent maxillofacial anomalisms.

**Keywords:** orthognathic surgery, deformities of jaws, morphometric analysis.

**Relevance of the problem.** The analysis of the data of clinical studies of domestic and foreign authors shows that the search for the best algorithm for the treatment of patients with congenital and acquired deformities of the facial skeleton has been going on for more than 40 years and does not lose its relevance to present day (Drobyshev A. Yu., 2007; Gunko V. I., 2009; Nabiev F. Kh., 2009; Senyuk A. N. 2010; Syomkin VA, 2011; Posnick J. C., 2008; Costa F., Politi M., 2008). The importance of this problem is primarily determined by the high frequency of this pathology (Shamsudinov A. Kh., 2001; Balin V. N., 2007; Medvedev Yu.A., 2009).

Nowadays, the issues of diagnosis and treatment of patients with various deformities of the facial skeleton are widely covered. However, the issues of aesthetic rehabilitation of this category of patients remain open. These patients undergo orthognathic and reconstructive surgery, orthodontic treatment, cosmetic interventions, but little attention is paid to the accompanying functional and aesthetic changes in the surrounding structures (Pshenysnov K. P. et al., 2004; Pavlyuchenko L. L. 2005; Oganesyan S. S., 2008; Higuera S. et al., 2007; Becker D. G., Bloom J., 2008; Kantas I., et al., 2008).

**Purpose of research**. To characterize the morphometric parameters of the maxillofacial region in patients with gnatic forms of occlusion abnormalities (GFOA).

**Material and methods of research.** To assess the morphometric parameters of the maxillofacial region of patients with GFOA, an analysis of archival material was carried out in 38 patients-ethnic Uzbeks who were on dispensary observation in the Department of pediatric maxillofacial surgery of the hospital of Tashkent State Dental Institute. To identify deformities of the facial skeleton depending on the severity in one or another plane, a typical accessory, we used the classification of malocclusion proposed by E. Engle (1898).

Depending on the type of malocclusion patients after diagnosis, were divided into the following 2 groups: 1 group comprised of the class II patient (E. Engel, 1898) distal oc-

clusion (upper macro prognathia, lower micro retrognathia); 2 – group – class III – class III occlusion (lower macro prognathia, top micro retrognathia). All patients underwent clinical and x-ray examination: clinical examination, detection of complaints, assessment of the state of the dental-jaw system and tissues of the maxillofacial area, anthropometry of facial proportions, telerentgenography in direct and lateral projections.

Table 1.– Distribution of patients according to age and sex

| Group | Sex | Age groups (years) | | | In total | |
|---|---|---|---|---|---|---|
| | | 14–19 | 20–24 | 25–35 | | |
| 1 группа | male | 4 | 2 | 1 | 7 | 16 |
| | female | 5 | 4 | – | 9 | |
| 2-группа | male | 3 | 6 | – | 9 | 22 |
| | female | 7 | 4 | 2 | 13 | |
| Total | | 19 | 16 | 3 | 38 | |

To assess the skeletal signs of jaw development, symmetry of facial skull bones, the main cephalometric parameters, we used cephalometric indicators of the computer program Dolphin and studied the following indicators – the absolute length of the upper jaw (PNS-ANS), the absolute length of the lower jaw (Go –Pg), the height of the middle third of the face (N-ANS), the height of the lower third of the face (ANS-Gn) and the position of the upper and lower jaw and interdigital differential (SNA, SNB, ANB) (Fig. 2). As control indicators of cephalometry of norm of persons of the Uzbek population (S. S. Murtazayev, 2017) are taken (Fig.1)

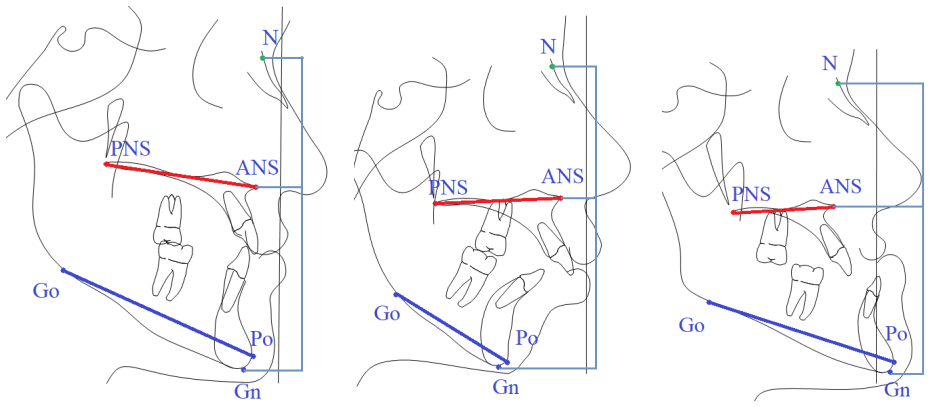


Figure 1. Schematic representation of the length of the facial skeleton: PNS-ANS –absolute length of the upper jaw, Go-Pg –the absolute length of the mandible, N-ANS-height of the middle third of the face, ANS-Gn is the height of the lower third of the face. A-the size of the facial skeleton in patients with orthognathic bite, B-the size of the facial skeleton in patients with distal occlusion, C dimensions of the facial skeleton in patients with mesial occlusion

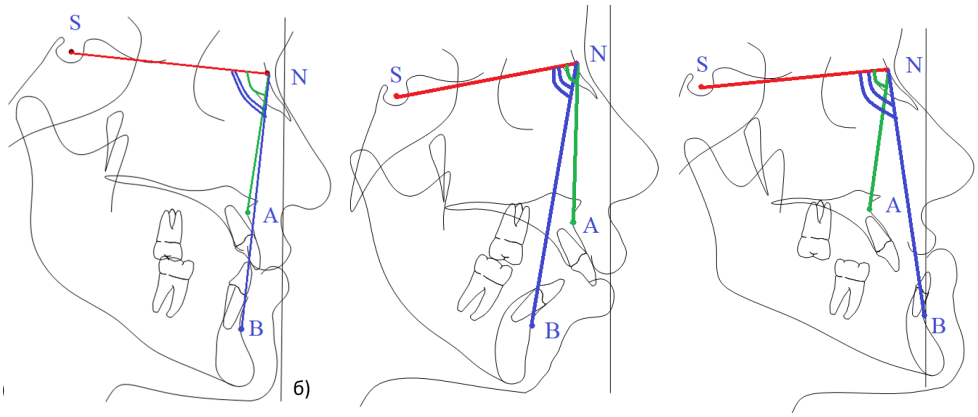


Figure 2. Schematic representation of angles: SNA, SNB, ANB: A – with orthognathic bite, B – with distal occlusion, C – with a mesial bite

In our opinion, these examinations allow us to make a comparative assessment of skeletal signs of jaw development, to assess the symmetry of the bones of the facial skull, to assess the main cephalometric parameters of the patient with GFOA.

**Result of research.** Analysis of the results of the study of aesthetic parameters before surgery in patients of group 1 shows that the ratio of the average height of the face is more than 1 in relation to the lower height (normally 1:1), which indicates an increase in the size of the upper jaw or a decrease in the size of the lower jaw.

In this study group, 14 patients presented aesthetic complaints (87.5%), which were expressed in a decrease in the lower third of the face and the crowding of the dentition in 11 patients (68.8%), insufficient visualization of the incisors of the upper jaw with a smile in 5 patients (31.3%). Patients of this group are characterized by complaints of clicking in the area of temporomandibular joints-3 patients (18.7%), fatigue of masticatory muscles in 4 patients (25%) and difficulty of nasal breathing in 6 patients (37.5%).

In patients of this group, the characteristic features of the face were revealed: there was a violation of the proportions of the face due to the shortening of its lower part. Lobopodia crease located high and deep. All patients were characterized by a distal position of the chin relative to the middle part of the face. With a pronounced retroposition of the lower jaw in the resting position, the closing of the lips was disturbed: the mouth is half-open, from under the upper lip the incisors of the upper jaw are visible. The examination of the oral cavity in 1 patient (6.25%) revealed a small vestibule of the oral cavity in the anterior part of the lower jaw and a high attachment of the lower lip frenulum and oral mucosa strands. 2 patients (12.5%) had protrusion of incisors of both jaws, 3 patients (18.8%) – retrusion of the upper incisors, while all patients had a close position of the front teeth. In addition, all patients noted a deformity of the occlusal plane, distal occlusion of posterior teeth, the cartridge disocclusion (sagittal slot reached an average of 7 to 13 mm). The majority of patients had deep incisor disocclusion, and 2 patients (12.5%) had vertical incisor disocclusion. There was also a deformation of the dental arches of the jaws: shortening of the lower dental arch, narrowing of the dental arches in the lateral parts.

The results of the study of aesthetic parameters before surgery in patients of group 2 show the presence of a variety of skeletal disorders. In patients of this group, the ratio of the average height of the face is less than 1 in relation to the lower height, which indicates an increase in the size of the lower jaw or a decrease in the size of the upper jaw.

In this group, all 22 patients complained of cosmetic defects (100%), which were expressed in excessive intensity of the chin Department – 21 cases (94.5%), and lengthening of the lower third of the face – 18 cases (81%). In addition, 4 patients (18%) complained of insufficient expression of gonial angles, the crowded position of the teeth worried 12 patients (54%), the tension in the closing of the lips and the presence of a "gingival" smile was observed in 13 patients (58.5%). Also, patients complained of "hump" in the back of the nose 7 (31.5%) and difficulty in nasal breathing 14 (63%), 9 patients (40.5%) noted the presence of difficulties in biting off food.

In patients of this study group was dominated by an increase in body length, which was combined with an increase in gonial angle over 123–124°. The height of the chin of the lower jaw was increased. The height of the branches was within normal limits. In such patients, there was a decrease in the volume of the oral cavity and the wrong position of the tongue. The disproportion of anterior and posterior facial height is revealed. t should be noted that in patients with a pronounced increase in the gonial angle, the height of the lower jaw and the anterior facial height, "long face syndrome" was revealed and an increase in the inclination of the front teeth and vertical disocclusion of the dentition with a reverse overlap was observed.

Analysis of the results of the study of cephalometric parameters in patients of group 1 shows (tab. 2) what the average length of the maxilla (PNS-ANS) in patients of this group was 50.5 ± 0.31 mm, mean value of the absolute length of the mandible (Go-Gn) amounted to 74.5 ± 1,21 mm, which indicates the small size of the lower jaw, the front elevation of the middle third of the face (N-ANS) amounted to 52,45 ± 1,83 mm. The average value of the height of the lower third of the face (ANS-Gn) amounted to 61,1 ± 1,88 mm, indicating that the underdevelopment of the lower third of the face.

Table 2.– Linear cephalometric parameters of patients with GFOA, M+m (mm)

| Recearch group | Sex | ANS-PNS (мм) | Go-me (мм) | Go-Gn (мм) | N-ANS (мм) | ANS-Gn (мм) | Ar-Go (мм) |
|---|---|---|---|---|---|---|---|
| *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* |
| 1st Gr | M | 52.0 ± 0.51 | 71.6 ± 0.64 | 75.9 ± 0.83 | 53.1 ± 0.72 | 63.3 ± 0.47 | 54.7 ± 1.27 |
| | F | 49.1 ± 0.3 | 68.7 ± 0.17 | 73.1 ± 0.53 | 51.8 ± 0.97 | 58.9 ± 0.81 | 48.9 ± 0.94 |
| | Average | 50.5 ± 0.31 | 70.1 ± 0.39 | 74.5 ± 1.21 | 52.45 ± 1.83 | 61.1 ± 1.88 | 51.8 ± 0.78 |

| *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* |
|---|---|---|---|---|---|---|---|
| 2nd Gr | M | 50.1 ± 0.72 | 75.8 ± 1.14 | 82.6 ± 0.92 | 52.2 ± 0.24 | 72.5 ± 0.19 | 59.3 ± 0.61 |
| | F | 46.9 ± 0.51 | 71.3 ± 0.62 | 76.7 ± 0.88 | 50.1 ± 0.78 | 65.7 ± 0.37 | 52.1 ± 0.48 |
| | Average | 48.5 ± 0.59 | 73.5 ± 0.58 | 79.6 ± 0.63 | 51.1 ± 1.36 | 69.1 ± 1.09 | 55.7 ± 0.14 |
| Control | M | 51.9 ± 0.52 | 73.9 ± 0.82 | 79.7 ± 0.82 | 54.93 ± 0.58 | 68 ± 0.84 | 54.9 ± 0.74 |
| | F | 47.8 ± 0.44 | 68.5 ± 0.65 | 74.0 ± 0.69 | 50.02 ± 0.81 | 61.5 ± 1.12 | 48.5 ± 0.56 |
| | Average | 49.8 ± 0.4 | 71.2 ± 0.59 | 76.8 ± 0.61 | 52.62 ± 0.5 | 64.98 ± 0.77 | 51.7 ± 0.57 |

*Note: the control group is study of S. S. Murtazayeva (2018)*

In patients of 2nd group, the results of the study of cephalometric parameters show that the average length of the upper jaw (PNS-ANS) was 48.5 ± 0.59 mm, indicating a small size of the upper jaw (tab. 2). The average length of the mandible (Go-Gn) was 79.6 ± 0.63 mm, indicating an increase in the size of the mandible. The mean height of the middle third of the face (N-ANS) was 51.1 ± 1.36 mm, indicating a small size of the middle third of the face. The average height of the lower third of the face (ANS-Gn) was 69.1 ± 1.09 mm, indicating an increase in the size of the lower third of the face. The spread of indicators in the study group was very significant (the maximum size of the lower third varies from the maximum – 76.3 mm to the minimum –57mm). This indicates a large variability of the original data.

The results of studies of jaw angles in patients of group 1 show that the average value of SNA was 83.5 ± 2.49 (tab. 3), which indicates a tendency to the anterior position of the upper jaw. The average value of the SNB angle was 77.3 ± 2.38°, which indicates a decrease in the angle due to the small size of the lower jaw. The average value of the ANB angle index in patients with distal occlusion was 7.15 ± 0.66°, which indicates an increase in the angle value.

In patients of 2nd group SNA angle had an average of 81.47° ± 0.71° (tab. 3), indicating the normal position of the upper jaw, the average angle SNB was 86.5 ± 1.01°, indicating an increase in the angle and the size of the lower jaw. The average ANB angle representing the difference between SNA and SNB angles was –5.8 ± 0.64°.

Table 3.– Angular cephalometric parameters of patients with GFOA, M+m (degrees)

| **Research** | **Sex** | **SNA angle (°)** | **SNB angle (°)** | **ANB angle (°)** |
|---|---|---|---|---|
| 1st Gr | M | 84.1 ± 0.83 | 77.8 ± 1.19 | 8.1 ± 0.33 |
| | F | 82.9 ± 0.79 | 76.9 ± 0.85 | 6.2 ± 0.73 |
| | Average | 83.5 ± 2.49 | 77.3 ± 2.38 | 7.15 ± 0.66 |
| 2nd Gr | M | 81.4 ± 0.27 | 87.9 ± 0.54 | –6.2 ± 0.42 |
| | F | 80.2 ± 0.65 | 85.1 ± 0.81 | –5.4 ± 0.78 |
| | Average | 80.8 ± 0.71 | 86.5 ± 1.01 | –5.8 ± 0.64 |
| Control | M | 82.9 ± 0.53 | 80.3 ± 0.53 | 2.7 ± 0.28 |
| | F | 82.1 ± 0.44 | 79.6 ± 0.44 | 2.6 ± 0.23 |
| | Average | 82.5 ± 0.35 | 79.9 ± 0.34 | 2.7 ± 0.18 |

*Note: the control group is study of S. S. Murtazayeva (2018)*

Thus, the data obtained by us confirm the idea that cephalometric analyses are often based on comparison of the data obtained as a result of examination of a particular patient (group of patients) with the average values in this population. The data obtained will serve as the basis for the judgment about the deviations of the norm in the facial skeleton and, in particular, in its gnatic Department among ethnic Uzbeks. These parameters will be the norm criteria in cephalometric studies in the treatment of patients with dentoalveolar anomalies, in particular patients with GFAO, which ultimately facilitates the clinical diagnosis, the preparation of a rational plan of orthodontic, surgical treatment and evaluation of their immediate and long-term results.

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# PECULIARITIES OF SECRETION OF DIGESTIVE PEPTIDASES OF THE STOMACH AND PANCREAS IN CHRONIC VIRAL HEPATITIS C

**Abstract.** It remains unclear the question of multidirectional changes in secretory and endocrine activity of the digestive glands of the stomach and pancreas in chronic liver diseases. At the same time, the study of changes in the endocrine function is of interest for practical diagnosis. as in diseases of the stomach and pancreas, and the violation of their function in chronic liver diseases. A comprehensive assessment of the state of the pancreas in the group of patients with chronic viral liver lesions revealed a violation of the functional state of the organ in 80% of cases with chronic hepatitis and in 96.3% of cases - with liver cirrhosis.

**Keywords:** endocrine activity, stomach, pancreas, chronic viral liver, chronic hepatitis, amylase and lipase, stimulated secretion, liver cirrhosis.

Despite the long period since the sixties of the last century, the study of the influence of chronic liver diseases on the changes in the functional state of the stomach and pancreas, to date there is no clear idea of changing their exosecretion and incretion. It remains unclear the question of multidirectional changes in secretory and endocrine activity of the digestive glands of the stomach and pancreas in chronic liver diseases. At the same time, the study of changes in the endocrine function is of interest for practical diagnosis. as in diseases of the stomach and pancreas, and the violation of their function in chronic liver diseases. A comprehensive assessment of the state of the pancreas in the group of patients with chronic viral liver lesions revealed a violation of the functional state of the organ in 80% of cases with chronic hepatitis and in 96.3% of cases – with liver cirrhosis [4; 6].

With combined infection with hepatitis B and C viruses, more pronounced changes in the proteinase activity of the blood (activity of trypsin and kallikrein), a more distinct decrease in antitryptic activity were noted. Exocrine function of the pancreas in patients with hepatitis was also impaired to a greater extent, which was manifested in some studies by a decrease in basal and stimulated secretion, enzyme secretion (especially trypsin and amylase) and bicarbonate production [4; 6], in others – by an increase in the activity of amylase and lipase. Disorders of external secretion increase with the severity of the main clinical and biochemical syndromes. The content of glucagon and somatostatin in the blood of patients with chronic hepatitis was increased [5; 6].

In alcoholic liver disease, exocrine pancreatic secretion tends to increase with the severity of liver damage, but does not correlate with the severity of chronic pancreatitis. It is assumed that alcohol abuse and the influence of hepatitis virus have an equal pathogenic effect on the liver and pancreas [3].

Levels of pancreatic enzymes – serum and pancreatic amylase, and serum lipase levels increase with the progression of liver disease in patients diagnosed with viral hepatitis. Pancreatic disease, asymptomatic in most cases, can be an extrahepatic manifestation of chronic viral hepatitis. It is suggested to reduce liver metabolism of amylase and lipase from the blood in patients with chronic infectious liver diseases, especially in patients with liver cirrhosis, which can lead to the accumulation of these enzymes in the blood [12; 18].

As for the stomach, it was shown that in patients with liver cirrhosis, the average rate of free and total acidity, as well as pepsinogen 1 in serum were lower than under normal conditions. Also in the gastric mucosa, a decrease in blood flow was noted, and the gastrin content was significantly lower than in the group of healthy patients. Whereas the concentration of serum gastrin and somatostatin in patients with liver cirrhosis was significantly higher [7].

In another study on dogs with liver disease was revealed hypergastrinemia and frequent manifestations of gastrointestinal disorders, which can be caused by ulceration. The paper suggests that the liver is important for inactivation of some forms of gastrin. Therefore, hypergastrinemia is involved in the pathogenesis of gastrointestinal ulceration associated with liver dysfunction [15].

**Purpose of research**. To study the features of changes in the content of blood hydrolases, incretilli stomach and pancreas, in chronic viral hepatitis C and to analyze the mechanisms of these changes.

**Material and methods.** 112 men and women aged 20 to 70 years were examined. For comparison, a group of healthy 42 people with no markers of HCV infection was formed, and liver samples were normal. Of the examined 70 had positive serological markers, 38 had markers related to post-HCV infection, 32 had markers related to chronic HCV infection. In all examined in serum by IFA (standard sets of JSC "Vector-best", Russia) was determined: pepsinogen-1 (PG1) and pepsinogen- II (PG II). Biochemical methods were used to determine amylase pancreatic (standard sets of JSC "Vector-best", Russia) and lipase pancreatic "HUMAN", Germany. In all patients hepatic samples were studied: alanine transaminase (ALT), aspartate aminotransferase (AST), total and direct bilirubin.

Results and discussion. It was found that in the examined healthy individuals the indicators of amylase, lipase, pepsinogen-1 and pepsinogen- II in the blood were within normal limits (table. 1).

In persons with HCV postinfection (table. 1) indicators of liver tests were within the norm, but higher than in healthy ones. In the same individuals, despite the absence of an active HCV process, the blood levels of amylase and lipase were significantly higher than normal and compared to healthy ones. At the same time, pepsinogen-1 indicators were within normal limits, but were lower than in healthy, and pepsinogen-II indicators were slightly higher than in healthy, but within normal limits.

Table 1.– Changes in the content of gastric and pancreatic hydrolases in the blood of healthy and patients with viral hepatitis C

| Serum markers Healthy | Healthy HCV | postinfection | Chronic HCV infection |
|---|---|---|---|
| **Liver function tests** | | | |
| AST (mmol/h*l)<br>Norm 0.1–0.68 | 0.36 ± 0.04 | 0.47 ± 0.05 | 1.26 ± 0.13 |
| ALT (mmol/h*l)<br>Norm 0.1–0.68 | 0.21 ± 0.02 | 0.38 ± 0.04 | 0.89 ± 0.09 |
| Total bilirubin (μmol/l)<br>Norm 8.5–20.5 | 13.6 ± 1.2 | 18.3 ± 1.9 | 61.5 ± 6.7 |
| Direct bilirubin (μmol/l)<br>Norm 0–5.02 | 2.0 ± 0.1 | 3.9 ± 0. 4 | 34.2 ± 4.27 |
| **Blood hydrolases** | | | |
| Amylase pancreatic<br>Norm 0–60 E/l | 41.6 ± 5.8 | 85.2 ± 11.4 | 129.7 ± 15.2 |
| Pancreatic lipase<br>Norm 0–53 E/l | 26.8 ± 3.7 | 69.5 ± 8.1 | 94.4 ± 12.6 |
| Pepsinogen-I (μg /l)<br>Norm 40–130 | 98.6 ± 12.5 | 48.9 ± 6.3 | 19.5 ± 2.3 |
| Pepsinogen-II (μg/l)<br>Norm 4–22 | 16.9 ± 1.8 | 18.4 ± 2.1 | 11.2 ± 1.4 |

In patients with chronic HCV infection rates of all considered hepatic samples were higher than normal. In these patients, there was a marked increase above the norm of amylase and lipase compared with patients with HCV postinfection. At the same time, pepsinogen-1 indicators were less than the lower limit of the norm and significantly lower than in persons with HCV post-infection. At the same time, pepsinogen-II levels were within normal limits, but were slightly lower than those with HCV post-infection.

The presented data demonstrate that in healthy individuals all the considered indicators were within the norm. At the same time, the blood levels of amylase and lipase are higher than normal in persons with HCV post-infection, and pepsinogen-1 and pepsinogen-II are within normal limits, indicating the absence of significant changes in the function of the digestive glands of the stomach and a slight increase in the functional activity of the pancreas, which may be associated with a hidden form of pancreatitis.

In patients with chronic HCV infection, a marked increase in blood above the norm of amylase and lipase indicates an increase in the functional activity of the pancreas, and possibly a latent form of pancreatitis. The observed values below the norm of pepsinogen-1, which is produced by the main cells of the glands of the bottom and the body of the stomach, indicate a decrease in the enzymatic activity of the stomach, with a decrease in the concentration of serum

pepsinogen-1 (PG1) to values less than 40 μg/l, observed with a marked decrease in the secretion of hydrochloric acid and the development of atrophic gastritis [10]. The available indicators within the norm of pepsinogen- II (PG II), which is produced by mucin-forming cells of the glands of all parts of the stomach, indicates the absence of changes in the mucin-forming function of the stomach. At the same time, the change in the ratio PG1 /PG2 (19.5/11.3) below the coefficient 3 is an additional indicator of the development of atrophic gastritis.

Thus, in patients with chronic HCV infection, there is a marked increase in the functional activity of the pancreas, which may be a manifestation of a hidden form of pancreatitis and a decrease in the functional activity of the digestive glands of the stomach, which may be a manifestation of a hidden form of atrophic gastritis. However, the mechanisms of these changes are not covered in the literature.

In our opinion, this is due to the physiological metabolism of the liver of low molecular weight peptides, in particular, CCK-8, which was shown by us in previous publications [1; 2] and which is confirmed by a number of other researchers [8; 9].

It is shown that the liver affects the metabolism of CCK-8 and this metabolic effect can vary significantly in liver diseases. It was found that CCK-8 is metabolized to a large extent in healthy individuals and to a lesser extent in patients with liver cirrhosis. Due to this, the content of CCK-8 in the blood of patients with liver cirrhosis increases [17].

The physiological role of CCK-8 as a stimulator of pancreatic secretion is known [11; 16]. At the same time, the results of the study of the physiological role of cholecystokinin as a regulator of gastrin secretion show that CCK-8 can play a crucial role in inhibiting stimulated secretion of gastric acid and controls the production of gastric acid, gastrin content in blood plasma and somatostatin secretion [13].

It was found that cholecystokinin inhibits acid secretion by activation of type A CCC receptors and a mechanism including somatostatin production [14].

Thus, it can be assumed that in the norm of CCK-8, it is more utilized by the liver, and in chronic hepatitis C, its utilization in the liver is disturbed and the concentration in the blood increases. Due to what is noted above mechanisms stimulation of pancreatic secretion and the development of pancreatitis, with simultaneous inhibition of gastric secretion, and the development of atrophic gastritis.

**Conclusion.** In patients with chronic HCV infection by increment, an increase in the functional activity of the pancreas and the development of a hidden form of pancreatitis, with a simultaneous decrease in the functional activity of the digestive glands of the stomach, which is a sign of a hidden form of atrophic gastritis. We assume that CCK-8 is the main factor contributing to the development of these violations.

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# ROLE OF THE NEUROHUMORAL FACTORS IN THE PROGRESSION OF CHRONIC HEART FAILURE AND KIDNEY DYSFUNCTION

**Abstract.** The interrelation of the levels of brain natriuretic peptide (BNP) and aldosterone (Al) in serum with the parameters of left ventricular remodeling, the degree of chronic heart failure (CHF) and the parameters of kidney dysfunction in patients with CHF were studied. Revealed a significant increase in neurohumoral factors of BNP and Al associated with functional class (FC) of the CHF, the degree of left ventricular (LV) systolic dysfunction and kidney dysfunction.

**Keywords:** chronic heart failure, kidney dysfunction, brain natriuretic peptide, aldosterone, prognosis.

Chronic heart failure (CHF) is not only a medical, but also a social problem due to the significant prevalence, high mortality rate and high costs of treating patients with CHF [11]. The prevalence of CHF among people over 45 years old is 2.5%, while its frequency increases with age and about 50% of patients, and, despite the use of combination therapy, dies within 5 years [5]. The risk of sudden death in patients with CHF is 5 times higher than the rate of persons not suffering from heart failure [9]. The mortality of patients depends on the functional class (FC) of CHF and, according to the data of the Framingham study, is about 20% per year, and 4–5 year survival rate is 25–50% [11].

With the development of CHF, left ventricular (LV) dysfunction is the main trigger, and the LV ejection fraction (EF) is the main factor determining the prognosis of CHF, kidney dysfunction is also a major predictor of poor prognosis in patients with CHF, even more significant than the severity of HF and EF LV [2].

With glomerular filtration rate (GFR) < 60 ml/min/1.73 m$^2$, the risk of mortality increases by 2.1 times, with reduced LV systolic function, the risk of death for patients with renal insufficiency increases by 3.8 times, with unchanged systolic function – 2.9 times [3]. In case of pronounced impairment of LV myocardial contractility, the decrease in GFR, as a rule, coincides with the appearance of another unfavorable marker – an increase in the concentration of natriuretic peptides (NP) and aldosterone (Al) in plasma [3; 9]. Evaluation of the functional status of the kidneys and biomarkers in the serum of patients

with CHF is important for the selection of prophylactic and therapeutic measures [6; 8].

As a biological marker in the diagnosis of CHF, brain NP (BNP) is used, besides BNP and Al plays an important role in the pathogenesis of CHF, and the increase in their level begins with the asymptomatic LV dysfunction [8; 13]. Biological markers allow you to optimize the processes of screening patients, assessing the prognosis and choosing the optimal treatment strategy and evaluating its effectiveness [4; 8].

**Purpose.** To study the relationship of BNP and Al levels in blood serum with the degree of CHF and the functional state of the kidneys, and their role in the progression of CHF and kidney dysfunction (KD).

**Material and methods**

Were examined 52 patients with coronary heart disease (CHD) with CHF with I (19 patients), II (21 patients) and III (12 patients) FC CHF, according to the classification of the New York Association of Cardiology. Average age of patients was 62.5 ± 7.96 years. Control group was 30 healthy individuals. All patients were carried out echocardiography (echocardiography), was determined creatinine (Cr) in the serum, calculated by GFR (cGFR) in the formula CKD-EPI [12], the level of amino-terminal pro-brain natriuretic peptide (NT-proBNP) and Al [13]. Well as all patients were distributed on the 2 groups according to the cGFR: 30 < cGFR ≤ ≤ 60 мл/min/1.73м$^2$–14 patients, consistent with 3 stage CKD, and cGFR ≥ 60 мл/min/1.73м$^2$–38 patients. Definition of the level of NT-proBNP and Al serum was carried out by immunoassay (Elisa) with the use of the test system to determine the NT-proBNP used CJSC "Vector Best" (Russia), to determine Al used test system – "Diagnostics Biochem Canada" (Canada) on an immunoassay analyzer Humareader HS "Human" (Germany). Normal indicators were evaluated in the values of NT-proBNP less than 125 pcg/ml, aldosterone – less than 199 pcg/ml.

For statistical data processing, the software package Microsoft Office Excel – 2013 is used. Methods of variational parametric and non-parametric statistics are used with the calculation of the arithmetic average of the studied indicator (M), standard deviation (SD), standard errors of the mean (m), relative values (frequency,%), the statistical significance of the measurement results when comparing the average values determined by the criterion Student (t) with the calculation of the error probabilities (p) when checking the normal distributions (by the criterion excess) and the equality of the general variances (F is the Fisher criterion). For a statistically significant changes have taken the level of confidence p < 0.05. Compared groups on the quality characteristics used criteria $\chi^2$. For the study of dependence between the quantitative variables used correlation analysis with the calculation of the coefficient of linear Pearson's correlation.

**Results and discussion**

Analysis of data echocardiography showed that with increasing the degree of CHF progressively decreased EF LV as the main index of systolic function. The results of studies have shown that фв was: in patients with I FC CHF – 51.68 ± 1.63, with II FC CHF – 47.9 ± 2.02, III FC CHF – 35.7 ± 7.68%. In patients with II and III FC CHF marked reduction EF 7.9% (p<0.001) and 44.9% (p<0.001), respectively, in comparison with the indicators I FC CHF.

Final systolic volume (FSV) in patients I, II and III FC CHF was: 56.47 ± 12.63, 74.9 ± 23.99 and 124.75 ± 42.87 ml, respectively. Index of FSV in patients with II and III FC CHF to 24.3% (p < 0.01) and 52.5% (p < 0.001), respectively, more than indicators I FC CHF. Final diastolic volume (FDV) in patients I, II and III FC CHF was: 118.3 ± 25.1 ml, 147.1 ± ± 46.5 ml and 199.00 ± 58.2 ml, respectively. Indicators of FDV in patients with II and III FC CHF to 19.2% (p < 0.05) and 40.3% (p < 0.001), respectively, more than indicators I FC CHF. Growing signs of CHF in patients with III FC accompanied by the more pronounced structural restructuring LV increased the degree of dilatation LV. When analyzing the obtained indicators of EF and their relationship with GFR in the examined patients, a reliable direct correlation dependence of FV and cGFR (r = 0.953) was revealed. The development of CHF is a consequence of an imbalance in the system of the most complex biochemical mechanisms of vasoconstriction and vasodilation. The root cause of such molecular changes is a direct damaging effect on myocardial ischemia and pressure overload. Against this background, physiological compensatory mechanisms are triggered: activation of the sympathoadrenal system (SAS), the renin-angiotensin-aldosterone system (RAAS), the natriuretic peptide systems, the endothelin-1 system, and others. Neurohumoral imbalance leads to the progression of LV dysfunction by accelerating myocardial remodeling processes and to a general cardiac overload [4].

Analysis of the initial level of neurohumoral parameters in patients with II and III FC CHF revealed a significant increase in indicators: NTproBNP and Al in the blood plasma compared with the control group, and patients with I FC CHF, which correlated with the degree of CHF (Tab.1).

As can be seen from table 1, in CHF, a significant increase in plasma NT-proBNP and Al was observed, which correlates with an increase in FC CHF: patients with I FC CHF showed an increase in the content of NT-proBNP and Al by 89.5% (p < 0.001) and 70.4% (p < 0.001). in patients with II FC CHF – by 94.6% (p < 0.001) and 78.2% (p < 0.001). and in patients with FC III – by 96.3% (p < 0.001) and 80.3% (p < 0.001). respectively. compared with the control group. Also, as the increase in FC CHF, a significant increase in NT-proBNP and AL was noted: in patients with FC II CHF by

48.6% ($p < 0.05$) and by 26.2% ($p < 0.01$). in patients with FC III CHF – by 65.2% ($p < 0.001$) and by 33.4% ($p < 0.001$), respectively, compared with indicators of the first FC CHF patients.

Table 1.– Content of NT-proBNP and Al in plasma in patients with I–III FC CHF (M ± SD)

| Indicators | Control group (n=30) | I FC CHF (n=18) | II FC CHF (n=21) | III FC CHF (n=13) |
|---|---|---|---|---|
| NT-proBNP (pcg/ml) | 18.5 ± 9.98 | 175.37 ± 97.28 *** | 341.26 ± 242.77 *** | 504.2 ± 86.36 *** |
| Al (pcg/ml) | 54.47 ± 22.66 | 184.0 ± 46.56 * | 249.39 ± 56.84 **** | 276.3 ± 45.64 **** |

*Note: where * – the accuracy of $p < 0.05$, ** – the accuracy of $p < 0.01$, *** – the accuracy of $p < 0.001$ from indicators of the control group*

Our results are confirmed by a number of previous studies [6; 15] and showed that in patients with CHF a significant increase in neurohumoral factors: NT-proBNP and Al is associated with the progression of CHF and is a predictor of poor prognosis, reflecting the degree of LV systolic dysfunction. A direct correlation relationship was established between NT-proBNP and Al in patients with FC II and FC III CHF ($r = + 0.88$ and $r = + 0.89$, respectively).

Fluctuations in the content of NT-proBNP in patients with I FC CHF ranged from 128 to 556 pcg/ml, and in patients with II FC CHF from 180 to 1023 pcg/ml, and in patients with III FC CHF from 415 to 731 pcg/ml. Similar changes were observed when studying the aldosterone content: fluctuations in the Al content in I FC CHF from 126 to 258 pcg/ml, in II FC CHF from 234 to 334 pcg/ml, and in III FC CHF from 232 to 346 pcg/ml.

The high level of NT-proBNP and Al corresponded to values above the median. Taking into account the fluctuations of these indicators, the distribution of the examined patients according to the content of NT-proBNP and Al was studied within smaller values of the median (medium-high level) and large values of the median (high level).

When analyzing these results, a slight increase in NT-proBNP and Al was found in patients with I FC CHF, while high values were observed in 5.2% and 21% of patients, respectively, in patients with II FC CHF, a high increase in NT-proBNP and Al was noted in 19% and 90% of the examined patients, respectively, in patients with III FC CHF, a high increase in NT-proBNP was observed in 100% of the examined patients, Al – in 93% of patients. These data suggest that in patients with II FC of CHF, medium-high values of neurohormones prevail, whereas in patients with III FC of CHF, a high level of NT-proBNP and Al increase prevails. Thus, patients with I FC CHF registered low NT-proBNP and Al values, but exceeding the norm, medium-high NT-proBNP and Al values prevailed in patients with II FC CHF and high NT-proBNP and Al values from III FC CHF.

The parameters of neurohormones were analyzed depending on cGFR (Tab. 2). It was noted that NT-proBNP and Al in patients with cGFR ≤ 60 ml/min/1.73 $m^2$ by 56.3% ($p < 0.05$) and 16.5% ($p < 0.05$), respectively, were higher by compared with these indicators in patients with cGFR > 60 ml/min/1.73 $m^2$. The correlation relationship between the level of NT-proBNP, Al and EF, FDV was studied. An association of the neurohormones level was revealed: NT-proBNP and Al with heart remodeling: high inverse correlation with EF ($r = 0.76$ and $r = 0.72$, respectively) and direct correlation with LV FDV ($r = 0.75$ and $r = 0.70$ respectively).

Table 2. The content of NT-proBNP and Al in the blood plasma of patients with cGFR ⩽ 60 and cGFR > 60 ml/min/1.73 $m^2$

| Indicators | Patients with cGFR ≤ 60 ml/min/1.73 $m^2$ | Patients with cGFR > 60 ml/min/1.73 $m^2$ | p |
|---|---|---|---|
| NT-proBNP (pcg/ml) | 409.9 ± 236.97 | 302 ± 180.0 | $p < 0.05$ |
| Al (pcg/ml) | 262.3 ± 138.7 | 223.97 ± 61.4 | $p < 0.05$ |

Thus, in patients with CHF, a significant increase in the neurohumoral factors NT-proBNP and Al is associated with FC CHF and indicators of LV remodeling and dysfunction (EF and FDV), as well as kidney dysfunction. In patients with cGFR ≤ 60 ml/min/1.73 $m^2$, the indicators NT-proBNP and Al by 56.3% ($p < 0.05$) and 16.5% ($p < 0.05$), respectively, were higher compared with these indicators in patients with cGFR > 60 ml/min/1.73 $m^2$.

**Conclusion**

In patients with CHF, a significant increase in the neurohumoral factors NT-proBNP and Al is associated with FC CHF, the degree of LV systolic dysfunction and KD. In patients with II FC CHF, the medium-high NT-proBNP and Al values prevailed, and from III FC CHF, a high level of NT-proBNP and Al elevated. A correlation relationship was found between the NT-proBNP, Al and EF levels ($r = – 0.70$ and $r = – 0.72$, respectively), between the NT-proBNP, Al and FDV LV ($r = 0.78$ and $r = 0.70$, respectively).

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# THERAPY OF CHRONIC HEPATITIS IN CHILDREN WITH DIFFERENT HBSAG STATUS

**Abstract.** For the assessment of the efficacy of three-stage antiviral therapy of chronic hepatitis B we observed 32 sick children in the age from 7 to 18 years old. In fourteen of them we revealed HBsAg (–) negative seroprofile, and these children composed comparison group for the children with HBsAg (+) positive hepatitis (18 children). as a result of the research it was determined that, application of three-stage scheme of antiviral therapy of chronic hepatitis B in children using α-Interferon (Viferon) agents and Lamivudine demonstrated diverse efficiency for both suppression of viral replication and decrease of cytolytic activity. The best virologic effect was achieved in HBsAg-positive patients.

**Keywords:** children, chronic hepatitis B, HBV markers, antiviral therapy.

In spite of the successful results in the control of HBV infection, wide spread implementation of specific immune prophylaxis and significant decrease in the registration of acute forms of the disease, chronic hepatitis B is still one of the most complex problems of the world health care [1; 3; 5; 11]. Every year about million people die because of liver pathologies conditioned by HBV. Hepatitis B is the reason of the greater part (up to 65%) of chronic pathologies of liver in children. At the same time increase in the duration of infecting in the infection foci leads to the growth of a specific weight of mutant strains, which in its turn causes formation of the high concentration of chronic infection with development of primary latent forms of the pathology (above 50.0%), with difficult diagnostics, and, finally, genotype variety and capability of the virus for various gene mutations, and that in some cases is the reason of non-effective vaccination (2–40%) [3; 4; 6; 8; 9]. Today the therapy of chronic hepatitis B (CHB) is the most difficult and unsolved problem in children's hepatology. The therapy of chronic HBsAg-mutant hepatitis B almost is not developed. Reference data are limited by single researches [2; 7; 10; 12]. That makes it necessary to search actively for new agents affecting the virus and its replication, to create various schemes and possible combinations of therapy, especially severe forms of CHB associated with mutant HBV strains. Majority of antiviral agents, except α-Interferon possessing mostly immune stimulating effect, cannot be used in pediatric practice due to the absence of special permission. Exclusion is permitted in children's hepatology Lamivudine, the mechanism of action of which is based on the suppression of viral DNA polymerase. As a rule, its one-moment intake together with α-Interferon therapy was considered effective for children with CHB. According to some data Lamivudine by means of suppressing viremia can restore distorted T-cell mediated immune response to HBV epitopes, and thus, promote immune modulating effect of interferon [5; 10]. Variation of its efficacy varies within 17–57%.

In relation to that, **the objective of** this work was to assess the efficacy of three-stage antiviral therapy of CHB in children with various HBsAg statuses.

**Materials and methods:** 80 children suffering CHB in the age from 7 to 18 years old were studied. 32 sick children were selected into therapeutic group, among whom there were 18 patients with HBsAg (+) positive hepatitis and 14 with HBsAg (–) negative one, linked with gene S-mutation, in our opinion. All studied children had HBV-DNA in blood serum with viral load rate 105–108 copies/mL. Classification of the patients according to the activity of the pathology revealed minimal degree in 31.2% of the children, moderate one in 43.7%, and expressed one in 25.0% of the children. The duration of CHB among the studied children was equal to 4.5 ± 0.4 years. 30 almost healthy children served to be the control.

