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Section 1. Clinical medicine

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CALCIFICATION OF INTACT EAR PINNA`S TISSUE AS A CONSEQUENCE OF SURGICAL OPERATION PERFORMED WITHIN NEARBY AREA

Abstract. Many manipulations and diagnostic procedures can lead to different and sometimes unexplained outcomes, like elongation of patient`s uvula after an esophagogastroduodenoscopy [1]. One of such examples could be calcification in different areas of our body without obvious reasons. Tissue calcification in most cases is considered to be pathological. This process can arise due to tissue trauma, surgical operations, chronic diseases (for ex. chronic pancreatitis), or due to some infections like tuberculosis. Most reasons, which could be the causes of calcification are well-known nowadays. For example, in case of mammary gland trauma, calcification of it`s tissue is expected outcome. This is also could be true in case of chronic pancreatitis, in which during saponification processes, the calcification remnants are stored in gland`s parenchyma. Nevertheless, predisposition of some parts and tissues of organism to this process had been observed, for example, in tissues rich in fat, like mammary gland or abdominal pad. Bacterial infection, for example, endocarditis can be complicated not only by septic embolism, but also by tissue calcification [2]. Also as examples: glands of inner and outer secretion, as also different types of tumors, for example Sertoli cell tumor [3]. However, in some cases no clear reasons can be established. The case of calcification of intact ear pinna`s tissue after an operation performed within nearby area is discussed in this article.

Keywords: pathology, plastic surgery, medicine, calcification.

Calcification is a complex process, which occurs due to a trigger. These triggers could be traumas, infections, surgical operations, or chronic diseases.

Mechanisms differ between each other. In case of metastatic calcification the leading cause is hypercalcemia, which can lead to decreased ability to excrete calcium. In this case, all tissues and organs are included in pathological process.

In calcium dystrophy a.k.a. petrification, there is only local involvement. This type of calcification is common in tuberculosis, infarctions or in areas of chronic inflammation like endocarditis. One of the

trigger is a tissue trauma like surgery or an injury. In this case there is a partial injury and death of some parts of tissue. Denaturated proteins bind phosphate, which binds calcium and makes insoluble particles. In normal state these particles are excreted via blood vessels, however, if a process is highly active, calcium particles are stored in damaged areas

By the way, there are no research, which could explain why calcium is stored in undamaged areas without any triggers. An example of calcification of normal tissues is represented below.

A 24-year-old woman came to plastic surgery clinic «Capital-Med» due to aesthetic defect in her ear`s pinna after she was wearing jewelry tunnels. She was complaining about inability to wear earrings. During examination, no abnormalities were observed. According to her words, she has not got any chronic diseases like Diabetes mellitus, Ehlers-Danlos syndrome, different types of coagulation pathologies and so on. Her blood count, coagulation profile studies and ECG did not reveal any abnormalities. Her siblings haven`t got any history of chronic diseases also.

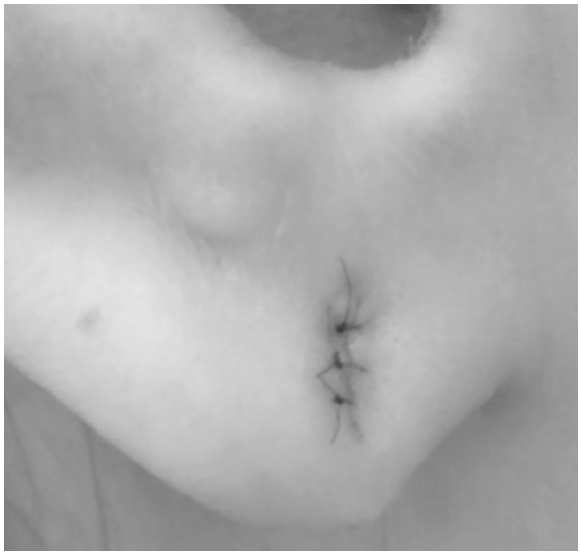

Figure 1. Initial closure of aesthetic defect

The decision was made just to close the aesthetic defect via deepidermisation and Prolen 7\0. No intradermal sutures were used. Sutures were removed on the 7th day. There were no any abnormalities noticed next two months.

She came back after 2 months due to strange feelings in her pinna. During examination, there was a dense component, 1 mm. and the distance from initial operation site was about 0.7 cm. No translummination and fluctuance were observed. The lesion was harmless and fixed. According to her words, it appeared after 2.5 months after a surgical operation. At first, it was assumed that the lesion was just an intradermal stich, however, no intradermal sutures were used. According to her words, the lesion has appeared just in one day, and has not been increasing or decreasing in size. She also has not mentioned similar episodes before.

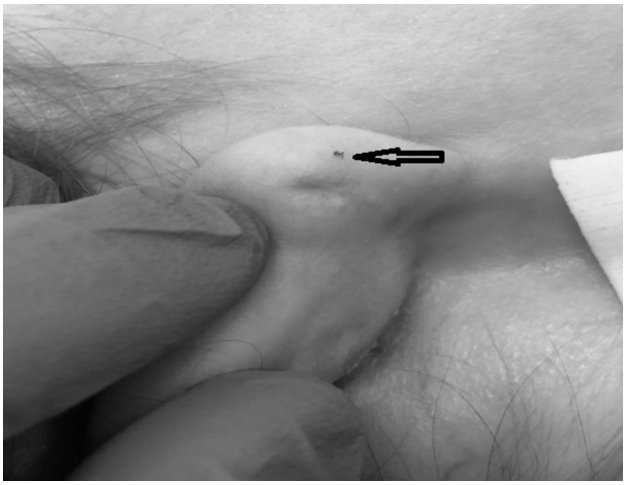

Figure 2. The area of calcification (arrow). Note the distance between the original scar and calcification area

The decision was made to excise the lesion through posterior side of pinna. There was no opportunity excise the whole lesion and we did it step by step. That is why we did not take a picture of a lesion due to lack of clinical significance. After excision, the lesion had been taken to a pathology department. It was confirmed that calcification had occurred in a healthy, previously undamaged area. One of the shot is below. We used Levenhook camera to make a shot. Hematoxylin and eosin stain were used to made a specimen. There were many similar shots like we have represented below. After an excision, there was no recurrence of this or similar conditions even after her blepharoplasty 3 months later.