CHB diagnosis was confirmed on the basis of clinical, epidemiological, common clinical laboratory and instrumental tests for liver. Testing of biochemical parameters and serological data of HBsAg, HBsAb, HBeAg, HBeAb, total HBcorAb was performed in clinical-experimental laboratory of the RSSPMC of Pediatrics of the MH of the RUz with the help of HUMAN commercial kits (Germany) and ROCHE test systems (Switzerland). HBV-DNA definition was performed by means of PCR in real-time mode using Vector-West test system (Novosibirsk) with «iCyclerQ5» (Bio-Rad, USA) thermo cycler for the amplification of nucleic acids.

Inclusion of the patients was performed taking into account the predictors of the efficacy of the stability of the response to antiviral therapy: more than 2 folds increased level of amino transferases, moderate viremia, and high histological activity. For all children we applied three-stage scheme of antiviral therapy the duration of which was 12 months: I stage – Lamivudine for 20 weeks, II stage – Lamivudine combined with α-interferon for 1 month, and later only α-interferon for 24 weeks. Lamivudine was prescribed to the children under 12 calculated 3mg\kg\day, and above 12 one hundred mg per os once a day after meal every day. Viferon per rectum 100 thousand IU/kg/day twice a day for 10 days with further transfer to double dose three times a week. Assessment of the therapeutic efficacy was performed on the basis of the criteria recommended by European Liver Pathologies Study Association (2011), taking into account AlAT and HBV-DNA values in the process of the therapy – primary remission (PR), during 6 months after its finish – stable remission (SR), and for 24 months after the end of the therapy – long-lasting one (LLR).

Statistical processing of the data was performed by means of variation statistic method using Student's t-criterion with special Excell-2012 software.

Results of the study. Application of the step-by-step partially combined scheme of antiviral therapy of CHB in children using α-interferon agents and nucleoside analogue (Lamivudine) showed significant efficacy according to clinical laboratory data, and dependence on serological status of HBV S-gene. That scheme of the therapy had the most notable impact on the dynamics of clinical symptoms in children with CHB-HBsAg (+) hepatitis (Table 1). Analysis of asthenovegetative syndrome symptoms (weakness, prostration, fatigue, etc.) showed decrease of the registration of these symptoms more than 2.6 folds compared to these values before the therapy ($p < 0.001$).

Table 1. – Dynamics of clinical syndromes at the background CHB therapy applied in children (% ± m)

| Clinical syndromes | HBsAg (+) hepatitis (n=18) | | | HBsAg (–) hepatitis (n=14) | | |
|---|---|---|---|---|---|---|
| | Before therapy | After therapy | P | Before therapy | After therapy | P |
| Asthenovegetative syndrome | 64.7 ± 5.4 | 5.5 ± 7.4 | < 0.001 | 96.4 ± 9.3 | 44.0 ± 13.2 | < 0.001 |
| Dyspeptic syndrome | 67.3 ± 11.7 | 11.1 ± 7.4 | < 0.01 | 88.0 ± 10.9 | 52.3 ± 13.2 | > 0.05 |
| Extra hepatic symptoms | 72.2 ± 8.7 | 20.8 ± 9.7 | < 0.001 | 100.0 | 76.7 ± 10.9 | > 0.05 |
| Cholestatic syndrome | 25.9 ± 11.1 | 3.6 ± 5.3 | < 0.05 | 78.5 ± 9.3 | 42.8 ± 13.2 | < 0.02 |
| Hepatomegaly | 33.3 ± 11.7 | 25.9 ± 9.8 | < 0.05 | 57.2 ± 0.0 | 33.2 ± 9.3 | > 0.05 |
| Splenomegaly | 55.5 ± 11.7 | 11.1 ± 7.4 | < 0.01 | 100.0 | 64.2 ± 12.8 | < 0.05 |

*P –reliability of differences between the values before and after the therapy*

Positive dynamics was also noted in the manifestations of dyspeptic syndrome; only in the comparison group these values were non-reliably decreased compared to the group of children before the therapy ($p > 0.05$). During the therapy extra renal symptoms such as palmar erythema, capillary net on cheeks, venous collaterals, and vascular spiders diminished together with the frequency of detection in all studied patients registered before the therapy, and at the end of the therapy varied only within 16.6%-27.7% ($p < 0.05$–$0.001$). The frequency and expression of hepatic-lienal syndrome clearly decreased in both groups. So, hepatomegaly was noted only in 25.9% of the children and only under 3cm ($p < 0.05$). At the same there was notable tendency for decrease of the density of liver consistence. Splenomegaly was registered more than 5 times less among treated patients ($p < 0.01$).

The applied scheme had a positive effect on the dynamics of the cytolysis syndrome indicators. So in children with HBsAg positive CHB the average AlAT diminished 2.7 folds and was equal to 0.69 ± 0.03 mmol/ls ($p < 0.001$, compared to ore the therapy 1.92 ± 0.09 mmol/ls), reaching normalization in 17 (94.4%) children. Similar changes were observed in AsAT values, the average amount of which before the therapy was 1.18 ± 0.08 mmol/ls, and after the therapy 0.41 ± ± 0.02 mmol/ls ($p < 0.001$). That allowed us judge about the development of biochemical response in that category of children in 94.4% cases.

Table 2. – Dynamics of biochemical parameters during the applied therapy of CHB in children

| Values | HBsAg (+) (n=18) | | | HBsAg (–) (n=14) | | | Control |
|---|---|---|---|---|---|---|---|
| | Before therapy | After | P | Before therapy | After | P | |
| AlAT, mkmol/ls | 1.92 ± 0.09 * | 0.69 ± 0.03 * | < 0.001 | 2.53 ± 0.19 * | 0.82 ± 0.03 * | < 0.001 | 0.39 ± 0.03 |
| AsAT, mkmol/ls | 1.18 ± 0.08 * | 0.41 ± 0.02 * | < 0.001 | 1.53 ± 0.11 * | 0.44 ± 0.02 * | < 0.001 | 0.23 ± 0.02 |
| Total bilirubin, mkmol/ls | 16.2 ± 0.31 * | 14.7 ± 0.41 | < 0.001 | 31.8 ± 1.83 * | 23.2 ± 0.46 * | < 0.01 | 14.8 ± 0.57 |
| Conjugated bilirubin, mkmol/ls | 4.32 ± 0.40 * | 1.95 ± 0.25 | < 0.05 | 13.4 ± 1.83 * | 5.7 ± 0.29* | < 0.001 | 1.8 ± 0.06 |
| Total protein, g/L | 65.3 ± 0.63 * | 71.2 ± 0.63 | < 0.001 | 62.9 ± 0.80 * | 66.3 ± 0.43 * | < 0.01 | 71.3 ± 0.86 |
| Albumin, % | 48.8 ± 0.73 * | 52.3 ± 0.59* | < 0.01 | 44.1 ± 1.21 * | 48.6 ± 0.31 * | < 0.01 | 54.5 ± 0.72 |
| Gamma-globulin,% | 19.3 ± 0.53 * | 15.7 ± 0.22 | < 0.001 | 24.5 ± 0.62 * | 19.7 ± 0.36 * | < 0.001 | 15.7 ± 0.47 |
| Thymol test, U. | 6.09 ± 0.26 * | 4.4 ± 0.14 | < 0.001 | 11.5 ± 0.54 * | 7.95 ± 0.26 * | < 0.001 | 4.5 ± 0.28 |

*P – reliability of differences between the values before and after the therapy;*

** – reliability of differences compared to control group (p < 0.05–0.001)*

Under the influence of the performed therapy the values of cholestatic syndrome changed. Reliable decrease was registered in the values of total and conjugated bilirubin, the amount of which after the therapy was 14.7 ± ± 0.41 mkmol/ls (p < 0.001) and 1.95 ± 0.25 mkmol/ls (p < 0.05), respectively (Table 2). The rise of liver synthetic function (hepatoprive syndrome) was indicated by a reliable (p < 0.01–0.001) increase of average albumin (up to 52.3 ± 0.59%) and total protein (up to 71.4 ± 0.63 g/L). In the values characterizing mesenchymal inflammatory syndrome we also registered clear normalizing effect of the applied therapy, expressed in the decrease in the results of gamma globulin (up to 15.7 ± 0.22%) and thymol test (up 4.4 ± 0.14 U, p < 0.001).

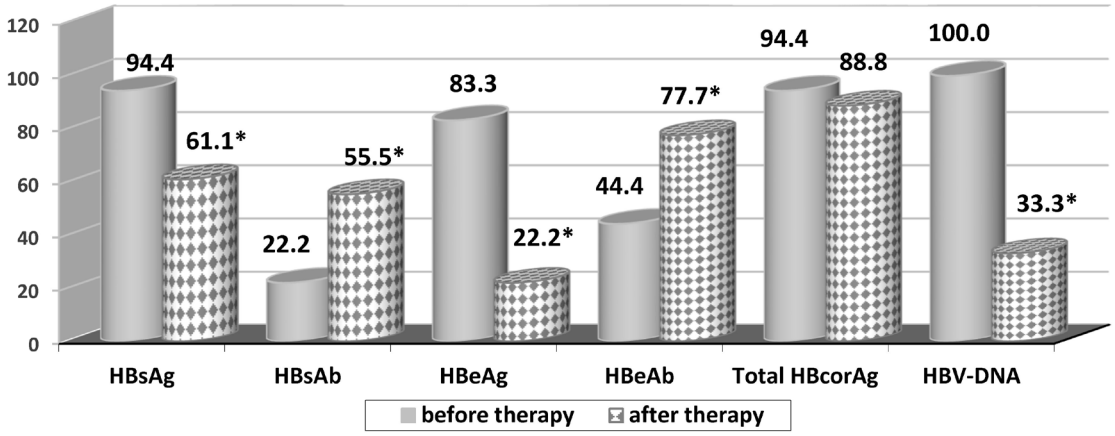


Figure 1. Marker profile of HBsAg (+) children during the therapy (%):* – reliability of differences between the values before and after the therapy (p < 0.05–0.001)

These changes were revealed in the children with HBsAg-negative CHB. Though the values of biochemical parameters did not approach the control ones, these reliably improved compared to the values registered before the therapy. For instance, the average AlAT diminished 3.0 folds and was equal to 0.82 ± 0.03 mkmol/ls, reaching normalization in 12 (85.7%) children with CHB with negative seroprofile (p < 0.001, compared to the values before the therapy 2.53 ± ± 0.19 mkmol/ls). Similar dynamics was noticed also in ASAT, the average amount of which before the therapy was 1.53 ± ± 0.11 mkmol/ls, and after the therapy 0.44 ± 0.02 mkmol/ls (p < 0.001). In the manifestation of cholestatic syndrome there was notable decrease of the concentration of hepatic enzymes, and particularly, total and conjugated bilirubin up to 23.2 ± 0.46 mkmol/ls and 5.7 ± 0.29 mkmol/ls, respectively (p < 0.01 to the values before the therapy). After the therapy we observed reliable rise (p < 0.01–0.001) of the average albumin (up to 48.6 ± 0.31%) and total protein (up to 66.3 ± 0.43 g/L), and decrease of gamma globulin (up to 19.7 ± 0.36%) and thymol test (up to 7.95 ± 0.26 U).

Results of the assessment of the dynamics of marker profile during the therapy indicate its positive impact on the elimination of HBV (Fig.1). So, in patients with HBsAg (+) CHB, after three-stage therapy the frequency of HBeAg detection significantly decreased, and it was determined in the blood of 4 (22.2%) children ($p < 0.001$). Seroconversion of HBeAg to HBeAb occurred in 33.3% of the children (before the therapy 44.4%; after the therapy 77.7%, $p < 0.05$). Decrease of the frequency of detection was registered in case of HBsAg persistence in 33.3% ($p < 0.02$), which was verified in 11 (61.1%) children at the end of the therapy, and that correspondingly led to the increase of HBsAb (55.5%, $p < 0.05$). However, in the values of HBcorAb we followed insignificant decrease of detection (to 5.6%, $p > 0.05$). Expressed dynamics was registered in the values of HBV-DNA (before the therapy 100.0%, after the therapy 33.3%, $p < 0.001$), which indicated development of virologic remission in 66.7% children with HBsAg (+) hepatitis.

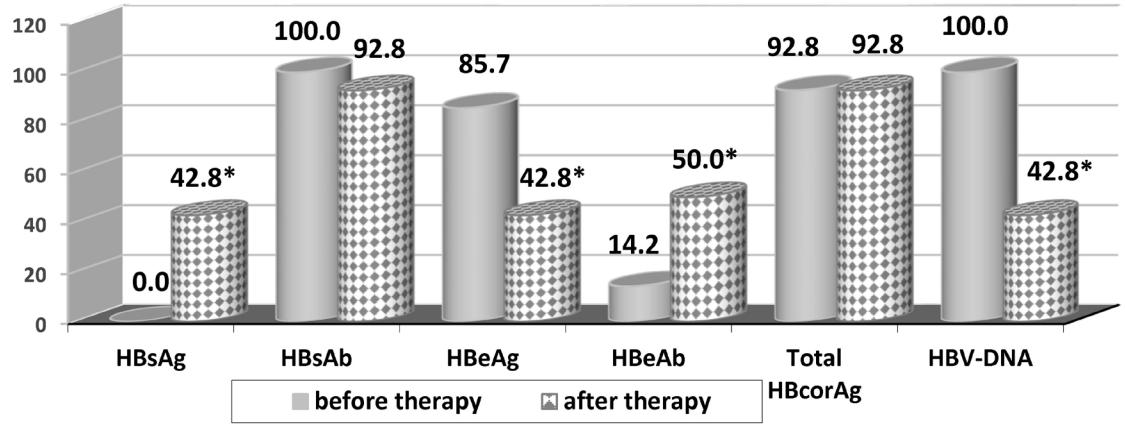


Figure 2. Marker profile of HBsAg (–) children during the therapy (%):* – reliability of differences between the values before and after the therapy ($p < 0.05$–$0.001$)

In the group of children with HBsAg negative it was possible to notice similar effect of the therapy on HBV markers (Fig. 2). After the therapy in the mentioned group six (42.8%) children had synthesis of HBsAg ($p < 0.01$). While HBsAb almost did not change (before the therapy 100.0%, after the therapy 92.8%). Summary HBcorAb stayed at the original level. In the process of the therapy the number of HBeAg-positive patients decreased to 42.9%, among whom 35.8% pf the children had seroconversion to HBeAb ($p < 0.05$). Similar to HBsAg-positive group of children, patients with HBsAg (–) CHB had expressed dynamics in HBV-DNA (before therapy 100.0%, after therapy 42.8%, $p < 0.001$), and that let us note the development of virologic remission in 57.2% cases.

Thus, the data obtained in the process of our research indicate positive effects of the proposed three-stage therapy, application of which led to the improvement of feeling; most of the studied biochemical indicators reached normal values, and as a result, that promoted development of remission judged according to clinical indicators in children with HBsAg (+) hepatitis in 50.6% cases and HBsAg (–) CHB in 40.9% cases. Biochemical response was received in 94.4% and 85.7%; virologic one in 66.7% and 57.2% cases, respectively.

Allergic reactions or side effects were not registered in any child. Development of Lamivudine-resistant strains was not revealed as well.

In follow-up observation for 12 months the efficacy of the performed antiviral therapy was assessed in compliance with EUROHEP Consensus program. Analysis of AlAT and HBV-DNA in the process of the observation provided determination of more stable response in children with HBsAg+ hepatitis. Primary remission was registered in 66.7% cases, stable in 61.1%, and long-lasting one in 55.5% cases. And absence of remission was noted in one third (33.3%) of the children. A little bit less expressed dynamics was observed among the children with HBsAg (–) CHB, in 57.1%, 50.0% and 35.7% cases, respectively. Absence of remission was observed in 42.8% of the children.

**Conclusion.** Thus, the data obtained in the process of our research indicate positive effects of the proposed three-stage therapy of CHB, application of which led to the improvement of feeling; most of the studied biochemical indicators reached normal values, and as a result, that promoted development of remission judged according to clinical indicators in children with HBsAg in blood serum in 50.6% cases and HBsAg (–) hepatitis in 40.9% cases. Biochemical response was received in 94.4% and 85.7%; virologic one in 66.7% and 57.2% cases, respectively. But the best effect was achieved in HBsAg-positive patients.

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# SLEEP DISORDERS IN PATIENTS WITH HYPERTENSION AND DIABETES MELLITUS

**Abstract.** Epidemiological studies show a link between insomnia and risk of development of hypertension and diabetes mellites as well as with a prognosis in people suffering these diseases. The study included 43 patients. Mean age of study subjects was 57.2 ± 11 years. All patients received standard therapy: valsartan, metformin and atorvastatin. Sleep disorders were assessed using the International Sleep Disorder Classification, edition 3, developed by the American Academy of Sleep Medicine, 2014 and Epworth Sleepiness Scale. Statistical analysis was performed using SPSS software, version 17.0. Sleep disorders were observed in both study groups, however, patients with hypertonic disease and type 2 diabetes mellitus reported reliably more difficulties in falling asleep (10 (40%) vs 2 (11.1%), p = 0.038) and early rising (18 (72%) vs7 (38.9%), p = 0.032), and consequently, behavioral problems were predominant among daily symptoms: increased emotionality, irritability, frequent mood swings. According to Epworth Sleepiness Scale, sleepiness in patients with combined course of hypertonic disease and type 2 diabetes mellitus was 6.7 points, while in control group of healthy volunteers, the score was 4.1 points. In patients with hypertonic disease and type 2 diabetes mellitus, disorders were more frequent in falling asleep and early rising, while impairment of usual sleep-awake regimen and inability to maintain continuous sleep were observed with similar frequency in both groups.

**Keywords:** diabetes mellitus, hypertension, sleep disorders, insomnia, day sleepness.

Currently, hypertonic disease and type 2 diabetes mellitus are among the most common chronic non-infectious diseases and are of special interest among scientists and investigators in terms of determination of risk factors affecting their development, course and complications. Thus, within the last few years, epidemiologic studies demonstrated interrelation between insomnia, development of hypertonic disease, type 2 diabetes mellitus, life expectancy and body ageing in general. At the same time, these studies applied various methodic approaches to assessment of sleep disorders. Also, sleep disorder risk factors were not assessed. It should be noted that sleep disorders are quite common within general population and by no means always cause development of non-infectious diseases. Therefore, the purpose of this work was to study the relation between sleep changes and their day-time consequences with hypertonic diseases and type 2 diabetes mellitus.

**Materials and methods.** The study included 25 patients with combined course of hypertonic disease and type 2 diabetes mellitus. Type 2 diabetes mellitus was diagnosed based on the criteria by ADA/European Assotiation for the Study of Diabetes (EASD) Position Statement on Management of Hyperglycemia in Type 2 Diabetes – Update January 2015. Hypertonic disease was diagnosed in accordance with definition laid down in the Guideline of European Society of Cardiology ESC2013 Arterial Hypertension (Management of) ESC Clinical Practice Guidelines. All patients received standard therapy: valsartan, metformin and atorvastatin. Mean age of study subjects was 57.2 ± 11 years. Height, weight, waist circumference were measured in all patients enrolled into the study. Control group included 18 patients without hypertonic disease and type 2 diabetes mellitus. Body mass index (BMI) was measured by the formula: weight (kg)/ height (m2). Physical activity was assessed by the number of steps made daily using Omron Walking style III step counter HJ-203-EK pedometer. Study subjects measured the number of steps made in three days, and then calculated the mean number of steps per day. Body composition, fat and muscle

mass ratio were studied using bioelectric impedance method using Omron Body Composition Monitor BF511. Muscle and fat tissue ratio was measured together with visceral fat share. Sleep disorders were assessed using the International Sleep Disorder Classification, edition 3, developed by the American Academy of Sleep Medicine, 2014 and Epworth Sleepiness Scale. Statistical analysis was performed using SPSS software, version 17.0. The data corresponded to normal distribution and were presented as the mean value and standard deviation; intergroup difference reliability was assessed by Student's test, and sign incidence was compared by $\chi^2$ test.

**Results.**

Patients with hypertonic disease and type 2 diabetes mellitus were comparable in terms of age (57.2 ± 11 vs. 55.1 ± 4.6 years old, p=0.49). Blood pressure values were reliably higher in study group vs. control group. Thus, SBP and DBP in hypertonic disease and diabetes mellitus group were 136.5 ± ± 12.6 and 86.5 ± 9.2 mm Hg, while in control group, SBP and DBP were reliably lower: 114.5 ± 8.6 (pSBP1–2 = 0.001) and 66.5 ± 8.7 (pDBP1–2 = 0.001). It should be noted that in 44% patients with hypertonic disease, blood pressure failed to achieve target values and was above 130/80 mm Hg, despite standard therapy conducted. Also, patients with hypertonia and diabetes had high glucose and cholesterol levels (Table 1).

Table 1. – Indicators of carbohydrate metabolism and cholesterol in patients with hypertension and type 2 diabetes mellitus

| Index | Hypertension + Diabetes Millitus (n=25) M±d | Control group (n=18) M±d | χ2 P |
|---|---|---|---|
| Total cholesterol, mmol/l | 5.4±1.1 | 4.2±0.9 | 0.001 |
| HDL cholesterol, mmol/l | 1.25±0.6 | 1.89±0.7 | 0.01 |
| TG, mmol/L | 1.8 ±1.1 | 1.34±0.9 | 0.153 |
| LDL cholesterol, mmol/l | 3.4 ±1.0 | 2.4±1.0 | 0.002 |
| Glucose, mmol/l | 7.3 ±3.3 | 4.3±1.6 | 0.001 |
| HbA1C,% | 7.0 ±0.8 | 4.7±0.7 | 0.01 |

Body mass index, waist circumference and content of visceral fat were reliably higher in patients with hypertonic disease and diabetes vs. control group (Table 2).

Table 2.– Anthropometric indicators of the examined patients

| Index | Hypertension + Diabetes Millitus (n=25) M ± d | Control group (n=18) M ± d | χ2 P |
|---|---|---|---|
| Body mass index, kg/m$^2$ | 32.3 ± 6.9 | 19.2 ± 4.1 | 0.03 |
| Waist measurement, cm | 105 ± 16.5 | 73 ± 9.1 | 0.02 |
| Hips, cm | 118.9 ± 13.4 | 101 ± 5.8 | 0.7 |
| Adipose tissue,% | 41.7 ± 9.2 | 30.9 ± 4.2 | 0.06 |
| Visceral fat,% | 12.3 ± 4.7 | 7.2 ± 2.3 | 0.03 |
| Muscle,% | 24.5 ± 5.5 | 30.7 ± 3.9 | 0.06 |
| Dynamometry, kg | 31.3 ± 11.3 | 34.2 ± 6.5 | 0.06 |
| Caliperometry, mm | 27.4 ± 11.3 | 23.4 ± 7.6 | 0.9 |

Control group subjects were undertaking reliably more physical activities and walked reliably longer distances on a daily basis.

Table 3.– Behavioral risk factors in patients with combined course of hypertension and type 2 diabetes mellitus and in the control group

| Index | Hypertension + Diabetes Millitus (n=25) | Control group (n=18) | χ2 P |
|---|---|---|---|
| *1* | *2* | *3* | *4* |
| Age, years | 57.2 ± 11 | 55.1 ± 4.6 | 0.451 |
| Smoking, n(%) | 3(12%) | 2(11.1%) | 0.0002 p=0.657 |
| Alcohol abuse, n(%) | 1(4%) | 0(0%) | 0.017 p=0.581 |

| *1* | *2* | *3* | *4* |
|---|---|---|---|
| Regular workouts, n(%) | 5(20%) | 13(72.2%) | 0.273<br>p=0.0008 |
| Walking with small children, n(%) | 1(4%) | 3(16.7%) | 0.046<br>p=0.190 |
| Cleaning of the apartment, n(%) | 22(88%) | 1 (77.8%) | 0.019<br>p=0.314 |
| Walking on foot per day, meters, steps | 3292 ± 245 | 6553 ± 178 | 0.0001 |

Patients with hypertonic disease and diabetes mellitus more often reported night-time meals (Table 4). Female patients had more frequent sleep disorders in the first years after labor.

Table 4.– Risk factors for sleep disorders

| **Questions** | **Hypertension + Diabetes Millitus (n=25) n(%)** | **Control group (n=18) n(%)** | **$\chi^2$<br>P** |
|---|---|---|---|
| Night / shift work | 15(60%) | 13(72.2%) | 0.016<br>p=0.308 |
| Daytime sleep | 6(24%) | 1(5.5%) | 0.061<br>p=0.114 |
| Eating at night | 8(32%) | 0(0%) | 0.165<br>p=0.008 |
| Sleep disturbances in the first years after childbirth | 21(84%) | 10(55.5%) | 0.098<br>p=0.044 |
| Abuse of caffeinated drinks | 3(12%) | 1(5.5%) | 0.012<br>p=0.438 |
| Frequent changes of time zones | 0(0%) | 0(0%) | 0 |

Sleep disorders were observed in both study groups, however, patients with hypertonic disease and type 2 diabetes mellitus reported reliably more difficulties in falling asleep and early rising, and consequently, behavioral problems were predominant among daily symptoms: increased emotionality, irritability, frequent mood swings (Table 5). According to Epworth Sleepiness Scale, sleepiness in patients with combined course of hypertonic disease and type 2 diabetes mellitus was 6.7 points, while in control group of healthy volunteers, the score was 4.1 points.

Table 5.– Assessment of sleep disorders by the American Academy of Sleep Medicine

| **Characteristics of sleep disorders and their daily manifestations** | **Hypertension + Diabetes Millitus (n=25) n(%)** | **Control group (n=18) n(%)** | **$\chi^2$<br>P** |
|---|---|---|---|
| ***1*** | ***2*** | ***3*** | ***4*** |
| ***Sleep assessment*** | | | |
| Difficulty falling asleep | 10(40%) | 2(11.1%) | 0.1<br>p=0.038 |
| Difficulties in maintaining a continuous sleep | 11(44%) | 6(33.3%) | 0.50<br>p=0.480 |
| Early Awakenings | 18(72%) | 7(38.9%) | 4.60<br>p=0.032 |
| Inability to fall asleep according to the usual routine of the day | 13(52%) | 6(33.3%) | 0.82<br>p=0.366 |

| *1* | *2* | *3* | *4* |
|---|---|---|---|
| ***Daytime Symptoms*** | | | |
| Nausea / vomiting | 2(8%) | 0(0%) | 0.04 p=0.332 |
| Violation of attention, concentration or memory | 13(52%) | 8(44.4%) | 0.03 p=0.857 |
| Violations in the social, family or professional sphere | 5(20%) | 3(16.7%) | 0.002 p=0.553 |
| Mood disturbance | 11(44%) | 4(22.2%) | 0.051 p=0.124 |
| Daytime sleepiness | 10(40%) | 8(44.4%) | 0.08 p=0.983 |
| Behavioral problems | 13(52%) | 4(22.2%) | 0.09 p=0.047 |
| Reducing motivation / energy / initiative | 17(68%) | 7(38.9%) | 0.083 p=0.056 |
| Propensity to errors | 10(40%) | 5(27.8%) | 0.016 p=0.309 |
| Concentration on dissatisfaction with your sleep | 7(28%) | 4(22.2%) | 0.004 p=0.475 |
| ***Frequency and duration of symptoms*** | | | |
| Sleep disorders and associated daytime symptoms are present at least 3 times a week | 15(60%) | 4(22.2%) | 0.141 p=0.015 |
| Sleep disorders and associated daytime symptoms persist for at least 3 months | 12(48%) | 5(27.8%) | 0.042 p=0.154 |
| ***Other causes of sleep disorders*** | | | |
| Night awakenings, not explainable by sleep disorders | 2(8%) | 0(0%) | 0.035 p=0.332 |

**Discussions:**

It is well-known that sleep duration and quality disorders adversely affect health condition and are associated with risk of chronic non-infectious diseases [2]. Experts from American Academy of Sleep Medicine demonstrated that in order to maintain healthy condition, night-time sleep should be at least 7–8 hours [6].

Relation between night-time apnea and development risk of hypertension, and with resistant course of hypertension is well-studied in the literature [8]. At the same time, it is confirmed that even if no obstructive sleep apnoe is observed, short sleep duration, insomnia, restless legs syndrome, shift-work are connected to hypertension [7]. It is established that sleep disorders may cause increased blood pressure as early as in adolescence [11]. Chronic insomnia is considered by several authors as hypertension development risk factor [16]. Vgontzas A. N. et.al. In the study among 1741 male and female patients, it was established that sleep duration for less than 5 hours is associated with hypertension development risk. In NHANES study, 4810 patients without arterial hypertension were followed-up (aged 25–74 years). Within observation period for 8–10 years, close relation between hypertonic disease and sleep duration less than 5 hours was observed [2]. One of the potential mechanisms of hypertension development in sleep disorders are inevitable circadian activity disorders in sympathetic and parasympathetic systems. In normal physiological circadian cycle of vegetative nervous system activity during sleep, blood pressure is reduced by 10% and more [17]. Impaired function of hypothalamo-pituitary-thyroidal axis is as important, and, consequently, impairment of circadian and ultradian rhythm of cortisol production [19]. These pathogenetic mechanisms may cause both development of hypertension, and development and maintenance of insomnia itself.

Hypertension and type 2 diabetes mellitus are the diseases which are most commonly observed simultaneously. Yadav D. And Cho K. H., having analyzed the results of several epidemiologic studies, reached the conclusion that the relation between sleep disorders and type 2 diabetes mellitus risk is seen as U-shaped curve. Both high sleep duration and its shortness are associated with the risk of type 2 diabetes mellitus [14]. These data are correlated with the results obtained in the analysis of disorders performed by Kim C. E. et al. In their work, investigators demonstrated that sleep duration of less than 6 hours is associated with waist increase in both male and female patients, and with metabolic syndrome development in male patients only. Sleep duration of more than 10 hours is also associated with waist increase, growth of triglycerides and development of metabolic syndrome in both male and female patients. In women, increased sleep duration was also associated with increased glucose levels and reduction of high-density lipoprotein cholesterol [17]. Relation between development risk of diabetes mellitus and sleep disorders was demonstrated in one Japan study among 38,987 patients. The relation was observed in only young and middle-aged patients, while in elderlies, no reliable evidence was obtained [21]. Possibly, in elderlies, other pathogenetic mechanisms are involved. It is also known that in patients with existing diabetes mellitus, sleep disorders impair glycaemia control [20].

Our study demonstrates that patients with hypertonic disease and type 2 diabetes mellitus were reliably more often subject to such sleep disorders as night-time meals and sleep disorders in the first years after giving birth. At the same time, sleep disorders in patients with hypertonia and diabetes was reliably more commonly manifested as only difficulties while falling asleep and early rising. However, these disorders consequently caused day-time symptoms and behavioral disorders. Our work is different from previous studies in that it analyzes not only sleep duration and quality, but also those day-time symptoms the patients had. It is demonstrated that it were day-time symptoms that helped distinguishing sleep disorders in patients with hypertonic disease and diabetes mellitus and those in control group.

**Conclusion**

1. In patients with hypertonic disease and type 2 diabetes mellitus, disorders were more frequent in falling asleep and early rising, while impairment of usual sleep-awake regimen and inability to maintain continuous sleep were observed with similar frequency in both groups.

Prospective trends. Assessment and development of sleep disorder correction methods is an important stage to prevent development and severe course of hypertonic disease and diabetes mellitus.

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# THE ROLE OF PREVENTIVE MEASURES FOR EARLY DETECTION OF PRECANCEROUS AND CANCEROUS DISEASES OF THE CERVIX

**Abstract.** Cervical cancer remains one of the most common cancers in the female population. Main the cause of the development of precancerous and tumor diseases of the cervix, vagina, penis, vulva, larynx, etc. is a virus the human papilloma virus. Now the family doctor plays an important role as in the organization of detection of precancerous pathology reproductive tract, and in improving the education of the population regarding the prevention of precancerous and tumor diseases cervix uteri.

**Keywords**: cervical cancer, human papillomavirus, diagnosis, prevention.

The last decade was marked by the evolution of views on many issues of diagnosis and treatment of oncogynecological pathology. Cervical cancer (cervical cancer) remains one of the most common cancers in the female population. Rshm is the second most common cancer among women aged 15–45 years, the third cause of death among women after breast cancer and lung cancer. Every year, more than 500 thousand new cases are registered in the world, both in the early stages of development and in the advanced stages, when it is not possible to achieve a cure. Analysis of risk factors, mortality rates, incidence of LSM, features of viral carcinogenesis can predict that by 2050 this figure could double. In 2012, the world diagnosed about 14.1 million new cases of cancer and recorded 8.2 million deaths from cancer, while in 2008 these figures were 12.7 and 7.6 million, respectively [1; 2]. The modern dynamics of the incidence of LSM is characterized, first of all, by a significant change in the age structure, revealing a clear trend towards rejuvenation. World experts note the dramatic difference between morbidity and mortality in Western and Eastern Europe. The lowest incidence rates are recorded in Finland, Denmark, new Zealand, Iceland and other countries where effective screening programmes covering a large segment of the female population are actively implemented. The highest incidence of cervical cancer is observed in Latin America and the Caribbean, East and South Africa, South and South-East Asia. Very low frequency was also noted in China and Western Asia, in Asian countries, this fact 47 scientists associate with the procedure of circumcision in men. Survival of patients with LSM is associated with the stage of the disease, methods of treatment, the period of time after treatment and other factors. According to the summary data of population cancer registries in Europe, 1-year survival of patients with RSM in the 90-ies was 84%, 3-year – 66%, 5-year – 62%. The lowest 5 – year survival rate was observed in Poland (51%), the highest-in Iceland (84.7%) [2; 3; 4]. To date, the role of oncogenic strains of the human papillomavirus (HPV 16, 18) in the formation and development of severe lesions of the cervix and LSM has been proved [5; 6; 7; 8; 9]. Cervical cancer relates to clinical forms of human papillomavirus infection. The main condition to start the process of cervical carcinogenesis is the presence of HPV in an integrated form (integrated in the DNA of the host cell), the rest of Exo and andfactory are treated as cofactors, providing the impact and implementation of the oncogenic properties of HPV in cervical tissue. The main cofactors include: early sexual activity, promiscuity model of behavior (both men and women), Smoking, frequent recurrent genital infections. Special attention is required for women with immunodeficiency conditions: HIV infection, severe forms of diabetes, hepatitis C, autoimmune and systemic diseases, in such patients, subject to the

presence of HPV, cervical disease occur more aggressively and very quickly progressing pre-tumor changes in more severe forms [4; 7]. Recently, there has been an increase in HPV infection: according to EUROGIN, infection has increased almost 10 times worldwide, both among women and men. HPV is the cause of precancerous and tumor diseases of the cervix, vagina, penis, vulva, larynx, etc. [4; 5; 6; 10]. The role of HPV in the development of cervical cancer in 1974–1976. prof. Harold Zur Hausen first suggested the possible participation of human papilloma viruses (Human 48 Papilloma Virus, HPV, HPV) in the pathogenesis of cervical cancer and began work on finding viruses in tumor cell cultures and bioptates.

It was found that in malignant tumors of the cervix, two types of papillomavirus are most often detected-HPV 16 and HPV 18 (cloned in 1983–1984), while in benign lesions (flat, pointed condylomas) there are mainly HPV 6 and 11 types, in connection with which it was proposed to distinguish between papillomavirus "high" and "low" carcinogenic risk (WRC, NKR) [11; 12]. Research on HPV infection formed the basis for understanding the mechanisms of carcinogenesis induced by the papilloma virus, for which Harold Zur Hausen was Awarded the Nobel prize in physiology or medicine in 2008. Recent studies have shown that most women become infected with the virus throughout their lives. According to various studies, the incidence of HPV infection in the age group of 16–29 years is 45–81% [11; 12; 13]. Among people living an active sex life, especially those under the age of 30, HPV infection affects both men and women with the same frequency. However, these figures reflect only the frequency of clinical manifestations of HPV, and not the true extent of infection in the population, as subclinical and latent forms of infection are not recorded. In 30% –40% of cases, the virus is spontaneously eliminated and cured within 6–12 months. In other cases, there is a long recurrent course, due to the persistence of the virus, in which it is possible to form a malignant transformation of the cervical epithelium. The peculiarity of the infection is not the ability to detect the virus in the blood and the fact that the production of antibodies by the immune system occurs only in half of the cases. At the same time, the level of antibodies is very low and is not able to provide long-term reliable protection against re-infection [7; 12]. A thorough study of HPV negative tumors revealed new rare types of HPV. Variations in the geographical distribution of papillomaviruses were found: HPV 16 prevails in European and American women, while HPV 18 was found in more than 50% of cases in Indonesia [14; 15; 16; 17]. In addition, the following epidemic features of HPV infection in Ukraine were revealed: high frequency of circulation of 16 genotypes (25.1%), as well as HPV 53 (14.3%) and 31(14%); for all age groups characteristic mix of 2 and MORE HPV genotypes, women under 25 years of age have the highest percentage of detection (48% of the total number of HPV-positive results) [18]. The main problem of HPV-associated pathology of the genitals is that the latent period can last from 3 months to several years, a very complex and expensive diagnosis of HPV, to date, there is no specific etiotropic treatment of the virus. After removal or ablation of pathologically altered cervical tissue within healthy tissues, the virus remains in the body, which can lead to a relapse of the disease after some time. Cervical cancer screening in different countries cervical Cancer is a visual form of cancer, the cervix is as accessible as possible to perform any diagnostic and therapeutic procedures. Thus, cervical cancer is one of the few forms 50 malignancies who satisfy all of the requirements for the conduct of population-based screening. Today, cytomorphological examination (PAP test) is the gold standard of cytological screening worldwide. For the first time cytological screening of rshm was conducted in the canadian province of British Columbia (since 1949). Then screening programs began to be implemented in other countries of the world: in the 50s-in the USA, in China, since the early 60s – in Japan, Finland, Sweden, Iceland, since the early 70's-in Germany, Brazil and other countries [6]. Cervical screening is a complex of organizational and medical measures aimed at early detection of precancerous and tumor diseases of this localization and at reducing the mortality of this category of patients. There are 2 screening systems for cervical cancer: organized (systematic) screening and unorganized (sporadic) screening. When organized at the state level cytological screening is determined by the population of women to be screened, its frequency and women are actively invited to participate in the survey. In case of unorganized screening, only women are examined who have applied to medical institutions for any reasons. In recent decades, in our country, the system of strictly organized cytological screening has lost its control levers, and screening has become opportunistic, which has led to a low coverage of the female population with cytological examinations, and, accordingly, an increase in the number of cervical tumor diseases among women. High efficiency of organized cervical screening is noted [19; 20; 21]. The criteria for evaluating the effectiveness of screening are the reduction of morbidity and, especially, mortality from cervical cancer, as well as changes in the structure of morbidity by increasing the number of early stages of cancer and reducing advanced forms. Analysis of the literature shows that with properly organized, documented and widely conducted screening, its effectiveness is quite high [22]. Among European countries, a significant decrease in the frequency of LSM (from 15 to 30% every 5 years) was observed in Switzerland (Geneva), Finland, Sweden, Slovenia, New Zealand and other countries with well-organized screening programs. In these countries,

the effectiveness of cytological screening is much higher than in those countries where it is carried out spontaneously by private doctors and independent laboratories, for example in France, Macedonia [23; 24]. Thus, well-organized screening programs to detect cervical pathology, providing high coverage (70–80%) and including follow-up and treatment of women with abnormal Cytology, reduce the incidence of cervical cancer by more than 80%. Thus, the age of the beginning of screening is a controversial issue until today and should depend on the age associated with the risk of cervical cancer in the population, the characteristics of sexual behavior of women, the middle age of sexual debut. It is necessary to take into account the cost of quality screening, ensuring its availability in different countries.

Preventive HPV vaccination new approaches to fighting cervical cancer through primary prevention have Recently emerged. The first preventive HPV vaccine 6, 11, 16 and 18 was approved by the European medicines Agency (EMEA) (Gardasil®, Sanofi Pasteur MSD) in 2006. By October 2007, the vaccine had been licensed in 80 countries in the region. The second, bivalent vaccine (Cervarix®, GlaxoSmithKline Biologicals) received "marketing" approval from EMEA in September 2007 and in October 2007 was licensed in 35 countries of the region. This vaccine protects against HPV 16 and 18. These vaccines showed promising results in large randomized placebo-controlled double-blind studies involving adolescent girls and young women [8; 10; 15; 25]. Combined analysis of the results of the study and subsequent four-year follow-up showed: 94.7% effectiveness in preventing infection; 96.0% effectiveness against cervical infection, 53 persistent for at least 6 months; 100% effectiveness against cervical infection, persistent for at least 12 months; 95.7% effectiveness against the development of cytological disorders; 100% protection against the development of all degrees of CIN [12; 15; 26; 27; 28]. Clinical trials of these HPV vaccines have shown that both drugs are well tolerated, with only minor, self-limiting side effects. Since the registration of Quadri – and bivalent vaccines in the period up to 2011, about 120 million doses of the vaccine have been used worldwide. Australia is one of the first countries in the world where since 2007 universal HPV vaccination has been introduced in accordance with the national immunization programme. Vaccination coverage was about 70% of persons (the maximum coverage was 12–13 years old adolescents). A year after the introduction of the vaccine into the national vaccination calendar, the incidence of genital warts decreased by 25% by the end of 2009.– by 59%, by the end of 2010 – by 73%, and in 2011 (4 years after the start of routine vaccination) almost complete disappearance of genital warts was noted. Vaccination against HPV 6, 11; 16; The 18$^{th}$ serotype has been on the U.S. national immunization schedule since 2006. The decrease in genital warts among women younger than 21 years was 19.4%. Female vaccination coverage in the United States is less than 30%. The difference between the level of genital warts reduction in the United States and Australia confirms the fact that the maximum effect of routine vaccination can be achieved only with a high level of vaccination coverage. In 2011, routine vaccinations of 11–12 year old boys with tetravalent vaccine and catch-up vaccination at the age of 13–21 years were recommended in the US. In Australia, it was also proposed to introduce routine vaccination of boys in 2013 [27; 28; 29; 30]. The use of Gardasil ® vaccine is allowed to women from 9 years of life to 45 years, men-from 9 to 26 years, vaccination Cervarix® is allowed to girls and women from 10 years of life to 25 years. The vaccine is administered intramuscularly (by injection) at a dose of 0.5 ml for all age groups. It is desirable to start vaccination before the beginning of intimate life, i.e. before the first sexual contact [27; 31]. Today, many schools hold health classes for high school students, but these lessons are not always conducted by specialists who know where to place psychological and medical accents. At the moment, the screening of LSM is carried out sporadically, that is, only those women who themselves have applied to medical institutions for any reasons are examined [35; 36]. In order to reduce the morbidity and mortality rate of women from cervical cancer in Ukraine, a program "screening of cervical pathology for 2005–2010" was developed, which is still in effect [37]. At the same time, it is clear that no order will force a woman to see a gynecologist. The priority direction in medical specialties of our country belongs to family medicine. Family medicine doctor is an important link between the patient and a specialist. The first contact of the patient, as a rule, occurs with the family doctor, to him he presents his complaints and problems. In turn, the family doctor is obliged to correctly build a conversation, collect anamnesis, pay attention when the patient visited a gynecologist, underwent cytological examination, examined the mammary glands. Therefore, a family doctor in this situation plays an important role both in the organization of detection of pre-tumor pathology of the reproductive tract, and in increasing the education of the population regarding the prevention of cervical cancer [36; 38]. At the stage of primary health care to provide primary and secondary prevention of cervical cancer. Primary prevention includes: 1) identification of risk factors for the development of LSM and their elimination, including through the promotion of healthy lifestyles, health education and counseling of women and men, improving the education of the population in the field of sexual behavior, intimate hygiene; 2) organization of preventive vaccination against HPV [19; 38]. 57 Secondary prevention is cervical screening, i.e. examination of women in order to identify and

timely treatment of benign and precancerous cervical pathology. In Uzbekistan, all women from the age of 18 or 6 months from the beginning of sexual life are subject to screening.

If a malignant disease is suspected, the patient should be sent to an Oncology center or a medical institution that has the right to diagnose and treat the cancer process (University clinics, research institutes, cancer treatment centers). Thus, special training, as well as training of highly qualified specialists of family doctors will help to ensure greater coverage of the female population with cytological screening, as well as to reduce the burden on the work of offices of cervical pathology of medical institutions, which in turn will make it possible to reduce the incidence and mortality of cervical cancer among the female population. And also to increase the detectability of CMM pathology at the stages to be fully cured.

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# EFFCIENCY OF THE USE OF PHOTODYNAMIC THERAPY IN COMPLEX TREATMENT

**Abstract.** A comparative research of treatment of 60 patients at the age from 22 to 55 years old with generalized periodontitis of moderate severity with the use of photodynamic therapy (FDT) was carried out. Analysis of received data showed increased efficiency of treatment of generalized periodontitis (GP) of moderate severity when including of FDT. PDT is an effective antimicrobial treatment system that can be used in conjunction with standard procedures for the mechanical removal of supra- and subgingival dental plaque to increase the efficiency of treatment of patients with GP.

**Keywords:** periodontitis, periodontopathogenic microorganisms, photodynamic therapy, biocenosis, treatment, disease.

The problem of treatment of periodontal diseases remains relevant, despite the advances in medical science of recent years. Recent studies indicate that the development of periodontitis is associated with increasing of quantity and persistence of periodontopatogenic microorganisms (PDPM) [1; 2].

Antibiotic therapy as a method of etiotropic therapy still occupy a leading position in the treatment of GP, but they may develop resistant to microorganisms. However, the most aggressive PDPM, as Act. comitans и P. gingivalis, are very resistant to mechanical and antiseptic processing, which is associated with their ability to invade gum epithelial cells, connective tissue and bone marrow spaces [4].

In recent years, new approaches to the suppression of pathogenic microflora in periodontal diseases are of particular interest, in particular the use of PDT, as a result of which the selective destruction of pathogenic microflora in the inflammatory focus is occurring [5]. This procedure is based on a photochemical reaction leading to the generation of reactive oxygen species that have a cytotoxic effect on bacteria, viruses, and fungi [3; 6].

**Purpose of the research** was to study the dynamics of changes in microbiosis of periodontal pockets (PP) in patients with moderate periodontitis under the influence of PDT.

**Materials and research methods.** The study involved 60 patients with GP at the ages of 22 and 55 years old (26 men and 34 women). The patients included in the study were divided into 2 groups. The basic treatment in all groups consisted of sanation of the oral cavity (OC), removal of supra-subgingival dental plaque; smoothing and polishing the root surface of teeth; selective grinding. Then the patients of the 1st control group (30 patients) received traditional antiseptic treatment of the OC using 0.05% chlorhexidine solution digluconate and gel "Metrogil-Denta" was applicated in PP in amount of 10 g for 5–7 days.

In the 2nd main groups (30 people) PDT was performed. After occupational hygiene measures, the photosensitizer was slowly injected into the PP with a syringe until they were maximally filled and left to act for 10 minutes. To activate the photosensitizer we used the device "UFD-1" (Uzbekistan). At the end of the procedure the oral cavity was rinsed to remove the photosensitizer, PP were washed with saline.

For objectification of the periodontal status and assessment of the efficiency of treatment, a comprehensive dental examination of patients was performed according to the traditional scheme, which included the collection of complaints and anamnesis, examination, determination of the oral hygiene index (OHI-S) (Green J.C., Vermillion J. R., 1964), and index of bleeding (IB) Muhlemann (1971) in modification of I. Cowell (1975), PI (Russel A., 1956) index. The depth of PP, the amount of gingival recession, the degree of tooth mobility, and furcation lesions were evaluated. To clarify the diagnosis and assess the condition of the bone structures of the periodontal tissues an X-ray examination was performed.

Composition of periodontal microflora was explored by polymerase chain reaction (PCR). Clinical examination of patients and analysis of the composition of the subgingival microflora by PCR were carried out before treatment, immediately after on -treatment, then after 3 and 6 months after conservative treatment.

**Results and discussion.** During clinical examination after 3 and 6 months after treatment, in patients of the 2nd group who received PDT, the OHI-S and IB were significantly lower than in group 1. In addition, patients of the 1st group showed a significant decrease in the depth of PP and the degree of tooth mobility. On apparently, it can be explained by a pronounced and long-lasting antimicrobial effect of PDT. In the control group in moderately severe GP patients, the anti-inflammatory effect of conservative treatment after 3 months almost disappeared or significantly decreased.

According to our results, in the initial study of the contents of PP in patients with GP of moderate severity, both groups revealed the presence of markers of the main periodontopatogens.

Table. Effect of PDT on the incidence of periodontal pathogens

| Periodontal pathogens | 1st group (n = 30) | | | | 2nd group (n = 30) | | | |
|---|---|---|---|---|---|---|---|---|
| | Before-treatment | After treatment | After 3 month-streatment | After 6 months treatment | Before treatment | After treatment | After 3 months treatment | After 6 months treatment |
| Act. comitans | 1.33 | 0.17 | 0.8 | 1.6 | 1.35 | – | – | 0.15 |
| P. gingivalis | 5.64 | 4.5 | 4.8 | 5.4 | 6.4 | – | 2.4 | 4.0 |
| Pr. intermedia | 6.37 | 5.0 | 5.6 | 6,6 | 6.7 | – | 2.8 | 4.6 |
| T. forsythensis | 7.08 | 5.3 | 6,6 | 7.1 | 7.4 | 2.3 | 4.6 | 5.2 |
| Tr. denticola | 6.57 | 3.5 | 4.1 | 6.2 | 7.2 | 1.8 | 2.8 | 3.2 |

As can be seen from the table 1, the ability of laser PDT to reduce the levels of bacterial infectious agents was significantly higher than that of occupational hygienic therapy using a 0.05% chlorhexidine solution and gel "Metrogil-Denta".

Inclusion in the complex conservative treatment of GP of moderate severity PDT can significantly reduce the frequency of detection in the composition of the subgingival microflora of PP. The remote terms of antimicrobial effect of carried out treatment decreased in both groups of patients, even in 6 months after the treatment the frequency of occurrence PDPM in patients of 2nd group received PDT was significantly lower than in patients of 1st group (control). Especially high antimicrobial effect of PDT was observed in relation to two types of microorganisms: P. gingivalis and Pr. intermedia. High bactericidal effect against chromogenic microflora, such as P. gingivalis, Pr. intermedia, was apparently due to the content of light-sensitive porphyrin molecules in the cells of these bacteria which, when activated by corresponding light wave lengths, produce oxygen radicals. In this connection, a part of microorganisms dies upon irradiation with laser light, even if they were not in contact with the photosensitizer.

By the end of PDT in the study group pain intensity decreased by 77.58% ($P < 0.01$); bleeding gums – by 73.73% ($P < 0.01$); intensity of breath – by 87.63% ($P < 0.01$); and the depth of the PP, tooth mobility and the quantity of exudation from the PP, respectively – by 48.50% ($P < 0.01$); 48.74% ($P < 0.01$) and 76.54% ($P < 0.01$).

At the same time reduction OHI-S decreased by 57.08% ($P < 0.01$); index of inflammation in periodontium, (PMA) – by 81.06% ($P < 0.01$) and periodontal destruction index (PI) – by 46.52% ($P < 0.01$).

Apparently, the high antimicrobial effect of PDT is due to the fact that part of the pathogenic microorganisms, having the ability to invade, penetrates into the epithelial cells of the gum. They are not available for mechanical treatment and the action of antiseptics, therefore, are the cause of the recurrence of the inflammatory process. The destruction of such microorganisms using PDT is possible due to the ability of the photosensitizer and laser radiation to penetrate the gingival tissue to a certain depth.

**Conclusions:** PDT is an effective antimicrobial treatment system that can be used in conjunction with standard procedures for the mechanical removal of supra- and subgingival dental plaque to increase the efficiency of treatment of patients with GP. In our opinion, PDT in periodontology can be applied after the initial phase of treatment as an addition to professional hygiene measures, as an alternative to the traditional antibacterial and anti-inflammatory treatment.

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# PREDICTION OF PROGRESSION OF CARDIOVASCULAR DISEASE IN PATIENTS WITH RHEUMATOID ARTHRITIS

**Abstract.** The objective of this paper was to predict the development of cardiovascular diseases in patients with rheumatoid arthritis. Conducted study of the common cardiovascular diseases risk factors revealed that in patients with rheumatoid arthritis arterial hypertension was the most common in 98 (62.4%) patients examined. Coincidently, the occurrence of such risk factors as arterial hypertension, hypercholesterolemia and obesity depends on age: in patients aged 50–60, the occurrence of arterial hypertension was 4.4 times more often, hypercholesterolemia was 4.8 times, and obesity was 2.4 times more when compared to the group of patients aged 35–49 years. In patients with rheumatoid arthritis, the determination of total cardiovascular risk on the mSCORE chart has important prognostic significance.

**Keywords:** rheumatoid arthritis, cardiovascular disease, risk factors, prediction, prognosis.

Rheumatoid arthritis (RA) is a widespread autoimmune disease of unknown etiology characterized by symmetrical erosive synovitis, destruction of cartilage and bone tissues, and also often by a broad spectrum of systemic symptoms. In most cases, the disease has a chronicity, which may lead (in the absence of timely and adequate therapy) to progressive destruction, deformity and dysfunction of the joints, a significant reduction in the quality of life and premature death. RA is known for a high risk of cardiovascular complications (CVC) [1; 2]. It is important for fundamental applied medicine to study of the immunopathogenesis of cardiovascular diseases (CVD), the specifics of their diagnosis and treatment in RA. Aforementioned requires an interdisciplinary approach to managing patients, with the participation of rheumatologists, cardiologists and therapists. To solve this problem, it is necessary to evaluate the morbidity of CVD, cardiovascular risk factors and metabolic disorders; to group patients predisposed to the development of CVC; to study the effect of antirheumatic drugs on the cardiovascular system; to develop a complex of preventive and therapeutic measures aimed at reducing the risk of CVC; to create a system of dynamic control and monitoring of the cardiovascular pathology development in this category of patients [3; 4]. An array of scientific data, obtained as a result of large multicenter studies, suggests that the immune-inflammatory cascade in systemic connective tissue diseases (SCTD) contributes to the progression of the atherosclerotic processes [5]. These patients have a high level of cardiovascular morbidity. Evaluation of traditional risk factors for cardiovascular diseases (CVD) does not reflect the true prognosis of these patients [6]. The cause of premature death in half of the deceased patients with rheumatological diseases is the pathology of the cardiovascular system associated with atherosclerosis (AS) of blood vessels, and not with inflammatory damage to the structures of the heart. One of the main causes of mortality in RA is cardiovascular accidents (myocardial infarction (MI), stroke, and sudden cardiac death), due to the early development and rapid progression of atherosclerotic vascular lesions [7]. Recent studies have shown that an increase in the risk of cardiovascular complications (CVC) in RA is associated not only with traditional risk factors (RF), but also with immune-inflammatory mechanisms underlying the pathogenesis of RA and atherosclerosis [8]. Arterial hypertension (AH) is the most important modifiable risk factor for the development of cardiovascular diseases (CVD). The presence of hypertension in RA patients is associated with an increase in subclinical manifestations of the carotid arteries atherosclerosis and is one of the main independent predictors of CVC [9; 10].

**Objective.** Prognosis of cardiovascular disease development in patients with rheumatoid arthritis.

**Materials and methods**

157 patients with RA aged from 35 to 60 years old (mean age is 51.6 ± 0.5) were examined. RA was diagnosed using ACR (1987) and ACR/EULAR (2010) classification criteria. 129 (82%) of examined patients were women and 28 (18%) were men. 113 (72%) of the patients had seropositive RA and

44 (28%) had seronegative RA. 51 of the examined were aged 35–49 years old and 106–50–60 years old.

**Results**

Analysis of the results has shown that most common risk factor was arterial hypertension present in 98 (62.4%) of the examined patients. Hypercholesterolemia was detected in 35 (22.3%) and obesity in 54 (34.4%) patients. Considering that 82% of the surveyed women, such RFs as smoking occurred in 10.8% of cases. Coincidently, the occurrence of such RF as AH, HCS and obesity depends on age: in patients aged 50–60, the occurrence of AH was 4.4 times more often, HCS was 4.8 times, and obesity was 2.4 times more when compared to the group of patients aged 35–49 years. Comorbidity with diseases such as coronary heart disease and diabetes mellitus is also more common in patients aged 50–60 years.

We used the SCORE risk chart to predict the risk of cardiovascular diseases, which classifies patients according to age, gender, total cholesterol, systolic blood pressure (SBP), and smoking/non-smoking using low and high risk matrices. Cross-checking data for each patient generates a cell containing a number representing the numerical value of the SCORE risk chart, and a color representing the 10-year risk of fatal cardiovascular complications of each patient. The SCORE risk chart should not be used for patients in the high and very high cardiovascular risk category. To calculate the cardiovascular risk in patients with rheumatoid arthritis (RA), the mSCORE risk chart was used, which compiles the results of the SCORE risk chart multiplied by 1.5. Based on calculations of SCORE and mSCORE, patients with a 10-year risk of fatal cardiovascular complications less than 1% were stratified as "low risk", from ≥ 1 to 5% as "moderate", from ≥ 5% up to 10% as "high risk", ≥ 10% as "very high risk".Among the examined 157 patients with RA were 6 patients with coronary artery disease and 9 diabetes mellitus who were excluded from the study to predict cardiovascular complications, the SCORE and mSCORE charts were used for 146 patients (Table 1).

Table 1.– Cardiovascular events prognosis

| **Total patients 146** | **SCORE** | **mSCORE** |
|---|---|---|
| Low < 1% | 45(30.8%) | 45(30.8%) |
| Moderate < 5% | 84(57.5%) | 81(55.5%) |
| High < 10% | 12(8.2%) | 8(5.5%) |
| Very high > 10% | 5(3.2%) | 12(8.2%) |

The results of mSCORE analysis showed that patients with RA had a low risk of cardiovascular disease in 45 (30.8%) patients, moderate in 81 (55.5%), high in 8 (5.5%) and very high in 12 (8.2%). When comparing the results of the SCORE and mSCORE risk charts, the very high risk by the mSCORE chart is 8.2%, which is 2.5 times more than by the SCORE chart. Cardiovascular risk by mSCORE among patients aged 50–60 years was more common than in patients aged 35–49 years. Predicting the development of CVDs and their prevention is a set of coordinated activities aimed at the entire population or certain groups of the population to prevent the development and progression of CVDs or minimize the burden of CVDs and related disability [11; 12]. In this regard, the use of the mSCORE chart in patients with RA will help predict the development of cardiovascular events, assess the risk and develop preventive measures.

**Conclusion**

In summary, the early detection of cardiovascular diseases risk factors in patients with rheumatoid arthritis and the cardiovascular events prognosis will help prevent the development and progression of cardiovascular diseases.

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# MULTISLICE TOMOGRAPHY IN THE COMPARATIVE ASSESSMENT OF THE RATE OF PRIMARY TUMOR REGRESSION AGAINST THE BACKGROUND OF CHEMORADIATION THERAPY FOR LOCALLY ADVANCED CERVICAL CANCER

**Abstract.** To evaluate possibilities of multislice tomography in determining the estimate of the rate of regression of chemoradiation therapy in patients with locally advanced cervical cancer.

***Rationale:*** Multislice tomography and magnetic resonance tomography, as some non-invasive methods of radiodiagnostics, can greatly facilitate the evaluation of the prevalence of this localization of malignant process allowing to increase the accuracy of the clinical staging and evaluate the effectiveness of the selected treatment.

***Materials and Methods:*** The work is based on the results of a survey of 42 patients in the period 2016–2017. MSCT was performed at Somatom Definition AS20 (Siemens, Germany 2015). The work is based on the results of a survey of 42 patients in the period 2016–2017. Multispiral tomography was performed on Somatom Definition AS20 (Siemens, Germany 2015).

***Results*:** When analyzing the diagnostic value of multislice tomography, the technique is a highly informative method that can be used for monitoring in the process of complex chemoradiation treatment for patients with cervical cancer. Multislice imaging performed on the SOMATOM DEFINITION AS20 (SIEMENS, Germany, 2015.), it allows you to receive objective information about the dynamics of tumor regression, the rate of change of its blood supply and changes in metastatic regional lymph nodes during treatment.

***Conclusion:*** The obtained data allows us to optimize the timing of MSCT monitoring for the chemoradiation treatment of locally advanced cervical cancer.

**Keywords:** locally advanced cervical cancer, multislice tomography, tumor regression.

**Introduction.** Malignant tumors of the female genital organs occupy a special place in clinical oncology: they are the most common malignant tumors in women [1]. Every year 12.7 million new cases of cancer are registered in the

world, of which more than 1 million are diseases of the female genitalia [10]. Among the countries of Central Asia and the Russian Federation for the period 1991–2016. the increase in the absolute number of cases of cervical cancer ranged from 9% (in Belarus) to 44–92% (in the Russian Federation, Kazakhstan, Kyrgyzstan). In 2016, the highest incidence rates were registered in the Russian Federation, Kazakhstan and Kyrgyzstan (15.4 and 16.4 per 100 thousand of the female population); at the level of 10–11 per 100 thousand – in Armenia, Uzbekistan, Moldova and Tajikistan; less than 7 per 100,000 – in the Republic of Azerbaijan [2]. Long-term results of treating patients with cervical cancer are not satisfactory, relapses after special treatment often occur after 12–20 months. and observed in 32–78.3% of cases. Up to 45% of patients die within the first 5 years of disease progression [7].

According to the State Institution Republican Specialized Scientific-Practical Medical Center of Oncology and Radiology, in 2017 the number of women with malignant tumor diseases in the population was the highest in cases of breast cancer – 9.9; cervical cancer-4,8; 2.4 ovarian cancer, respectively. From 2013 to 2017, 7201 new cases of cervical cancer were detected in the Republic of Uzbekistan. The average incidence rate was 4.6 per 100,000 population. Despite the progress made in the diagnosis and treatment of this localization, there is an increase in the incidence and an increase in the aggressiveness of the course of the disease. There is a decrease in 5-year survival in the period from 2013 to 2017 from 45.3 to 42.6, and the mortality rate increased from 2.4 to 2.6 per 100.000 population (Cancer register). This requires improving the quality of early diagnosis and improving the treatment of locally advanced forms of cervical cancer in order to predict the recurrence of the disease. Multislice tomography and magnetic resonance tomography, as some non-invasive methods of radiodiagnostics, can greatly facilitate the evaluation of the prevalence of this localization of malignant process allowing to increase the accuracy of the clinical staging and evaluate the effectiveness of the selected treatment [4; 16; 17].

In 2009, the International Federation of Obstetricians and Gynecologists recommended for the first time to take into account data of computer tomography and / or magnetic resonance imaging in planning the treatment of cervical cancer patients [14]. It was established that the tumor volume, the spread of the tumor on the body of the uterus, the state of the pelvic and retroperitoneal lymph nodes, as determined by MSCT, MRI are independent predictors of overall and without recurrent survival with locally advanced cervical cancer [6; 12].

The possibility of using MSCT to reliably exclude the spread of the tumor to the adjacent pelvic organs, identify the level and determine the cause of the obstruction of the ureters led to a decrease in the need for the use of X-ray diagnostic methods. MSCT proved to be useful in planning and preparing for radiation treatment [5; 18]. The presence of metastases in the regional lymph nodes is an extremely unfavorable prognostic factor that significantly reduces survival in cervical cancer. However, the possibilities of using pathological studies to assess the state of lymph nodes are significantly limited, since many patients with cervical cancer do not show surgical treatment, and therefore non-invasive diagnostic methods become relevant [13]. The analysis will improve the effectiveness of clinical examination and qualitatively influence the tactics of patient management, depending on the results obtained. The analysis of literature data indicates a significant variability of the results of MSCT, the complexity of interpreting the visual picture in the monitoring of chemoradiation treatment in order to assess its effectiveness.

**The aim** of the study was the possibilities of MSCT, a comparative assessment of the rate of regression of the primary tumor on the background of chemoradiation therapy and the closest prognosis for locally advanced forms of cervical cancer.

**Material and methods:** The work is based on a survey of 42 patients with cervical cancer, IIB-IIIAB stages of FIGO classification (2009), who received chemoradiotherapy in the State Institution Republican Specialized Scientific-Practical Medical Center of Oncology and Radiology of Uzbekistan from 2016 to 2017. The diagnosis of the disease in all cases is verified histologically. Morphologically, all women were diagnosed with squamous cell carcinoma. The age of 72.4% of patients accounted for 4–5 decades of life. All patients received chemoradiotherapy; 3 courses of neoadjuvant chemotherapy (cisplatin + 5 ftorouracil), followed by a course of combined radiation therapy, including remote gamma therapy, SFD of 2 Gy, TFD of 46 Gy (TERABALT type 80 model SCS2012 Czech Republic) and intracavitary radiation therapy (BEBIG apparatus Multisourse Co 602013. Germany) SFD5 Gy, eq TFD to point A 70–90 Gy, to point B50–58 Gy.

Evaluation of the effectiveness of chemoradiation treatment was carried out according to RECIST criteria using MSCT. On sagittal sections, the spread of the tumor along the long axis of the uterus, its transition to the body, as well as the relationship between the tumor and the posterior wall of the bladder and / or the anterior wall of the rectum was evaluated. Axial and coronary sections were used to assess the transition of the tumor to the walls of the pelvis and visualize the lymph nodes. The best visualization of the parametric invasion was achieved using oblique axial slices oriented perpendicular to the long axis of the cervix. At MSCT, infiltration was manifested by tyazhy consolidations of the structure of parametric fiber and an increase in the densitometric density of tissues by 40–70 X units. The obstruction of the ureters was well defined using the CT-urography technique (obtaining a thick section in the coronary plane). This technique allowed for a few seconds, without

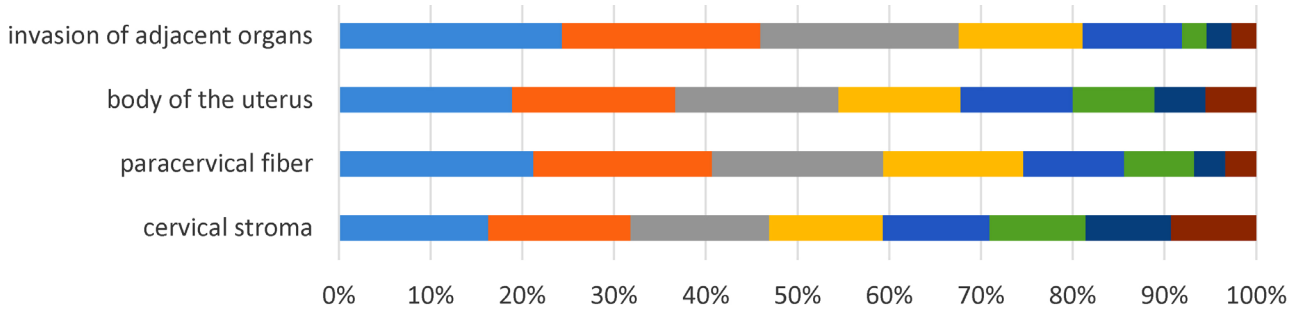
resorting to contrast, to obtain an image of the bladder and dilated ureters. A good contrast between the lymph nodes and the surrounding fatty tissue provided the lymph nodes better differentiated from skeletal muscles, ovaries and blood vessels. The advantage of the frontal plane was the ability to explore the retroperitoneal space from the pubic symphysis to the level of the renal vessels. Sagittal images were used to visualize enlarged aortic lymph nodes. Axial sections for adequate assessment of the structure of the lymph nodes covered the region from the pubic symphysis to the renal vessels.

When performing MSCT to reduce artifacts from intestinal motility, patients were advised to abstain from food intake for 5–6 hours prior to the study using antiperistaltic drugs the evening before. Artifacts from the respiratory movements of the anterior abdominal wall were eliminated by software (using a saturation band) or mechanical compression of the abdomen with an elastic belt.

In all cases, the control CT of the pelvic organs was performed after 3 courses of neoadjuvant chemotherapy, before and after combined radiation therapy and 3, 6, 9 and 12 months after treatment. Statistical data analysis was performed using Microsoft Excel and the SPSS13.0 statistical software package. Data are presented as absolute frequencies and percentages.

**Research results and discussion:** Evaluation of the effectiveness of the treatment was carried out taking into account the analysis of changes in the following parameters: tumor size, the degree of para infiltration of cervical fiber, involvement of the uterus and neighboring organs, the state of regional lymph nodes. Before treatment, in all cases there was a lesion of the cervical stroma, characterized by a lesion that ruptures the hypointensive stroma ring. Tumor sizes ranged from 5 to 60 mm, on average – 32 ± 3 mm. The transition of the cervical tumor to the body of the uterus was determined in 40.5% (17) cases, while on the tomograms the tumor masses were visualized through the internal pharynx into the uterine cavity with disruption of its normal zonal anatomy with a change in section. During the MSCT, in all cases, bilateral infiltration was detected, while the defeat of one of the parties in some cases was significantly greater than the opposite. Infiltration of the paracervical tissue was perched in 59.5% (25) patients. Using MSCT, invasion of the bladder in the form of local uneven thickening of its wall and tumor invasion of the rectum was suspected in 21.4% (9).

Table 1. – Dynamics of regression of the primary tumor in patients with cervical cancer




| | cervical stroma | paracervical fiber | body of the uterus | invasion of adjacent organs |
|---|---|---|---|---|
| before treatment | 42 | 25 | 17 | 9 |
| after 3 courses of chemotherapy | 40 | 23 | 16 | 8 |
| before radiation therapy | 39 | 22 | 16 | 8 |
| after radiation therapy | 32 | 18 | 12 | 5 |
| after 3 months | 30 | 13 | 11 | 4 |
| after 6 months | 27 | 9 | 8 | 1 |
| after 9 months | 24 | 4 | 5 | 1 |
| after 12 months | 24 | 4 | 5 | 1 |

After 3 courses of neoadjuvant chemotherapy, before and after combined radiation therapy, the size of cervical stroma infiltration according to MSCT was 95.2% (40), 92.8% (39), 76.2% (32), respectively. Preservation of vapor infiltration of cervical fiber during treatment 54.7% (23), 52.4% (22), 42.8% (18) cases. The transition of the cervical tumor to the uterus body after 3 courses of neoadjuvant chemotherapy disappeared to 2.5% (1), 2.5% (1) and 12% (5), respectively, show before and after combined radiation therapy.

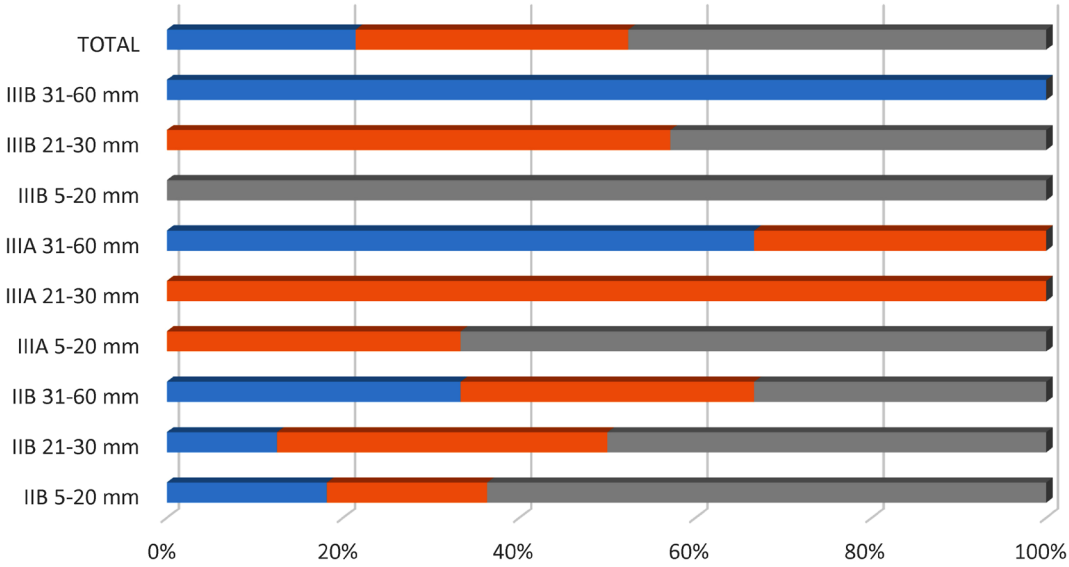
Under dynamic observation, 3 months after chemoradiation treatment in 28.6% of cases, according to MSCT, inflamed stroma of the cervix disappeared in patients. The incidence of vapor infiltration of cervical fiber was reduced from 59.5 to 30.9% (13). The transition of the tumor process to the body of the uterus was preserved in 26.2% (11) cases and was visualized as an area of increased intensity without clear contours in the region of the lower segment of the uterus in violation of its normal zonal anatomy. In half of the women with the initial spread of the tumor to adjacent organs, a positive trend was recorded in the form of a decrease in the degree of infiltration.

After 6 and 9 months after the end of treatment, the phenomena of tumor size regression (from 25 ± 3 mm to 15 ± 3 mm), reduction in the size of vapor infiltration of cervical tissue (in 9.5% (4) patients) continued, and the transition of the tumor process to the body the uterus was preserved in 19% (8) and 11.9% (5) cases, respectively.

After 12 months after treatment, infiltration of the cervical stroma disappeared in 42.9% (18) patients. The spread of the tumor on paracervix was preserved in 9.5% (4) cases. The frequency of transition of the tumor to the body of the uterus decreased from 26.2 (11) to 11.9% (5) cases. A decrease in tumor infiltration into adjacent organs was recorded in 2.4% of cases (Table 1).

According to the MSCT monitoring, a significant regression of the tumor process was noted in the majority of patients. Moreover, a decrease in tumor size after chemoradiation treatment, more than 50% was noted in 20 (47.6%), from 25 to 50% in 13 (30.9%), less than 25% in 9 (21.4%) patients. Complete tumor regression was achieved in 14 (33.3%), partial regression – in 7 (16.6%), process stabilization – in 13 (30.9%) patients (Table 2).

Table 2. – The degree of regression of the tumor of the cervix after 12 months after chemoradiation treatment, depending on the stage and size




| | IIB 5-20 mm | IIB 21-30 mm | IIB 31-60 mm | IIIA 5-20 mm | IIIA 21-30 mm | IIIA 31-60 mm | IIIB 5-20 mm | IIIB 21-30 mm | IIIB 31-60 mm | TOTAL |
|---|---|---|---|---|---|---|---|---|---|---|
| <25 % | 2 | 1 | 1 | 0 | 0 | 2 | 0 | 0 | 3 | 9 |
| ≥25-50 % | 2 | 3 | 1 | 1 | 1 | 1 | 0 | 4 | 0 | 13 |
| ≥50-100 % | 7 | 4 | 1 | 2 | 0 | 0 | 3 | 3 | 0 | 20 |



According to our data, a decrease in the degree of infiltrative changes was determined during and after treatment. In most patients, tumor size reduction in the process of combined chemoradiation treatment occurred in parallel and in proportion to the decrease in the degree of accumulation of the contrast agent, which indicated a decrease in the blood supply to the tumor.

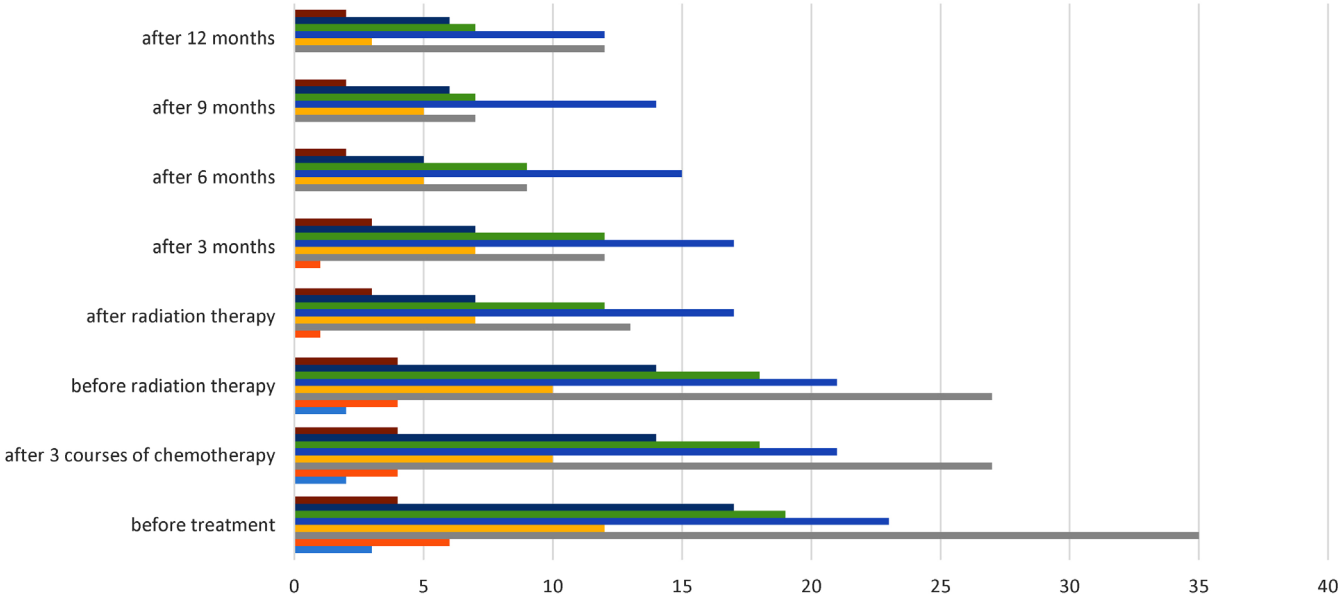
With complete remission, restoration of the normal anatomical structure of the cervix and the proximal part of the vagina was observed, which was determined by the picture of recovery of a homogeneous signal of low intensity from the stroma, visualization of the even mucous membrane against the background of a decrease in the size of the cervix. When conducting a bolus contrast enhancement, it was found that in the projection of a previously defined tumor there was an accumulation of contrast, visually identical to the unchanged stroma.

Assessment of the lymph nodes is also one of the most important tasks of a CT scan in cervical cancer. Unfortunately, the accuracy of traditional MSCT in the diagnosis of lymph node metastatic lesions is assessed as low.

MSCT sensitivity in the diagnosis of lymphadenopathy varies from 83% to 95%, specificity – 88% [15]. The main criterion for the evaluation of lymph nodes using any tomographic method is the size, with preference given to the transverse size.

As a separation point, values in the range from 6 to 15 mm are used, but most often the upper limit of the norm for the pelvic lymph node is 10 mm. A minimum diameter of more than 10 mm serves as the most reliable criterion for lymph node metastatic damage, although some authors consider pelvic lymph nodes with a maximum size of more than 10 mm suspicious [3, 9]. In addition, there is evidence that in the metastatic lesion of the lymph node its shape is rounded [8]. Therefore, as an indirect sign of a lymph node metastatic lesion, it is proposed to use the criterion of increasing the ratio of smaller to larger diameter of more than 0.8 [8; 11].

Table 3. – Dynamics of changes in the size of regional lymph nodes in patients with cervical cancer




| | before treatment | after 3 courses of chemotherapy | before radiation therapy | after radiation therapy | after 3 months | after 6 months | after 9 months | after 12 months |
|---|---|---|---|---|---|---|---|---|
| parakavalnye | 4 | 4 | 4 | 3 | 3 | 2 | 2 | 2 |
| paraaortic | 17 | 14 | 14 | 7 | 7 | 5 | 6 | 6 |
| inguinal | 19 | 18 | 18 | 12 | 12 | 9 | 7 | 7 |
| common iliac | 23 | 21 | 21 | 17 | 17 | 15 | 14 | 12 |
| internal iliac | 12 | 10 | 10 | 7 | 7 | 5 | 5 | 3 |
| external iliac | 35 | 27 | 27 | 13 | 12 | 9 | 7 | 12 |
| pararectal | 6 | 4 | 4 | 1 | 1 | 0 | 0 | 0 |
| paracervical | 3 | 2 | 2 | 0 | 0 | 0 | 0 | 0 |



However, even small lymph nodes may be affected by metastases, and enlarged lymph nodes may not contain tumor tissue [8,;11]. At the same time, when large conglomerates of lymph nodes are detected (more than 20 mm) with the presence of sections of disintegration and hemorrhages in their structure, the metastatic nature of their damage is beyond

doubt. There is evidence that the presence of central necrosis in the lymph node can be used to diagnose its metastatic lesions. The positive predictive value of this feature, regardless of the node size, is 100% [12].

Changes detected by MSCT in the lymph nodes, allowed to adequately stratify the lymphogenous spread of the process according to the criterion N of the TNM system (Table 3). In the series of presented observations for locally advanced cervical cancer, single metastatic lymph nodes or packages of enlarged lymph nodes were more characteristic. Both the first and the second group of lymph nodes were characterized by a round or ovoid shape, clear and even contours, a homogeneous structure and reduced echogenicity. At the same time, in 7.1% of cases an increase in lymph nodes was detected by more than 10 mm in diameter in the pair of cervical cellulose, in 14.3% in rectal cellulose. The lymph nodes along the external iliac vessels were enlarged by 83.3%, along the internal iliac vessels – by 28.6%, along the common iliac vessels – by 54.7% of cases; an increase in the pair of aortic lymph nodes was noted in 40.5%, paracaval – in 9.5%, inguinal – in 45.2% of observations. The contours of the lymph nodes were lumpy in 82%.

During treatment, it became known that after chemoradiation therapy, all lymph nodes decreased significantly. Paracervical lymph nodes disappeared. A pair of rectal 14.3% (6) by 2.4% (1). External iliac lymph nodes decreased 83.3% by 28.6%. After chemoradiation therapy, the internal iliac lymph nodes unsharply decreased 28.6% – 16.6%. General ileal lymphocytes after treatment are almost preserved 54.7% – 40.5% and inguinal lymph nodes 45.2% – 28.6%, respectively. The number of aortic and para lymphatic nodes during treatment decreased by almost two times: 40.5% – 16.2%, 9.5% –7.1%, respectively.

When the control MSCT after 3 months. after treatment, it was found that lymph nodes in a pair of cervical cellulose were not visualized in 100%, in a pair of rectal cellulose lymph nodes remained in 2.4% (1) of cases. The increase in lymph nodes along the external iliac vessels remained in 28.6%, along the internal iliac vessels – in 16.6%, along the common iliac vessels – in 40.5% of cases, the increase in a pair of aortic lymph nodes continued to be determined in 16.6%, paracavalny – in 7.1%, inguinal – in 28.6% of patients.

12 months after treatment, an increase in the lymph nodes along the external iliac vessels was observed in 28.6%, along the internal iliac vessels – in 7.1%, along the common iliac vessels – in 28.6% of cases; an increase in lymph nodes of the aortic group remained in 14.3%, in the paracaval group in 4.7%, and in the inguinal group in 16.6% of patients. The contours of the lymph nodes remained bumpy in 43%.

**Conclusion:** Thus, the results of the study suggest that MSCT is a highly informative diagnostic method that can be used to monitor the combined chemoradiation treatment of patients with locally advanced cervical cancer, which allows obtaining objective information about the dynamics of regression of the size and condition of regional lymph nodes.

Analysis of the dynamics of tumor prevalence during the monitoring showed that the maximum reduction in the size of the tumor was recorded after chemoradiation therapy, a decrease in the vapor infiltration of cervical fiber and the restoration of the structure of the walls of the uterus body – from 3 to 6 months after treatment. At the same time, in the course of dynamic observation, it was possible to determine the progression of the disease 12 months after treatment, which was manifested by an increase in tumor size by 25% or more and the appearance of multiple liver metastases in 2 (4.7%) patients.