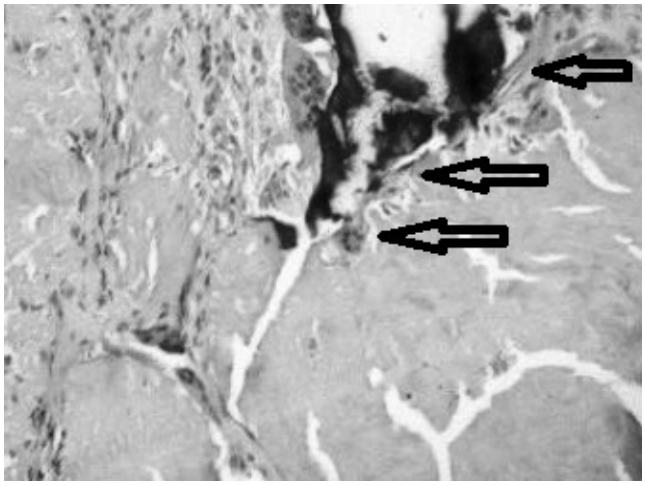

Figure 3. Histological appearance of excised tissue. Calcification (arrowed) is surrounded by healthy, intact tissue

This case report could be an example of a calcification process in a healthy area. Authors linked this process with the previous surgery, but the question 'Why calcification took place in a healthy area instead of the surgery area?' remains unanswered. At first, authors can suggest that this is could be an example of "reactive" calcification, in which damage to nearby tissue could increase an amount of inflammatory mediators, which could trigger any area in our body, especially the area which is near the site of the previous surgery. During tissue trauma, there is sudden release of huge amount of cytokines. After initial phase of inflammation, there is the phase in which granulation tissue forms. During this phase, an exposed and previously damaged area is prone to calcification since granulation tissue has an acidic environment in which calcium is more likely to bind a phosphate [2]. This phase ususally takes 3 weeks to resolve completely. This is highly unlikely that in a healthy person without any history of connective tissue disease this process could last longer. Even if it is, there were no data found about this type of pathological process. Secondly, this could be just a coincidence. There are many articles about spontaneous calcification, for example, calcification of arteries and cartilage in mice. However, it can not be exactly compared to a human`s body, but the structure of cartilage in mice and in humans remains almost the same [4]. There is also one more thing to consider – calcinosis cutis. It is well known, that calcinosis cutis can occur in any part of a skin including eyelids, finger pads and ear`s pinna without obvious reasons. However, this process is rarely isolated and spontaneous. In general, calcinosis cutis tends to occur in chronic and periodic way. It also can be linked to many autoimmune conditions like Systemic Lupus Erythematosus, Ehlers-Danlos syndrome, CREST syndrome, Scleroderma and so on [5]. However, there was not either evidence of these diseases in the patient or family history of any kind of skin and connective tissue pathology. Additionally, reduced blood flow can be a reason of this pathological process. However, it is not linked with calcification directly. Lack of sufficient blood flow can lead to chronic inflammation and can be a reason of poor wound healing [6]. Poor wound healing and chronic inflammation are the main reasons of local calcification process due to, as was mentioned before, acidic environment in which calcium is more prone to be stored in tissues. However, in this case, it is impossible to consider because the pathological process took place in healthy and undamaged tissue, which was not touched during surgery and the blood flow was not reduced. The last point to consider is an infection. Many local and systemic infections can lead to chronic inflammation and to granulated and calcificated areas [2]. Besides chronic inflammation, there is one more pathway in which calcification can take place. The similar mechanism we can see in tuberculosis, where macrophages attack Mycobacteria, but due to its thick cell wall, they can not eliminate the bacteria completely. The result is the Ghon complex, in which caseous necrosis takes place. Many other infections can also lead to similar granulomatous pattern, but it has its own characteristic microscopic appearance, which haven`t been observed by authors. Moreover, during regular appointment visits after surgery, there were no signs and symptoms of any kind of infection or inflammation. To sum it up, there are no obvious reasons, which could explain calcification of intact tissue in this case.

Conclusions: This clinical example demonstrates that a calcification process after tissue trauma could arise not only within exposed tissue, but also within healthy tissues, which takes place near the exposed ones. This conclusion could suggests that a calcification process, in some cases, can be chaotic and could not have an obvious explanation or any association with a trigger.

It also could be assumed, that a similar phenomenon could take place in any other surgical procedure. No similar case reports were discovered by authors.