The reaction of lymph nodes after chemoradiation treatment was most pronounced in terms of 3 to 6 months, with the most pronounced changes recorded in groups of external iliac and a pair of rectal / para cervical lymph nodes, which were not visualized 3 months after chemo-radiation therapy.

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# RADIOLOGICAL PROGNOSTIC FACTORS OF BREAST CANCER

**Abstract.** This article analyzed the main mammographic and ultrasound signs affecting the outcome of the disease, as well as their proportion. From mammographic signs, worm-like, treelike microcalcifications, star-shaped tumors were mainly found in patients with an unfavorable outcome of the disease. Heterogeneity of the tumor with ultrasound diagnosis, posterior darkening, hyperechoic ring and hypoechoic ring around the tumor are also considered unfavorable signs and are more common in patients with early progression of the disease.

**Keywords:** Breast cancer, mammography, ultrasound, prognosis.

**Introduction**

In developed and developing countries, there is a tendency to an increase in the incidence of breast cancer, due to a change in the reproductive behavior of the population, a change in lifestyle and an increase in the life expectancy of the population. According to forecasts of GLOBACAN2012 (International Cancer Research Institute), by 2020 in low- and middle-income countries, the number of newly detected cases of breast cancer will be about 1 million cases per year [2].

According to the IARC, mortality from breast cancer varies depending on the income level of the country, in high-income countries the mortality rate is 24%, while in low- and middle-income countries, 48%, 38%, respectively. With about 1.5 million deaths from breast cancer, it might be preventable [2].

Breast cancer is a heterogeneous disease with a different clinical course, response to therapy and prognosis.

The complex of diagnostic measures for breast cancer includes clinical examination and palpation, ultrasound, mammography, MRI of the mammary glands.

By mammography, one can judge the pathological changes in the anatomical structure and density of the mammary glands, the biological aggressiveness of the tumor, the presence of concomitant pathologies of the mammary glands. The advantage of mammographic research is the ability to detect intraductal formations, as well as various kinds of microcalcifications. Mammographic features of the structure of the tumor provide prognostic data on the nature of the course of the disease. According to Tot T., Tabar L. et al 2000, breast cancer mortality rates are higher in patients with mammograms of which there were cast-type microcalcifications compared with patients without them [3].

The use of ultrasound in addition to mammographic examination increases their sensitivity and specificity, and is also a convenient method for visualizing and controlling minimally invasive procedures (fine-needle aspiration biopsy, core-biopsy, etc.). The joint use of mammographic examination with ultrasound increased the diagnostic accuracy up to 100%. However, as an independent method of diagnosing breast cancer, it cannot be used, since it is not able to determine microcalcifications, and is less effective in visualizing solid formations. According to Bassett et al, only in 63% of cases, ultrasound allowed visualization of solid formations.

One of the most pressing and complex problems of modern oncology is the problem of individual forecasting.

A personalized approach to treating patients is most often based on the physician's personal experience, which takes into account only a few factors that characterize the tumor and the organism-tumor carrier. At the same time, only an individual prognosis makes it possible in each individual case to most accurately determine the tactics of patient management.

Objective: to determine the effect of mammography and ultrasound signs on the prognosis of breast cancer.

**Materials and methods**

To study the causes and conditions of generalization in patients with breast cancer and the characteristics of the course, a censored study of 350 case histories of patients who

had previously undergone combined and complex treatment was carried out. Selected case histories of 95 patients for retrospective analysis. Of these, the main group of 32 patients in whom within 5 years after the combined and complex treatment, progression of the process was noted. For comparison (control group), 63 case histories of patients who lived for more than five years after combined and complex treatment without signs of disease progression were identified.

Mammography was performed in two standard (craniocaudal and medio-lateral) projections with breast compression.

Ultrasound examination was carried out according to the standard method on a Toshiba-xario-200 device with a frequency of 7.5 MHz linear sensor.

The basis of evidence-based statistics was: to highlight common factors – factor analysis with the determination of the proportion of each symptom affecting the outcome of the disease; to determine the relationship between indicators nonparametric (rank) correlation analysis by the method of Kendall (Rk); to determine the differences – the criterion of the angular Fisher transform (F *), the criterion of compliance (consent) of Pearson ($\chi 2$), the criterion of relative risk (RR and 1/RR).

To determine the differences, four main levels of statistical significance were adopted: high – $p < 0.001$, average $p < 0.010$, low (marginal) $p < 0.05$, insignificant (unreliable) – $p > 0.05$. The main verifiers of the reliability of the differences were the results of multifunctional (universal) methods – Fisher.

**Results**

A mammographic examination revealed a star-shaped tumor in the majority of patients with an unfavorable outcome of the disease.

Adverse symptoms in mammographic studies were wormlike, treelike microcalcifications (casting type calcification) ($p < 0.01$), star-shaped ($p < 0.01$) tumors that had a high factorial effect. Such mammographic signs, such as the absence of calcifications ($p < 0.01$), in patients were associated with a favorable outcome of the disease and had a significant $\chi 2$ distribution. Powder calcification microcalcifications, crushed stone-like calcification microcalcifications, the round shape of the tumor and unifocal growth were not reliably associated with the outcome of the disease ($p < 0.05$).

Table 1. – $\chi 2$ – distribution of patients depending on the mammographic picture of the tumor and the probability of generalization of breast cancer

| Mammographic picture | Main group n = 32 | Control group n = 63 | Total n = 95 $\chi^2$/p |
|---|---|---|---|
| Lack of calcifications | 10*(18.6)** | 44(35.4) | 6.08; $p < 0.01$ |
| Round shape of the tumor | 10(17.6) | 41(33.4) | 1.74; $p < 0.05$ |
| Unifocal growth | 28(30.4) | 60(56.6) | 0.393; $p > 0.05$ |
| Star shape | 19(10) | 10(18.9) | – 12.3; $p < 0.01$ |
| Worm-like, treelike microcalcifications | 20(10.4) | 10(19.6) | – 13.7; $p < 0.01$ |

*Note: * Actual result, ** In quote, Expected result*

As is known, the growth of cancer in the mammary gland occurs in three directions:

1) on milk courses;

2) in the lymphatic crevices and vessels;

3) through the blood vessels.

The progression of the tumor can be carried out by continuous growth through the vessels and intercellular gaps and transfer of the rejected tumor cells by the flow of lymph and blood. For the progression of a tumor, many conditions are needed that create a favorable background for the rejection of the tumor complex from the main node, its penetration into the blood or lymph flow, filtration of the tumor in organs and tissues, followed by the growth of the secondary node.

Table 2. – The distribution of patients depending on the relationship of the ultrasound picture of the tumor and the probability of generalization

| Ultrasound picture | Main group n=32 | Control group n=63 | Total n=95 $\chi^2$/p |
|---|---|---|---|
| Heterogeneity | 22*(25.1)** | 26(22.9) | – 0.801; $p < 0.05$ |
| Posterior shadowing | 18(15.2) | 11(13.8) | – 1.08; $p < 0.05$ |
| Hyperechoic ring | 15(14.7) | 13(13.3) | – 0.01; $p > 0.05$ |

*Note: * Actual result, ** In quote, Expected result*

The complex of compulsory studies of patients with suspected breast cancer includes ultrasound examination. Ultrasound examination was carried out according to standard methods. With ultrasound, heterogeneity

(RR = –10.688, p < 0.050), posterior shadowing (RR = –6.354, p < 0.050), hyperechoic ring (RR = –7.389, p < 0.050) had a major equity in patients with an unfavorable outcome of the disease. In the statistical processing of these characteristics, the correlation coefficient for the third degree of freedom was 0.9678, which is a highly reliable result (r = 0.01). The most significant ultrasound sign associated with an unfavorable outcome was the rear blackout.

Breast cancer is a heterogeneous disease, including malignant neoplasms of the breast with a different clinical course, response to treatment and prognosis.

It is interesting to note that the prognosis of a tumor with the same traditional histological characteristics, as well as in patients with the same stage of the disease, varies widely.

One of the most pressing and complex problems of modern oncology is the problem of individual forecasting.

In a generalized form, the purpose of forecasting in medicine, in particular in oncology, is to predict the nature of the course of pathological processes both at the stages of treatment and later in the course of its progression. The final results of predicting the nature of the course, outcomes and complications of any of the considered nosological forms directly depend on the competent choice of reliable diagnostic features that most fully reflect the clinical, functional, morphological, social and many other features of the pathological process.

According to Cil T. et al., high breast density on mammograms is associated with a high risk of relapse after radical surgery [1]. In addition, an association was found between breast density and tumor pathomorphism after neoadjuvant chemotherapy. The lower the density of the breast, the higher the probability of a pathologically complete response and the survival of patients. According to numerous studies, dense mammary gland refers to a biologically inferior phenotype, in which breast cancer is aggressive.

According to Tot T., Tabar L. et al., mortality from breast cancer is higher in patients with mammograms of which there were cast-type microcalcifications compared with patients without them [3].

**Conclusion**

1. From mammographic signs, worm-like, treelike microcalcifications, star-shaped tumors were mainly found in patients with an unfavorable outcome of the disease.

2. Tumor heterogeneity with ultrasound diagnosis, posterior darkening, hyperechoic ring and hypoechoic ring around the tumor are also considered to be unfavorable signs and are more common in patients with early tumor progression.

3. Thus, in our work, it has been shown that the nature of the correlation relationship between mammographic and ultrasound characteristics of a tumor reflects its biological potency and indicates its ability for early progression.

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## HYPOTHERMIA IN COMPLICATIONS OF CARDIOVASCULAR DISEASES

**Abstract.** This report focuses on cardioprotection and describes the advantages and disadvantages of various methods of inducing therapeutic hypothermia (TH) with regard to neuroprotection and cardioprotection for patients with cardiac arrest and ST-segment elevation myocardial infarction (STEMI). TH is recommended in cardiac arrest guidelines. For patients resuscitated after out-of-hospital cardiac arrest, improvements in survival and neurologic outcomes were observed with relatively slow induction of TH. More rapid induction of TH in patients with cardiac arrest might have a mild to modest incremental impact on neurologic outcomes. TH drastically reduces infarct size in animal models, but achievement of target temperature before reperfusion is essential. Rapid initiation of TH in patients with STEMI is challenging but attainable and marked infarct size reductions are possible. To induce TH, a variety of devices have recently been developed that require additional study. Of particular interest is transcoronary induction of TH using a catheter or wire lumen, which enables hypothermic reperfusion in the absence of total-body hypothermia. At present, the main methods of inducing and maintaining TH are surface cooling, endovascular heat exchange catheters, and intravenous infusion of cold fluids. Surface cooling or endovascular catheters may be sufficient for induction of TH in patients resuscitated after out-of hospital cardiac arrest. For patients with STEMI, intravenous infusion of cold fluids achieves target temperature very rapidly but might worsen left ventricular function. More widespread use of TH would improve survival and quality of life for patients with out-ofhospital cardiac arrest; larger studies with more rapid induction of TH are needed in the STEMI population.

**Keywords:** Hypothermia; Circulatory cardiac arrest, Myocardial infarction; Myocardial protection; Ischemia-reperfusion injury.

The effectiveness of achieving low-grade hypothermia (HT), which is defined as a decrease in body temperature to 32–35 °C, was evaluated in many experimental models of brain damage, in particular, in ischemic and hemorrhagic stroke, spinal cord injury, hepatic encephalopathy, traumatic brain injury and hypoxic ischemic encephalopathy of newborns. In turn, the results of randomized control trial (RCT) including patients, who have circulatory cardiac arrest (CCA)

[5; 42], as well as newborns with ischemic hypoxic encephalopathy [3; 60], may indicate the possibility of using HT in clinical practice. Given the data on the possible protective effect of HT on the myocardium, it is believed that the role of HT may not be limited to the protective effect on the nervous system in the development of coma after CCA in patients hospitalized for acute myocardial infarction (MI).

Experimental and clinical data confirmed the protective effect of HT on the nervous system. The mechanisms responsible for the positive effects of HT are multifactorial and include a decrease in glucose metabolism in the brain and oxygen consumption [14; 24], as well as a decrease in the severity of factors such as accumulation of excitotoxic neurotransmitters, development of intracellular acidosis, calcium intake into cells and the formation of free oxygen radicals [36; 54], a change in the expression of "cold shock proteins" [5; 54]. In addition, HT leads to a decrease in the severity of cerebral edema [10; 32], minimizing the risk of thrombosis, as well as reducing the risk of epileptic activity due to increased electrical stability [54].

In the course of several preclinical studies, such positive effects of HT as a reduction in the MI zone were noted; and the most pronounced advantages of HT were revealed with cooling of the heart to the development of reperfusion, which suggests a connection between the degree of viable myocardial preservation and the temperature of the myocardium at the time of reperfusion [60]. Despite the fact that the mechanisms by which HT enhances myocardial protection have not been studied to the same extent as the mechanisms of its protective effect on the brain, suggest a number of explanations for this effect of HT on the myocardium. These include reducing the metabolic needs of the myocardium, which is at risk of damage [46], increasing the integrity of cell membranes by maintaining adenosine triphosphate [8; 46], increasing the stability of mitochondrial membranes [11; 45] and improving blood flow in the vessels of the microcirculatory bed [20; 26; 52].

After receiving the results of observational studies that suggested that the use of HT had a positive effect on the survival of patients who underwent CCA [53], during the implementation of 2 RCTs, data on the efficacy of using HT in such a clinical situation were confirmed [5; 42]. The results of the first study [42] indicated a link between the use of HT and the improvement of neurological outcomes and survival within 6 months after the CCA due to ventricular fibrillation (VF) or ventricular tachycardia in the absence of a pulse. During the second RCT [5], the use of HT initiated in an ambulance was also accompanied by an improvement in neurological outcomes compared with the absence of such intervention. The results of a meta-analysis performed later to assess the effectiveness of HT use indicated that the number of patients needed to treat for discharge from hospital with improvement of neurologic symptoms was 6 at 95% confidence interval from 4 to 13 (ie, to improve the neurological symptoms 1 patient who underwent CCA, HT should be used in 6 patients) [28]. Experts from the International Committee for the Links of Reanimation Specialists recommend, on the basis of the results of such studies, the use of HT (with the maintenance of body temperature in the range of 32 to 34 °C for 12–24 hours) in patients unconscious in restoring spontaneous circulation after of the hospital CCA, if FV was initially recorded (class of recommendations II a). Cooling was also recommended to be used in patients who survived after CCA, not due to VF [48; 49]. This tactic of using HT is also included in more modern versions of the reanimation recommendations [27; 47].

The possibility of using HT and its positive effect on neurological outcomes have been confirmed in the course of carrying out numerous observational studies [1; 62]. Presented by M. Holzer et al. [29] The results of a retrospective study that included all comatose patients who survived the CCA developed against any heart rhythm indicated that HT was associated with improved survival and improved neurologic outcomes within 1 month of follow-up. Data from the ERC HACA (European Resuscitation Counc il Hypothermia After Cardiac Arrest), which collected information on 650 patients who were comatose after an CCA developed against any heart rhythm, also confirmed the view that the use of HT leads to increasing survival at the time of hospital discharge and improving neurological outcomes [2]. Similar results confirming the clinical effectiveness of HT use were obtained in the analysis of the Hypothermia Network Registry registry database, which included data on all 986 patients who underwent CCA at any heart rhythm [44].

The results of experimental animal studies suggested a positive effect of HT in cardiogenic shock due to influence on the processes of inflammation, apoptosis and remodeling [21; 41]. Despite the fact that in a person the shock that develops after CCA belongs to quite frequent complications, such patients were not included in RCTs, and the interpretation of the results of observational studies is difficult due to the great variability of the applied shock criteria, as well as the lack of reports on these studies of data on the impact of HT on the incidence of adverse clinical outcomes in these patients. In the course of 2 retrospective studies involving patients hospitalized with shock, which developed after resuscitation, the use of HT did not adversely affect the clinical outcomes studied [30; 61].

The results of several on observational studies indicated the possibility of combined use of HT and immediate coronary angiography both in combination with percutaneous coronary artery intervention and in its absence, and that such combined use of these interventions can improve clini-

cal outcomes in patients successfully resuscitated after CCA, developed against a background of acute myocardial infarction with ST segment elevation (AMI-ST) [33; 56; 63; 64]. In the course of one of the earliest studies evaluating the effectiveness of the combined use of such interventions [63] improvement in neurological outcomes and survival at the time of discharge following the introduction into clinical practice of a standardized protocol for the treatment of patients who underwent resuscitation, which included HT.

The results of experimental animal studies using the MI model suggested that the use of HT may be effective in reducing the size of MI [12; 25]. In several studies in humans, the effects of HT as a method of reducing myocardial damage in patients with AMI-ST have been studied [13; 20]. Based on data on the possibility of using HT, which were obtained by S. R. Dixon et al. [13], studies of COOL–MI (Cooling as an Adjunctive Therapy to Percutaneous Intervention in Patients with Acute Myocardial Infarction) [22] and ICE-IT (Intravascular Cooling Adjunctive to Percutaneous Coronary Intervention) [50] were performed. Their results were to answer the question of whether the use of HT leads to a decrease in the size of myocardial infarction estimated with a single-photon emission computed tomography 30 days after the development of AMI-ST. However, these studies failed to identify the benefits of using HT to reduce the size of myocardial infarction. Nevertheless, it should be noted that in a subgroup of patients with AMI-ST who had an internal body temperature of less than 35 °C, there was a favorable tendency to decrease the size of myocardial infarction. Moreover, the results of the analysis in the subgroups of patients included in the ERC HACA study [34] indicated the absence of a statistically significant effect of the use of HT on blood concentration of creatine phosphokinase and its CF fraction, as well as electrocardiographic parameters. It should be noted, however, that in a subgroup of patients with a shorter duration of the period before reaching the target temperature (8 hours or less), a statistically significant decrease in the concentration of creatine phosphokinase and its CF fraction was observed. Perhaps the earlier onset of cooling, rather than its duration, may be a key factor in reducing the size of MI [12; 25]. The results of experimental and clinical studies suggest that in addition to early cooling, the optimal protective effect of HT can be achieved by achieving an internal body temperature of less than 35 °C [12; 19]. Additional confirmation of this hypothesis was obtained by M. Gotberg et al. [20]. The results of their study showed that in patients who perform primary PCI for AMI-ST, achieving internal body temperature of less than 35 °C can be achieved without increasing the period between the development of clinical manifestations of myocardial infarction and the time to inflation of the balloon, but also is accompanied by a 38% decrease in the size of myocardial infarction according to the evaluation using magnetic resonance imaging (MRI). Despite the relatively small number of patients included in this study, this was the first study, during which data were obtained on the benefits of using HT in this category of patients. The achievement of internal body temperature of less than 35 °C and the use of MRI, which is now considered a "gold standard" for measuring the size of MI [6; 7], can be suggested in As an explanation of the effectiveness of HT in this study. In contrast to single-photon emission computed tomography, which was used in most of the studies mentioned above, the benefits of MRI include information on not only geometric characteristics such as the volume of the ventricles, but also violations of local contractility and left ventricular function, and its remodeling. However, despite such encouraging results, the optimal method and timing for the use of HT in patients with AMI-ST should be studied during RCT with sufficient statistical power.

Until the results of such studies are obtained, the utility of HT may be considered conjectural and this intervention cannot be recommended as a standard tactic for treating such patients in conditions of actual clinical practice. Currently available cooling methods have mainly been developed for use in patients who are in a coma after CCA; detailed descriptions of such methods are presented in the relevant publications [9; 57]. There is evidence that infusion of cold solutions can be an effective method of cooling patients, especially during the introductory phase, given the availability of its use in the prehospital stage. Several protocols have been proposed, for example infusion of cold solution 0.9% ice solution (4 °C) sodium chloride with lactate 30 ml per 1 kg body weight for 30 min [57] or 500–2000 ml 0.9% chloride solution sodium, cooled to 4 °C, as soon as possible after the completion of Reanimation [4]. The use of external cooling refers to inexpensive, easy-to-use methods that are achieved by placing ice packs in the groin, trunk, axillary and neck and / or applying moistened in ice water towels and the use of fans. The use of such methods can be taken into account both during the introductory and supporting phases in intensive care units, but their drawbacks include the inability to regulate the rate of warming of the patient, as well as the need for careful monitoring and experience to prevent hypothermia [55]. Currently, several cooling devices are sold, including cooling mattresses filled with circulating air or water, blankets for cooling and special clothes with a device cooling its surface [40]. Methods of intravascular cooling include the installation of a cooling catheter, which is usually inserted transdermally into the lower vena cava and connected to a cooling system that automatically maintains the desired temperature. Such a system absorbs heat directly from the so-called core of the body and

its functioning does not depend on vasoconstrictor reactions of the skin that participate in thermoregulation [39]. This allows the use of such devices to quickly and accurately set the desired body temperature, and also maintains a stable temperature after the intervention starts and allows for effective observation of the temperature regime during the warming phase [16; 17; 59]. These new methods include rinsing the stomach with ice salt solution [18], using a cooling helmet [23], a system for general immersion cooling with cold water [15], as well as cooling devices introduced through the nose [31], the use of which allows you to quickly reduce the internal temperature of the body to 34 °C. The possibility of using more modern methods of cooling is taken into account in the implementation of the study CHILL–MI (Efficacy of Endovascular Catheter Cooling Combined With Cold Saline for the Treatment of Acute Myocardial Infarction), which is funded by Philips Innercool. The use of HT can be divided into 3 phases: introductory, supporting and warming phase. Use of HT is accompanied by a change in a number of physiological parameters and the possibility of complications development [40; 54]. Trembling refers to natural physiological responses to HT and can hamper HT during both the introductory and maintenance phases due to heat generation, as well as increased oxygen consumption of tissues and their metabolic needs [38]. In addition to the narrowing of the peripheral vessels, tremor appears to be the "last resort" that the body uses to counteract a decrease in internal body temperature of less than 35.5 °C. The use of several therapeutic interventions aimed at counteracting such a reaction of the organism is suggested [39]. In patients reanimated after CCA, a combination of benzodiazepines is widely used to achieve a sedative effect, as well as opioid analgesics and drugs that cause systemic blockade of neuromuscular conduction to achieve muscle relaxation [5]. In contrast, the combined use of meperidine (both in combination with buspirone and in its absence) and skin warming to reduce the threshold temperature at which the trembling develops, as well as the prevention of discomfort associated with HT, has become a standard approach in the treatment of conscience patients [13; 37; 50].

The effect of HT on the cardiovascular system is complex [40; 54]. After completion of the introductory phase, HT may be accompanied by the development of bradycardia and an increase in the contractility of the myocardium [35; 40]. Such a decrease in the heart rate may, in turn, lead to a decrease in the minute volume of the heart, which, however, is not sufficiently pronounced to lead to hemodynamic disturbances [40; 54].

Despite the fact that during the RCT, the use of HT was not accompanied by the development of arrhythmias, and the stable arrhythmias developing during the observational studies could be the result of excessive cooling (with a decrease in the internal temperature of the body to 32 °C or less), an electrolyte balance disorder and dysfunction tubules [54]. Although the use of HT may lead to an increase in the incidence of infectious complications due to a disorder of cellular and humoral immunity caused by HT [58], the results of clinical studies do not give an unambiguous answer to the question of whether the hypothetical risk of developing such complications is clinically important. The results of several studies indicated an increase in this risk [29; 64], while in other studies such data were not confirmed [43; 51; 63]. The use of HT may lead to an increased risk of bleeding due to impaired platelet function, thrombocytopenia, and clotting system disorders [40]. It should, however, be noted that an increase in this risk was not observed in clinical practice, both in the isolated use of HT and in the use of HT in combination with PCI.

Thus, based on the available evidence and in accordance with current clinical guidelines, the possibility of using HT as a standard treatment for patients who undergo CCA, regardless of the baseline heart rate, should be considered. At the same time, many questions remain, the answers to which have not yet been received. In particular, the question of the optimal duration of HT, the depth of cooling, as well as the speed of warming, the best method of cooling and the cost-effectiveness of the intervention. At present, there are no convincing data that could serve as a basis for recommendations on the use of HT in clinical practice in the treatment of patients hospitalized for acute myocardial infarction if its development was not accompanied by CCA.

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# HYPOTHERMIA IN COMPLICATIONS OF CARDIOVASCULAR DISEASES

**Abstract.** This report focuses on cardioprotection and describes the advantages and disadvantages of various methods of inducing therapeutic hypothermia (TH) with regard to neuroprotection and cardioprotection for patients with cardiac arrest and ST-segment elevation myocardial infarction (STEMI). TH is recommended in cardiac arrest guidelines. For patients resuscitated after out-of-hospital cardiac arrest, improvements in survival and neurologic outcomes were observed with relatively slow induction of TH. More rapid induction of TH in patients with cardiac arrest might have a mild to modest incremental impact on neurologic outcomes. TH drastically reduces infarct size in animal models, but achievement of target temperature before reperfusion is essential. Rapid initiation of TH in patients with STEMI is challenging but attainable and marked infarct size reductions are possible. To induce TH, a variety of devices have recently been developed that require additional study. Of particular interest is transcoronary induction of TH using a catheter or wire lumen, which enables hypothermic reperfusion in the absence of total-body hypothermia. At present, the main methods of inducing and maintaining TH are surface cooling, endovascular heat exchange catheters, and intravenous infusion of cold fluids. Surface cooling or endovascular catheters may be sufficient for induction of TH in patients resuscitated after out-of hospital cardiac arrest. For patients with STEMI, intravenous infusion of cold fluids achieves target temperature very rapidly but might worsen left ventricular function. More widespread use of TH would improve survival and quality of life for patients with out-ofhospital cardiac arrest; larger studies with more rapid induction of TH are needed in the STEMI population.

**Keywords:** Hypothermia; Circulatory cardiac arrest, Myocardial infarction; Myocardial protection; Ischemia-reperfusion injury.

The effectiveness of achieving low-grade hypothermia (HT), which is defined as a decrease in body temperature to 32–35 °C, was evaluated in many experimental models of brain damage, in particular, in ischemic and hemorrhagic stroke, spinal cord injury, hepatic encephalopathy, traumatic brain injury and hypoxic ischemic encephalopathy of newborns. In turn, the results of randomized control trial (RCT) including patients, who have circulatory cardiac arrest (CCA)

[5; 42], as well as newborns with ischemic hypoxic encephalopathy [3; 60], may indicate the possibility of using HT in clinical practice. Given the data on the possible protective effect of HT on the myocardium, it is believed that the role of HT may not be limited to the protective effect on the nervous system in the development of coma after CCA in patients hospitalized for acute myocardial infarction (MI).

Experimental and clinical data confirmed the protective effect of HT on the nervous system. The mechanisms responsible for the positive effects of HT are multifactorial and include a decrease in glucose metabolism in the brain and oxygen consumption [14; 24], as well as a decrease in the severity of factors such as accumulation of excitotoxic neurotransmitters, development of intracellular acidosis, calcium intake into cells and the formation of free oxygen radicals [36; 54], a change in the expression of "cold shock proteins" [5; 54]. In addition, HT leads to a decrease in the severity of cerebral edema [10; 32], minimizing the risk of thrombosis, as well as reducing the risk of epileptic activity due to increased electrical stability [54].

In the course of several preclinical studies, such positive effects of HT as a reduction in the MI zone were noted; and the most pronounced advantages of HT were revealed with cooling of the heart to the development of reperfusion, which suggests a connection between the degree of viable myocardial preservation and the temperature of the myocardium at the time of reperfusion [60]. Despite the fact that the mechanisms by which HT enhances myocardial protection have not been studied to the same extent as the mechanisms of its protective effect on the brain, suggest a number of explanations for this effect of HT on the myocardium. These include reducing the metabolic needs of the myocardium, which is at risk of damage [46], increasing the integrity of cell membranes by maintaining adenosine triphosphate [8; 46], increasing the stability of mitochondrial membranes [11; 45] and improving blood flow in the vessels of the microcirculatory bed [20; 26; 52].

After receiving the results of observational studies that suggested that the use of HT had a positive effect on the survival of patients who underwent CCA [53], during the implementation of 2 RCTs, data on the efficacy of using HT in such a clinical situation were confirmed [5; 42]. The results of the first study [42] indicated a link between the use of HT and the improvement of neurological outcomes and survival within 6 months after the CCA due to ventricular fibrillation (VF) or ventricular tachycardia in the absence of a pulse. During the second RCT [5], the use of HT initiated in an ambulance was also accompanied by an improvement in neurological outcomes compared with the absence of such intervention. The results of a meta-analysis performed later to assess the effectiveness of HT use indicated that the number of patients needed to treat for discharge from hospital with improvement of neurologic symptoms was 6 at 95% confidence interval from 4 to 13 (ie, to improve the neurological symptoms 1 patient who underwent CCA, HT should be used in 6 patients) [28]. Experts from the International Committee for the Links of Reanimation Specialists recommend, on the basis of the results of such studies, the use of HT (with the maintenance of body temperature in the range of 32 to 34 °C for 12–24 hours) in patients unconscious in restoring spontaneous circulation after of the hospital CCA, if FV was initially recorded (class of recommendations II a). Cooling was also recommended to be used in patients who survived after CCA, not due to VF. [48; 49]. This tactic of using HT is also included in more modern versions of the reanimation recommendations [27; 47].

The possibility of using HT and its positive effect on neurological outcomes have been confirmed in the course of carrying out numerous observational studies [1; 62]. Presented by M. Holzer et al. [29]. The results of a retrospective study that included all comatose patients who survived the CCA developed against any heart rhythm indicated that HT was associated with improved survival and improved neurologic outcomes within 1 month of follow-up. Data from the ERC HACA (European Resuscitation Counc il Hypothermia After Cardiac Arrest), which collected information on 650 patients who were comatose after an CCA developed against any heart rhythm, also confirmed the view that the use of HT leads to increasing survival at the time of hospital discharge and improving neurological outcomes [2]. Similar results confirming the clinical effectiveness of HT use were obtained in the analysis of the Hypothermia Network Registry registry database, which included data on all 986 patients who underwent CCA at any heart rhythm [44].

The results of experimental animal studies suggested a positive effect of HT in cardiogenic shock due to influence on the processes of inflammation, apoptosis and remodeling [21; 41]. Despite the fact that in a person the shock that develops after CCA belongs to quite frequent complications, such patients were not included in RCTs, and the interpretation of the results of observational studies is difficult due to the great variability of the applied shock criteria, as well as the lack of reports on these studies of data on the impact of HT on the incidence of adverse clinical outcomes in these patients. In the course of 2 retrospective studies involving patients hospitalized with shock, which developed after resuscitation, the use of HT did not adversely affect the clinical outcomes studied [30; 61].

The results of several on observational studies indicated the possibility of combined use of HT and immediate coronary angiography both in combination with percutaneous coronary artery intervention and in its absence, and that such combined use of these interventions can improve clinical

outcomes in patients successfully resuscitated after CCA, developed against a background of acute myocardial infarction with ST segment elevation (AMI-ST) [33; 56; 63; 64]. In the course of one of the earliest studies evaluating the effectiveness of the combined use of such interventions [63] improvement in neurological outcomes and survival at the time of discharge following the introduction into clinical practice of a standardized protocol for the treatment of patients who underwent resuscitation, which included HT.

The results of experimental animal studies using the MI model suggested that the use of HT may be effective in reducing the size of MI [12; 25]. In several studies in humans, the effects of HT as a method of reducing myocardial damage in patients with AMI-ST have been studied [13; 20]. Based on data on the possibility of using HT, which were obtained by S. R. Dixon et al. [13], studies of COOL-MI (Cooling as an Adjunctive Therapy to Percutaneous Intervention in Patients with Acute Myocardial Infarction) [22] and ICE-IT (Intravascular Cooling Adjunctive to Percutaneous Coronary Intervention) [50] were performed. Their results were to answer the question of whether the use of HT leads to a decrease in the size of myocardial infarction estimated with a single-photon emission computed tomography 30 days after the development of AMI-ST. However, these studies failed to identify the benefits of using HT to reduce the size of myocardial infarction. Nevertheless, it should be noted that in a subgroup of patients with AMI-ST who had an internal body temperature of less than 35 °C, there was a favorable tendency to decrease the size of myocardial infarction. Moreover, the results of the analysis in the subgroups of patients included in the ERC HACA study [34] indicated the absence of a statistically significant effect of the use of HT on blood concentration of creatine phosphokinase and its CF fraction, as well as electrocardiographic parameters. It should be noted, however, that in a subgroup of patients with a shorter duration of the period before reaching the target temperature (8 hours or less), a statistically significant decrease in the concentration of creatine phosphokinase and its CF fraction was observed. Perhaps the earlier onset of cooling, rather than its duration, may be a key factor in reducing the size of MI [12; 25]. The results of experimental and clinical studies suggest that in addition to early cooling, the optimal protective effect of HT can be achieved by achieving an internal body temperature of less than 35 °C [12; 19]. Additional confirmation of this hypothesis was obtained by M. Gotberg et al. [20]. The results of their study showed that in patients who perform primary PCI for AMI-ST, achieving internal body temperature of less than 35 °C can be achieved without increasing the period between the development of clinical manifestations of myocardial infarction and the time to inflation of the balloon, but also is accompanied by a 38% decrease in the size of myocardial infarction according to the evaluation using magnetic resonance imaging (MRI). Despite the relatively small number of patients included in this study, this was the first study, during which data were obtained on the benefits of using HT in this category of patients. The achievement of internal body temperature of less than 35 °C and the use of MRI, which is now considered a "gold standard" for measuring the size of MI [6; 7], can be suggested in As an explanation of the effectiveness of HT in this study. In contrast to single-photon emission computed tomography, which was used in most of the studies mentioned above, the benefits of MRI include information on not only geometric characteristics such as the volume of the ventricles, but also violations of local contractility and left ventricular function, and its remodeling. However, despite such encouraging results, the optimal method and timing for the use of HT in patients with AMI-ST should be studied during RCT with sufficient statistical power.

Until the results of such studies are obtained, the utility of HT may be considered conjectural and this intervention cannot be recommended as a standard tactic for treating such patients in conditions of actual clinical practice. Currently available cooling methods have mainly been developed for use in patients who are in a coma after CCA; detailed descriptions of such methods are presented in the relevant publications [9; 57]. There is evidence that infusion of cold solutions can be an effective method of cooling patients, especially during the introductory phase, given the availability of its use in the prehospital stage. Several protocols have been proposed, for example infusion of cold solution 0.9% ice solution (4 °C) sodium chloride with lactate 30 ml per 1 kg body weight for 30 min [57] or 500–2000 ml 0.9% chloride solution sodium, cooled to 4 °C, as soon as possible after the completion of Reanimation [4]. The use of external cooling refers to inexpensive, easy-to-use methods that are achieved by placing ice packs in the groin, trunk, axillary and neck and / or applying moistened in ice water towels and the use of fans. The use of such methods can be taken into account both during the introductory and supporting phases in intensive care units, but their drawbacks include the inability to regulate the rate of warming of the patient, as well as the need for careful monitoring and experience to prevent hypothermia [55]. Currently, several cooling devices are sold, including cooling mattresses filled with circulating air or water, blankets for cooling and special clothes with a device cooling its surface [40]. Methods of intravascular cooling include the installation of a cooling catheter, which is usually inserted transdermally into the lower vena cava and connected to a cooling system that automatically maintains the desired temperature. Such a system absorbs heat directly from the so-called core of the body and

its functioning does not depend on vasoconstrictor reactions of the skin that participate in thermoregulation [39]. This allows the use of such devices to quickly and accurately set the desired body temperature, and also maintains a stable temperature after the intervention starts and allows for effective observation of the temperature regime during the warming phase [16; 17; 59]. These new methods include rinsing the stomach with ice salt solution [18], using a cooling helmet [23], a system for general immersion cooling with cold water [15], as well as cooling devices introduced through the nose [31], the use of which allows you to quickly reduce the internal temperature of the body to 34 °C. The possibility of using more modern methods of cooling is taken into account in the implementation of the study CHILL–MI (Efficacy of Endovascular Catheter Cooling Combined With Cold Saline for the Treatment of Acute Myocardial Infarction), which is funded by Philips Innercool. The use of HT can be divided into 3 phases: introductory, supporting and warming phase. Use of HT is accompanied by a change in a number of physiological parameters and the possibility of complications development [40; 54]. Trembling refers to natural physiological responses to HT and can hamper HT during both the introductory and maintenance phases due to heat generation, as well as increased oxygen consumption of tissues and their metabolic needs [38]. In addition to the narrowing of the peripheral vessels, tremor appears to be the "last resort" that the body uses to counteract a decrease in internal body temperature of less than 35.5 °C. The use of several therapeutic interventions aimed at counteracting such a reaction of the organism is suggested [39]. In patients reanimated after CCA, a combination of benzodiazepines is widely used to achieve a sedative effect, as well as opioid analgesics and drugs that cause systemic blockade of neuromuscular conduction to achieve muscle relaxation [5]. In contrast, the combined use of meperidine (both in combination with buspirone and in its absence) and skin warming to reduce the threshold temperature at which the trembling develops, as well as the prevention of discomfort associated with HT, has become a standard approach in the treatment of conscience patients [13; 37; 50].

The effect of HT on the cardiovascular system is complex [40; 54]. After completion of the introductory phase, HT may be accompanied by the development of bradycardia and an increase in the contractility of the myocardium [35; 40]. Such a decrease in the heart rate may, in turn, lead to a decrease in the minute volume of the heart, which, however, is not sufficiently pronounced to lead to hemodynamic disturbances [40; 54].

Despite the fact that during the RCT, the use of HT was not accompanied by the development of arrhythmias, and the stable arrhythmias developing during the observational studies could be the result of excessive cooling (with a decrease in the internal temperature of the body to 32 °C or less), an electrolyte balance disorder and dysfunction tubules [54]. Although the use of HT may lead to an increase in the incidence of infectious complications due to a disorder of cellular and humoral immunity caused by HT [58], the results of clinical studies do not give an unambiguous answer to the question of whether the hypothetical risk of developing such complications is clinically important. The results of several studies indicated an increase in this risk [29; 64], while in other studies such data were not confirmed [43; 51; 63]. The use of HT may lead to an increased risk of bleeding due to impaired platelet function, thrombocytopenia, and clotting system disorders [40]. It should, however, be noted that an increase in this risk was not observed in clinical practice, both in the isolated use of HT and in the use of HT in combination with PCI.

Thus, based on the available evidence and in accordance with current clinical guidelines, the possibility of using HT as a standard treatment for patients who undergo CCA, regardless of the baseline heart rate, should be considered. At the same time, many questions remain, the answers to which have not yet been received. In particular, the question of the optimal duration of HT, the depth of cooling, as well as the speed of warming, the best method of cooling and the cost-effectiveness of the intervention. At present, there are no convincing data that could serve as a basis for recommendations on the use of HT in clinical practice in the treatment of patients hospitalized for acute myocardial infarction if its development was not accompanied by CCA.

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# MORPHOLOGICAL CHARACTERISTICS OF BONE TISSUE WITH EXPERIMENTAL OSTEOPOROSIS AND ITS TREATMENT

**Abstract.** As the average life expectancy in the world increases and the proportion of the elderly and elderly people increases, the incidence of osteoporosis (OP) also increases [10]. One of the factors affecting the pharmacodynamic and pharmacokinetic parameters of calcium preparations used in OP can be the peculiarities of metabolic activity and hormonal background [6]. As is well known, the use of substances containing calcium of natural origin can have a positive effect on the hormonal levels of experimental animals, as well as on the absorption of calcium, which, as is well known, depends on the state of the gastrointestinal tract (GIT) [5]. When OP is observed a change in the qualitative structure of bone tissue, which is associated with a decrease in bone mass and mechanical failure. As it is known, estrogen deficiency is one of the main causes of accelerated bone loss and the development of OP. In this regard, the development of OP is typical for women in the postmenopausal period, as well as with hyperprolactinemia, hypogonadism, after removal of the ovaries and with the development of amenorrhea caused by hypoestrogenia [8].

**Keywords:**

**Purpose of the study**. To study the morphofunctional changes in the structure of bone tissue in rats using organic calcium compounds in the treatment of experimental osteoporosis (OP).

**Materials and methods.** The experiments were performed on 100 white outbred rats weighing 170–220 g in which a model of experimental OP was reproduced by the generally accepted method of ovariectomy. Experimental animals removed the ovaries and after 2 months made the study. The animals were kept in the Vivarium of the Tashkent Pharmaceutical Institute with free access to food and water. The research work was carried out in accordance with the European Convention for the Protection of Vertebrate Animals used for experiments or for other scientific purposes (Strasbourg, March 18, 1986). In carrying out research, the basic ethical principles of animal welfare and the main provisions of the Helsinki Declaration were observed [1, 10]. At the end of the experiment, animals were killed under light ether anesthesia. The animals were divided into equal groups: Group I – before reproduction of the experimental OP (intact), Group II (control) – animals with experimental OP without treatment, Group III (comparison) – with experimental OP after calcium chloride administration and Group IV (main, experienced) – with experimental OP after the introduction of calcium alginate.

Confirmation of the presence of osteoporotic changes in bone tissue was performed by morphological examination of sections of the skeleton bones using the method of preparing bone tissue preparations and their microscopy according to the standard technique [3]. For histological examination, bone tissue pieces were placed in a 4% neutral formalin solution, then decalcification was carried out in 15% nitric acid and then fixed in alcohols. After sufficient fixation, paraffin blocks were prepared from the materials. The finished sections were stained with hematoxylin and eosin.

**Results and discussion.** As shown by morphological studies of bones in rats in group II (control) – animals with experimental OP without treatment, in samples of the epiphyseal part of the tibial bone taken after ovariectomy, bone resorption, areas of rarefaction due to leaching of calcium salts and porosity, softening of bone tissue with

the presence of primitive poorly identified bone beams (Fig. 1), which corresponds to the data of the authors [6; 7]. At the same time, the processes of bone tissue resorption, foci of lysis, osteomalacia in the central areas are noted. In microscopy, it is necessary to note the predominance of uniform elements and poorly identified primitive bone beams [2].

The introduction of calcium alginate in group IV led to the restoration of bone structure (Fig. 2), as evidenced by the absence of obvious morphological signs of OP. Thus, in group IV, the growth of osteogenic fibrous tissue was noted, followed by compaction of compact bone tissue with repair sites, disappearance of porosity and osteomalacia due to saturation of calcium salts during therapy with calcium alginate (Fig. 2).

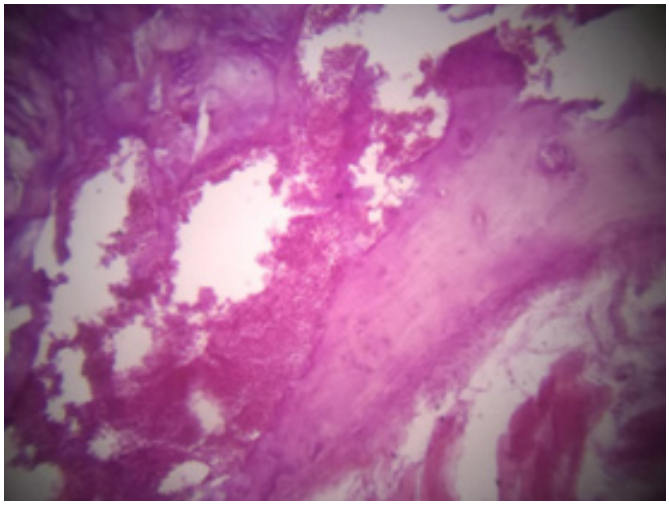

Figure 1. Group II (control) – animals with experimental OP without treatment. Bone tissue resorption, foci of lysis and osteomalacia, poorly identified bone marrow in areas of destruction are noted. Color: hematoxylin and eosin. H. about 10.0

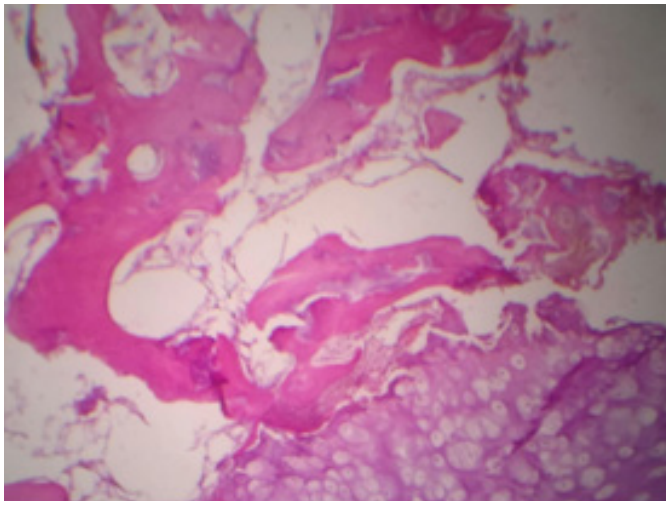

Figure 2. Group IV (basic, experimental) – with experimental OP after the introduction of calcium alginate. Cartilage plate layers and fragments of dense bone tissue with areas of growth of the osteogenic fibrous structure (left section). Color: hematoxylin and eosin. H. about 10.0

Lots of compact bone tissue lack porosity and have a uniform color. The growth of fibrous connective bone tissue is one of the main indicators of the intensity of recovery processes. Also, there are seals of bone beams, providing bone strength characteristics, which indicates the effectiveness of therapy with the use of calcium alginate. All this testifies to the positive effect of calcium alginate therapy on bone structure, which is confirmed by the proliferation of osteogenic connective tissue, the basis of the future bone.

Thus, in the treatment of experimental OP with calcium alginate, areas of bone marrow consolidation were observed, which may be the result of calcium deficiency replenishment, and foci of osteogenic fibrous connective tissue are observed, which indicates osteogenic recovery processes [7]. At the same time, fragments of dense bone tissue and layers of cartilaginous plates alternate with areas of growth of the osteogenic fibrous structure, which indicates regenerative processes in the bone that occur during the treatment with calcium alginate.

**Conclusion.**

During the treatment of experimental OP with calcium alginate, there is an improvement in the basic morphostructural parameters of bone tissue, which are determined in the Open Field test.

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# DEVELOPED METHODS OF SURGICAL TREATMENT OF POST-BRAIN DEFECTS OF SOFT AND BONE TISSUES OF THE CRANIAL VAULT

**Abstract.** This article is devoted to the introduction into clinical practice of the conventional method of surgical treatment of patients with cicatricial defects and deformities of the soft and bone tissues of the cranial vault. The results of surgical practice were studied in 22 patients. In the long-term period in the main group (n-10) patients, where improved methods of surgical treatment were used, good functional and aesthetic results were observed in 9(90%) patients, satisfactory in 1(10%) patients.

**Keywords:** scar, defect, soft tissue, bone tissue, cranial vault, surgical treatment, combined plastics, flap.

**The urgency of the problem.** Defects of the soft and bone tissues of the cranial vault arise mainly after injures, burns and excision of tumors. Head burns account for about 40% among other sites, and their consequences, due to the opennes of zones and the tendency of scars to pathological growths, put the problem of rehabilitation of these patients in the first place (Gurlek A. et al., 2004). The main ways to solve the problem is the development and introduction of new methods of surgical correction of cicatrical deformations, defects (balloon stretching of tissues, plastic with flaps on the vascular pedicle, microsurgical auto transplantation of tissue complexes) (Azolova V. V. and co-author (2002)).

**Materials and research methods.** The research is based on the results of surgical treatment of 22 patients with post-burn defects and deformities of the soft and bone tissues of the cranial vault area, who were in the ward of the injures of the multidisciplinary medical center of Andijan region from 2010 to 2015 yy.

Of the 22 patients,18(83.9%) had a soft tissue defect with exposure of the bones of the cranial vault, 4 (16.1%) had a defect of soft tissues and bones with exposure of the brain tissue.

In 12 (54.8%) patients, soft tissue defects with exposure of the bones of the cranial vault were eliminated by traditional combined plastics.

**Combined plastics technique:**

Before the operation, the boundaries of excision of the soft tissues defect of the cranial vault, as well as the boundaries of the skin-aponeurotic flap, were marked with a marker. Under general anesthesia, an incision of a skullap defect was dissected within the limits of healthy tissues. In cases of exposure of the bones of the cranial vault in 12 (54.8%) patients, a skin flap was cut out from the unaffected tissues next to the defect. After the rotation of the flap to the defect, the edges of the wound and the flap were sutured with interrupted a-traumatic sutures.

The donor wound was closed with a split autodermal graft, 5 mm thick, taken from the anterolateral thigh. At the edges of the graft and donor wounds, nodal a-traumatic tensile

stitches were also applied with a 'pilot' pressure bandage. The under-patchwork space was drained by vacuum drainage.

In the post-operative period, local hypothermia and antibiotic therapy were prescribed.

Figure 1. Defect of the soft and bone tissues of the cranial vault with the exposure of dura mater. The boundaries of the skin aponeurotic flap are outlined

Figure 2. Pathologically altered tissues dissected, skin aponeurotic flap cut

Figure 3. Defect is closed by a skin aponeurotic flap by rotation. The donor wound is covered with a free split autodermal graft

Figure 4. Post-burn scar alopecia and soft tissue defect with exposure of bone tissue

Figure 5. The same patient has the closest result of plastic surgery of the defect with a skin aponeurotic flap on the leg

**An improved method of combined plastics of soft and bone defects of the cranial vault** was used in 10(45.4%) patients. In cases when the patients had bone defects with exposure of the dura mater and liquorrhea, for vital reasons an urgent operation, using **an improved method of combined plastics.**

**Operation techniques:** Before the operation, using a marker, the boundaries of the skin aponeurotic flap were outlined, respectively, the area and contour of the defect next to it were used to cut out the skin-aponeurotic flap from the unaffected tissues. The end of the flap was taken on the handles. The edges of the bone defect were carefully treated in the traditional way.

According to the size and contour of the defect, a graft was formed from a carbon plate. The latter was fixed to the edges of the bone defect of the cranial vault using prolene threads. After washing the surgical wound with an antiseptic solution (Tsiteal), the latter was closed with a previously formed skin aponeurotic flap. Under the patchwork space drained vacuum

drainage. In 2 (50%) patients, intra-operatively stretched tissues were used to close the donor site.

Figure 6. Defect of the soft tissues of the temporal region with the exposure of the bone tissue. The boundaries of the skin aponeurotic flap and excised pathological tissues are outlined

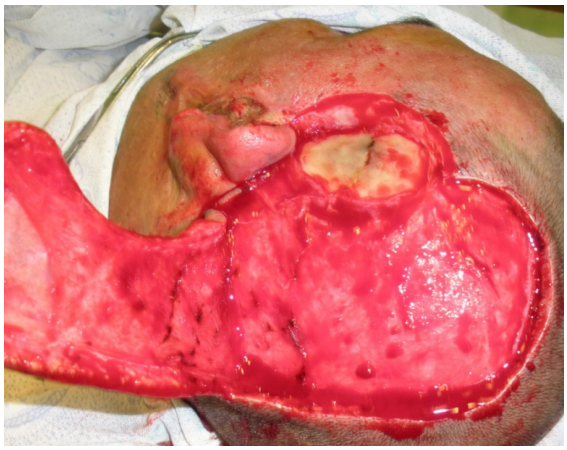

Figure 7. The defect in the temporal region is closed by a skin-aponeurotic flap by rotation, the donor wound is closed by a free full-layer skin bone

Figure 8. post-burn scar alopecia with the exposure of the skull bone

Figure 9. The same patient. The closest result of the plastic repair of the defect is a rotated skin aponeurotic flap. The donor wound is covered with a free full-layer skin flap

**Results:** In the main group of patients (n-10), there was no necrosis of the flap and no cases of suppuration. Subcutaneous hematoma occurred only in 1 (10%) patient. Observations for periods of up to 3 years showed that the thus-closed, long-exposed bone was not sequestered, and no osteomyelitis recurred.

In the control group, necrosis of the distal end of the flap was observed in 1(8.3%) patients after the final plastic surgery. Hair loss along the suture line was found in 1(11.7%)patient. Under-scrap hematoma occurred in 2(16.6%)patients.

In the long-term period in the main group (n-10) patients, where improved methods of surgical methods were used, good functional and aesthetic results were observed in 9(90%) patients, satisfactory in 1(10%) patients.

In the control group, using traditional methods of surgical treatment due to complications, good results were observed in 10(88.2%) patients, satisfactory in 2(11.8%) patients.

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# THE URGENCY OF THE PROBLEM OF EMERGING AND RE-EMERGING VIRAL INFECTIONS, STUDY IN UZBEKISTAN

**Abstract.** Uzbekistan is an area with varied terrain, variety and large number of blood sucking vectors (mosquitoes, ticks, black flies, etc.), and their vertebrate hosts, mammals and birds, which may serve as reservoirs and vectors and viral pathogens of dangerous, new and reemerging viral infections. WNF infection is either asymptomatic (about 80% of infected people) or can lead to the development of West Nile fever or severe West Nile disease. Over the past five years of research on the problem of arbovirus infections in our country, scientists – virologists have identified the circulation of the WNF virus in Uzbekistan; found antibodies to the virus in human serum, identified the virus antigen in mosquitoes, ticks and mites, isolated strains of the WNF virus from birds, and patients with meningitis and meningo-encephalitis. The research Institute of Virology plans to conduct molecular genetic studies of isolated strains in order to establish the genotypes of the pathogen circulating in the country.

**Keywords:** WNF, natural foci, arbovirus infections, carriers, extremely, dangerous infections, morbidity.

Today the world is in the position where the epidemics again spread uncontrollably across the globe, but this time at an unprecedented rate – as a result of the globalization of modern life. Watch and ward is the price of survival in the fight of humans against pathogenic microorganisms [12].

On the threshold of XXI century, the humankind has come to realize the importance of global objectives – security of people's lives. These tasks, in a number of security issues came to the fore among the most important priorities of countries and the international community. The most acute need to address these problems emerged in connection with the threats and challenges that have arisen in the demographic, environmental, political and social spheres of human activity.

Among them – the threat of new and emerging infectious diseases and epidemics, the consequences of which could be catastrophic for humanity. This tragic threat to modern civilization was quite unexpected, since modern medicine, although it assumed the possibility of new infections as a result of the ongoing evolutionary processes and microbial mutations, but not enough reliable assessed the extent of the danger. It seemed that everything will be accomplished with "traditional" dangerous infections that are well studied and largely defeated. The emergence of new infections was considered unlikely, not as dangerous, in any case do not threaten with fatal consequences [6].

The only way to prepare for infectious crises that inevitably occur in the XXI century – is to prepare specialists who are able to identify a new disease, assess the epidemiological situation and to develop preventive measures and new drugs.

According to the World Health Organization (WHO), infectious parasitic diseases caused the death of 16 million out of 51 million people dying each year in the world. Considered problem lies in the fact that, in spite of the modern sanitation capabilities of medical science, and seemingly streamlined health system over the past decade new and still unrevealed, previously unknown dangerous infections began to emerge.

New infections (Emerging Infections, synonym emerging pathogens.) – the common name of infectious diseases that have been identified and classified taxonomically recently. In the last quarter of the twentieth century, more than 30 such infections been identified, many of which can cause dangerous epidemics. Among them HIV, Ebola virus, hantavirus pulmonary syndrome, hemorrhagic fever with renal syndrome and other viral fevers, Campylobacteriosis, transmissible spongiform encephalopathy, Legionnaires' disease, Lyme disease. Some new infections are presented as "new" diseases of people, for example, HIV infection is probably formed as a human disease in the second half of the twentieth century. Other diseases, such as viral hemorrhagic fever, they are existed for centuries and have been discovered only recently due to changes in environmental conditions, which led to an increase in the risk of infection of humans. Remerged infections – it is some "old" diseases such as tuberculosis and syphilis, which its wave comes again after the change of conditions and the host state, agent and environment factors [17].

For the first time in the early 90's XX cen. J. Lederberg et al. (1992) proposed the term defining them as the disease that became known in the past two decades or significance of which may increase in the near future. It is known that by far described only 15% of microbes and 5% of viruses that exist on Earth [12]. It is not surprising that almost every year

identified a new disease and their pathogens. Since many new infections are extremely dangerous, often fatal completed and fraught with epidemics, the problem of dealing with them, along with other serious global problems is a priority at the international and national levels.

By the middle of the XX century it became apparent increase in the role of viruses in human infectious diseases. Of particular relevance got the problem of so-called new types of recurring infections, as Infectious diseases not only has not lost its socio-economic importance, but also requires more attention by national and international health care systems due to the weakening position of medicine in the fight to reduce morbidity and mortality, especially against viral diseases with natural foci.

Among these infections the arbovirus infections – infections transmitted by arthropods occupy a key place. At least 100 of the known natural focal viruses, which include mosquito (mosquito), fever, cause disease in humans. This is an epidemic of dengue fever, O' Nyong-Nyong, equine encephalomyelitis, Japanese, tick-borne and Murray Valley encephalitis, Rift Valley fever, a mosquito, Karelian, West Nile, and others.

Ecological interactions may be complex, a number of factors often interact together or in any sequence one after the other. However, they are the most common of the identified factors that contributes to emerge of one or the other infectious disease [10]. Especially they are often noted when large number of deaths accompanied with the outbreaks of previously unrecognized infections originating from the terrestrial reservoir. Environmental factors commonly accelerate the emergence of infectious diseases by establishing contact humans with the natural reservoir or with the infection host, the infection host could be unknown until the outbreak [21].

This issue is fully relevant for our country and its landscape diversity, the active economic development of uninhabited areas, the influx of population into these areas.

If we consider that through Uzbekistan lies two bird migration route – from East Africa and Indochina to the north of Siberia and back, as well as all the increasing migration of the population, it will be clear to the need for further systematic survey of the territory of the Republic in respect of the natural foci of arboviruses.

It is believed that arboviruses have enormous pathogenic potential. However, the actual medical importance to humans, tend to have only those that were isolated in terms of epidemic outbreaks and are the cause of permanently recorded disease [12].

Uzbekistan is an area with varied terrain, variety and large number of blood sucking vectors (mosquitoes, ticks, black flies, etc.), and their vertebrate hosts, mammals and birds, which may serve as reservoirs and vectors and viral pathogens of dangerous infections. All this contributes to the formation of natural foci of viral diseases. To date, Uzbekistan detected circulation of more than 20 arboviruses, some of them causes severe disease with high mortality. An example is the Crimean-Congo hemorrhagic fever, the natural foci of which are revealed in almost all landscape zones of regions except for mountainous areas.

If we consider that in the neighboring countries bordering on the territory of the Republic of Uzbekistan on the climatic and geographical conditions, revealed the circulation of many other pathogens of viral infections, there is a possibility registration of these viruses on the territory of Uzbekistan.

Due to the fact that northern – west part of the country (the Republic of Karakalpakstan, Khorezm region) lies on the migration route of birds from East Africa to Kazakhstan and western Siberia; and from Ceylon, India and Afghanistan through the south – east part of the Republic(Surkhandarya and Kashkadarya regions) to the Eastern Siberia, there is a high possibility of occurrence of infections which causes severe diseases in humans with a high mortality rate like Japanese encephalitis virus, Dengue fever, WNF, Rift Valley, Kiassanur forest disease, yellow fever, hemorrhagic fever with renal syndrome, Omsk hemorrhagic fever, tick-borne encephalitis and others in the territory of the Republic.

Active moving of large number of people across countries and continents during possibilities of air fleet poses a risk in the sense of circulation of such exotic highly contagious hemorrhagic fever for us as Lassa, Marburg, Ebola, Argentinean and Bolivian fevers.

West Nile virus was first isolated from a woman in the West Nile district of Uganda in 1937. In 1953, it was diagnosed in birds (crows and Columbiformes) in the region of the Nile delta. Until 1997, WNV was not considered as pathogenic for birds. At that time in Israel, the death of different species of birds, which had signs of encephalitis and paralysis, resulted in a more virulent strain. Human infections caused by WNV have been registered in many countries of the world for more than 50 years.

In 1999, the WNF virus circulating in Tunisia and Israel was imported to New York, where it resulted in a major and dramatic outbreak, which in the following years spread to the mainland of the United States of America (USA). Outbreak of WNF in the United States (1999–2010 y.) Has shown that the import and fixation of vector-borne pathogens outside their current habitats represent a serious danger to the world.

The largest outbreaks occurred in Israel, Greece, Romania, Russia and the United States. Major migratory pathways of birds are being laid through the outbreak sites. The WNF virus was originally distributed in Africa, in some parts of Europe, the Middle East, Western Asia and in Australia. Since its introduction in 1999, the U.S. virus has spread and is now widely entrenched in the territory from Canada to Venezuela [9].

Human infection is most often caused by bites of infected mosquitoes. Mosquitoes are infected during feeding with the blood of infected birds – in their blood the virus circulates for several days. Eventually the virus gets into the salivary glands of the mosquito. During its subsequent feeding with blood (during mosquito bites) the virus can enter the body of humans and animals, where it can multiply and lead to disease.

The virus can also be transmitted by contact with other infected animals, with their blood or other tissues.

A very small proportion of human infections occur during organ transplant, blood transfusion and breastfeeding. One case of transplacental transmission of the WNF virus (from mother to child) has been registered.

To date, there are no documented cases of transmission of WNV virus from person to person in safe contacts.

WNF infection is either asymptomatic (about 80% of infected people) or can lead to the development of West Nile fever or severe Western Nile disease.

Approximately 20% of infected people develop West Nile fever. Its symptoms include fever, headache, fatigue and body aches, nausea, vomiting and sometimes a skin rash (on the trunk) and swollen lymph nodes.

The symptoms of severe disease (also called neuroinvasive disease), such as encephalitis or West Nile meningitis or West Nile poliomyelitis, include headache, high fever, neck stiffness, stupor, disorientation, coma, tremors, convulsions, muscle weakness and paralysis. According to estimates, the most severe form of the disease occurs in approximately in one out of 150 people infected with West Nile virus. Serious illness can occur at any age, however people over age 50 and some people with weakened immune systems (for example, transplant patients) are at the highest risk of developing severe disease as a result of infection with WNV virus.

The incubation period is usually 3 to 14 days. The virus contains a single-stranded, unsegmented RNA, its replication occurs in the cytoplasm of infected cells.

Since the discovery of the WNF virus for several decades, there has been a predominantly sporadic incidence of human morbidity within the tropical and subtropical endemic foci of Africa [16; 15] and Asia [24], although in some cases there have been large outbreaks. Thus, in 1974, there was an outbreak of West Nile fever in South Africa, where about 3000 cases were reported [27].

The situation has changed radically since 1996, when in Bucharest and surrounding areas, that is, outside the tropical and subtropical zone there was a large outbreak of West Nile fever. 835 patients with CNS lesions were hospitalized, laboratory confirmed 393 cases, of which 7 (4.3%) Were deadly. The virus was isolated from the cerebrospinal fluid by PCR [18]. Antibodies to the WNV virus among the inhabitants of Bucharest were found in 4.1% of cases, and in other regions-in 0.9%.

Outbreaks of West Nile infection were also observed in other European countries: in 1997 in the Czech Republic in 1998 in Italy, in 1999–2000 in Israel, in 2000 and in 2004 – in France [22; 15; 28; 30].

In recent years, the WNF virus has become increasingly aggressive and causes disease even in regions where it has not been known before. The epidemic outbreak caused by the WNF virus occurred in New York in 1999, for the first time in the American continent. The disease originated at the end of July – September with a peak in the second half of August in New York and its environs. There were 62 cases reported, 7 of which were fatal [30].

By 2002, WNF virus has spread almost throughout the United States, while described 4156 human cases, including 286 deaths. In 2003, the US has already been registered 9862 cases of the disease, of which 264 – lethal in Canada – 1335 cases, including 10 deaths.

Every year in the Americas, cases of the western Nile infection among humans are identified. In 2006, 4269 cases were identified, of which 177 were fatal, and in 2007, 3576 cases, 115 were fatal [30]. In 2003–2004. The circulation of the WNF virus in Cuba was established [14].

Epidemic outbreaks caused by the WNV virus have also occurred in Russia. In July-September 1999 in the Russian Federation there was a sharp worsening of epidemiological situation on incidence of viral fevers, complicated meningitis and meningoencephalitis.

Outbreaks of disease caused by WNV virus, accompanied by severe clinical course, and even death. Laboratory tests in 190 cases in Volgograd, 89 – in Astrakhan areas and 31 in Krasnodar region identified antibodies to WNV, i.e. it confirmed diagnosis of West Nile infection [23].

It should be noted that the outbreak in Romania, the USA and Russia, caused by WNF virus, characterized by a high proportion of meningitis and meningoencephalitis (over 50%), high mortality (about 10%). Patients with Western Nile infection in endemic areas of Russia are identified every year. In addition, the WNF virus began to be discovered in those areas of Russia, where it had not previously met [2]. For example, in 2004, in Novosibirsk region, three laboratory-confirmed cases of infection caused by the WNV virus in humans were registered for the first time [11].

During an outbreak of WNF in 1996 in Romania, the main carrier of infection in anthropogenic biocenoses was Culex pipiens [26].

In the US in 1999, when WNF virus was first detected in the transmission cycle involved only a few species of mosquitoes, common in North America: Aedes vexans, Culex

pipiens, Culex restuans. However, after 4 years the virus has already been detected in 43 different types of genera Aedes mosquito, Anopheles, Coquillettidia, Culex, Culiseta, Deinocerites, Ochlerotatus, Orthopodomyia, Psorophora, Uranotaenia [13]. Infection with such a large number of different species of mosquitoes most likely was one of the decisive factors in the spread of the WNF virus in the United States. It is assumed that in America infection with WNV in birds takes place with the participation of C. pipiens and C. restuans, among people – C. salinarius, among horses – mosquito genera Aedes and Ochlerotatus [29].

The WNF virus also adapts to the local species of argasidae and ixodidae mites involved in the preservation of the viral population in the inter-episodic period [1]. Representatives of a huge number of species of vertebrates, from amphibians and reptiles to birds and mammals can be infected with the virus WNV, but not all of them achieve the level of viremia, sufficient to infect the feeding on them Mosquitoes. In particular, humans are not a source of mosquito infection, which, like some mammals, does not play a significant role in maintaining the natural foci of the WNF virus [7]. Apparently raising levels of viraemia is insufficient to infect mosquitoes [3]. The main reservoir of the WNF virus is considered to be birds, including migratory birds, which can carry out the introduction of the virus into non-endemic areas, as well as birds of aquatic and near-water ecological complexes [3; 5; 25].

WNF virus was isolated in different geographical areas, from the rock-pigeon, crow, barred warbler, glossy ibis and a rook, blackbird and nuthatch. The commensal foci WNF virus main hosts are Raven – crows, rooks, Jay et al. [7; 30]. In an epidemic outbreak of West Nile infection in Romania, 41% of domestic and 7% of wild birds were found to have specific antibodies to the virus [26]. France had isolated the virus strains of WNF from the magpies and Sparrow [20]. The outbreak caused by WNF virus in the United States in 1999, has not affected only wild birds, but also some birds of Bronsk and Kvinsk zoos (Chilean flamingos, cormorants, bald eagles, magpies, ducks, pheasants, white owls, and others) [24].

As mentioned above, in recent years there has been an increase in the number of diseases related to the pathogen virus WNF, the weighting of the course and the involvement of new regions, previously "not familiar" with this disease.

Most researchers attribute this to the process of "emerging infections", when in a certain area of the disease reappear, which was not in the last 20 years, or when the incidence of common infections is increasing as a result of long-term changes in the epidemiological process. It is believed that the main cause of these phenomena is complex natural and socio-economic factors leading to an increase in the number of populations of vectors of disease – mosquitoes (irrigation activities, heavy rains followed by flooding, increased average temperature, the formation of the ecological niches that promote a mass feeding mosquitoes, etc.) [18].

Global warming with a predominance of warm and wet weather leads to an increase in the number and distribution of disease vectors [27, 8].

In order to control the incidence of arbovirus infections is necessary to conduct the complex epidemiological, entomological and preventive measures, including monitoring of the number of vector populations, determining the level of infection, serological monitoring of animals – feeders and inhabitants of endemic areas, an adequate level of training and literacy of medical professionals in relation to the WNF infection.

Over the past five years of research on the problem of arbovirus infections in our country, scientists – virologists have identified the circulation of the WNF virus in Uzbekistan; found antibodies to the virus in human serum, identified the virus antigen in mosquitoes, gnats and mites, isolated strains of the WNF virus from birds, and patients with meningitis and meningoencephalitis. The research Institute of Virology plans to conduct molecular genetic studies of isolated strains in order to establish the genotypes of the pathogen circulating in the country.

The recent outbreaks of WNF virus in Romania, Russia, America, Spain and other countries, accompanied by severe course of the disease, a high proportion of meningitis and meningoencephalitis, CNS lesions and high mortality, especially in the group of patients with meningoencephalitis.

In order to prevent human infection with WNV virus necessary to carry out non-specific prevention: treatment of breeding sites of mosquitoes (reservoirs, basements of residential buildings) and personal protection from mosquito attacks while visiting natural arrays, to carry out the health education work among the population.

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# ULTRASOUND SEMIOTICS OF BIKER CYSTS

**Abstract.** The ultrasound data of 80 patients with Baker cysts aged 10 to 60 years were analyzed. Baker's cyst was visualized in the form of a distended fluid of the synovial bag of the popliteal fossa and was very often combined with various pathologies of the knee joint. Synovial cysts of the subcortical region are pathological formations that have arisen as a result of the influence of polythetic factors causing chronic irritation of the synovial membrane of the knee joint and synovial bags.

**Keywords:** Baker's cyst, arthrosonography, knee joint.

The anatomical diversity of the popliteal region, the abundance of mucous bags in terms of the differential diagnosis of their pathological conditions presents certain difficulties for the clinician. However, Baker's cyst is not such a rare disease and accounts for 3.9% of all injuries and diseases of the knee joint [1; 2; 5].

In connection with the expansion of indications for adequate surgical interventions on the knee joint, especially in its posterior part, arthrosonography is currently gaining interest. At the present level of knowledge, sonography, as a non-invasive method of research, has become more important in the diagnosis of Baker cysts with a high degree of reliability [3; 4].

Considering the above, the purpose of our study is to study the ultrasound semiotics of Baker's cyst.

**Material and methods**. The data of an ultrasound study of 80 patients with Baker's cysts aged from 10 to 60 years were analyzed using a SonoScape-S-50 ultrasound scanner with a linear format sensor with an operating frequency of 7.5 MHz.

The study was performed in the position of the patient lying on his stomach and on his back, necessarily in comparison with the intact side. In the position of a patient lying on his back, the state of the upper inversion, its size, the presence of an intra-articular effusion, the synovial membrane were evaluated. The dorsal part of the knee joint, where Baker's cyst is located, was examined in the position of the patient lying on his stomach. The study was carried out in the transverse and longitudinal directions in many sections of the entire dorsal surface of the knee joint with the proximal part of the leg and the distal part of the thigh, in the position of extension and flexion of the knee joint.

**The results of the study.** In the examined patients with knee joint pathologies, in the history of which different types of knee injuries were noted, a Baker cyst was revealed in 80 patients. The duration of the disease in the examined patients ranged from one to six years. Mostly the cyst was noted in the left knee joint, which made 50% (40 patients). In 24 patients (30%) left-sided localization was observed, and in 20% of cases (16 patients), bilateral cyst localization was observed.

During ultrasound examination, Baker's cyst was visualized as a stretched by fluid synovial bag of the popliteal fossa, located in its medial section between the inner head of calf and semi-membranous muscles and communicating with the knee joint by means of fistula. Baker cyst of small size usually had a painless course. With relatively large sizes of cysts, patients

mostly complained of sensation of pain along the posterior surface of the knee joint during physical exertion, discomfort, and the presence of a tumor-like mass in the subtile fossa. The of symptoms complex sometimes included pain in the calf muscles or impaired sensitivity along the back of the leg.

In the popliteal area, all patients were found to have different sizes of clearly defined low-painful elastic swelling, disappearing or diminishing in size when the knee joint was bent at rest and increased after physical exertion.

In ultrasound of symptoms Baker cyst is often combined with various pathologies of the knee joint. Thus, in 17.5% of cases (14 patients), sonographic symptoms of arthritis were marked, in which Baker's cysts are often visually obliterated, and in the presence of effusion, they are prone to rupture due to marked degenerative changes in the walls. Determining the severity of intraarticular effusion according to ultrasound data, as a rule, presents no difficulty [4; 5] if the border between the fluid layer and the hypoechoic thickened synovial membrane is clearly visible.

In addition to marked hyperplasia of the synovial membrane in the upper torsion and in Baker's cysts, significant thickening of the synovial membrane in the infrapatellar zon in the area of the fat body and pterygoid folds is typical for arthritis. When scanning the infrapatellar zone of a bent more than 90° of knee joint, a typical symptom is noted – the hypoechoic layer of the thickened synovial membrane over the supporting surface of the articular cartilage, which was not noted by us in any other diseases.

In 10 patients (12.5%), gonarthrosis was diagnosed predominantly of the first and second stages of degenerative-dystrophic changes on the part of the articulating surfaces of the knee joint and was characterized by the formation of small hyperachroic marginal osteophytes of the fibrocartilaginous echo structure, with the normal size of the joint space and the thickness of hyaline cartilage;

In combination with a Baker cyst, the states of the upper synovial twisting of the knee joint are typical for gonarthrosis, indicating a different degree of obliteration or an increase in its volume, especially with synovitis revealed in 8 cases (10%). Also, in 8 observations (10%) ultrasound signs of bursitis were noted. Prepatellary bursitis is a frequent complication that occurs after injuries of the knee joint, especially the anterior sections and the patella, with a tendency to chronicity. Almost always there was swelling of the subcutaneous fatty tissue over the entire front surface of the knee joint with hypoechoic layers between the segments of adipose tissue, and therefore it was not possible to determine the boundaries of the bag at times.

Sinovitis is a provocative moment in the development of cysts, leading to increased intra-articular pressure, which increases the risk of developing of recurrences. Constant stimulation of the synovial membrane and accumulated fluid stretch the synovial sac, forming a cyst, and its size can reach large sizes (12 × 8 × 6 cm).

As shown by our research, Baker cyst formation occurs in stages. We have identified 3 periods of the sonographic organization of cysts. In the first period – early structural changes – the cyst had a wall up to 2.6 mm thick, without intraluminal structures. In longitudinal scanning, an oval-shaped cyst with homogeneous anechoic contents was determined. These changes were noted in 26 patients (32.5%). The second period – the progression of structural changes – was characterized by a thickening of the cyst wall up to 7.9 mm, a heterogeneous content structure with "gentle" septa and inclusions. In the study of the popliteal fossa, a cyst, divided by a semimembranose, having a crescentic shape during transverse scanning, was visualized in the form of two longitudinal elongated ellipses with longitudinal scanning. These changes were noted in 30 patients (31.5%). In the third period – the final structural organization – the walls of the cyst are thicker than 8.0 mm, in the cavity there were septa and inclusions with a small amount of "liquid" content, which we found in 24 patients (30%).

The earliest stage of the cyst was a type of hernia of the synovial sac. Hernia of the synovial sac occurred in 15% of cases. Light signs of knee joint synovitis have always been identified. The later bursitis stage of the cyst occurred in most cases (85% of cases). There have always been marked signs of chronic synovitis of the joint.

3 patients (3.75%) had a Baker cyst that communicates with the joint cavity through the fistula. In the predominant percentage of observations (80%), single-chamber formation was characteristic. In 16 cases (20%), multi-chamber Baker cyst was revealed. In rare cases, in sonography connective tissue bridges in the cavity of cystic formations, were differentiated with a small amount of "liquid" content and a wall thickness of more than 8 mm, which is typical of the inflammatory process.

In chronic inflammation of the cyst (35% of observations) on the arthrosonogram, an echo-negative formation with clear contours, a moderately increased echogenicity of the synovial membrane, thickened to 6–8 mm, with villi and single soft septa was visualized on the arthrosonogram. The content presented inhomogeneous, with echo dense, without acoustic shadow, inclusions. The neck of the cyst was less clear.

Interpretation of the results of the study showed that in 35% of observations (28 patients) there was a combination of several pathologies, against the background of which Baker cyst was differentiated.

As can be seen, synovial cysts of the subcortical region are pathological formations resulting from the influence of polythetic factors that cause chronic irritation of the synovial membrane of the knee joint and synovial bags. Cysts

are formed from the popliteal pits or are formed as "hernial" protrusions of the synovial membrane through the weakened areas of the fibrous capsule of the knee joint. The basis of the pathological process is a chronic productive inflammation. It should be noted that this pattern was combined with ultrasound signs of arthritis in 14 cases (17.5%).

Thus, ultrasound examination makes it possible to establish the presence of a Baker cyst, which is increasingly found in the practice of a rheumatologist, its location in the popliteal fossa, to visualize the contours and contents, boundaries and extent, connection with the joint cavity of the, signs of rupture and inflammation of the wall, and also ultrasound signs of damage to the intra-articular structures of the knee joint. Ultrasound makes it possible to establish a link between the stage of gonarthrosis and the stage of the structural organization of the cyst, which consists in the fact that with an increase in the severity of degenerative processes in the tissues of the knee joint, the severity of structural changes in Baker's cyst increases. When examining the popliteal area, ultrasound is necessary not only to diagnose cystic formations, but also to identify the following common pathological conditions, such as deep vein thrombosis (thrombophlebitis), femoral and popliteal aneurysms, abscesses, tumors, and muscle ruptures.

**Conclusions.** Ultrasonography with high settling is not inferior to magnetic resonance imaging in the diagnosis of Baker cysts, and taking into account the possibility of choosing the scanning plane, conducting a polypositional study, portability and accessibility, relatively low cost, no contraindications, ultrasound can be considered the optimal method of diagnosis and dynamic observation of patients with Baker cyst, including the course of treatment.

Due to the new high-informative ultrasound devices with broadband high-frequency ultrasound sensors and taking into account non-invasiveness, lack of radiation load, efficiency, availability and lack of contraindications to sonography, this method can be recommended as mandatory in patients suspected of injury and disease of the knee joint and especially if they have cystic formations.

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# SELECTION OF OPTIMAL CARBON AND NITROGEN SOURCES FOR ENHANCED POLYSACCHARIDES PRODUCTION BY *LENTINUS EDODES*

**Abstract.** In this paper the effect of carbon and nitrogen sources on the endopolysaccharides production by *Lentinus edodes* 2541 strain was investigated. Medium composition is the most important aspect to take into consideration when growing any microorganism. It was found that cellobiose was the best carbon source for fungal growth and endopolysaccharides production by *L. edodes 2541* strain. Maximal endopolysaccharides production (5.5%) was detected in media with cellobiose as a carbon source. Among the various nitrogen sources used, peptone was a suitable nitrogen source for maximal endopolysaccharides production by *L. edodes 2541*. The medium had the following composition g/l: cellobiose –30; $KH_2PO_4$–1; $K_2HPO_4$–1; $MgSO_4$–0.25; peptone – 3.5; yeast extract – 20 ml. Selection of carbon and nitrogen sources allowed increase polysaccharides production by *Lentinus edodes.*

**Keywords:** Lentinus edodes, Polysaccharides, Selection.

**Introduction.** Mushrooms such as *Ganoderma lucidum* (Reishi), *Lentinus edodes* (Shiitake), *Inonotus obliquus* (Chaga) and many others are extensively known for their immunomodulatory, hepatoprotective, antinociceptive, antidiabetic, antiviral, and antimicrobial properties [1; 2]. Shiitake is the common Japanese name for *Lentinus edodes*, and is also the common name now used in the West. Indigenous to Asia, shiitake is now cultivated and is the second most commonly produced edible mushroom in the world. Besides being a culinary delicacy, there is a long tradition of use of shiitake as medicine in Asia, dating back > 2000 years. Shiitake contains protein (26% of dry weight), lipids (primarily linoleic acid); carbohydrate; fiber; minerals; vitamins B-1, B-2, and C; and ergosterols [3]. Besides its nutritive content several important compounds have been isolated from shiitake that have immunomodulatory, lipid-lowering, and antimicrobial properties. These include lentinan, *Lentinus edodes* mycelium (LEM), KS-2, and eritadenine [4]. Another compound isolated from shiitake is eritadenine, which has been shown to lower serum cholesterol and lipid concentrations in various studies in rodents [5]. Besides the well-studied compounds other potentially beneficial compounds have been found in shiitake.

In spite of many researchers' efforts for the production of bioactive metabolites by mushrooms, the physiological and engineering aspects of submerged cultures (production kinetics, structural features, biological activity and biosynthesis control methods of some bioactive compounds) are still far from being thoroughly studied. Existing studies of the artificial cultivation of higher mushrooms are concerned to increase in the yield of the target products (biomass, protein, amino acids), the development of new cheap and simple nutrient media for the biosynthesis of biologically active compounds. In this regard, the primary role is given to the composition of the nutrient medium (carbon and nitrogen sources), which

influence both the constructive exchange of cultures and the synthesis of polysaccharides.

**Materials and methods.** The object of present research was the *L. edodes 2541* strain from the collection of higher mushrooms of the Institute of Botany, Kiev, Ukraine. Extracellular endopolysaccharides were produced in synthetic glucose-peptone-yeast medium. Mycelia biomass was be assessed after 7 days of submerged cultivation in 250 ml flasks containing 50 ml of medium. The mycelia biomass was separated by centrifugation (4 °C, 3000 rpm, 30 min), washed by $dH_2O$, dried at 50 °C until constant weight was obtained, and measured as g L-1 of the medium. Biomass production was estimated at 3, 5, 7 days of cultivation in liquid medium. Biomass and endopolysaccharides production were evaluated in artificial culture media with different carbon and nitrogen sources.

The effect of various carbon and nitrogen sources on the endopolysaccharides production was determined. Mono-, di-, and polysaccharides such as glucose, arabinose, xylose, galactose, mannose, fructose, lactose, maltose, sucrose, mannitol, sorbitol, and cellobiose in concentration equal to 30 g/l glucose were used as carbon sources. Inorganic and organic sources such as $NaNO_3$, $NH_4NO_3$, $NH_4Cl$, $(NH_4)_2SO_4$, peptone, asparagine and urea in concentration equal to the amount of nitrogen in 2g of $NaNO_3$, were used as nitrogen sources.

Total content of polysaccharides was determined by the phenol-sulfuric acid method [6]. The content of polysaccharides was calculated in% of absolutely dry biomass (a.s.m.). All the analyses were performed in triplicate, and the results were expressed as mean SD values of the three sets of observations. The mean values and standard deviation will be calculated using STATISTICA 6 [7].

**Results and discussion.** At the first stage, the effect of the carbon sources on the endopolysaccharides production in *L. edodes 2541* strain was studied (Table 1).

Table 1. – The effect of various carbon sources on endopolysaccharides production by *L. edodes 2541* in submerged cultivation

| Carbon source | Biomass, g/l | Endopolysaccharides,% a.s.m. |
|---|---|---|
| Glucose | 13.5 ± 0.2 | 4.5 ± 0.2 |
| Arabinose | 3.0 ± 0.3 | 2.8 ± 0.2 |
| Galactose | 3.5 ± 0.4 | 2.5 ± 0.1 |
| Xylose | 3.2 ± 0.2 | 2.9 ± 0.3 |
| Mannose | 4.6 ± 0.4 | 2.0 ± 0.2 |
| Fructose | 3.3 ± 0.2 | 2.3 ± 0.1 |
| Lactose | 6.2 ± 0.3 | 3.2 ± 0.3 |
| Maltose | 6.4 ± 0.2 | 2.8 ± 0.2 |
| Sucrose | 5.8 ± 0.2 | 2.8 ± 0.2 |
| Cellobiose | 14.8 ± 0.4 | 5.5 ± 0.3 |
| Mannitol | 3.2 ± 0.3 | 2.5 ± 0.1 |
| Sorbitol | 4.5 ± 0.2 | 2.0 ± 0.2 |

The results indicate that the best carbon source for the endopolysaccharides production in *L. edodes 2541* was cellobiose. The yield of endopolysaccharides in the medium with cellobiose was 5.5%.