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COURSE OF GLOMERULONEPHRITIS IN CHILDREN WITH CONNECTIVE TISSUE DYPLASIA

Abstract. The clinical and laboratory features of acute glomerulonephritis in children with connective tissue dysplasia in the environmentally unfavorable Surhandarya region were studied. Multiple stigmas of connective tissue dysplasia and dysembryogenesis were more common in patients with acute glomerulonephritis with nephrotic syndrome and nephrotic syndrome with hematuria. In children with acute glomerulonephritis and multiple stigmas of connective tissue dysplasia and dysembryogenesis, pronounced and more prolonged edema, significant proteinuria was more often noted, and there were high indicators of process activity. The presence of multiple stigmas of connective tissue dysplasia and dysembryogenesis in patients with acute glomerulonephritis can be an indirect criterion for predicting the severe course of acute glomerulonephritis and the high activity of the process, which is important to consider when prescribing therapy.

Keywords: Children, glomerulonephritis, connective tissue, dysplasia, immunology.

Introduction

Connective tissue dysplasia (CTD) is a violation of the development of connective tissue in the embryonic and postnatal periods, a genetically determined condition characterized by defects in fibrous structures and the basic substance of connective tissue. Dysplastic changes in the connective tissue significantly affect homeostasis, metabolism and immunity at the tissue, organ, and body levels in the form of various morphological and functional disorders of the visceral and locomotor organs with a progressive course and determine the characteristics of the associated pathology, as well as the pharmacokinetics and pharmacodynamics of drugs [1]. Connective tissue (CT) performs numerous functions: morphogenetic, biomechanical, trophic, barrier, plastic, etc., the leading of which is the integration of various organs and tissues of the body into a single whole [2; 4]. Morphological changes in the CT itself, changes in metabolic processes, immunogenesis cause the occurrence of secondary disorders from the internal organs, which often determines the severe course and prognosis of the underlying pathological process [6]. Connective tissue dysplasia syndromes (CTDS) are genetically heterogeneous, and according to several authors, they are detected with a high frequency in children with renal pathology, incl. in patients with pyelonephritis, interstitial nephritis, cystitis, nephroptosis, glomerulonephritis [3; 4; 5]. Unfavorable environmental factors leading to the formation of "secondary environmental immunodeficiency" affect the metabolism of connective tissue, the state of cell membranes, therefore, in such patients, the negative effect of connective tissue dysplasia should be more pronounced [1; 7; 8]. CTDS are manifested not only by external signs, but also by the features of the immune status with a decrease in the activity of T-lymphocytes, deficiency of CD3+, CD4+, impaired phagocytosis, changes in the level of IgA, IgM, IgG, impaired formation, and elimination of circulating immune complexes (CIC), due to a decrease in activity and intensity of macrophage-monocytic

immunity [1; 4]. This leads to the development of immunopathological and immunocomplex diseases, including acute glomerulonephritis (AGN), which has a specific clinical course.

The aim of the work was to study the clinical and laboratory features of AGN in children with connective tissue dysplasia living in the environmentally disadvantaged Surhandarya region.

Materials and research methods

We examined 94 children with AGN living in the Surhandarya region, aged from 1 to 7 years, who were treated at the Regional Children's Clinical Association and City Children's Hospital № 1. In 50 patients, AGN proceeded with nephritic syndrome, in 26 – with nephrotic syndrome (NS), in 18 – with NS and hematuria. All patients underwent a conventional clinical and laboratory examination, which included the identification of connective tissue dysplasia stigmas and dysembryogenesis. The degree of disorganization of the basic substance of the connective tissue was determined by the level of sialic acids, seromucoids, C-reactive protein, CIC.

Results and its discussion

During the examination of 94 children with AGN, CTD stigmas were detected in 84,04 ± 3,78% of patients, multiple connective tissue dysplasia stigmas (3 or more) were detected in 39,3 ± 5,04%, that is, in every third patient with AGN.

Of the connective tissue dysplasia stigmas, anomalies of the hands and feet (41.5 ± 5.08%) and flat feet (40.4 ± 5.06%) were the most common. Age spots and hypermobility of the joints occurred with the same frequency (33.9 ± 5.0%), and postural disorders, scoliosis were detected in 20.2 ± 4.14% of patients. Other connective tissue dysplasia stigmas (deformation of the chest, hernias, myopia, tall stature and long fingers, sandal gap, deformity of the gallbladder, mitral valve prolapses) occurred in less than 10% of the examined patients. More than 5 stigmas of CTD had 3 out of 94 children. The absence of CTD stigmas was found in 16.0 ± 3.8% of children with AGN. In various forms of AGN, CTD stigmas occurred with almost the same frequency ($p > 0.05$). Three or more CTD stigmas occurred with equal frequency in patients with nephritic syndrome (39.6 ± ± 6.4%) and nephrotic syndrome (41.0 ± 10.7%). This may indicate that the characteristics of metabolism and immunity in children with CTD predispose to the development of AGN, but do not determine its form. Since CTD is genetically determined, the peculiarities of connective tissue metabolism can occur in utero, which affects the formation of some stigmas of dysembryogenesis. Disembryogenesis stigmas were detected in 9.4 ± 2.9% of patients with AGN, multiple dysembryogenesis stigmas (3 or more) were detected in 51.0 ± 5.1% of children, that is, in every second patient with AGN.

Of the stigmas of dysembryogenesis, the tendency to syndactyly II, III toes were most common (78.7 ± 4.2%), with the same frequency – gothic palate and hypertelorism (respectively 56.3 ± 5.1 and 52.1 ± 5.1%), somewhat less often – deformation of the earlobes (20.2 ± 4.1%), low hair growth on the forehead (18.0 ± 3.9%). Other stigmas of dysembryogenesis, such as anomalies in the shape of the skull, epicanthus, anomalies of the kidneys, anomalies of the eyes, cryptorchidism, an additional nipple on the chest, hypertrichosis, occurred in less than 5% of the examined children. More than 5 stigmas of dysembryogenesis had 8 out of 94 children (8.5 ± 2.9%).

The incidence of dysembryogenesis stigmas in various forms of AGN had several differences. In the nephrotic form of AGN, more often than in the nephritic form, there were 3 or more dysembryogenesis stigmas, which were detected in 68.18 ± 10.2% of patients with the nephrotic form and in 41.3 ± 6.4% with the nephritic form ($p < 0,05$). At the same time, 1–2 stigmas of dysembryogenesis were more often detected in nephritic syndrome (28 patients, 48.2 ± ± 6.5%) and only in 5 out of 22 patients with nephrotic syndrome ($p < 0.05$). he presence of multiple dysembryogenesis stigmas in patients with nephrotic syndrome indirectly indicates a negative effect of connective tissue metabolism, membrane permeability,

immunity, its regulatory systems (cytokines) on the occurrence of nephrotic syndrome in AGN.

In isolated urinary syndrome, the incidence of dysembryogenesis stigmas did not differ from the frequency in AGN with nephritic syndrome, so these two groups of patients were not separated. The nature of dysembryogenesis stigmas in groups of patients with various forms of AGN did not differ significantly ($p > 0.05$).

The presence of a combination of CTD stigmas and dysembryogenesis was found in almost all patients with AGN (98.9 ± 1.0%). Only one child did not have CTD stigmas and dysembryogenesis. It was a boy of school age who fell ill after suffering a sore throat. AGN in this child proceeded with nephritic syndrome. Most children (84.0 ± 3.7%) had more than 3 stigmas of CTD and dysembryogenesis, only 14.9 ± 3.6% of children, mainly with AGN nephritic syndrome, had 1–2 stigmas of CTD and dysembryogenesis. No child with nephrotic syndrome had less than 3 stigmas of CTD and dysembryogenesis. At the same time, all children with nephrotic syndrome and the vast majority (13 out of 14) of children with nephrotic syndrome with hematuria had more than 3 stigmas of CTD and dysembryogenesis. The combination of more than 5 stigmas of CTD and dysembryogenesis had 54.2 ± ± 5.1% of patients, that is, every second patient with AGN. he presence of 5 or more stigmas of CTD and dysembryogenesis was significantly more common in nephrotic syndrome (68.18 ± 10.20%) and nephrotic syndrome with hematuria (78.5 ± 11.4%) than in nephritic syndrome (43.1 ± 6.5%, $p < 0.05$).

Thus, the presence of multiple stigmas of CTD and dysembryogenesis in a patient with AGN can be an indirect criterion for predicting a severe course of the process with damage not only to the glomerular apparatus, but also to the basement membrane. Since AGN with nephrotic syndrome and AGN with nephrotic syndrome with hematuria were more common in patients with multiple stigmas of CTD and dysembryogenesis, the clinical manifestations in these patients had certain features. Edema syndrome in patients with AGN with CTD stigmas was more often expressed in the form of anasarca (39.2 ± 5.4%) and moderate edema (16.4 ± 4.1%, $p < 0.05$), and in children with AGN without stigma of CTD, pastosity of the eyelids and shins prevailed (80.0 ± 10.69%, $p < 0.01$). Edema was longer in patients with AGN with CTD stigmas (12.3 ± 1.0 days), and in patients without CTD stigmas, the duration of edema was 8.0 ± 1.3 days ($p > 0.05$). The number of CTD stigmas did not affect the severity of the edematous syndrome and its duration. Hypertension syndrome did not differ significantly in these groups of patients ($p > 0.05$). Gross hematuria was somewhat more common in patients with AGN without CTD stigmas (86.70 ± ± 9.08%, $p > 0.05$). Its duration did not depend on the presence or absence of CTD stigmas. Proteinuria up to 1 g/l was more common in patients with AGN without CTD stigmas (73.4 ± 11.8%), in patients with CTD, proteinuria more than 2 g/l prevailed ($p < 0.05$). The average level of daily proteinuria in patients with CTD stigmas was 2.6 times higher than in patients without CTD stigmas. The incidence of leukocyturia in patients with AGN did not depend on the presence of CTD ($p > 0.05$). Acute phase parameters (sialic acids, diphenylamine test, seromucoid, C-reactive protein), levels of CIC and cryoglobulins, fibrinogen were increased more significantly in patients with AGN who had CTD stigmas. This is since the presence of CTD stigmas reflects some features of the metabolism of connective tissue structures, acute phase parameters, the level of CIC and cryoglobulins, fibrinogen were analyzed depending on the presence or absence of CTD stigmas.

Thus, in patients with AGN with CTD stigmas, sialic acids were elevated in 62.8 ± 6.77% of cases, their average level was 261.0 ± 11.0 units; diphenylamine test increased in 70.5 ± 6.3%, the average level of diphenylamine test was 0.290 ± 0.011 units; seromucoid was elevated in 49.02 ± 7.0% of patients, its average level was 0.32 ± 0.01 u.op.pl. In patients with AGN without CTD stigmas, sialic acids, diphenylamine test, and seromucoid were elevated only in

1/6 patients, and the average level of sialic acids was 182.5 ± 17.0 arb. units, diphenylamine test – 0.2 ± ± 0.01 u.p.m. ($p < 0.01$), seromucoid – 0.3 ± 0.02 op.pl. ($p < 0.001$). The average level of C-reactive protein in the presence of CTD stigmas was 4.6 times higher than in patients without CTD stigmas ($p < 0.01$). The mean fibrinogen level was somewhat higher in the presence of CTD stigmas (5.0 ± 0.3 g/l, $p > 0.05$). The number of CTD stigmas had some effect on the degree of increase in acute phase parameters, CIC, cryoglobulins, fibrinogen. In patients with multiple CTD stigmas, all these indicators were higher. Probably, more pronounced metabolic and immune changes in patients with multiple stigmas of CTD and dysembryogenesis affect the degree of connective tissue destruction in patients with AGN.