Further experiments were aimed at studying the effect of various nitrogen sources for endopolysaccharides production in *L. edodes 2541* strain. The data obtained are presented in (Table 2).

Table 2. – Effect of nitrogen sources on endopolysaccharides production by *L. edodes 2541* strain in submerged cultivation

| Nitrogen source | Biomass, g/l | Endopolysaccharides,% a.s.m. |
|---|---|---|
| $NaNO_3$ | 4.4 ± 0.3 | 2.9 ± 0.1 |
| $NH_4NO_3$ | 5.2 ± 0.2 | 2.5 ± 0.1 |
| $NH_4Cl$ | 4.9 ± 0.1 | 2.7 ± 0.2 |
| $(NH_4)_2SO_4$ | 6.0 ± 0.3 | 3.5 ± 0.1 |
| Peptone | 13.5 ± 0.2 | 4.5 ± 0.2 |
| Asparagine | 6.2 ± 0.4 | 2.5 ± 0.2 |
| Urea | 2.7 ± 0.1 | 2.4 ± 0.1 |

As can be seen from the data presented in (Table 2), peptone found to be optimal for the endopolysaccharides production by *L. edodes 2541*.

In conclusion, the optimal carbon and nitrogen sources in the nutrient medium were selected. The medium had the following composition (g/l): cellobiose – 30; KH2PO4–1; K2HPO4–1; MgSO4–0.25; peptone – 3.5; yeast extract – 20 ml. Quantitative assessment of the influence of nutrient optimization and cultivation conditions on the efficiency of the growth process and polysaccharide biosynthesis by *L. edodes 2541* strain indicates a significant increase in the content of endopolysaccharides in biomass by 60% as a result of optimization of biotechnological cultivation processes.

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# CEREBRAL HEMODYNAMICS IN PATIENTS WITH CEREBRAL VENOUS DYSFUNCTION

**Abstract.** The experience of using different methods of magnetic resonance study of the arterial and venous parts of the vascular bed of the head and neck is analyzed, and the feasibility and possibility of simultaneous assessment of the state of the brain and the study of the anatomy of the cerebral bed are shown.

**Keywords**: chronic cerebrovascular accident, venous hemodynamics, magnetic resonance imaging, duplex scanning.

Disorders of cerebral circulation in arterial hyperonia (AH) are one of the most pressing problems of modern cardiology and neurology, remaining the subject of discussion to date. It is known that disorders of the venous circulation play an important role in the reactions of cerebral autoregulation [8; 10].

Thus, with increasing blood pressure, there is an increase in the diameter of the veins and an increase in the permeability of the blood-brain barrier [9; 11]. According to many authors, when using magnetic resonance imaging (MRI) techniques focused on the study of the venous bed, patients with hypertension revealed the following changes: expansion of the superficial cerebral veins, lack of a signal from the blood flow or reduction in the size of the transverse and sigmoid sinus, combined with expansion of the sizes of the sinuses of the same name from the opposite side etc. [1; 4; 7]. Further research in this direction may allow developing new approaches to the prevention and treatment of hypertensive encephalopathy.

The advantages of MRI are not limited to the visualization of anatomical structures. Functional MRI created on the basis of angiographic techniques allows to evaluate the change in the velocity of the venous flow. This compares the change in the intensity of the signal on the angiograms obtained at rest and under conditions leading to the activation of a specific department or region of the cerebral cortex [4; 7].

Interest in studying the characteristics of the cerebral venous circulation and attempts to assess its significance in the violation of cerebral circulation are determined, on the one hand, by the existing trend of increasing the number of patients suffering from vascular diseases, on the other hand, by the active development and implementation of modern visualization technologies [2; 3; 5; 6].

In the available specialized literature, we were not able to find systematic data on the value of magnetic resonance angiography in assessing the arterial and venous circulation of the brain, which served as the basis for conducting this study.

**Purpose of the study**. Justify the possibility of conducting and determine the features of the magnetic resonance venography in violation of cerebral arterial blood flow.

Materials and methods. In 87 patients with chronic cerebral ischemia (CCI) on the background of hypertension were examined, of whom 36 were women and 51 men aged from 46 to 72 years old (mean age 57.2 ± 11.3 years). The patients were divided into 2 groups: CBI Stage I – 33 patients, CBI II – 54. In the examined patients, the mean systolic blood pressure was 181. 7 ± 9.3 mm Hg. Art., average diastolic – 112.3 ± 17.6 mm hg. art. The average duration of hypertension was 9.2 ± 8.2 years (0.7–25 year). The control group consisted of 20 healthy individuals aged from 36 to 64 years old (mean age 49.1 ± 9.7 years).

All patients underwent standard neurological examination, brain MRI with venography (MRV) of the brachiocephalic veins and venous sinuses of the brain, duplex scanning (DS) in the modes of color Doppler mapping and pulsed Doppler of extra- and intra-cranial vessels.

MRI and MRI were performed on a Magnetom Verio 3 T and Magnetom Avanto 1.5 T from Siemens according to a generally accepted method. Brain scans were performed in axial, sagittal and coronary projections with slice thickness from 4 mm with T1 – TR programs – 450 ms, T2 – TR – 6000 ms, tirm TR – 600 ms, TI – 110 ms, contrast enhancement occurred upon injection of 10–20 ml of a 5% magnneist solution (Schering). For MPA and MRI, a two-dimensional time-of-flight angiography (2DTOF) technique was used. Using fast T2-weighted programs, we evaluated the state of cerebrospinal fluid dynamics in sylvium aqueduct. To assess the CSF dynamics, the intensity of the signal from the pulsation of the cerebrospinal fluid in the sylvian aqueduct was compared with the intensity of the signal in the lateral ventricles at the same level.

Results and discussion. All patients complained of dull headaches, more pronounced in the morning. The pains were mostly of a diffuse nature, occipital localization and in most cases combined with pain in the neck. In 49(36%) patients, headaches were accompanied by a moderately pronounced "noise in the head".

32(36.8%) patients complained of pain in the cervical spine. Pain syndrome was more often characterized as chronic with periodic exacerbations. They noted the frequent connection of cervicalgia with headaches, a little less – with dizziness.

Along with the headache, the subjects noted difficulty concentrating, absent-mindedness. 61(70.1%) patients complained of sleep disturbance (superficial sleep, headaches on waking, a decrease in the level of daytime wakefulness) and dizziness. Dizziness were mostly non-systemic in nature, there was instability when walking, incoordination, which are especially clear when performing small movements.

During neurological examination, vestibulo-atactic disorders in the form of instability during walking, staggering in the Romberg position, elements of dysmetry, indistinctness when performing knee-heel and paltse- nose test tests were most often encountered. The deficiency of oculomotor innervation, consisting in the weakening of convergence and accommodation, was noted less often. Visual disturbances in the form of cattle-resistant, photopsies were also observed. Signs of pyramidal insufficiency manifested in the form of asymmetry of tendon and periosteal reflexes, pathological foot and hand symptoms.

DS and MRA revealed in patients the presence of occlusive processes in the form of tortuosity and stenosis. In chronic cerebral ischemia, grade 1, crimpiness occurred in 31.4%; with chronic cerebral ischemia 1 degree II Art.– in 38.2% of patients. Thus, the tortuosity of the carotid arteries was characteristic of all hypertensive patients, regardless of the stage of CBI. No statistically significant difference between the parties was obtained ($p > 0.5$).

Atherosclerotic changes were detected in 27% of patients. Atherosclerotic changes were detected in 27% of patients. At the same time, a seal of the arterial wall was noted, atherosclerotic plaques were detected, loosening and an increase in the intima of the vessels. The spread of indicators of the intima-media complex was significant and ranged from 0.6 to 2.7 mm with an average of $1.4 \pm 0.4$.

With CBI there was only a tendency to a decrease in the volumetric blood flow velocity against the background of a moderate decrease in the blood flow velocity in the posterior circulation arteries. At stage II of the disease, there was a decrease in the linear and volumetric blood flow rates in the ICA. In the arteries of the posterior circulation revealed a significant decrease in blood flow velocity. As for the DE III, there was a pronounced decrease in the linear and volumetric blood flow velocity, especially in the arteries supplying the back sections of the brain.

Taking into account the role of the common jugular vein as a collector of venous outflow from the cranial cavity, we analyzed the indicators of blood flow in it at different stages of CBI.

In all patients with CIM, the lumen of the internal jugular veins (IJA) was free. A valve was visualized in all cases at the mouth of the IJA. In most cases, a bicuspid valve was detected.

To assess the viability of the IJA valvular apparatus, a respiratory load test was performed: in response to a deep breath, closing of the valve leaflets was observed, accompanied by a significant reduction in blood flow to the IJA. In 59(67.8%) cases with functional test, reversal of blood flow in valvular insufficiency was noted. No cases of valvular insufficiency were detected in the control group.

In all patients examined in the control group and in the majority of patients with CBI, the blood flow in the IJA had a three- or four-phase character, synchronized with the act of breathing. In 1/3 of the cases, low-amplitude flow with reduced phasing was noted.

The study of the vertebral veins was performed in the supine position, and the flow of the PT was determined in patients with CBI, Stage I, in 26.4% of cases. CBI II Art.– 42.7%. When switching to orthostasis, in 100.0% of cases in both groups. The failure of visualization of the vertebral veins was associated with the quality of visualization in general. Thus, more often, vertebral veins was untenable in patients with CBI II ($p < 0.05$).

Comparative assessment of brain MRI results in patients with CBI revealed diffuse changes in the signal intensity from the white matter of the brain (periventricular, subcortical leucoarea, LA), single or multiple ischemic foci of 115 mm, external and internal cerebral atrophy (CA). Large ischemic foci (cortical and subcortical heart attacks) in the examined patients were absent. Patients with CBI II differed more pronounced periventricular LA of all localizations compared with the group of patients with CBI II ($p < 0.05$); symmetry of atrophic changes in the brain (the absence of significant differences in the index of the bodies of the lateral ventricles – ITBJ, the linear dimensions of the anterior horns and the bodies of the lateral ventricles on the right and left); the prevalence of single and small (up to 5 mm) ischemic foci in the brain substance (43.4% with 10.7% CBI II, $p < 0.05$). Compared to patients with CBI I, patients with CBI II were characterized by a greater ($p < 0.05$–$0.01$) severity of asymmetric internal cerebral atrophy with predominant left hemisphere involvement (average values of ITBI, linear dimensions of the anterior horns and bodies of the lateral ventricles significantly higher left than right); a high representation of multiple ischemic foci with a size of > 5 mm in the brain substance (39.3% with 10.4%, CBI II, $p < 0.01$), especially in the deep sections of the white matter of the frontal lobes (50% and 23.1 respectively%), the head of the caudate nucleus (60.7% and 33.3%), the thalamus (60.7% and 30.8%) and the brain bridge (46.0% and 20.5%), i.e. in structures that are functionally significant for developed KP [11].

According to MRI, the majority of patients were identified asymmetry of the main venous reservoirs; jugular veins and cerebral sinuses mainly on the right side were enlarged in 53% of patients, on the left side – in 27%. Analysis of the

MRI data showed that in 58% of cases an abnormal development of the drainage system of the brain was detected. Thus, in 36% of cases, hypoplasia of one of the transverse sinuses was diagnosed (12 in the left, 6 in the right), and 14% of the patients showed aplasia in the transverse sinus. In 6 cases revealed hypoplasia of the sigmoid sinuses (right – 4, left – 2). In all cases, abnormalities in the development of the venous sinuses noted a compensatory expansion of the lateral sinus, and in some cases, the upper and lower stony sinuses were visualized, and their detection is normally difficult.

Thus, in chronic cerebrovascular disease, along with changes in the arterial blood flow, changes in the regulation of the venous circulation are indicative. In chronic cerebral ischemia, both a comparative expansion of the VNV and a relative decrease in the intensity of blood flow in them is noted.

Based on the conducted research, the feasibility and the possibility of a one-stage assessment of the state of the brain and the study of the anatomy of the cerebral bed are substantiated. The need for an extended magnetic resonance study of the vascular system in the lesion of the arterial bed of the brain is due to certain anatomical and functional relationships between the arterial and venous sections.

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# VESTIBULAR NEURONITIS – THE PROBLEM OF SYSTEMIC DIZZINESS

**Abstract.** The Vestibular Neuritis is often mistakenly diagnosed pathology manifested by a sudden acute systemic dizziness, nausea, vomiting, unsteadiness when walking and peripheral nystagmus. The vestibular Neuritis is a quite rare pathology, which may cause diagnostic difficulties for physicians of different specialties. As the diagnosis of "vestibular neuritis" is primarily a "diagnosis of exclusion", it is necessary to know peculiarities of clinical picture, course and differential diagnosis with other similar netalogue. The diagnosis of the disease requires the joint and coordinated work of medical specialists: neurologists, ENT, specialists of functional and laboratory diagnostics and laboratory services. Due to the low awareness of this disease doctors of different specialties often make mistakes in diagnosis and treatment.

**Keywords:** vertigo, vestibular neuritis, ischemic stroke in the vertebral-basilar pool.

Vestibular neuronitis (VN) or sharp peripheral vestibulopatia is this disease of vestibular vehicle, that does not threaten to life of man. First clinical presentation of VN was described by Eric Ruttin in 1909, and a term is inculcated in 1949 by Dix and Hallpike. The met of VN is 3.5 case on 100000 persons [1]. Vestibular neuronitis (VN) or acute peripheral vestibulopathy is a disease of the vestibular apparatus that does not threaten human life. The age of onset of the disease is different, but more often it debuts within 30 to 60 years [2; 3]. The etiology is not entirely clear. The cause of the disease is associated with selective inflammation (viral or infectious–allergic Genesis) of the vestibular nerve, as indicated by the results of pathomorphological studies[1; 4]. Studies have shown serological signs of recent upper respiratory infections caused by hepatitis a virus, influenza virus, adenovirus, as well as infections caused by herpes simplex, cytomegalovirus, Epstein-Barr virus, rubella and parainfluenza [3]. Herpes simplex virus type 1 was isolated in 2/3 of cases in vestibular ganglion autopsy by PCR [3; 4]. The histological pattern of the vestibular nerve in LN is similar to that of the nerve in herpes zoster [4]. Much less common is the defeat of the lower branch of the vestibular nerve. The pathological picture is characterized by a decrease and degeneration of the vestibular nerve fibers, and sometimes changes in the scarp node [3].

The main complaints of a patient with VN are:

1. Incessant rotational vertigo.

2. Imbalance at rest and when walking with a tendency to fall towards defeat.

3. Nausea and vomiting.

For vestibular neuronitis characterized by monophasic course, when clinical symptoms develop acutely or subacutely and most pronounced from a few days to several weeks.

The patient should be specifically interviewed about the presence of neurological symptoms such as impaired speech, vision, severe headache, numbness or severe weakness in the limbs. These symptoms are typical for lesions of the brain stem and cerebellum and indicate a Central vestibular pathology, primarily a stroke.

In a clinical examination of a patient with VN pathognomonic for this disease are the following symptoms:

1. Sp N. Most often there is a horizontal nystagmus in the direction of a healthy ear with a rotator component, in which the upper pole of the pupil is twisted also in the direction of a healthy ear. This type of SpN is observed in the combined lesion of the upper and lower vestibular nerves, which explains the absence of a vertical component in SpN by the defeat of the receptors of both vertical channels [2].

2. The slope of the subjective visual vertical in the direction of the patient's ear. This occurs as a result of asymmetry of the tone of the vestibular nuclei with a unilateral violation of afferent impulses from the vertical channels, or from the otolith receptor, or from both of them with a joint lesion.

3. Positive head turn test (Halmagi test). During the fixation of the patient's gaze on the target with a sharp low-amplitude turn of the patient's head in the horizontal plane in the

affected direction, a corrective saccade is fixed, which returns the patient's eyes to the target after the turn.

4. Deviation in stato-coordination and stato-kinetic tests. In a simple pose Romberg, sensitized pose Romberg, walking in a straight line there is a deviation in the direction of the affected maze. In the finger-nose, finger-index and the Barre–Fisher sample, a harmonious deviation of the hands towards the affected labyrinth can be detected.

5. In oculomotor tests, such as the saccade test and smooth tracking, disturbances can be detected, especially when the target moves in a horizontal plane in the direction opposite to the affected ear.

6. There is no change in hearing. In the case of a combination of the described symptoms and unilateral acute hearing loss, the detected pathology is called labyrinthitis.

**Of the diagnostic tests used:** The caloric test.

1.With HF, Hypo – or areflexia is observed from the affected labyrinth. However, it should be taken into account that the caloric test assesses the functional state of only the vestibular-ocular reflex from the ampullary receptor of the horizontal semicircular channel at low frequencies (0.003 Hz) and does not reveal pathology in an isolated lesion of the lower vestibular nerve (with lower HF).

2. vHIT. A characteristic feature of HV is the asymmetry of gain more than 8% due to its reduction from the affected side and the presence of explicit and hidden corrective saccades [1; 2]. With the help of vHIT, the functional state of not only horizontal semicircular channels, but also vertical ones is investigated, which allows to assess whether both branches of the vestibular nerve are affected or isolated upper (upper) or lower (lower) VN.

3. Vestibular myogenic evoked potentials (VMVP). VMVP assesses the function of otolith sacculus and utriculus receptors. VN is divided into 3 stages: symptomatic, pathogenetic therapy and vestibular rehabilitation

4. In oculomotor tests, such as the saccade test and smooth tracking, abnormalities can be detected, especially when the target is moving in a horizontal plane in the direction opposite to the affected ear.

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2. vHIT. A characteristic feature of VH is the asymmetry of the gain of more than 8%, due to its decrease on the affected side and the presence of explicit and hidden corrective saccades [1; 2]. The functional state of not only horizontal semicircular channels, but also vertical channels is investigated with the help of vhit, which allows to assess whether both branches of the vestibular nerve are affected or the upper (upper) or lower (lower) VN are isolated.

3. Vestibular myogenic evoked potentials (VMVP). VMVP evaluates the function of otolith sacculus and utriculus receptors. VN is divided into 3 stages: symptomatic, pathogenetic therapy and vestibular rehabilitation.

Symptomatic therapy, primarily, is the use of vestibular suppressants to reduce vegetative symptoms, which include antihistamines, antiemetic agents and benzodiazepines.

Pathogenetic therapy is the appointment of high doses of corticosteroids with a gradual decrease in dose. The effectiveness of corticosteroids in NR was confirmed in several randomination kontroliruemykh studies [3].

Vestibular rehabilitation is an individual course of special physical exercises, compiled by a doctor and regularly performed by the patient under his control. First and foremost, uses exercises for adaptation based on the stimulation and consolidation of the responsiveness of the vestibular system to rotation of the head with the defeat of one of the mazes and, consequently, the vestibular-ocular reflex on the affected side through biofeedback in the form of slippage of the visual image from the retina by rotating the head. Another form of vestibular gymnastics are exercises on substitution, under which the patient is using duplicate Vestibulo-ocular reflex of the oculomotor system, such as smooth pursuit and saccades [3; 6]. Subsequently, the complex is expanded through the use of exercises that duplicate the most commonly used movements in the daily life of the patient, which helps him to quickly return to normal life.

**Conclusion**

VN is an acute disease of the peripheral vestibular system, manifested by rotational dizziness, nausea, vomiting, coordination disorders. The clinical picture is caused by acute unilateral lesion of the vestibular nerve and vestibular receptors. The main diagnostic criteria are the absence of hearing loss and neurological symptoms, the presence of peripheral nystagmus, a positive test of head rotation. Treatment consists in the appointment of vestibular suppressants and corticosteroids in the acute period and an individual course of vestibular rehabilitation.

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# MORPHOLOGICAL FEATURES OF THE DEVELOPMENT OF THE IMMUNE SYSTEM, THE RELATIONSHIP AND INTEGRATION OF EPITHELIAL CELLS AND IMMUNE CELLS OF THE SMALL INTESTINE OF STERILE RATS ASSOCIATED WITH LACTOBACILLI

**Abstract.** Accelerating the renewal of enterocytes in the crypt-villus system, enhancing the secretion of Paneth cells, fat and eosinophilic cells, enrichment of the villus stroma with plasma cells, formation of structural and functional areas of PB, the appearance of macrophages in the dome zone after the introduction of amicrobial lactobacillus rats, i.e. intestinal microflora indicate morphogenic and immunogenic effects of microorganisms on the functional morphology of the mucous membrane of the small intestine.

**Keywords**. Immune system, lactobacilli, morphology, cells.

The formation and development of the immune system is the basis of the stability of the child's body, its susceptibility to various diseases of a bacterial, viral, fungal nature, as well as immunodeficiency states and the development of allergies. The process of maturation of this global natural defense lasts for many years, since immunological memory is not inherited, but is acquired by man in the process of development.

The constant presence in the intestine of a sufficient number are attached to its wall resident microorganisms prevents propagation of pathogenic microorganisms, their invasion into enterocytes and passage through the intestinal wall by establishing their biotope unfavorable extraneous microflora pH, generating bacteriostatic low molecular weight metabolites, degradation, bacterial toxins, deconjugation of bile acids, production of a wide range of antimicrobial substances of the bactericin family [2; 3; 4; 5]. Lactobacilli are able to exhibit an inhibitory effect on clostridia, streptococci, enterobacteria, pseudomonads, listeria, candida, forming lactocins, lactobrevin, lactostrepcin, nisin, diplolocin and helveticin. Bifidobacteria actively suppress the reproduction of putrefactive and pyogenic bacteria, producing bifidine and bifilong.

Gnotobiotic animals are an excellent, if not to say, ideal model for solving the most diverse problems of medical microbiology, a model whose value can hardly be overestimated. After all, in this way, researchers get into the hands of another tool that allows them to penetrate the secrets of the microbial world, and, most importantly, it is the pathogenic microbes. But to know in detail how these microorganisms interact with each other and the highest organism – that means getting the key to creating new, more effective ways of dealing with them [1; 6; 7; 8; 9].

**Objective:** To evaluate the effect of intestinal microbiocenosis on the formation of integrative and adaptive properties of the mucous membrane of the small intestine and its immune system under experimental conditions.

**Materials and research methods**. The work was performed on 120 white male rats of the Fisher line at the age of 1, 3, 7, 14, 21 days and 4–6 months.

The morphological, morphometric, and ultramicroscopic parameters, as well as the immunomorphology of the small intestine of sterile rats were studied on the material obtained from the studies conducted in the laboratory of the Gnotobiology Research Institute of Epidemiology and Microbiology. N. F. Gamaley with the joint work of the staff of our department. Control animals with normal intestinal microflora were kept under normal vivarium conditions.

Taking into account the goal and objectives set for this work, two series of experiments were carried out.

In the first series, pieces of duodenal tissue, jejunum, ileum and Peyer's patches were studied in microbe free animals at the age of 1, 3, 7, 14, 21 -days and 4–6 months. after birth. The rats with normal intestinal microflora, born and kept in normal vivarium conditions, were selected as controls.

In the second series of experiments, the effect of normal intestinal microflora on the processes of proliferation and differentiation of the epithelium in crypts, their migration and extrusion from the surface of the villi in amicrobial rats, and amicrobic rats associated with lactobacilli associated

(Lactobacillus plantarum 8P-A3 and Lactobacillus fermentum 90T-90T and Lactobacillus fermentum 90T-90T), was studied.

A light-optical study was carried out after fixation in a mixture of Carnoy, FSU, 12% neutral formalin on paraffin (4–5 μm) and semi-thin (1 μm) sections, stained respectively with hematoxylin-eosin and pyronine G-methylene blue.

For electron microscopic studies, pieces of tissue of the small intestine, Peyer's plaque were fixed in a buffered 2.5% solution of glutar-aldehyde (20 min), 1% solution of OsO4 (1.5 h) at pH 7.2–7.3. Sections obtained on an ultratome 1 KV-4800 after contrasting in a solution of uranyl acetate and lead citrate were viewed in JEM-7 and JEM-100B electron microscopes.

In all series of radioautographic studies for each term used at least 3 animals. The index of labeled nuclei with single and repeated injections of H3 – thymidine was carried out when viewing 2–3 thousand. epithelial cells. The change in the percentage of labeled mitoses in time after a single injection of H3-thymidine is determined after studying 100 mitoses on average for each term.

In all series of experiments with morphometry, the number of statistical samples was carried out taking into account Avtandilov's criteria, statistical processing was carried out according to Student-Fisher. The difference in values is significant at $P < 0.05$.

**Research results**. In order to study the effect of normal intestinal microflora on the morphological, morphometric and ultrastructural features of the immune system of the small intestinal mucosa in the age dynamics, lactobacilli of the series: Lactobacillus plantarum 8P-A3 and Lactobacillus fermentum 90T-S4 were introduced to the microbeless rats. As a control, germ-free rats were taken.

In sexually mature, bacterial-free rats associated with lactobacilli, the lymphoid follicles of the Peyer's patches are located singly or in groups in their own mucous plate. In PB as well as in intact rats, the following structural and functional zones are clearly defined: follicular, parafollicular, dome. Between each follicle, there is a parafollicular zone, which, without sharp boundaries, passes into the surrounding loose connective tissue of the stroma of the mucous and submucous membranes. A dome extending to the follicle from above, bulging into the hemispheric lumen. Its surface is flat, lined with one layer of prismatic epithelium. On the periphery of the PB is surrounded by crypts and villi.

Detected layer-by-layer arrangement of cells in each area of the PB (table number 1). The separation of one zone from another is carried out by reticular cells. In the bright center of the cell are located loosely. The follicular zone surrounding the bright center is dense due to the dense location of the cells. The follicular and parafollicular zones, as well as the dome, consist mainly of small lymphocytes. In the light center of the follicle lymphoblasts are located, which are in contact with each other using shallow invaginations. In this zone, mitotic dividing lymphoid cells, single differentiated plasma cells, macrophages, in whose cytoplasm polymorphic inclusions are identified, are often detected.

The dome of the PB in ultrastructure differs significantly from other zones. In this zone, macrophages are relatively often detected, while plasma, mast and eosinophilic cells are isolated. Lymphocytes lie in groups, surrounded on the periphery with reticular cells. Occasionally lymphoblasts are found among them. Plasma cells are large, may be located near the epithelial layer, capillaries, on the border with the follicular zone. Everywhere they come in contact with lymphocytes and macrophages. Macrophages are more common, have a characteristic structure: in the cytoplasm of some, varying sizes and forms of lysosomes are detected, inside which digestible cells or their fragments are visible, resembling phagocytosed lymphocytes in structure.

Table 1.– The cellular composition of the structural and functional areas of the lymphatic nodule PB small intestine of mature sterile rats associated with lactobacilli (n = 6)

| Cell type | Germinal | Follicle | The parafol zone | licular | Zone Dome Epithelium |
|---|---|---|---|---|---|
| Small lymphocytes | 39.9 ± 3.5 | 61.9 ± 6.1 | 66.6 ± 6.9 | 50.0 ± 1.1 | 43.4 ± 2.6 |
| Large lymphocytes | 6.8 ± 0.3 | 1.2 ± 0.03 | 1.9 ± 0.06 | 10.2 ± 1.4 | 5.9 ± 0.6 |
| Lymphoblasts | 16.9 ± 1.2 | 3.2 ± 0.1 | 3.0 ± 0.1 | 5.8 ± 0.6 | – |
| Plasma cells | 8.2 ± 0.4 | 5.1 ± 0.2 | 1.0 ± 0.02 | 11.5 ± 1.6 | – |
| Reticular cells | 12.6 ± 0.8 | 12.4 ± 0.8 | 18.0 ± 1.5 | 11.3 ± 1.6 | – |
| Macrophages | 0.5 ± 0.1 | 0.2 ± 0.01 | – | 2.6 ± 0.02 | – |
| Mast cells | 0.5 ± 0.01 | 0.5 ± 0.01 | 0.3 ± 0.004 | 1.8 ± 0.1 | – |
| Nediffer- | 12.5 ± 0.8 | 15.5 ± 1.1 | 9.1 ± 0.6 | 9.1 ± 1.2 | – |
| cysed cells | – | – | – | – | 40.8 ± 0.9 |
| Enteric Enterocytes | – | – | – | – | 8.2 ± 0.1 |

Fat and eosinophilic cells of PB, as in their own plate of the mucous membrane of the small intestine, are in contact with macrophages, lymphocytes, are located near the blood capillaries, have a characteristic ultrastructure for them.

Compared to other zones, the dome is relatively rich in blood and lymphatic capillaries, in the lumen of which lymphocytes with processes occur, which are in contact with each other and endothelial cells. In the parafollicular zone, small and medium lymphocytes of typical structure are detected. Single macrophages, large, polymorphic, in contact with mast cells and lymphocytes own plate of the small intestine. Capillaries with flattened or high endothelium.

The surface of PB is lined with a single-layer prismatic epithelium, where poorly differentiated, limbate and single goblet cells differ. Between them in large numbers at different levels of the epithelium are lymphocytes.

The limbate cells have a highly prismatic shape, an oval elongated nucleus, which is located in the basal part of the cell, sometimes in the middle part of the cell, if they are displaced by interepithelial lymphocytes, so they look multi-core. The layer of mucus on the surface of the epithelial cells of the dome is thinned in its direction from the base to the top, sometimes fragmented. In the same direction, the number of interepithelial lymphocytes increases. They practically do not occur between epithelial cells located in the base area of the dome dome PB.

Among the modified epithelial cells in the area of the dome are M-cells. They differ from typical epithelial cells by the presence of microvilli on the apical surface and by invaginations of the plasmolemma in the region of the microvilli, which probably form pinocytosis vesicles. At the base of the M-cells often 1–2 lymphocytes.

Thus, a comparative study of the structure of the mucous membrane of the small intestine of rats without microbes and with normal microflora made it possible to establish a number of significant differences indicating the morphogenic influence of microorganisms. Normal microflora causes the acceleration of epithelial renewal in the villus-crypt system, reduces the linear parameters of the villi and increases the -crypt, the proximal-distal gradient becomes more distinct. In the lamina propria, the number of cells of loose connective tissue increases. Particularly noticeable increase in plasma cells and macrophages, their cooperation with other cells of the stroma, the number of infiltrating lymphocyte epithelial layer. Significantly reduced the number of secretory granules in them.

A comparative analysis of the morphological and functional rearrangements of the small intestinal mucosa of gnotobiont rats during contamination with representatives of the normal and pathogenic intestinal microflora suggests that pathogenic microbes have a more pronounced immunogenic effect than representatives of normal microflora.

In germ-free rats, there is a slow migration of cells in the crypt-villus system, a longer lifespan than in normal ones. Lactobacilli accelerate the migration of epithelial cells, but not as intensively as with normal microflora (in animals living under normal vivarium conditions). The life cycle of enterocytes in the crypt-villus system is shortened. This is accompanied by a deepening of the crypts and a decrease in the height of the villi. This is a universal mechanism of adaptation to changes in the microbiocenosis of the intestine, which is observed in various infectious and allergic enterocolitis, resection of the small intestine, aimed at maintaining the established relationship in the crypt-villus system, the architectonics of the small intestinal mucosa.

Thus, the study of the mucous membrane of the small intestine in early postnatal ontogenesis, in germ-free animals, after the introduction of various microbial associations, allowed the influence of intestinal microflora on the epithelium kinetics, linear parameters of the crypt-villus system, change in proximal-distal gradients, structure of the lamina propria and structurally – functional zones PB. Without touching upon the various complex, intensively developed aspects of their functioning, it was noted that under physiological conditions, the integration of the activity of PB cells, the lamina and the interepithelial lymphocytes ensures the homeostasis of the internal environment, protection from microorganisms, products of their vital activity, food antigens, intestinal microflora. The interaction of fat and eosinophilic cells in germ-free animals during all periods of postnatal life, various types of cooperation of connective tissue cells in the lamina of the small intestinal mucosa of adult rats with normal microflora expands the existing ideas about the immune function of the organ, its innate ability to form protective mechanisms.

**Conclusion**. 1. Structural and functional zones of PB of adult conventional rats differ in their cellular composition and lymphocyte kinetics. Lymphocytes synchronously, synchronously, with high speed, migrate from all areas of the PB to the dome area, from where they quickly, within a day, decrease.

2. Changes in the structure and function of the mucous membrane of the small intestine at different periods of ontogenesis in the dynamics of the process of absorption reflect its ability, respectively, to slow and fast adaptations.

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# PREVALENCE OF DISEASES OF VISUAL ORGANS AMONG CHILDREN: REVIEW

**Abstract.** In the various countries of the world, much attention is paid to studying the causes, development and prevalence of eye diseases, especially among children. The article provides a review of the literature in recent years and described current state the incidence of children and adolescents in ophthalmic pathology.

**Keywords**: diseases of the organ of vision, refractive pathology, children, prevalence, regional characteristics.

Currently, a person faces the growing effects on his body of various external, chemical and biological factors. Organ of sight, as part of the body, is also subject to the influence of given factors that might include environmental. These factors affect not only the structure of the organ of vision, but also violate its activity, which is expressed by the development of various pathologies.

In various countries of the world, much attention is paid to the study of the causes, development and prevalence of eye diseases, especially among children. There is also an acute problem regarding the study of eye injuries, disability from eye diseases and the influence of various harmful factors on the organ of vision of children of different ages.

To date, clinical features, diagnosis, conservative and surgical treatment of various eye diseases studied extensively, with the development and supply in the practice of modern, advanced methods of diagnosis and treatment of diseases [1; 17; 21].

The study of the prevalence of eye diseases, as well as the problems of clinical examination, disability and prophylaxis with them, is devoted to the study of some scientists from near and far abroad [16; 25].

A special place in the state of health of the children's population was occupied by diseases of the organ of vision. In the structure according uptake incidence proportion eye diseases whether composed of 4–5%. In the Russian Federation, children with physical and mental disabilities made up about 4.5% of the children of the population, of whom 18% are children with visual organ damage. Pathological affected children in Russia diseases of the eye and its appendages was compiled 144.6. The structure of the pathological affection whether prevailing refraction and accommodation disorders (74.1%), strabismus and other disorders binocular movement (10.6%), inflammatory diseases (7.7%). Observe that with increasing age, an increase in the pathological infestation of children from 73.0‰ (up to 3 years) to 364.6‰ (during adolescence). Due to violations of refraction and accommodation, the incidence of girls is higher than boys. The prevalence of diseases of the organ of vision had regional features [17].

Disability of the child population is an important medical and social problem. Among the children of the Russian Federation revealed a trend of growth prevalence eye diseases, while in children in the first year of life in 11.1%, in children under 14 years old in 12.1%, in adolescents 15–17 years old in 5.9%. Occupying a dominant place if disturbances in visual acuity (32.8% among children, 56.1% of adolescents). A significant impact of the socio-economic development of the regions on the formation of ophthalmologic pathology in children has been established [15; 20].

In the Republic of Azerbaijan, the total number of newly recognized disabled people was 3015 children. The level of primary disability ranged from 2.7 to 1.8 per 10,000 children. The total number of children re-recognized as disabled due to ophthalmopathology was 4090 children. The level of disability ranged from 1.9 to 4.2 per 10,000 children [18].

Isakhanov A. L. [12] studied in detail the causes of reduced vision in schoolchildren with different motor activity. The influence of the motor activity of schoolchildren on the development of their shortsightedness was proved, which should seriously affect the preparation of methodological manuals for the prevention of this disease.

According to WHO, there are currently 45 million blind people in the world and 135 million people with serious visual impairments, the number of blind children may double by 2020. At the same time, according to WHO experts, 80% of cases of blindness can be avoided. The WHO initiative aims to fight the diseases of the eye, which causes blindness and can be prevented and treated [8].

Mirskaya N. B. et al. [19] believe that the high prevalence of pathological conditions of the organ of vision in modern schoolchildren is an objective medical and social prerequisite for developing effective measures for the prevention and correction of disorders and diseases of the organ of vision in schoolchildren.

Research has established [2; 14] that the prevalence of diseases of the organ of vision in children in Kazan was on average 205.4 ± 0.3‰. The most frequent were refractive errors, conjunctivas diseases and eyelid pathology. The prevalence of diseases of the organ of vision among children living in the area with heavy traffic was higher and amounted to 223.1 ± ± 0.3‰, whereas in the control area 97,9 ± 0,4‰. In the area with heavy traffic in the structure of the pathology of the organ of vision, the first place was occupied by refractive errors, the second – conjunctivas diseases, the third – eyelid pathology.

When analyzing diseases of the organ of vision in children living in ecologically unfavorable conditions, the authors noted functional and organic changes in the visual analyzer, indicating the negative role of air pollution. There were violations of microcirculation, biochemical metabolism, affecting the sclera frame properties. The authors assumed that the effect of anthropogenic pollution on the organ of sight of children was mediated and caused various ophthalmologic diseases, including refractive errors [3,10].

The increased proportion of refractive pathology in the structure of low vision is due to the fact that due to the great advances in computer technology, the increasing visual load, especially in children aged 10–14 years, non-compliance and discrepancy of the elementary physiological and hygienic requirements for the organization of the educational process contribute to changes and worsening of many health indicators, including acquired eye diseases in schoolchildren [13; 20].

Analyzing the data of Lin L. L. et al. from Taiwan, it was concluded that from 1983 to 2000, there was an increase in myopia from 5.8% to 21% in 7-year-old children. When examining schoolchildren at the age of 12, an increase in the number of patients with myopia from 36.7% to 61% was revealed [20].

A survey of Singaporean schoolchildren aged 7–9 years from 1999 to 2002 revealed a progression of myopia (47.7%) from 1.0 to 2.5 diopters. As a result of studies conducted in Mexico, it was found that among 1035 schoolchildren of Mexico City at the age of 12–13 years, visual impairment is represented mainly in the form of refractive pathology.

A study of the prevalence of ocular pathology among schoolchildren in the eastern part of Sydney by Australian scientists revealed the predominant role of ametropia, mainly myopia – 8.3% in 12-year-olds. However, the percentage of patients with myopia among multiethnic groups of students in eastern Sydney was much lower compared with the same type of students in the United States and Asia. During the examination of 217 students aged from 6 to 18 years old school for the blind in Saudi Arabia, cases of bilateral blindness were detected in children with retinal degeneration, congenital glaucoma and optic nerve atrophy. In 89% of children, blindness was due to hereditary or congenital diseases [4; 5; 11].

By Djalilov E. D. et al. [7] were examined 29 children aged 4–8 years. The prevailing number of sick children (62%), were children from related and closely related marriages. Microphthalmos and atrophy of optic nerve were the leaders in the structure of diseases of the organ of vision. It should be noted that these diseases are registered in children born from closely related marriages.

Many different risk factors have caused impairment of normal retinal vasculogenesis in very premature babies. It is the violation of retinal vasculogenesis that underlies the development of retinopathy of prematurity, in connection with which it can rightfully be called the disease of the developing vessels [24].

According to G. Nikolaev [22] retinopathy premature is given the third place in the nosological structure of children's disability. The main forms of pathology leading to childhood blindness: optic nerve atrophy (32%), congenital cataract (20%), retinopathy premature (18%), degenerative myopia (18%), congenital glaucoma (4%), others (8%).

The significant influence of the socio-economic development of the regions on the formation of the ophthalmological morbidity of children and adolescents has been established. High incidence rates were noted in economically and medically-well-organized regions. The incidence rates were associated with the development of transport infrastructure in the territory and the provision of telephony to the apartments [9; 20].

Daynogo V. N. et al. [6] believe that the presence of children and adolescents in a light environment with an excessive dose of blue light can lead to degradation of the retina 10 years earlier than when exposed to natural light. When LED lighting white first-generation LEDs (blue crystal and yellow phosphor), which have a dip in the spectrum at 480 nm, there is a significant increase in the area of illumination of the retina in the blue part of the spectrum. For maternity homes, children's institutions and schools, it is preferable to use the latest generation of lamps with a biologically adequate spectrum of white light. But according to Polish researchers, refractive pathology in 3636 children aged 6 to 18 years revealed, regardless of sanitary conditions on sight – the use of fluorescent lamps. The authors have not established a link between the type of room lighting and the prevalence of violations of the optical structure of the eye.

WHO expert [27] conducted a meta-analysis of the epidemiology of eye injuries: 55 million injuries occurred each year leading to disability for more than 1 day, 750000 injuries requiring hospitalization, 200000 open eye injuries. Due to eye injury 19 one million people lost sight in one eye; 2.3 million had bilateral vision reduction and 1.6 ml n. lost sight in both eyes.

In the Russian Federation in large ophthalmological centers, the proportion of patients with eye injuries and their consequences accounts for up to 1/3 cases. About 22% of hospitalized patients are children under 16 years old.

In Kazakhstan, among working-age people, amongst the causes of disability, eye injuries are in the first place, and in children – in the third place. Up to 50% of all accidents of eye injury occur at the age of 18 years. It turned out that boys aged 5–7 years in relation to girls are most prone to eye injuries. The group of children aged 3–9 males had the highest frequency of injuries at home, at school and on the street [26].

In the Khabarovsk Territory of the Russian Federation, the proportion of pediatric ophthalmic injuries was 46% among all treated children [23]. In Tajikistan, the proportion of children's eye injuries was 27–35%, while in Kyrgyzstan this figure was 20.5–35% [28].

The above problems are relevant in the Republic of Uzbekistan, in the literature there are few scientific works devoted to this problem. Rare scientific works devoted to environmental issues incidence of eye diseases, problems am forecasting the development of eye diseases. In addition, there are practically no works related to modern aspects, a conceptual approach to the prevention, correction of disorders of eye diseases in children of preschool and school age.

In connection with these arguments, the solution of the above problems through the implementation of research and development works is a modern, relevant and sought-after.