Findings

Most children with AGN have CTD and dysembryogenesis stigmas, while every third child has multiple CTD stigmas, and every second child has multiple dysembryogenesis stigmas. Significantly more often, 5 or more stigmas of CTD and dysembryogenesis are detected in AGN with nephrotic syndrome and AGN with nephrotic syndrome with hematuria and hypertension. In children with CTD stigmas, the edematous syndrome is more pronounced and longer, with significant proteinuria, and higher rates of process activity. Thus, the presence of multiple stigmas of CTD and dysembryogenesis, on the one hand, indicates an adverse effect in the ante- and postnatal period, predisposing to the development of AGN. On the other hand, the presence of multiple stigmas of CTD and dysembryogenesis in patients with AGN may be an indirect criterion for the severe course of AGN, the high activity of the process, which is important to consider in prognosis and therapy. Determining the stigmas of CTD and dysembryogenesis is a simple, informative method, publicly available and not difficult for a pediatrician. The study of the detection of CTD stigmas and dysembryogenesis is especially important at the present stage due to the deterioration of the environmental situation and the change in the classical clinic of the disease.

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CHARACTERISTICS OF THE IMMUNOLOGICAL PROPERTIES OF THE EFFECT OF ACUTE EXPOSURE ON THE ORGANISM OF EXPERIMENTAL ANIMALS

Abstract. The aim of the study was to determine the effect of acute irradiation on the immune status of experimental animals, taking into account the degree of influence of biocorrection on this process. It was found that in white outbred male rats that received and did not receive acute irradiation, distinctive results were obtained in the relative values of immune system cells. This was observed in the total number of lymphocytes, cells – CD3+-, CD4+- and CD8+. A key indicator of the development of secondary immunodeficiency is a decrease in IRI by 2.01 times in the main group. No changes were found in CD20+ cells, in the main group of laboratory animals the number of CD16+ cells increased by 1.35 times, and in CD95+ cells it decreased by 1.51 times. The deficiency of the immune system in the biocorrection group was relatively shallow, the biological product used had an immunostimulating effect. It has been proven that its use reduced the negative impact of acute irradiation on the quantitative indicators of immune system cells.

Keywords: acute irradiation, immunocompetent cells, laboratory animals, secondary immunodeficiency, biocorrection.

Introduction

It is known that the negative impact of irradiation on all organs and systems of the body leads to irreversible consequences [3; 10]. often detrimental effect on these organs [5; 9].

Acute exposure depends on the frequency and duration of exposure to ionizing radiation and develops at different levels depending on the radiation sensitivity of the organs. The organs of the immune system, mucous membranes of the gastrointestinal tract, exo- and endocrine glands, and sex glands are the most sensitive organs to acute irradiation. Organs with low sensitivity to radiation include the heart, kidneys, liver, brain and spinal cord, bone tissue, and joints [4; 11].

The purpose of the research work is to determine the effect of acute irradiation on the immune status of experimental animals and to show the degree of influence of biocorrection on this process.

Materials and methods. To achieve the goal, 60 adult white male rats weighing 160–180 grams took part in the study. Laboratory animals were kept in plastic cages under standard vivarium conditions at relative humidity (50–60%), temperature (19––220 °C), with a light regime of 12 hours of darkness and light. The care of laboratory animals was carried out according to Nuraliev N. A. et al. [6].

When working with laboratory animals, the rules of biological safety [2; 6] and the ethical principles of working with laboratory animals were strictly observed.

All laboratory animals were divided into the following groups:

the main group consisted of white rats (n = 30) on a standard vivarium diet, which received a single acute irradiation at a dose of 5 Gy;

the control group consisted of intact white outbred rats kept under standard vivarium conditions that did not receive acute irradiation (n = 30).

The main group, in turn, was divided into two small groups: 1a subgroup – white outbred rats that received a single acute irradiation at a dose of 5 Gray with the addition of a biologically active additive "Lactopropolis-AWL" as a biocorrection (n=15); 1b subgroup – white outbred rats without biocorrection, who received a single acute irradiation at a dose of 5 Gray (n=15).

In the course of the experiment, laboratory animals were irradiated with the AGAT-R1 gamma-therapeutic apparatus (made in Estonia), while the source of irradiation was Co-60. Studies on animal irradiation were carried out in the Bukhara regional branch of the Republican Specialized Scientific and Practical Center of Oncology and Radiology, Ministry of Health of the Republic of Uzbekistan.

The drug "Lactopropolis-AWL" was administered once, every morning, based on the body weight of all laboratory animals. Those who received acute irradiation were given the drug for 20 days, on the last day they were irradiated, and then on the 5th day they were mortified and immunological studies were carried out. The biologically active additive "Lactopropolis-AWL" contains probiotic bacteria Lactobacillus rhamnosus 925, Enterococcus durans and an extract of biologically active compounds of propolis with antimicrobial, immunostimulating, anti-inflammatory properties (product of the Institute of Microbiology of the Academy of Sciences of the Republic of Uzbekistan and LLC "AllWellLab").

The state of the immune system of laboratory animals was assessed by the expression of CD-differentiating and activating antigens. The following markers of immunocompetent cells were identified: CD3+-, CD4+-, CD8+-, CD16+-, CD20+-, CD95+-lymphocytes. The expression of CD receptors was carried out according to the rosette formation reaction with monoclonal antibodies of the LT series according to the method of Garib F. Yu. et al. (1995) developed by Sorbent LLC (RF). The immunoregulatory index (IRI, CD4+/CD8+) was calculated.

The materials were statistically processed using the methods of traditional variational statistics. For this, a software package for biomedical research on a personal computer based on the Pentium IV processor was used. The principles of evidence-based medicine were used in organizing and conducting the study.

Obtained results and discussion. In order to study the effect of acute irradiation, first of all, the main parameters of the immune system of intact white outbred male rats that were not exposed to this effect were studied, the results were analyzed and interpreted, a total of 9 indicators (table 1).

Table 1.– The main parameters of the immune system of intact white rats involved in the study, n=30

Indicators	Relative (%)	Absolute
Leukocytes, $\times 10^9$/л	–	4680±36
total number of lymphocytes	49.8±1.1	2331±51
CD3+ cells	50.3±1.2	1172±28
CD4+ Cells	32.7±0.9	762±21
CD8+-Cells	12.9±0.8	301±19
Measure, IRI	2.53±0.01	2.53±0.01
CD16+ Cells	18.1±1.3	422±30
CD20+ Cells	19.6±1.4	457±33
CD95+ Cells	17.8±1.2	415±28

Table 1 shows the quantitative and relative (%) parameters. These results were identical to those previously reported by the investigators [one].

The results obtained on the fifth day after irradiation on the main indicators of the immune system of white outbred rats that received a single acute irradiation in the amount of 5 Gray are shown in (table 2).

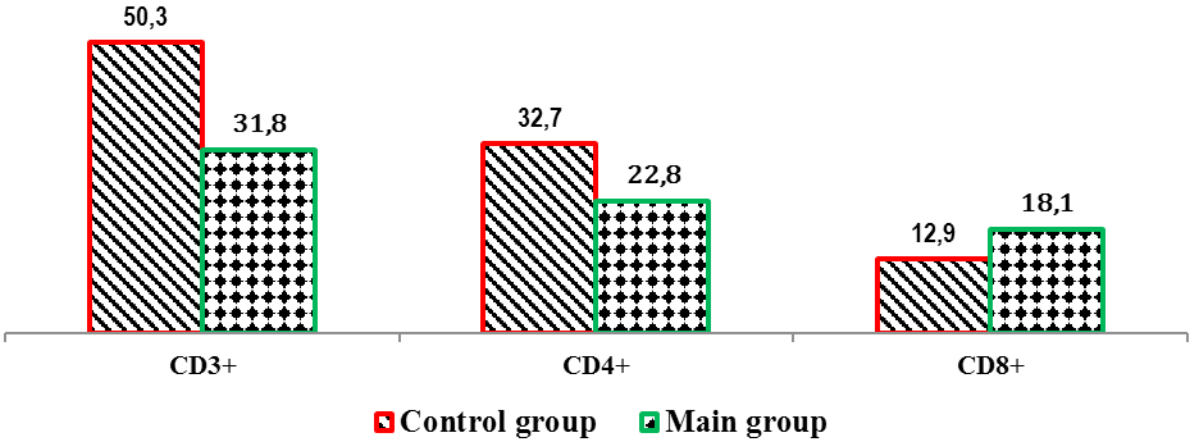
Table 2. – Quantitative indicators of the main immunocompetent white outbred rats treated with acute irradiation, n=30

Indicators	Relative (%)	Absolute
Leukocytes, $\times 10^9/л$	–	4600±49
total number of lymphocytes	35.3±1.4	1624±64
CD3+ cells	31.8±1.5	516±24
CD4+ Cells	22.8±1.1	370±18
CD8+-Cells	18.1±1.2	294±19
Measure, IRI	1.26±0.02	1.26±0.02
CD16+ Cells	24.2±1.6	396±26
CD20+ Cells	21.9±1.7	356±28
CD95+ Cells	11.8±1.5	192±24

The results obtained showed that the quantitative index of leukocytes in the main and control groups of laboratory animals did not have a significant difference ($P > 0.05$). In our opinion, this condition is explained by a short period after irradiation (5 days).

When comparing the quantitative and relative amounts of lymphocytes, we observed a completely different picture. A decrease in relative indicators by 1.41 times ($P < 0.05$) was established in experimental animals that received acute irradiation compared with the relative indicators of the control group (intact) experimental animals.

When comparing the absolute indicators of this cell, an almost similar trend was observed, the decrease was 1.44 times ($P < 0.05$). The decrease in the relative and absolute number of lymphocytes is explained by the effect of acute irradiation on the proliferation, differentiation of these cells, and a decrease in their activity.



Picture 1. Comparative characteristics of relative indicators in the system of T-lymphocytes in white outbred rats that received (basic) and did not receive (control) acute irradiation in%

As for the analyzed immunocompetent cells of the body's immune system, changes in T-lymphocytes (CD3+ cells) and their main subpopulations (CD4+ + and CD8+ cells) had different forms. There was a significant decrease in the relative and quantitative indicators of CD3+ cells compared with the control group (picture 1).