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# THE EXPERIENCE OF TREATMENT OF CHILDREN WITH CONGENITAL ABNORMALITIES AND TRAUMATIC INJURIES OF THE CRANIO-MAXILLOFACIAL AREA WITH NICKEL-TITANIUM MATERIALS

**Abstract.** The article describes the results of clinical application of nickel-titanium materials (threads, straps, bars) in children's maxillofacial surgery. The main properties of nickel-titanium alloy, comparative characteristics of "Prolene" and "Ti-Ni" threads in the treatment of wounds are given. The clinical cases and observations of using of nickel-titanium in the removal of tissue defects in the cranio-maxillofacial area in children are presented.

**Keywords:** nickel-titanium, clinical effectiveness, treatment, wounds, defects, congenital pathology, cranio-maxillofacial surgery, children.

The choice of suture material in the removal of tissue defects in the practical cranio-maxillofacial surgery is still an actual problem, which is determined by the high frequency of such defects (due to congenital pathology, traumatic injuries, tear-contused and tear-bite wounds of face, tumors and tumor-like processes) and a large selection of suture materials for their riddance. The disadvantages of natural suture materials are insufficient mechanical endurance, manifestation of the properties of wick effect, high reactivity and allergenicity, expressed absorption ability. The other kinds of materials behave like foreign bodies after placing in the organism owing to the lack of biocompatibility characteristics. Therefore, it is necessary to create and implement in clinical practice suture materials that have not only the optimal physical, biological and corrosive features in the environments of the organism, but also positive clinical properties.

The **purpose** of this research is to study the clinical efficacy of nickel-titanium materials in the elimination of congenital pathology and traumatic injuries of the cranio-maxillofacial area in children.

There are two types of suture and plastic materials, which were used in the research:

1. "Prolene". This is a monofilament synthetic nonabsorbable surgical suture material. It is made of isotactic crystal stereoisomer of polypropylene, synthetic linear polyolefin. It has good manipulation characteristics, elasticity, relative biological inertness and mechanical strength, atraumaticity.

2. Threads, straps, bars with a shape memory of nickel-titanium alloy of the mark "TH-10". "Ti-Ni" materials were developed in the Tomsk Research Institute of Alloys. There are only positive reviews, good reparation of wounds, absence of inflammation in tissues and complications, early rehabilitation of patients.

18 children at the age of 5 to 11 years were observed in the unit of children maxillofacial surgery of the Ivano-Matreninskaya Children's Clinical Hospital of Irkutsk. Patients were divided into 3 groups.

**The first group** is 8 children with traumatic injuries of soft tissues of maxillofacial area, whose treatment was carried out with suture material "Prolene" of sizes of threads 4, 0, 5, 0 and 6.0.

**The second group** is 7 people. The same injures were carried out by threads of fiber nickel-titanium with the sizes of 80–120 microns.

**The third group** included 3 observations – the children with congenital facial and oral pathology and combined cranio-maxillofacial trauma.

The comparative analysis of wound healing (reduction of infiltration, cessation of exudation, appearance of proliferation) was made in the postoperative period (7 days) in the first and in the second groups. Clinical efficiency was compared of using of "Prolene" and "Ti-Ni" threads with a shape memory.

In the treatment of children with congenital pathology (the third group) and combined cranio-maxillocerebral trauma the behavior of "Ti-Ni" materials in the tissues of organism was explored, and long-term results of their employment were fixed.

The following positive characteristics of "Ti-Ni" materials were found during the research: high biochemical and biomechanical compatibility, hypoallergenic properties, atraumaticity, super elasticity in conditions of body temperature, mechanical strength, good handling attributes, the effect of "memory shape" with temperature changes, high corrosion resistance. The advantages of using this material were found out in comparison with classical "natural" threads:

1. Inflammatory infiltration of surrounding tissues with using of "Ti-Ni" threads remained for 2–3 days, and with using of "Prolene" – 3–4 days;

2. Exudation disappeared in 3 days with using of "Ti-Ni" threads;

3. Reparation of wounds was faster when their edges were approached with the threads from "Ti-Ni", so removal of sutures from the threads on its basis was carried out on the 6$^{th}$, and from "Prolene" – on the 7$^{th}$ day;

4. Using of suture material from "Ti-Ni" gave a more optimal cosmetic result in comparison with stuff from "Prolene". The post-traumatic hems have good cosmetic properties, flat structure. They also are not visible on the aesthetically important areas (face and neck). All these qualities of nickel-titanium suture material allow accelerating rehabilitation of children with traumatic injuries of the cranio-maxillofacial area.

After using staples, bars and threads of "Ti-Ni" in the third group of patients the full integration of these materials with the tissues of organism, absence of postoperative complications, optimal functional and aesthetic results in the distant terms were noted.

Figure 1. The result of treatment of bilateral congenital transverse cleft of mouth with employment of treads from "Ti-Ni" and a distant result after two years of observation

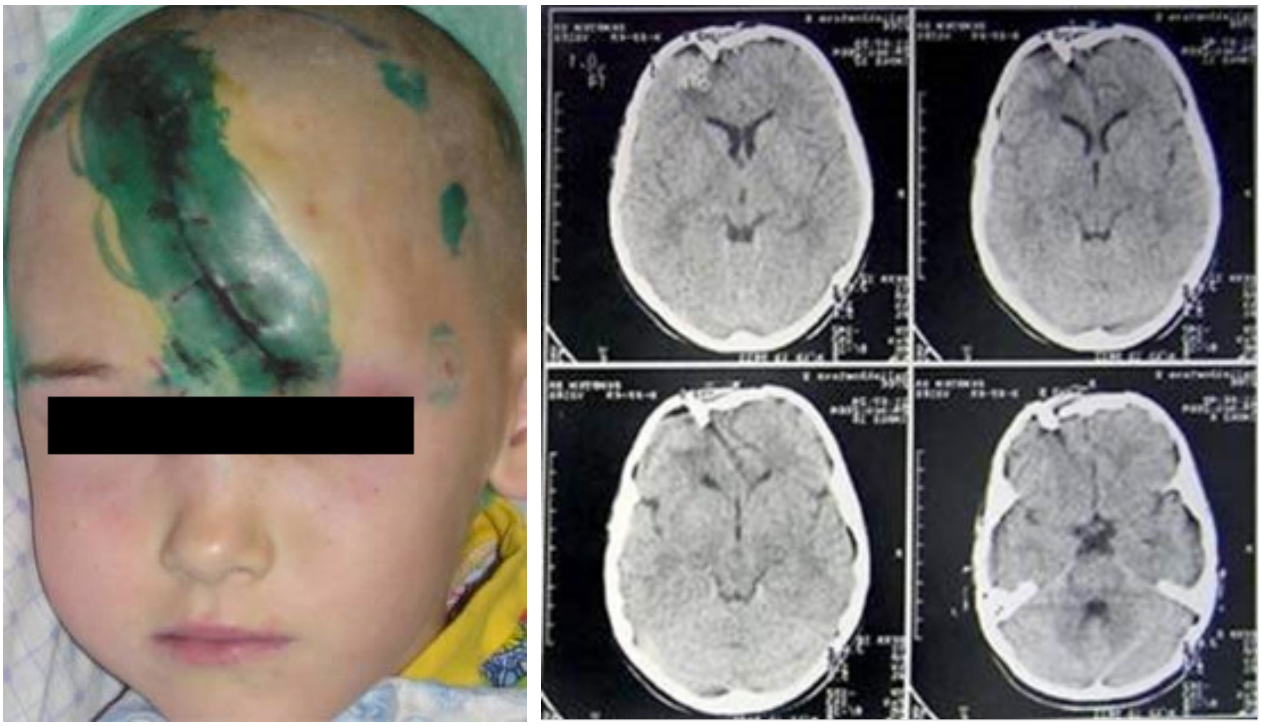

Figure 2, 3. Patient, 7 years old. Diagnosis: open cranio-cerebral injury of the frontal region and left cranial roof

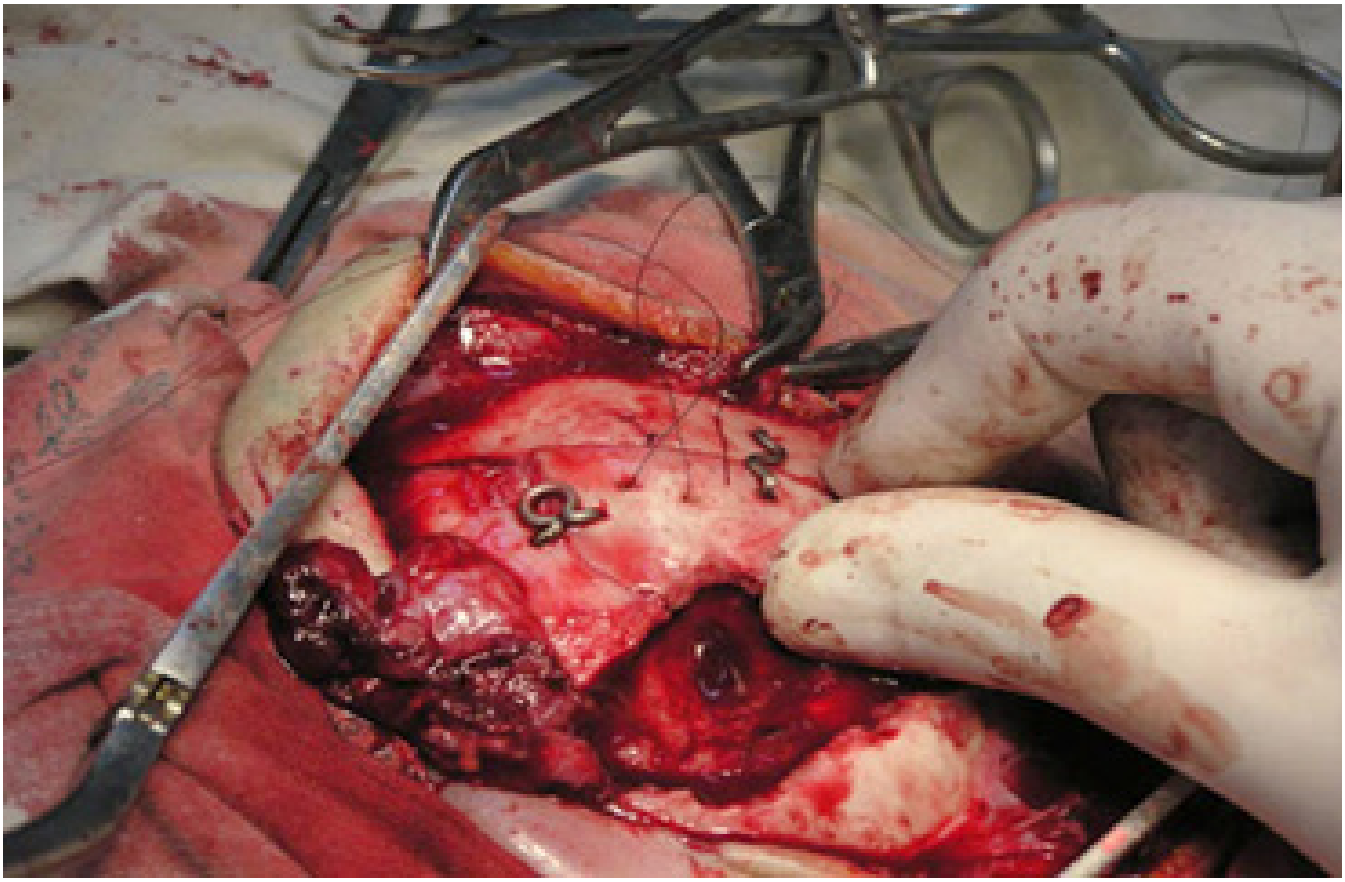

Figure 4. Surgery: osteosynthesis of forehead bones, frontal sinus, plastic of skull defect with porous and permeable “Ti-Ni” bars, threads and staples, stitching of dura mater with “Ti-Ni” threads, the creation of frontal sinus, fixation of bone elements with “Ti-Ni” materials

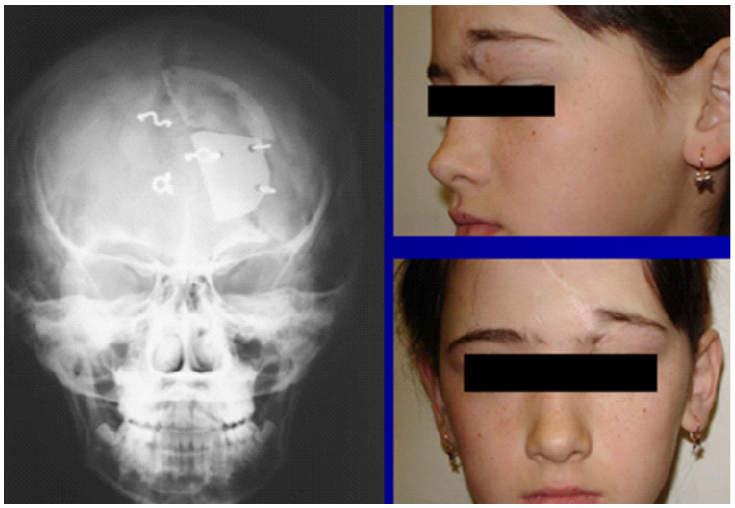

Figure 5. Radiological control of the result of the operation and the appearance of the patient after elimination of the skull defect

Figure 6. The distant result after 13 years of observation

Thus, "Ti-Ni" materials have optimal properties for the treatment of congenital and acquired defects of cranio-maxillofacial area in children. In addition, the using of "Ti-Ni" materials differs by the significant positive results and excellent clinical effectiveness as well. It gives grounds to create and introduce into medicine modern materials for treatment of various pathologies more widely. Their employment increases the quality of medical care in the cure of cranio-maxillofacial injuries in children's maxillofacial surgery.

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# SCREENING OF THE CHRONIC OBSTRUCTIVE PULMONARY DISEASE UNDER THE CONDITIONS OF LARGE INDUSTRIAL CENTER

**Abstract.** Chronic obstructive pulmonary disease is the fourth cause of mortality in all over the world. The main risk factors for development COPD in young population are registered smoking, bronchial hypersensitivity, frequent respiratory infection in the childhood. There has been performed investigation by program of the modern pulmonological screening of 3000 persons of the age 20–60 years working at the enterprises in Tashkent. This program allowed active identification of individuals with risk factors of COPD and respiratory symptoms even slightly expressed and qualitative performance of spirometry allows for specialist of the primary stage of medical care to diagnose COPD at early stages.

**Keywords:** chronic obstructive pulmonary disease, screening, risk factors, early diagnosis.

Chronic obstructive pulmonary disease (COPD) at present is one of the most significant diseases taking into account the burden of social problems, which is beard by society connected with progressing of disease and its systemic effects [1].

COPD is the fourth cause of mortality in all over the world, and how it is predicted, in the nearest decay it will be observed increased prevalence and mortality from it.

The main risk factors for development of COPD appeared to be smoking, bronchial hypersensitivity, frequent respiratory infection in the childhood [2]. Hypodiagnosis of COPD is usually characteristic for individuals of young and adult age and often connects with absence or insignificant expressions of respiratory symptoms in them [3].

The formation of disease is developing during many years and manifests in the period when it is impossible to restore the functions of the bronchopulmonary system.

It is known how important the role of early diagnosis of COPD and prescription of timely adequate starting therapy. According to the data of European Respiratory Society only 25% cases of disease is diagnosed in time [4]. COPD is frequently diagnosed missed or remained to be unrecognized. At early stages of COPD the patients frequently have no complaints.

The early diagnosis (stage 1) is possible only in active identification of the patients in the groups of risk with methods of special questionnaire and functional investigation of the lungs.

The complexicity of timely diagnosis of the obstructive pulmonary disease justified to perform this investigation the purpose of which was early diagnosis of COPD.

**Materials and methods:** According to tasks there was studied morbidity due to COPD, and there was performed examination according to the program of the current pulmonological screening of 3000 persons of the organized population working at the different enterprises of Tashkent at the age from 20 to 60 years.

Assessment of the system of external respiration was performed with method of computed pneumatachometry on the apparatus "Masterlab" (Erich Jaeger, Germany), providing automatic analysis of the parameters of the structure of the lung volumes (FJEL), momentary maximal volumetric velocities at expiration 25.50/75% (MOC25, MOC50, MOC75), expressed in percents.

**Results of research:** We tried to study prevalence rate of COPD at various stages of disease. For this purpose there were examined 3000 individuals of the organized population of Tashkent. Females were 1400 persons (46.7%), males – 1600 persons (53.3%). The mass screening examination showed, that prevalence of COPD in the studied population accounted for 8.7%. A number, character of the clinical course of disease provided possibility of the representative analysis of the results of the investigations performed from various positions.

All patients with COPD were divided into 4 groups in relation to severity degree. At distribution there was used system of severity degree proposed by GOLD (2003). The main part of patients comprised of only persons with I and II severity degree, and only insignificant part were on III and IV stage of severity degree. The investigation was performed on the enterprises, so the main part of patients consisted of contingent with working ability, while individuals with III and IV stages appeared to be disabled.

We concider the fact the majority of patients with COPD were revealed for the first time appeared to be very important moment (75.2%). Only small quantity of patients before our examination were under observation in

the therapeutic institutions in Tashkent. It was very important that they were persons with severe and extremely severe stage of disease.

Analysis of the data of medical history and results of the functional investigation showed verification of COPD in 263 patients, that accounted for 8.7% of all the interviewed. Among the women COPD was diagnosed in 6.4% of cases (n – 90), among the men COPD was found in 10.8% of cases (n – 173). The incidence of COPD with regard to the stages of disease is presented in (table 1).

Table 1.– The incidence of COPD with regard to stages of disease in men and women

| Gender | n | COPD is diagnosed | COPD | | | |
|---|---|---|---|---|---|---|
| | | | I ст. | II ст. | III ст. | IV ст. |
| Men | 1600 | 173 | 103 | 38 | 25 | 7 |
| | 100% | 10.8 ± 0.8* | 6.4 ± 0.6* | 2.3 ± 0.3 | 1.5 ± 0.3** | 0.4 ± 0.1 |
| Women | 1400 | 90 | 37 | 38 | 10 | 5 |
| | 100% | 6.4 ± 0.6 | 2.6 ± 0.4 | 2.7 ± 0.4 | 0.7 ± 0.2 | 0.3 ± 0.1 |
| Totally | 3000 | 263 | 140 | 76 | 35 | 12 |
| | 100 | 8.7% | 4.6 ± 0.3 | 2.5 ± 0.2 | 1.2 ± 0.2 | 0.4 ± 0.1 |

*Note: in the numerator –absolute number; in the denominator –percent;*

**difference reliability between men and women p<0,001; ** reliability of differences p < 0.05*

Table 1 shows that COPD is reliably more often met among men at the first stage of disease (6.4%), and among women – at the second stage of disease (2.7%).

Analysis of COPD incidence with regard to age (table 2) showed that in women of age above 49 years COPD was noted 2 times more often, than at age of 40–49 and younger. In men the frequency of COPD increases 2.8 times with age growing (from 6.7% to 18.9%). It was noted that with age increasing both among women and men the specific weight is also increasing in patients with more severe stages of disease. Comparative analysis of the frequency rate of COPD in patients in the age group of 50–59 years showed that among the men the frequency of COPD was 1.9 times higher than among the women of age 40–49 years – 2.3 times and of age 30–39–1.6 times.

Table 2.– Characteristic of the patients in relation to age and gender

| Gender | Age groups | n = 3000 | COPD | I st. | II st. | III st. | IV st. |
|---|---|---|---|---|---|---|---|
| Women | **20–29** | 143 | 7 | 5 | 1 | – | 1 |
| | | 100% | 4.8% | 3.4 ± 1.5 | 0.7 ±0.7 | – | 0.7 ± 0.7 |
| | 30–39 | 247 | 12 | 4 | 4 | 1 | 3 |
| | | 100% | 4.8% | 1.6 ± 0.8 | 1.6 ± 0.8 | 0.4 ±0.4 | 1.2 ±0.7 |
| | 40–49 | 488 | 20 | 12 | 7 | 1 | – |
| | | 100% | 4.1% | 2.4 ± 0.7 | 1.4 ± 0.5 | 0.2 ± 0.2 | – |
| | 50–59 | 522 | 51 | 16 | 26 | 8 | 1 |
| | | 100% | 9.8% | 3.0 ± 0.7 | 5.0 ± 0.9 | 1.5 ± 0.5 | 0.2 ± 0.1 |
| | Всего | 1400 | 90 | 37 | 38 | 10 | 5 |
| | | 100% | 6.3% | 2.6 ± 0.4 | 2.7 ± 0.4 | 0.7 ± 0.2 | 0.3 ± 0.1 |
| Men | 20–29 | 371 | 25 | 20 | 5 | – | – |
| | | 100% | 6.7% | 5.4 ± 1.1 | 1.3 ± 0.5 | – | – |
| | 30–39 | 339 | 26 | 15 | 5 | 4 | 2 |
| | | 100% | 7.7% | 4.4 ± 1.1 | 1.4 ± 0.6 | 1.8 ± 0.7 | 0.6 ± 0.4 |
| | 40–49 | 483 | 45 | 33 | 4 | 7 | 1 |
| | | 100% | 9.3% | 7.0 ± 1.1 | 0.8 ± 0.4 | 0.6 ± 0.3 | 0.2 ± 0.2 |
| | 50–59 | 407 | 77 | 35 | 24 | 14 | 4 |
| | | 100% | 18.9% | 8.6 ± 1.4 | 5.6 ± 1.1 | 3.4 ± 0.8 | 1.2 ± 0.5 |
| | Всего | 1600 | 173 | 103 | 38 | 25 | 7 |
| | | 100% | 10.7% | 6.5 ± 0.6 | 2.3 ± 0.3 | 1.3 ± 0.2 | 0.7 ± 0.2 |

*Note: in the numerator –absolute number; in the denominator –percent;*

It has been seen in (table 3), that diagnosis of COPD was made for the first time that that indicates about hypodiagnosis and possible outcomes of disease in 8,4% of men and 4.5% of women.

Table 3. – Characteristics of studied patients

| Gender | Diagnosis of COPD has been made | | Totally |
|---|---|---|---|
| | Previously | For the first time | |
| Men | 38 | 135 | 173 |
| n=1600 | 2.4% | 8.4% | 10.8 ± 0.7 |
| Wome | 27 | 63 | 90 |
| N=1400 | 1.9% | 4.5% | 6.4 ± 0.7 |
| Total | 65 | 198 | 263 |
| n=3000 | 2.1% | 6.6% | 8.7 ± 0.5 |

Comparative data about patients with COPD, being under dispensary observation and revealed for the first time, are presented in table 4, of which it is seen that as among males, so as among females, being earlier under observation, there are prevailed severe forms of disease, stage III (52.6% and 33.3%) and IV (18.4%), and among the patients with identified for the first time stages I and II of disease in 96.3% of males and to 98,4% of females.

Table 4. – Comparative data of patients with COPD being under dispensary observation and revealed for the first time in relation to stages

| | | «I» | «II» | «III» | «IV» | Totally |
|---|---|---|---|---|---|---|
| Women | Identified for the first time | 34 | 28 | 1 | – | 63 |
| | | 54.0 ± 6.3** | 44.4 ± 6.3 | 1.6 ± 1.6 | – | 100% |
| | Being under the observation | 3 | 10 | 9 | 5 | 27 |
| | | 11.1 ± 6.0 | 37.0 ± 9.3 | 33.3 ± 9.0 | 18.5 ± 7.4 | 100% |
| | **Totally** | 37 | 38 | 10 | 5 | 90 |
| | | 41.1 ± 5.2 | 42.2 ± 5.2 | 11.1 ± 3.3 | 5.6 ± 2.4 | 100% |
| Men | Identified for the first time | 102 | 28 | 5 | – | 135 |
| | | 75.6 ± 3.7** | 20.7 ± 3.5 | 3.7 ± 1.6 | – | 100% |
| | Being under observation | 1 | 10 | 20 | 7 | 38 |
| | | 2.6 ± 2.6 | 26.3 ± 7.1 | 52.6 ± 8.1** | 18.4 ± 6.2 | 100%* |
| | **Totally** | 103 | 38 | 25 | 7 | 173 |
| | | 59.5 ± 3.7 | 22.0 ± 3.1 | 14.4 ± 2.6 | 4.1 ± 1.4 | 100% |

*Note: in the numerator –absolute number; in the denominator –percent;*
**difference reliability between primary and earlier being under observation * $p < 0.05$; **$p < 0.001$*

Thus, among all studied population only 65 (2.1%) were under observation in the therapeutic institutions, that accounted for 24.7% out of all revealed patients. For the first time diagnosis of COPD was established in 198 studied patients (6.6%), that accounted for 75.2% out of all revealed patients. The data obtained indicate that majority of young individuals of the both gender having clinical symptoms of disease diagnosis of COPD was not made, and consequently the therapeutic and prophylactic measures were not performed. The patients who were under observation in the institution of public health service, as a rule, have already process of moderate and severe degree. So, only 30% of all women (n –27) and 22% of men (n –38) had established diagnosis of COPD before our investigation, out of them in 51.8% of women and 71.0% of men the disease had severe degree with bright clinical signs.

We conceder it is important that in these persons diagnosis of COPD was established rather lately, however these patients, as a rule, has diagnosis of chronic bronchitis. This moment appeared to be a cause of missed approaches to treatment, and as consequence, enhance development of disease.

We have studied critical role of the various risk factors such as professional harmful conditions: toxic-chemical and dusty, smoking, recurring diseases of the upper respiratory ducts and development of COPD. The research showed that 45.9% (n–1376) of patients had effect on the body of some or other studied factor or their combinations. With regard

to structure of the risk factors it was noted that factor of smoking occurred with frequency to 37.3%, recurring diseases of the upper ducts – to 11.8%, effect of toxic-chemical factor – to 17.7%, dusty – to 33.2%.

Table 5. Prevalence of the risk factors among the individuals with or without COPD

| Risk factors | | Totally n = 1376 | Presence of COPD diagnosis n = 263 | Absence of COPD diagnosis n = 1113 |
|---|---|---|---|---|
| Occupational harmfulness | Toxic-chemical | 244 | 72 | 172 |
| | | 17.7 ± 1.02 | 27.3 ± 2.7 | 15.5 ± 1.08* |
| | Dusty | 457 | 2 | 455 |
| | | 33.2 ± 1.26 | 0.8 ± 0.5 | 40.9 ± 1.4** |
| Smoking | | 513 | 156 | 357 |
| | | 37.3 ± 1.3 | 59.3 ± 3.02 | 32.1 ± 1.4* |
| Recurring diseases of the upper respiratory ducts | | 162 | 33 | 129 |
| | | 11.8 ± 0.8 | 12.5 ± 2.03 | 11.6 ± 0.95* |

*Note: in the numerator –absolute number; in the denominator –percent;*
*reliability (*p < 0.05; **< 0.002) between presence and absence of COPD*

On the basis of the results of research it was established that among the individuals with determined diagnosis of COPD the frequency of meeting of some risk factors prevailed reliably the level, than among the persons without diagnosis of COPD: toxic-chemical effect – by 1.8 times, smoking – by 1.8 times, recurring diseases of the upper respiratory diseases – by 1.07 times.

Analysis of the risk factors for development of COPD in the males and females is presented in table 6, from which it is seen, that among males the smoking (60.7%) and toxic-chemical effect (33.0%) appeared to be factors of COPD formation, the frequency among which is reliably higher, in comparison with individuals without COPD ($p < 0.01$). Among women the leading factors for development of disease may be presented by smoking (56.7%) and recurring diseases of the upper respiratory ducts (24.4%). However, while comparing significance of the risk factors among males and females, suffering from COPD, it is necessary to note that factor of smoking and toxic-chemical effects are reliably more frequently registered in males, suffering from COPD.

Table 6.– Frequency of the risk factors for COPD

| Risk factors | Determined diagnosis of COPD | | | Undetermined diagnosis of COPD | | |
|---|---|---|---|---|---|---|
| | Males n = 173 | Females n=90 | P | Males n = 711 | Females n = 402 | P |
| Toxic-chemical | 57 | 15 | P < 0.01 | 104** | 68W | P < 0.001 |
| | 33.0 ± 3.5 | 16.7 ± 3.9 | 1 | 14.6 ± 1.3 | 16.9 ± 1.8 | |
| Dusty | – | 2 | | 289 | 166ww | P < 0.05 |
| | – | 2.2 ± 1.5 | | 40.6 ± 1.8 | 41.3 ± 2.4 | |
| Smoking | 105** | 51ww | P < 0.01 | 244 | 113 | P < 0.01 |
| | 60.7 ± 3.7 | 56.7 ± 5.2 | 1 | 34.3 ± 1.7 | 28.1 ± 2.2 | |
| Recurring diseases of upper respiratory ducts | 11 | 22 ww | P < 0.01 | 74* | 55 | P < 0.05 |
| | 6.4 ± 1.8 | 24.4 ± 4.5 | 1 | 10.4 ± 1.1 | 13.7 ± 1.7 | |

*Note: in the numerator –absolute number; in the denominator –percent;*
*P – reliability between males and females with COPD;*
*w – reliability between females with COPD and without COPD;*
** – reliability between males with COPD and without COPD (**p < 0.001; P < 0.05)*

Analyzing the factor of smoking it was noted that out of all studied individuals 22% were males (n–349) and 11.7% women (n –164). The frequency of COPD among smoking males was found in 105 patients, among the smoking females – in 51 individuals. The patients smoking previously included 1.5% of males (n–24) and 0.85% of females (n –12) and frequency of COPD occurred in this group was 13.8% and 13.3%, respectively.

Table 7. Effect of smoking into COPD

| Smoking | Nonestablished COPD n = 2737 | Established COPD n = 263 |
|---|---|---|
| Active smoking people | 357 | 156 |
| | 100% | 43.6% |
| Smoking in the last time | 536 | 36 |
| | 100% | 6.7% |
| Not smoking | 1844 | 71 |
| | 100% | 3.8% |

Studying of the effect of smoking factor on COPD it was revealed that 43.6% of actively smoking had diagnosis COPD, at the same time among individuals smoking in the last time diagnosis of COPD was determined in 6.7% of cases. Not smoking people had the less risk of the COPD occurrence, because in this group COPD was noted in 3.8% of cases.

Studying the factor of smoking in relation to stage of disease it is necessary to note that at stages of COPD I and II there is met category of individuals not smoking and persons smoking in the last, and at stages III and IV of disease there is found high special weight of actively smoking patients.

Data shows that at the initial stages of disease index of smoking individual accounts for 10–20 years, while at the late stages there is noted index higher than 30 years. Consequently, it may be concluded that with growing index of smoking man the severity of disease increases too and this process has closed interrelation.

In our research the recurring diseases of the upper respiratory ways resulted in COPD among males in 12.8% of cases, and among women in 20.8% of cases. At the comparing of the risk factors of various origins it was clear that the main provocateur of COPD among males is smoking, and among women – the recurring diseases of the upper respiratory ways.

All the patients with verified diagnosis of COPD were registered in the pulmonological center, where they were offered programs of rehabilitation and constant regular observation of the specialist. In the conclusion it is necessary to note that the final purpose for performance of any epidemiological investigation is to introduce clarity into prevalence of this disease in the region, to study the gender-aged characteristics of the epidemiological characteristics. In its turn this will allow to know real parameters of morbidity and help to reduce growth of parameters of morbidity and mortality due to COPD.

Thus, active identification of the individuals with risk factors of COPD and respiratory symptoms even less marked, and qualitative, according to the current requirements, performance of spirometry will open possibility for doctor of the primary level of public health service to diagnose COPD at the early stages.

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# EVALUATION OF CARDIOVASCULAR EVENTS FOR THE PREVENTION OF CARDIOVASCULAR DISEASES

**Abstract.** It is recommended to determine the total cardiovascular risk for primary and secondary prevention of CVD. The implementation of the SCORE risk chart in primary health care will contribute to the evaluation of cardiovascular risk and the development of preventive measures to the main risk factors.

**Keywords:** prevention, prognosis, cardiovascular diseases.

At the present time, the following prevention strategies are distinguished: population strategy; high risk strategy; secondary prevention strategy. The population prevention strategy primary aim is to promote healthy lifestyles among members of society, to promote health protection knowledge, and to perform widespread informational work with the population, regardless of whether they have risk factors or chronic noncommunicable diseases. The role of the family doctor in the implementation of the population prevention strategy is to actively inform and promote healthy lifestyle among the population to a healthy life style and seek to medical advice if there are risk factors [1; 2]. It is important to engage in primary prevention of chronic diseases from childhood, as numerous studies have confirmed that the so-called risk factors are formed in childhood and adolescence, are sustainable and subsequently pass into the lifestyle of an adult. The concept of risk factors is based on the results of prospective epidemiological studies and is currently the methodological basis for planning and organizing primary prevention of cardiovascular pathology [3; 4]. The concept differentiates between modifiable and non-modifiable risk factors. Non-modifiable risk factors are: age, gender, genetic predisposition. They are used to develop a system for stratifying the risk of developing diseases. Those risk factors cannot be adjusted, but can only be taken into account when determining the degree of risk of developing diseases. Modified risk factors are subject to correction. They are divided into behavioral and biological risk factors. The behavioral risk factors include: smoking, unhealthy diet, low physical activity, excessive alcohol consumption, chronic psycho-emotional stress. These are the most common behavioral risk factors in the lifestyle of a modern person that contribute to the development of diseases. With prolonged exposure to behavioral risk factors on the human body, the following biological risk factors can form: arterial hypertension (AH), dyslipidemia, excessive weight, obesity and diabetes mellitus, which are important for the development of cardiovascular diseases. In addition to identifying risk factors for developing diseases, effective prevention strategies are being developed [5; 6].

Due to the fact that CVDs are considered as diseases with a multifactorial etiology, and the potentiating effect of risk factors on their development has been established, a total cardiovascular risk estimation system has been developed, which is based on taking into account the combination of certain risk factors. The determination of total cardiovascular risk is recommended for primary and secondary prevention of CVD, including during clinical examination of certain age groups of the population and preventive medical examinations. It was proposed to determine the total cardiovascular risk using the European SCORE risk chart, which estimates the 10-year risk of fatal cardiovascular complications [7]. Fatal cardiovascular complications include death from myocardial infarction and other forms of ischemic disease heart (IHD) and stroke. It is important that during any visit of patients that seek medical attention, an opportunistic screening is conducted to identify risk factors for the development of cardiovascular diseases and the total cardiovascular risk of developing fatal complications is determined in the next 10 years [3]. The purpose of our

study was to evaluate the role of determining the total cardiovascular risk on the SCORE risk chart in primary care in the prevention of cardiovascular diseases (CVD).

**Research methods**

400 individuals aged 40 to 55 years were surveyed. Risk factors were determined using a questionnaire and the risk of cardiovascular events was evaluated according to the SCORE risk chart.

**Results**

To study the total cardiovascular risk using the SCORE chart, different risk factors (such as smoking) were observed, which occurred in 226 individuals (56.5%), hypercholesterolemia to determine the level of total cholesterol was found in 134 individuals (33.5%) and hypertension was detected in 174 individuals (43.5%). The results of the study of the total cardiovascular risk by the SCORE chart revealed: low cardiovascular risk was detected in 82% individuals; mean is 9.0%, moderate risk in 4%, high in 4% and very high risk in 1% of patients. We also analyzed other risk factors of CVD: 274 (68.5%) of the patients had family history tainted with CVD. Other factors, such as excessive weight > 24.9 kg/m$^2$ had 314 (77.5%) patients, of which 151 (48%) were overweight, 84 (26.7%) had 1 degree obesity, 38 (12.1%) had 2 degree obesity, 165 has a visceral type of obesity with WHR1.3 ± 0.3. During survey and active questioning, low physical activity was detected in 294 (74.0%) people (lifestyle, habits, restriction due to pain or discomfort in the heart area, inspiratory dyspnea during exercise). All participants have participated in a discussion about the cardiovascular diseases risk factors and their prevention.

**Conclusion**

The implementation of the SCORE risk chart in primary health care will contribute to the evaluation of cardiovascular risk and the development of preventive measures to the main risk factors.

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# ADIPONECTIN AND ITS SIGNIFICANCE FOR THE DEVELOPMENT OF CLINICAL METABOLIC DISORDERS IN METABOLIC SYNDROME

**Abstract.** The article defines the role of adiponectin (ADN) in the development of clinical metabolic disorders in metabolic syndrome (MS).

The ADN level was significantly lower in patients with MS. Negative correlations were found between the ADN level and obesity, insulin resistance, free fatty acids, hyperlipidemia, blood pressure; positive correlation was found with the HDL cholesterol. Nevertheless, regardless of sex, age and, and body mass index, only the triglyceride level and diastolic blood pressure are in correlation with ADN.

**Keywords:** adiponectin, hypertriglyceridemia, insulin resistance, metabolic syndrome.

One of the key epidemiological trends, the significance of which will not lower and may even increase in the near future, is the steady growth of metabolic syndrome in the general population [1; 2; 5].

Metabolic syndrome (MS) is a clustering of pathogenetically interrelated symptoms and metabolic disorders that increase the likelihood of developing atherosclerosis and ischaemic heart disease (IHD). They often include obesity and/or the abdominal spread of adipose tissue, insulin resistance (IR), atherogenic dyslipidemia, arterial hypertension (AH), hyperuricemia, and a number of other medical conditions [2; 9; 14].

Currently, in the genesis of this clusterind of disorders, more and more attention is paid to the role of adipokines – biologically active proteins, which are expressed and secreted into the blood by adipose tissue [4; 6]. For example, there is evidence of a positive correlation between manifestations of MS and expression and plasma levels of such substances as tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), resistin, leptin and negative with adiponectin [7; 8; 10]. Results of tests on transgenic mice have shown that adinopectin has antiatherogenic and antidiabetogenic effects [16]. The antidiabetogenic effect of adiponectin is associated with an increase in the sensitivity of tissues to insulin under the effect of this protein, while the antiatherogenic effect is explained by a number of effects of adiponectin [13; 16]. These include lowering triglycerides (TG), increasing high-density lipoprotein cholesterol (HDL cholesterol), improving endothelial function, slowing down the transformation of macrophages and smooth myocytes of the vascular wall into foam cells, migration and proliferation of smooth medial myocytes, production of cytokines in the vascular wall, adhesion of monocytes to the vascular endothelium, reduction of free fatty acids (FFA) [12; 13; 15].

Despite the strong interest in the world, which manifested in the study of this adipokine, its role in the development of MC remains unexplained.

The aim of this article was to study the parameters and the role of adiponectin in the development of clinical metabolic disorders in metabolic syndrome.

**Materials and methods**

40 patients with MS were examined (18 men and 22 women) aged 35–67 years (mean 48.7 ± 5.6 years). The control group (volunteers) had 20 people of the same sex and age.

Metabolic syndrome was diagnosed according to the criteria proposed by the Experts of the US National Cholesterol Education Program (2005). The criteria for MS diagnosis were: waist circumference of more than 94 cm in men and more than 80 cm in women; blood pressure of 130/85 mmHg and above, the fasting plasma glucose of 5.6 mmol/l and more. The body mass index (BMI, Quetelet index) was calculated using the formula BMI = body weight (kg) / height ($m^2$).

Glucose-insulin homeostasis was determined by the level of fasting blood glucose (FBG), the level of insulin in the blood by the ELISA method in the radioimmune laboratory of the Republican Center for Endocrinology (Tashkent), using "Beckman Coulter" analyzers (Czech Republic). HOMA-IR was calculated (fasting insulin mcIU/ml × fasting blood glucose mmol/l:22.5). The patients with fasting insulin higher than 12.5 mcIU/ml were diagnosed with hyperinsulinemia. The patients with HOMA-IR above 2.27 were considered insulin-resistant.

Parameters of blood lipid composition – total cholesterol (TC), HDL cholesterol, TG was analyzed using Reflotron Plus express analyzer by Roshe (Germany), with Biocon diagnostic reagents (Germany). The content of LDL cholesterol, VLDL cholesterol was calculated by the Friedewald formula. The integral indicator – atherogenic index of plasma (AIP) – was calculated using the formula AIP = (TC – HDL cholesterol/HDL cholesterol).

The FFA concentration in the serum was determined using the NEFAFS testing system by Disus (Germany).

The level of adiponectin was determined using a competitive ELISA testing using analyzators by Bio Vender-Laboratorni medicina E.S. (Czech Republic), in the "Immunogen-Test" laboratory at the Institute of Immunology of the Academy of Sciences of Uzbekistan.

Statistical data processing was carried out by the variation system method using Student's t-test. The results were processed using the Statistica software. To identify the relation of the adiponectin level to different parameters, a Pearson correlation coefficient analysis and regression analysis were performed.

**Results**

The main clinical metabolic parameters are given in (Table 1). When comparing the content of adiponectin (ADN) in patients with MS and in control group it was discovered that the level of ADN was significantly reduced in patients with MS. In addition, a change in a number of biochemical, anthropometric, hormonal, and hemodynamic parameters was observed in patients with MS. For example, among the biochemical parameters in patients with MS, there was an increase in the levels of insulin, glucose, the NOMA index, TG, FFA, AIP, as well as a decrease in the level of HDL cholesterol. In addition, patients with MS had increase in BMI and WC, as well as a greater increase in DBP and SBP compared to control group.

Table 1. – Adiponectin content and clinical biochemical parameters in patients with metabolic syndrome

| **Parameters** | **Control (M ± m)** | **MS (M ± m)** |
|---|---|---|
| Absolute number | 20 | 40 |
| Age, years | 47.5 ± 6,6 | 48.7 ± 5.6 |
| Sex (m/f) | 10/10 | 18/22 |
| BMI, $kg/m^2$ | 23.5 ± 4.7 | 31.2 ± 4.6 |
| WC, cm | 80.0 ± 5.5 | 99.1 ± 13.6 |
| SBP, mmHg | 122.5 ± 10.2 | 191.6 ± 16.4 |
| DBP, mmHg | 80.3 ± 7.6 | 103.4 ± 13.2 |
| Glucose, mmol/l | 5.0 ± 0.5 | 6.5 ± 1.9 |
| Инсулин, mcIU/ml | 8.5 ± 3.1 | 16.3 ± 5.2 |
| HOMA-IR | 1.81 ± 0.92 | 3.43 ± 1.05 |
| FFA, mmol/l | 0.42 ± 0.15 | 0.87 ± 0.49 |
| TC, mmol/l | 4.2 ± 0.9 | 6.5 ± 1.7 |
| TG, mmol/l | 0.94 ± 0.1 | 2.76 ± 0.7 |
| HDL Cholesterol, mmol/l | 1.12 ± 0.18 | 0.85 ± 0.11 |
| LDL Cholesterol, mmol/l | 2.2 ± 0.8 | 5.11 ± 1.45 |
| AIP | 4.5 ± 0.9 | 6.1 ± 1.9 |
| Adiponectin, μg/ml | 10.2 ± 4.1 | 5.79 ± 2.2 |

In a detailed study of patients with low levels of ADN, men predominated to a greater extent. A direct correlation was found between the ADN level and the age of patients. With an increase in the ADN level, a decrease in the values of BMI and OT is observed. There is an inverse correlation between the ADN level and glucose and insulin levels, HOMA-IR. As the content of ADN increases, FLC and TG levels decrease. The correlation between the ADN level and the concentrations of LDL cholesterol and HDL cholesterol is much less pronounced.

For a more detailed study of the correlations of the ADN level with clinical metabolic parameters, a correlation analysis was performed (Table 2).

Its results confirm the data on the positive correlation of the ADN level with age and negative with BMI, OT, glucose levels, insulin, HOMA-IR, FFA and TG concentrations. The strongest correlation was found between TG level and ADN (r = –0.46). In addition, significant correlations of the ADN level with concentrations of HDL cholesterol and SBP were found.

Comparison of MS patients by sex and age led to a slight decrease in the correlation of ADN content with BMI, OT, FFA levels, TG, and correlations of ADN concentration with glucose – insulin homeostasis and HDL cholesterol levels were not detected (Table 2). Comparison by sex and age did not affect the correlation between the ADN level in blood plasma with DBP, while the correlation with the SBP was slightly higher, and acquired a reliable character.

Table 2. – Correlation of adiponectin levels with clinical metabolic parameters in patients with metabolic syndrome

| Parameter | Adiponectin (without matching) | Adiponectin (after matching by sex and age) |
|---|---|---|
| AGE | 0.28* | – |
| BMI | –0.37* | –0.28* |
| WC | –0.33* | –0.25* |
| Type 2 diabetes | –0.03 | – |
| Glucose | –0.26* | –0.18 |
| Insulin | –0.27* | –0.17 |
| HOMA-IR | –0.34* | –0.23* |
| FFA | –0.27* | –0.24* |
| TC | –0.00 | –0.12 |
| TG | –0.46* | –0.4* |
| HDL Cholesterol | 0.27* | 0.21 |
| LDL Cholesterol | 0.19 | 0.13 |
| AIP | –0.12 | –0.25* |
| SBP | –0.23 | –0.26* |
| DBP | –0.33* | –0.35* |

*Note: * – correlation is accurate (p < 0.05);*

Regression analysis has shown that only the TG content (r = –0.33, p = 0.04) and sex (r = –0.28, p = 0.04) are independent factors associated with the ADN level (r = 0.36, p = 0.04). ADN level (r = –0.31, p = 0.02), FFA (r = 0.44, p = 0.04) and HDL cholesterol (r = 0.26, p = 0.04) of all above parameters were independent factors associated with the concentration of TG in the blood. An independent link was established on sex, age and BMI, as well as a link between ADN levels and TG.

**Discussion**

In recent years, the role of ADN in the genesis of many disorders in MS [4; 8; 13; 14] has been often discussed in the literature. Identified by various authors of the connection of reduced levels of ADN with abdominal fat distribution and IR, hypertriglyceridemia, hypocholesterolemia, hypertension, prove the increasing role of this protein in the genesis of MS [3; 10; 11; 15].

Our analysis allowed us to identify a number of the ADN level correlations with some sex, age, clinical and biochemical parameters in patients with MS.

We were able to show that the ADN level is lower in men than in women, as well as its increase with age of patients. These data are consistent with the results of studies conducted by foreign authors [12; 13; 14]. Reduced levels of ADN in men can be one of the factors that predispose them to an increased incidence of MS [3; 7]. Moreover, once again data on the negative correlation of ADN levels with obesity, OT, glucose, basal insu-

lin, HOMA-IR, TG levels, FFA, BP and a positive correlation with HDL cholesterol was confirmed [11; 12].

The mechanisms responsible for reducing the level of ADN in patients with MS are still little studied. It is assumed that the main role may be played by TNFα and IL-6, the expression and secretion of which in adipose tissue increases with obesity [12; 14]. It is known that these cytokines reduce the expression of ADN [12; 13]. Moreover, a decrease in the ADN level may be mediated by hyperinsulinemia, since insulin also reduces the production of ADN [3; 8]. In addition to the effect of insulin on the ADN level, the reverse effect is also described in the literature – a decrease in the level of insulin under the effect of ADN. So in mice transgenic for ADN, as well as in mice that were injected with ADN, a decrease in insulin levels was observed, and this effect is related to an increase in tissue sensitivity to insulin [16]. However, despite the relation of the ADN level with the insulin content and HOMA-IR that we found, it decreased and became unsubstantiated after comparing patients by sex and age.

In general, our data do not confirm the findings of foreign researchers on the direct effect of ADN on the indices of glucose-insulin homeostasis in animals [6; 16]. Of all the parameters, the ADN level was correlated with the TG level. According to the results of regression analysis, this correlation did not depend on sex and age, parameters of lipid and carbohydrate metabolism. At the same time, the ADN level was an independent determinant only for TG. The mechanisms and their consequences which are realized independent of the listed factors, the correaltion between ADN and TG, remain unknown so far. However, the literature data suggest that this correlation can be realized through a direct effect of ADN on the formation of TG in hepatocytes, as a result of which VLNP production by the liver is reduced [16]. For example, transgenosis of leptyndefective mice (ob/ob) with ADN resulted in a decrease in TG accumulation in the hepatocytes of these animals [6; 16].

This effect is the product of the intracellular target of ADN-AMP-sensitive protein kinase, an enzyme that reduces the formation of intracellular TG in hepatocytes. These data are also confirmed by foreign researchers [8; 16].

**Conclusion**

In summary, data on the ADN level correlation with a number of clinical metabolic manifestations of MS were confirmed. Negative correlation was found between the ADN level and abdominal obesity, insulin resistance, FFA level, hyperlipidemia, ABP, and a positive correlation with HDL cholesterol. Nevertheless, regardless of sex, age and BMI, only the TG and DBP levels are in correlation with ADN. Once again it is confirmed that ADN, in turn, is an independent determinant only for TG.

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# QUALITY OF LIFE ASSESSMENT IN CHILDREN AND ADOLESCENTS WITH TYPE1 DIABETES MELLITUS ON INSULIN PUMP THERAPY IN UZBEKISTAN

**Abstract.**

***Background:*** Worldwide, 5–10% of diabetes cases are type 1 diabetes mellitus (T1DM). Despite intensive research, T1DM is presently incurable. Over the past three decades, diabetes management has increasingly benefited from innovations in technologies aimed at diabetes care.

***Purpose:*** The purpose of this study was to assess the quality of life in children and adolescents with type 1 diabetes mellitus on insulin pump therapy in Uzbekistan

Materials and methods: Twenty children with type 1 diabetes who were on insulin pump therapy participated in the study 12 boys and 8 girls (mean age 12.3 ± 0.7 years). Russian version of the Diabetes Quality of Life for Youth Pediatric Quality of Life (DQOLY-SF) questionnaire was used in our study.

***Results of the study:*** impact of diabetes symptoms decreased by 5%, impact of treatment by 8.2%, impact on daily activities improved by 7.7%, relationship with parents became better by 14.3%. Worries associated with diabetes decreased almost twice. Perceptions of health changed for the better side by 2.3%.Overall quality of life assessment showed an improvement in QOL by 7%.

***Conclusion*:** the results of the conducted study demonstrate that the use of modern technologies is accompanied by the improvement of not only of glycemic control, but also the quality of life of children and adolescents with type 1 diabetes.

**Keywords***:* quality of life, insulin pump therapy, diabetes mellitus in children and adolescents.

**Introduction**

According to IDF, 542,000 children (0–14 years) with type 1 diabetes mellitus (T1DM) were registered in the world in 2015, of which 86.000 were newly diagnosed. [1] The prevalence of type 1 diabetes varies considerably in different countries, within one country and in various ethnic groups. Most often it occurs in Finland [2], in Nordic countries [3; 4] and Canada [5]. Among Europeans living in Europe, the frequency of occurrence is 20-fold scatter [6] and correlates with the incidence of HLA genes in the population[7]. Of the approximately 500,000 children with T1DM which constituted about 26% from Europe and 22% from North America and the Caribbean. In Asia, the incidence of T1DM is very low: South-East Asia recorded 149,300 children and adolescents with type 1 diabetes. In 2017, according to the International Diabetes Federation, approximately 19,500 newly identified children and adolescents were registered. India is on the second place in the world with type 1 diabetes after the United States, the number of incidents is 128.500 [8; 12; 17]. In Republic of Uzbekistan by the period 01.01.2017, 2532 patients with type 1 diabetes mellitus were registered and added to dispensary record. Children with type 1 diabetes mellitus compromise 1791 and adolescents 741. On the period of 10 years, the prevalence of type 1 diabetes among children in the Republic increased from 10.6 to 19.8 per 100,000 children for the period 2006–2016. As for adolescents, this indicator has doubled from 22.2 to 41.2 per 100,000 adolescents. The incidence in 2016 was 2.3 per 100000 children, at the same time it should be noted that the incidence among adolescents for 10 years increased by 3 times. In 2006, the 100000 adolescent population had a morbidity rate of 2.6, in 2016 this figure was 6.9 [18].

In accordance with the "St. Vincent Declaration", the main directions of the medical and social policy regarding diabetes should be aimed at minimizing its growth, development of complications and improving the quality of life (QoL) in patients of all age groups [15]. From the moment of manifestation of type 1 Diabetes mellitus patients should be introduced with insulin therapy in the basal-bolus regimen (ISPAD2017).

Insulin pumps fundamentally new and progressive step in the treatment of diabetes [16]. Insulin pumps provide better

glycemic control compared to the multiple daily injections of insulin (MDI) regime and significantly reduce the incidence of hypoglycemia, which is one of an important aspects in the compensation of diabetes. Worldwide Insulin pump therapy is used quite often not only in type 1 diabetes, but also up to 34% of adult patients with DM 2 in the US and up to 25% in Europe use pumps to administer insulin. In Russia the number of pump users is progressively increasing and by 2014 it has been about 10.000 people [9]. Researchers from European countries have shown that QOL depends on many factors – age, gender, duration of the disease, family relationships, treatment methods and others. It is quite obvious that long-term maintenance of glycemic targets with low QOL or at the cost of its reduction, for example, the need to increase the frequency of self-monitoring and the number of daily injections often sharply reduces QOL. For a patient it may be more important to evaluate a happy family life, an opportunity to enjoy a hobby, personal finances rather than wellbeing. Patient-oriented questionnaires for assessment of quality of life, where a person with diabetes determines and evaluates important things for the patient and gives higher QOL score to those using continuous subcutaneous insulin infusion (CSII) compared to MDI [14]. Only one large multicenter prospective study was published that evaluated satisfaction with treatment and QOL in patients using the integrated continuous blood glucose monitoring system and continuous subcutaneous insulin infusion (RT-CGM / CSII) systems [10]. Along with the improvement of QOL, CSII is an effective and safe diabetes treatment method in children and adolescents, of which only a small part of patients continue insulin therapy in MDI regime after 6–12 months of using CSII) [11]. It is also important to emphasize that CSII provides better glycemic control compared with the MDI together with significant reduction in the incidence of hypoglycemia [13].

In order to extensive the use of intensive care methods such as MDI and insulin pumps in Uzbekistan, tables for assessing the carbohydrate value in Uzbek and Eastern cuisine in Bread Units (BU) were developed. An electronic base for integration into specialized computer programs for better calculation of type of bolus depending on food was prepared.

Thus assessment of QOL is very important when transferring patients with type 1 diabetes from MDI to insulin pump therapy.

**Purpose:** The purpose of this study was to assess the quality of life in children and adolescents with type 1 diabetes mellitus on insulin pump therapy, with consideration the carbohydrate value in Uzbek national food.

**Methods and materials of the research.**

Twenty children with type 1 diabetes who were on pump insulin therapy participated in the study. A group of patients with type 1 diabetes was formed from the number of patients at the city Endocrinology dispensary in Tashkent and the Region Endocrinology dispensary of the Tashkent.

Table 1.– Clinical characteristic of the patients

| **The indicators of the groups** | | |
|---|---|---|
| **The number of the patients** | | N = 20 |
| **Average age** | | 12.3 ± 0.7 |
| **Sex** | **Boys** | 12 |
| | **Girls** | 8 |
| **Duration of the disease** | | 4.5 ± 0.7 |
| **complications** | | no |
| **Duration of control** | | 12 months |
| **General clinical observation of the patients included:** | | Weight, height SDS, blood glucose and glycated hemoglobin |

All patients have been investigated by standardized clinical-laboratory observation, which included collection of anamnesis, the physical observation of the patients, laboratory and instrumental investigation, and assessment of the quality of the life with the questionnaire.

General clinical observational methods consisted of:

a) questionnaire, constructed protocol of research;

b) anthropometric methods of assessment of physical development, which is the measurement of the weight, height SDS by percentiles(WHO 2007);

c) functional methods of investigation (ECG);

d) Biochemical investigations (urine assay, creatinine);

e) Consultation of the oculist whit the direct ophthalmoscopy of the eyeground.

**Clinical methods of the investigation.**

Indicators of the compensation of the carbohydrate metabolism have been assessed by the recommendations of ISPAD (International Society for Pediatric and Adolescent Diabetes) published in 2014.

For the assessment of QOL of the patients with type 1 diabetes mellitus Russian version of the questionnaire of Diabetes Quality of Life for Youth Pediatric Quality of Life (DQOLY-SF) was used. This questionnaire is distinguished by high reliability, validity and sensitivity and allows to ob-

jectively assess the quality of life of children and adolescents with type 1 diabetes.

In the present study, blocks for the age groups 8–12 and 13–18 years were used. The DQOLY-SF questionnaire includes 22 questions relating to scales assessing quality of life factors: the impact of diabetes symptoms, the impact of treatment, the impact on daily activities, relationships with parents, experiences related to diabetes, health perception. In addition, during the survey, it is possible to count the total scores of various scales of the questionnaire.

Each question has five possible options for assessing the degree of one or another concern from 0 to 4, with 0 – never, and 4 – constantly. A higher score indicates a more negative impact of diabetes and a worse quality of life, lower scores are associated with good QOL. The evaluation of each subsection is made separately by summing up the scores for each sub-item question. The emphasis on the sum of points in each subsection, in contrast to the total score, makes it possible to assess the problem in more detail in a separate area.

The total number of points after recoding (transfer of raw data to life quality scores) was calculated on a 100-point scale; The lower the value, the higher the quality of life of the child. The following formulas were used in the explanation to the questionnaire:

This questionnaire was provided to patients for completion before group training on a structured program and after the completion of the annual follow-up period. All patients signed informed consent to participate in the study.

**Results:**

The use of insulin pump therapy has a positive impact on all aspects of the quality of life detected by the questionnaire DQOLY-SF. The greatest improvements were noted in such aspects of quality of life as the impact of diabetes symptoms, the impact of treatment, the impact on daily activities, relationships with parents. Moreover, worries associated with diabetes decreased by almost twice. Against background of investigation and modified therapy according improvement of carbohydrate metabolism there were registered positive dynamic of the main aspects of the QOL. For the children under 12 year and for the parents of the children younger 12 have been suggested to fill up the questionnaire of QOL before and after using 1 year of pump insulin therapy.

By evaluating of quality of life we got following results (table. 2).

Table 2. – Comparative assessment of quality of life of patients with type 1 diabetes mellitus before and after using CSII for 1 year

| Quality of life parameters | Score before CSII (%) | Score after 1 year of using CSII (%) | Score % | P value |
|---|---|---|---|---|
| Influence of symptoms of diabetes mellitus | 23 | 18 | ↓5 | < 0.05 |
| Effect of treatment | 27.8 | 19.6 | ↓8.2 | < 0.05 |
| Impact on daily activities | 13.6 | 5.9 | ↓7.7 | < 0.05 |
| Relations with parents | 62 | 47.7 | ↓14.3 | < 0.05 |
| Anxiety associated with diabetes | 40 | 22.4 | ↓17.6 | < 0.05 |
| Perception of health | 50 | 47.7 | ↓2.3 | < 0.05 |
| Overall assessment of QOL | 29.5 | 22.3 | ↓7.2 | < 0.05 |

Table 2 shows statistically significant differences in the quality of life indicators obtained when the questionnaire was filled by children and parents before the initiation of CSII and after 1 year. After transferring to pump insulin therapy, parents and children evaluated all the indicators higher:

– impact of diabetes symptoms decreased by 5%;
– impact of treatment by 8.2%;
– impact on daily activities improved by 7.7%;
– relationships with parents became better by 14.3%;
– Worries associated with diabetes decreased almost twice;
– Perceptions of health changed for the better side by 2.3%, while after transferring to CSII more patients and parents began to assess the health of children good and excellent;
– Overall quality of life assessment showed an improvement in QOL by 7%.

When comparing questionnaires filled with parents and children, parents were more concerned about the development of complications of diabetes than children.

Thus, the results of the conducted study reliably demonstrate that the use of modern technologies is accompanied by the improvement of not only glycemic control but also QOL.

**Discussion**.

The latest published meta-analysis of studies comparing CSII and MDI (multiple daily injection) [19; 20] demonstrated improvement in glycemic control using pump therapy in patients with T1DM. At the current time, there are

only a few reviews on the use of CSII in adults, adolescents and small children with T1DM.

In this study quality of life was assessed in children and adolescents with type 1 diabetes mellitus on insulin pump therapy, taking into account the carbohydrate value in dishes of Uzbek national cuisine. It was shown that the method of insulin administration plays a huge role in achieving compensation of type 1 diabetes, thereby improving the glycemic control and QOL parameters of the subjects. Attention is drawn to the more pronounced dynamics of a statistically significant improvement in QOL for a larger number of patient outcomes after transferring to the PIT regime after a year. Thus, the results of the conducted study demonstrate reliably that the use of modern technologies, such as CSII, is accompanied by an improvement not only in glycemic control, but also in QOL. Taking into account the data of earlier studies and the accumulated clinical experience, it can be assumed that pump insulin therapy has an ambiguous effect on patients: the repeatedly increasing amount of information on glycemia, its dynamic changes depending on various events and the possibility of flexible control of food intake by patients provides a great opportunity for them to look at diabetes with other eyes. QOL is an important result both in itself and because it can affect the patient's activity with regard to self-management of the disease. If the requirements for adherence to the treatment scheme do not coincide with how patients want to live, they can choose less strict glycemic control in order to maintain their QOL. Thus, patients on pump therapy in conventional clinical practice admitted improving thinking, mood and well-being after a transfer from MDI, and these and other psychosocial factors are increasingly being evaluated in scientific studies on CSII. Knight et al. showed that the improvement in HbA1c in children with type 1 DM after transition to CSII was accompanied by an improvement in a number of cognitive indicators, such as sensory perception, selective attention and short-term memory, relationship with parents, etc.

**Conclusions:**

1. The use of CSII has a positive impact on all aspects of QOLs on the DQOLY-SF questionnaire.

2. The greatest improvements were noted in relation to such aspects of QOL as the impact of the symptoms of diabetes mellitus, the impact of treatment, the impact on daily activities, relationships with parents. Worries associated with diabetes decreased in almost twice.

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# HYGIENIC JUSTIFICATION OF STUDYING THE EDUCATIONAL PROCESS OF PRESCHOOL CHILDREN OF PREPARATORY GROUPS

**Abstract.** Microclimate indicators, air frequency, the compliance of furniture to hygienic requirements and the educational process of preparatory groups in the children's educational institutions.

**Keywords:** microclimate, air frequency, furniture, educational process.

A feature of modern general education is the search for new methods, tools and forms of education. The widespread introduction into the preparatory groups of children's educational institutions characterized by the intensification of the educational process (complication and restructuring of the curricula in the preparatory groups) leads to an increase in the requirements for the functional state and health of the child [1; 2; 11; 12]. The level and harmony of physical development in any age period reveal the dialectic of the relationship between the organism and the environment, characterize the metabolic processes in the body and its functional state [8; 9; 10].

One of the urgent problems is the study of the influence of learning conditions and the educational process, acting on the level and harmony of physical development in group rooms of children's educational institutions [1; 2; 3; 4].

**Purpose of the research.** The study of learning conditions and educational process of preschoolers of preparatory groups.

**Materials and research methods.** The studies were conducted in the preparatory groups of children's educational institutions (№ 148, 134, 232, 270, 525, 546) of Mirzo-Ulugbek district of Tashkent. Initially, we investigated the hygienic conditions for the education of children in preparatory groups (microclimate, air frequency, furniture conformity, etc.). Hygienic assessment of the organization of the educational process was carried out on the basis of taking into account the compliance of its components with the requirements

«Sanitary Legislation and Regulations 0241–07» Sanitary rules for the organization and maintenance of preschool institutions in the Republic of Uzbekistan [8; 9; 11].

Also, there were established the hygienic assessment of furniture and compliance with the later height indicators (Sanitary Legislation and Regulations 0241–07).

Studies were conducted at the beginning and at the end of the school year (September), in the first half of the school day (from 8:30 to 12 o'clock), when there is a more effective functioning of all physiological systems of the body.

**Research results and discussion.** The results of the hygienic assessment of conditions in group rooms showed that during the day the physical properties of air (temperature, humidity, air movement and dustiness) gradually change in children's educational institutions, which can adversely affect children's health.

Insufficient attention is paid to the physical properties of air during the control (children's educational institutions), therefore, colds (bronchitis, sore throats, pneumonia) are often observed in children's educational institutions.

In those children's educational institutions, where there were high incidence rates of pneumonia (acute respiratory infection), angina and bronchitis, we measured the air temperature in group rooms at various levels. As a result of these studies, it was established:

At the level of 2 meters, the air temperature corresponded to 20°

At the level of 1 meter, the air temperature corresponded to 18°

At the surface of the floor, the air temperature corresponded to 13–14°

Consequently, the air temperature in these areas did not meet hygienic requirements. The next factor determining the microclimate in the premises of preschool institutions is the relative humidity, which should be in the range of 40–60%, and the speed of air movement – not more than 0.2 m/s. These requirements in the surveyed children's educational institutions are mainly met.

When assessing hygienic conditions, it is noted that the air of the enclosed spaces of preschool institutions during children's stay in them changes its chemical composition. The deterioration of the chemical composition of the air in the room is usually judged by the CO2 content in it. On the basis of a large number of studies, it was established that air should be

recognized as harmful to children in rooms if the CO2 content in it exceeds 0.1%.

Our studies of the air of preschool institutions have established that in some cases a slight increase in CO2, especially during the cold season (in early spring or autumn) and after a long stay of children in the room: after classes; after lunch; by the end of the stay of children in kindergarten (after lunch in afternoon groups), after a nap in a sleeping room (especially in crowded groups) happen. This was not observed in children's plants built according to standard designs.

Particular attention should be paid to the fight against dust in kindergartens, since microbes are found in the air along with dust.

The main reservoir of microflora in the premises is the nasopharyngeal microflora.

In group rooms, a living room, and sleeping rooms every hour before the arrival of children, wet cleaning is done with opened windows, transoms or air vents, with mandatory removal of cabinets and other furniture. After cleaning, wipe with a damp cloth moistened with a clarified bleach solution (2: 100) furniture, beds, tables, chairs, cabinets, toys, etc.

Despite conducting sanitary cleaning, our studies showed that the number of microbes in 1 $m^3$ of air, for example in the gym rooms, increases by 2–3 times by the end of lessons, twice in the bedroom, after the children have gone to bed.

In ensuring the purity of the air, an important role is played by the proper organization of room ventilation, which is one of the effective means of preventing aerogenic infections.

Hygienic assessment of furniture and its compliance with age and age indicators was conducted according to Sanitary Legislation and Regulations 0241–07. Studies have shown that furniture in preparatory groups, as a rule, does not meet hygienic requirements and standards for Sanitary Legislation and Regulations 02–41–07. Preparatory groups in all examined children's educational institutions are equipped mainly with one type of furniture. In addition, all caregivers seat children, not complying with any requirements.

The study of the day routine showed that for most preschoolers it was compiled without taking into account hygienic requirements and recommended standards. The main violations in the structure of the day regimen are: high training load, insufficient outdoor rest, inadequate sleep and low level of physical activity.

The weekly curriculum in preparatory groups significantly exceeds the load established for preparatory groups: 12 hours of music; 12 hours for math; Physical education classes on schedule 1 h 20 minutes. In addition, with the involvement of parental funds, the number of hours spent on teaching foreign languages is further increased. Among the factors negatively affecting the health of children of preparatory groups, it is necessary to note the violation of the principles of organizing the training schedule. In all surveyed children's educational institutions schedules are compiled without taking into account the dynamics of the physical and mental performance of children (work, optimal performance, fatigue) and the grade scale of lesson difficulty.

To determine the permissible duration of studies, we conducted time-keeping observations of the behavior in the classes of pupils of senior and preparatory groups. Timing observations were conducted in two types of groups, depending on whether "physical training" were conducted in class or not.

It was found that without a "physical training", in the middle of the class, signs of fatigue appeared (signs of motor restlessness increased – fidgeting, sinking, jumping from places – the number of distractions increased). Taking into account the time of occurrence of these signs, it was found that the duration of educational classes in the older groups should not exceed 25 minutes, and in preparatory classes –30 minutes, with the obligatory holding of "physical training" in the middle of the classes.

Breaks between classes are only 5–10 minutes. There are no walks at the end of autumn and in winter. Not all employees in children's educational institutions even comply with this mode of the day, because (physical training) time of 5–7 minutes are very rarely held, games-relay races, outdoor games are carried out mainly on holidays.

Thus, the revealed violations negatively affect the performance and are one of the main causes of fatigue of children, since they do not take into account the known periodicity of physiological functions, the reflection of which is the dynamics of mental performance.

**Findings**

1.The pedagogical process in children's educational institutions is accompanied by the impact on preschool children of a number of adverse factors (insufficient equipment, furniture that does not correspond to the growth of preschool children, an adverse microclimate, air pollution, etc.).

2. Regime of the day is made without taking into account hygienic requirements and recommended standards. The main violations in the structure of the day regimen are: high training load, insufficient outdoor rest, inadequate sleep and low level of physical activity.

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# COMPARATIVE ASSESSMENT OF NONSPECIFIC INFLAMMATION MARKERS AND VARIOUS KEY FACTORS IN PATIENTS WITH ACUTE CORONARY SYNDROME

**Abstract.** The article studied and compared the nonspecific inflammation markers of some key prognostic factors in patients with acute coronary syndrome (ACS).

In patients with ACS, the following correlated hyperstates are seen as the leading risk factors: hypercytokinemia (IL-6, IL-10), hyper-CRP-nemia, hyper-PAPP-A-nemia, and hyper-NT-proBNP-nemia. Correlation values of these factors can prognosticate the risk of developing ACS↑ST/AMI with Q, ACS↑ST/AMI without Q and ACSTUA, optimizing the strategy of clinical prognosis of early diagnosis and therapeutic and preventive interventions.

**Keywords:** acute coronary syndrome, nonspecific inflammation markers, key prognostic factors, early diagnosis.

The high frequency of acute coronary syndromes (ACS) indicates a lack of knowledge of the pathogenetic and prognostic role of various factors in the development of this disease. One of the most important factors in the pathogenesis of ACS is the cardiovascular risk markers play a special role. The most significant (key) among them are immune responses, nonspecific inflammation markers, markers of myocardial damage and markers of cardiovascular diseases adverse outcomes [1; 2; 3; 4]. However, the role of primary inflammation mediators and their relation to impaired catecholamine metabolism (CM) in the development of ACS or adverse outcomes in patients with this pathology has not yet been fully evaluated. The study and/or development of these issues can provide up-to-date information for the diagnosis, assessment, severity of ACS [5; 6; 7]. Literature data suggests that the pathogenetic mechanisms underlying cytokin-induced disorders in ACS are not quite clear. To date, issues of pathogenesis, clinical and diagnostic features and therapeutic and rehabilitation aspects for improving the effectiveness of treatment that considers cytokines, non-specific markers of inflammation, predictors of early myocardial damage of unfavorable prognosis (PPP-A, NT-proBNP) are insufficiently studied. Studies aimed at solving these issues seem to be a relevant issue.

The aim of the study was the analysis and comparative assessment of nonspecific inflammation markers and some predictive factors in patients with acute coronary syndrome.

**Materials and methods**

149 patients with ACS admitted to the Andijan State Medical Institute clinic and Republican Scientific Center of Emergency Medical Care participated in the study. ACS diagnosis was established using ESH/ESC (2015) classification. The criteria for participation in the study were: characteristic anamnestic and clinical signs in men and women aged 25–75 years who signed an informed consent to participate in the study. The exclusion criteria for the patients were: acute inflammatory and infectious diseases, exacerbation of chronic inflammatory diseases, symptomatic hypertension, acute disorders of cerebral circulation, acquired and congenital heart defects, rheumatism, cardiomyopathy, pericarditis, myocarditis, endocarditis, oncological and hematological diseases. The control group consisted of 20 healthy individuals. Urine sampling to determine the daily catecholamines (CA) excretion

and blood sampling was performed on the 1 day of admission to the hospital. On day 1, all patients underwent clinical laboratory and instrumental examination as a basic procedure: determination of CA in daily urine and serum, lipid factors, nonspecific inflammation markers (interleukins IL-6, IL-10, tumor necrosis factor TN-α, C-reactive protein hsCRP), matrix metalloproteinase (PAPP-A) and brain natriuretic peptide (NT-proBNP) in serum. The comparison of the studied values was carried out between the main groups of patients (control, ACS) and between subgroups of the main group: ACS↑ST/AMI with Q (acute coronary syndrome/myocardial infarction with ST elevation with Q wave); ACS↑ST/AMI without Q (acute coronary syndrome/myocardial infarction with ST elevation without Q wave); ACSTUA (acute coronary syndrome with transformation to unstable angina).

All studies were performed in accordance with Good Clinical Practice standards and Microsoft Excel 2010 statistical processing principles. Arithmetic and relative values (M), mean error and relative values (M), Student's coefficient (t), Student's t-test statistical differences significance (P), as well as the correlation coefficient (r) were calculated. Differences in values between means are significant at $p < 0.05$. Significance of differences between groups was found using the Mann-Whitney test.

**Results and discussion**

Elevated levels of IL-6 and IL-10 were determined in all three groups of patients with ACS (48.9%, 16.7%, 38.2%, respectively). An increased concentration of cytokines with a relatively high frequency is determined in patients with ACS↑ST/AMI with Q (I-group), which exceeds the values of patients with ACS↑ST/AMI without Q (II-group) and ACSTUA (III-group) from 6.5 up to 1.2 times ($p < 0.001$). Comparison of nonspecific inflammation markers in patients with ACS, depending on age, also showed some interesting data. The obtained data as a whole correspond in general with the data present in the world literature and confirm the existence of a relation with age and hypercytokinemia. For example, IL-6 and IL-10 values in patients with ACS ST/AMI with Q increase with age and this process looks like this: if in the age group of 30–39 years old IL-6 and IL-10 averaged – 162±66.8 and 7.9±4.8 pg/ml, in the patients group aged 40–49 years its levels are 166.1 ± 10.9 and 8.0 ± 0.6 pg/ml respectively (with an increase of 1.2 and 0.9 times; $p>0.05$), in 50–59–183.9 ± ± 20.8 and 10.1±0.7 pg/ml (with an increase of 1.2 and 1.4 times; $p_2<0.05$) in 60–69–200.0 ± 16.0 and 110.0 ± ± 0.6 pg/ml (with an increase of 1.2 and 1.5 times; $p_1 < 0.05$, $p_2 < 0.05$), in > 70 years – 229.8 ± 8.3 and 12.8 ± 0.4 pg/ml (with an increase of 1.4 and 1.8 times; $p_1 < 0.05$, $p_2 < 0.01$). The increase in cytokine indices was also observed in the group of patients with ACS ST/AMI without Q: the detectability of elevated levels of IL-6 and IL-10 increases from 3.4 times ($p < 0.001$) to 1.8 times ($p < 0.01$) with an increase in age. The lowest mean value of cytokines was determined in patients with ACSTUA from 8.5±1.1 to 29.2±1.6 pg/ml and from 4.2 to 8.3 pg/ml, IL-6 and IL-10 respectively.

However, there is a significant increase in the mean IL-6 values with age by 3.4 times ($p < 0.01$) and a statistically significant increase in the mean level and IL-10 by 1.9 times in patients with ACSTUA. Significant differences in groups of women and men by ACS categories were identified. The serum cytokines in patients with ACS were characterized by relatively higher levels in women than in men.

Comparative assessment of TNFα and hsCRP in serum in healthy and patients with ACS showed that in patients with ACS↑ST/AMI with Q, the levels of TNFα and CRP were 115.4 ± 3.2pg/ml and 6.7 ± 0.1 pg/ml, which is respectively 15.4 times ($p < 0.001$) and 6.1 times ($p < 0.001$) more than control values. The lesser trends were endured in the group of patients with ACS↑ST/AMI without Q. For example, the mean level of TNFα in patients was 29.5 ± 1.8 pg/ml, which is 4.1 times higher ($p < 0.001$) than control values, and the mean value of hsCRP was 4.8 0.1 mg/ml, which is 4.4 times higher ($p < 0.001$) than control values.

We noted a statistically significant, compared with groups of patients with ACS↑ST/AMI without Q, but a less significant increase in TNFα and hsCRP in patients with ACSTUA: TNFα in the blood was 19.7 ± 1.0 pg/ml, what is 2.7 times higher than the control, and the mean level of hsCRP was 6.7 ± 0.1 mg / ml, which is more than 6.2 times higher than the control ($p < 0.001$).

We noted that the mean values of TNFα, hsCRP in patients with ACS significantly increase with age statistically, which is most pronounced in groups I and II of patients with ACS.

It would not be an exaggeration to note that according to our data, TNFα and hsCRP have a special place among clinical and laboratory tests in patients with ACS. This is primarily due to their special properties, such as acute phase reactants.

The obtained data correspond to the results of other researchers, confirming the existence of a relation between TNFα, hsCRP, ACS. The findings also confirmed that the rates of both TNFα and hsCRP are characterized by higher levels among women with ACS than men. In general, the relation between a combination of ACS↑ST/AMI without Q and ACSTUA with the main nonspecific inflammation values was found, which have rational specific features and require research and analysis in population data.

It is known that the hyper-PAPP-A state (>10 mm E/l) is a sensitive marker of atherosclerotic plaque inflammation, which may be the cause of ACS and therefore the determination of this value significance can be used to diagnose acute coronary events.

We have studied and assessed the PAPP-A value in the serum of patients with ACS. The results of the study showed that the mean PAPP-A value in patients with ACS↑ST/AMI with Q was significantly increased and amounted to 9.8 ± 0.2 μg/l, which is 49 times more than the control values ($p < 0.001$). The content of PAPP-A in patients with ACS↑ST/AMI without Q and ACSTUA was also significantly increased: thus, the level of PAPP-A in patients with ACS↑ST/AMI without Q was 5.1 ± 0.2 μg/l, which is 25 times higher than the value of the control group ($p < 0.001$). Lower rates of PAPP-A were observed in patients with ACSTUA, averaging 1.9 ± 0.1 μg/l, which is 9.5 times higher than the control group ($p < 0.001$).

The data obtained by us makes it obvious that age is quite a powerful factor in the development of ACS against the background of pronounced changes in the concentration of PAPP-A in the blood toward a sharp increase. This trend is observed in all groups of patients with ACS. In all groups of patients, PAPP-A in the blood is higher in women than in men. For example, the average PAPP-A level in the group of men and women with ACS↑ST/AMI with Q was 9.4 ± 0.3 and 11.3 ± 0.2 μg/ml, respectively ($p < 0.05$), which statistically significantly higher than the control (0.2±0.04 and 0.2 ± 0.03) by 47.0 and 57.0 times ($p < 0.001$). The average level of PAPP-A in male and female patients with ACS↑ST/AMI without Q was –5.0 ± 0.0 and 45.6 ± 0.1 μg/ml ($p < 0.05$), which is 25.0 and 58.0 times the control level ($p < 0.001$). In general, groups of men and women with ACS were characterized by a pronounced increase in blood readings of PAPP-A At the same time, in the group of female patients with ACS↑ST/AMI with Q, ACS↑ST/AMI without Q and ACSTUA, significantly higher levels of PAPP-A were observed.

Among the important factors in the pathogenesis of ACS, a special role is played by the brain sodium-uretic peptide (NT-proBNP). At the same time, the participation of this factor in the development of ACS has not been studied enough. Therefore, the next task of our work was the study of NT-proBNP values in the serum of patients with ACS.

It should be noted that our version of the role of NT-proBNP in ACS initially to a certain extent receives its statistically reliable confirmation. For example, the mean value of NT-proBNP in patients with ACS↑ST/AMI with Q was 87.0 ± 3.1 pg/ml, which is 5.6 times more than the control ($p < 0.001$).

In patients with ACS↑ST/AMI without Q, the average content of NT-proBNP was also significantly higher (55.0 ± ± 2.8 pg/ml) than in the control group (15.6 ± 2.8 pg/ml) by 3.5 times ($p < 0.001$). In the group of patients with ACSTUA, it is also obvious that the average content of NT-proBNP is significantly higher, amounting to 30.6 ± 1.6 pg/ml, which is 23.0 times higher than the control ($p < 0.01$).

It should also be noted that the version confirms the diagnostic value of NT-proBNP, in both men and women with ACS. In patients with ACS↑ST/AMI with Q, the highest increase in the level of NT-proBNP was observed in women than in men (105.7 ± 4.0 pg/ml versus 82.0 ± 3.5 pg/ml) ($p < 0.01$).

In patients with ACS↑ST/AMI without Q, the highest increase in the level of NT-proBNP in women was also 966.2 ± ± 2.2 pg/ml versus 51.1±3.3 pg/ml ($p < 0.05$).

Table 1.–NT-proBNP values in in the serum of patients with ACS by age

| **Age (years)** | NT-proBNP | | |
|---|---|---|---|
| | **ACS↑ST/AMI with Q** (n=67) | **ACS↑ST/AMI without Q** (n=25) | **ACSTUA (n=57)** |
| 30–39 | 75.4 ± 32.7 | 25.5 ± 14.1*** | 8.7 ± 2.1ººº |
| 40–49 | 66.9 ± 4.4 | 25.5 ± 1.4*** | 27.8 ± 3.5ºº |
| 50–59 | 86.5 ± 7.6 | 55.6 ± 3.8*** | 31.3 ± 2.2ººº |
| 60–69 | 93.6 ± 5/7 | 61.7 ± 4.0*** | 32.1 ± 5.3ººº |
| > 70 | 106.6 ± 2.9 | 64.2 ± 1.8*** | 38.6 ± 1.8ººº |

* significance of $p < 0.05$ between ACS↑ST/AMI groups with and without Q;
** significance of $p < 0.01$ between ACS↑ST/AMI groups with and without Q;
*** significance of $p < 0.001$ between ACS↑ST/AMI groups with and without Q;
º significance of $p < 0.05$ between ACS↑ST/AMI without Q and ACSTUA groups;
ºº significance of $p < 0.01$ between ACS↑ST/AMI without Q and ACSTUA groups;
ººº significance of $p < 0.001$ between ACS↑ST/AMI without Q and ACSTUA groups.

The data in the table show that the NT-proBNP in patients with ACS↑ST/AMI with Q, depends on the age of patients: it increases from 75.4 ± 32.7 pg/ml (30–39 years) to 106.6 2.9 pg/ml (>70 years), which is 1.4 times higher ($p < 0.01$). The patients group with ACS↑ST/AMI without Q, the level of NT-proBNP also increases with age from 25.5 ± ± 14.1 pg/ml (30–39 years old to 64.2±1.8 pg/ml (>70 years), which is 2.5 times higher ($p < 0.001$). In patients with ACSTUA, lower values were observed in the patients group of 30–39 years old (8.7 ± 2.1 pg/ml) and 40–49 years old (27.8 ±

± 3.5 pg/ml), higher levels of NT-proBNP were observed in the groups of patients with ACSTUA – 50–59 years (31.3 ± ± 2.2 pg/ml), 60–69 years (32.1 ± 5.3 pg/ml) and >70 years (38.6 ± 1.8 pg/ml). Total increase of the NT-proBNP in patients with ACSTUA is 4.4 times ($p < 0.001$).

In summary, a strong relation between the levels of NT-proBNP and the formation of ACS was discovered. NT-proBNP is an important pathogenetic link in the development of all clinical forms of ACS.

**Conclusion**

In summary, it was shown that the following correlated hyper states are seen in ACS patients as leading risk factors: hypercytokinemia (IL-6, IL-10), hyper-CRP-nemia, hyper-PAPP-A-nemia, and hyper-NT-proBNP-nemia. They are in a strong direct (in patients with ACS↑ST/AMI with Q), moderate (in patients with ACS↑ST/AMI with Q), and weak (ACSTUA) correlation dependance on the level of other risk factors for patients with ACS. The nature of these relations is complex and cannot be viewed as definite proof of cause and effect relations, since these issues are the subject of long-term epidemiological and randomized studies. Consequently, our results can serve as objects of further research at the population level in different regions of the country. However, following the detected logic of the ACS development, we can assume that the correlative values of these studied factors can predict the risk of the development of ACS. The results of the study can be used to identify high-risk groups for the development of ACS↑ST/AMI with Q, ACS↑ST/AMI without Q and ACSTUA, optimizing the strategy of clinical prognosis of early diagnosis and therapeutic and preventive interventions.

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