In quantitative terms, the decrease in CD3+ cells was 1.58 times ($P < 0.001$), and the relative number of CD4+ cells decreased 1.43 times ($P < 0.05$). We observed the opposite picture in terms of the relative number of CD8+ cells; it was found that these cells significantly increased relative to the control in the main group – 1.40 times ($P < 0.05$). Both

lymphocytes responded to the same exposure with different changes.

The decrease in the relative number of CD3+ and CD4+ cells in the group of white outbred rats that received acute irradiation is explained by a decrease in the total number of lymphocytes, immunodeficiency in the T-lymphocyte system, and this condition was recognized as an exposure to acute irradiation, because other factors affecting laboratory animals were eliminated. Given that one of the main functions of CD8+ cells is to reduce the immune response, an increase in the number of these cells relative to other cells is one of the reasons for the development of secondary immunodeficiency.

Similar results were obtained for the quantitative indicators of the above-mentioned immunocompetent cells (except for CD8+ cells). If a significant difference of 2.27 times in favor of the control group ($P < 0.001$) was found between the absolute values of CD3+ cells between the main and control groups, then the same trend remained for CD4+ cells (difference by 2.06 times, $P < 0.001$). However, it was noted that no such trend was found in -CD8+ cells. No results were obtained in one or the other group of these data ($P < 0.05$). This distinction between relative and quantitative measures raises the question of what indicators should be relied upon for inference based on interpretation and analysis. If we take into account that the quantitative indicator is more dependent on the quantitative indicators of leukocytes and lymphocytes, it becomes clear that the trend of change in relative indicators allows us to obtain reliable results and draw reasonable conclusions. Therefore, in experimental studies it is recommended to use relative indicators in assessing the activity of the immune system, the state of immunocompetent cells.

Another scoring parameter used to evaluate the T-system of the immune system is IRI. This indicator indicates the ratio of T-lymphocytes to the main immunoregulatory cells in the same case, the higher the IRI, the less pronounced immunodeficiency in the body, the lower the level of secondary immunodeficiency [7]. Therefore, it is recommended to constantly use IRI when assessing the immune status. Studies have established that IRI in the control group is significantly higher than in the main group by 2.01 times ($P < 0.001$). The fact that this unit shows the same result both in relative and absolute parameters indicates that it can be used to assess the degree of depth of immunodeficiency. To assess the activity of the immune system, we believe that a comparative assessment of the relative parameters of immunocompetent cells and IRI is sufficient.

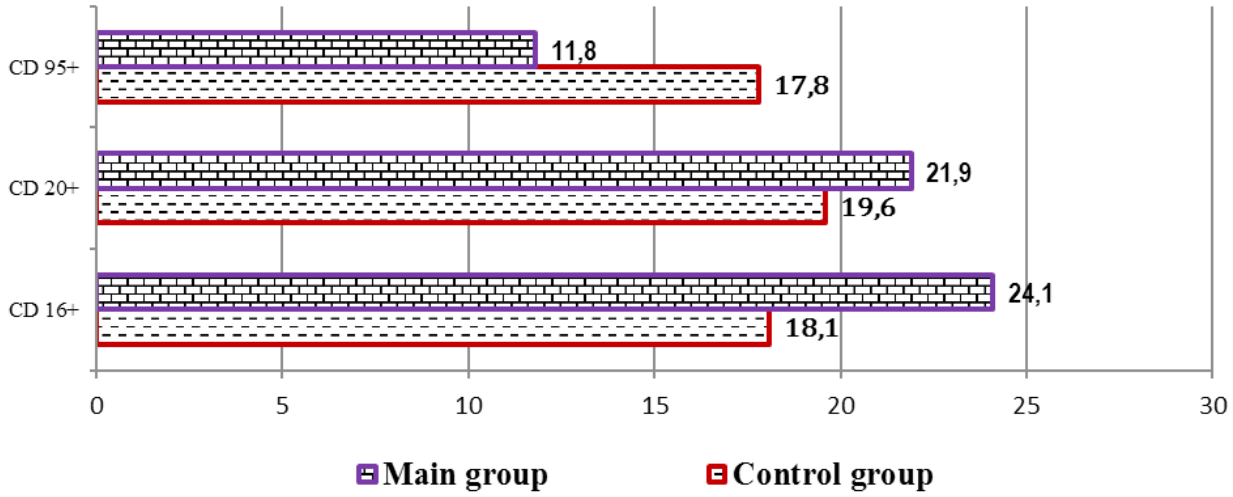
Since we considered that together with the T-system of immunity it is important to define the B-system of immunity, the relative and absolute values of cells – CD20+ were studied and analyzed. The results obtained showed no significant differences between groups compared to this immunocompetent cell ($P > 0.05$). Apparently, the difference of 1.12 times was in favor of the main group.

Although the results did not differ significantly from each other, white outbred rats exposed to acute irradiation showed a tendency to multiply in -CD20+ cells compared with intact laboratory animals. This situation showed that changes in the T-system of the immune system develop faster than the B-system seeks to compensate for the deficiency that occurs in the B-system of immunity. It is noteworthy that the results obtained in absolute terms differ from the relative parameters, the data in the control group were higher than in the main group ($P < 0.001$).

CD16+ cells, which are part of the nonspecific defense of the immune system, are allogeneic and xenogeneic cells that multiply in the body regardless of the antigen and perform the function of detecting and destroying tumor cells. Taking into account the need to eliminate tumor cells formed as a result of external influences (irradiation), taking into account the increase in their number and increase in their activity, the real reasons for the quantitative and relative changes in CD16+ cells become clear. The observations showed that in laboratory animals that received acute irradiation, the relative index of these cells increased

significantly compared to the control group – 1.35 times ($P < 0.05$). No significant difference was found between the absolute values ($P > 0.05$).

The CD95+ receptor is one of the apoptosis receptors, which is expressed on the surface of all cells of the immune system and is involved in the control (regulation) of the immune system. In our study, the relative number of – CD95+ cells was significantly reduced in white outbred rats of the control group – 1.5 times, $P < 0.05$ (Figure-2)



Picture 2. Comparative indicators of the relative number of immunocompetent cells of laboratory animals that received (basic) and did not receive (control) acute irradiation,%

Considering that a decrease in the number of lymphocytes with the expression of cells-CD95+ marker was observed in autoimmune and oncological pathologies [8], and this indicates a decrease in the level of readiness of lymphocytes for apoptosis, and a gradual decrease in immunity.

The next stage of the study was the assessment of the degree of influence of biocorrection on the cells of the immune system of experimental animals that received acute irradiation.

Biocorrection was carried out with the preparation "Lactopropolis-AWL", taking into account the serious condition of laboratory animals, it was prescribed once every morning, depending on the weight of the animals. The drug was administered for 20 days, on the last day, acute irradiation was performed at a dose of 5 Gray, on the fifth day after irradiation, laboratory animals were mortified, blood was taken, and immunological studies were performed.

The results obtained are shown in (table 3).

Table 3.– Comparative indicators of the main indicators of the immune system of laboratory animals that received acute irradiation in a biocorrected and uncorrected state

Indicators	**Those who received biocorrection, n=30**		**Those who did not receive biocorrection, n=30**	
	%	**Absolute**	**%**	**Absolute**
1	***2***	***3***	***4***	***5***
Leukocytes, × 10^9/l	–	4600±49	–	5650±6.1*↑
Total number of lymphocytes	35.3±1.4	1624±64	44.5±1.6*↑	2514±90*↑
CD3+ cells	31.8±1.5	516±24	39.9±1.7*↑	1003±43*↑
CD4+ cells	22.8±1.1	370±18	23.9±1.2↔	601±30*↑
CD8+ cells	18.1±1.2	294±19	16.3±1.1↔	410±28*↑

1	*2*	*3*	*4*	*5*
IRI	1.26±0.2	1.26±0.2	1.47±0.1*↑	1.47±0.1*↑
Cells-CD16+	24.4±1.6	396±26	22.3±1.5↔	561±38*↑
Cells-CD20+	21.9±1.7	356±28	23.6±1.8↔	593±45*↑
Cells-SD95+	11.8±1.5	192±24	15.5±1.0*↑	390±30*↑

*Note: * – signs of confidence between biocorrected and non-biocorrected groups: ↑ – direction of changes; ↔ – no significant difference*

It can be seen that the results obtained by relative and absolute indicators have differences, 4 of the relative indicators (out of 8 parameters) 50.0% of the indicator changed confidently in a positive direction, and no significant changes were detected for the remaining 4 indicators (50.0%), however, they tend to shift in the positive direction.

Reliable relative values are the total number of lymphocytes (increase by 1.26 times $P < 0.05$), the number of CD3+ cells (increase up to 1.25 $P < 0.05$), IRI (increase by 1.17 times $P < 0.05$) and the number of CD95+ cells (increase up to 1.31 times, $P < 0.05$) was not observed.

Significantly relative values were the total number of lymphocytes ($R < 0.05$, an increase of 1.26 times), the number of SD3+ cells ($R < 0.05$, an increase of up to 1.25 times), IRI ($R < 0.05$, increase by 1.17) and SD95+ cell count ($R < 0.05$, increase to 1.31).

In cells subjected to acute irradiation for the first time, sensitivity partially decreased after biocorrection.

Significant changes were observed in absolute amounts (100%) of 9 studied immunocompetent cells ($P < 0.05 – P < 0.001$). The indicators of the group of laboratory animals that underwent biocorrection prior to acute irradiation showed a positive shift in immune system cells from 1.17 to 2.03 times compared to non-biocorrected white outbred rats, we want to emphasize once again that all changes were significant.

If we compare the indicators of the biocorrected subgroup 1b with those of intact laboratory animals (control group), we observe that there are the following differences from this subgroup:

firstly, the absolute values of 9 studied immunocompetent cellular parameters of the immune system were significantly higher than in laboratory animals of the control group;

the second aspect was that the relative number of 9 immunocompetent cells studied by the immune system was close to that in intact laboratory animals, it was especially clearly manifested in the total number of lymphocytes and CD25+ cells;

the third aspect is that – CD4+ cells before and after biocorrection with the biologically active additive «Lactopropolis-AWL» are almost identical, far from normal;

the fourth aspect is that – CD20+ cells differ more than the normative values given. In general, the quantitative deficiency of the immune system in the group of outbred rats (subgroup 1b) that underwent biocorrection was observed to a lesser extent than in the comparison group (subgroup 1a).

Findings

1. Distinctive results were obtained on the relative and absolute values of the cells of the immune system of white outbred rats that received and did not undergo acute irradiation. These results were mainly observed in the ratio of the total number of lymphocytes, cells – CD3+-, CD4+- and CD8+, which were significantly reduced by 1.41, 1.58 and 1.43 times, respectively, in laboratory animals exposed to acute radiation ($P < 0.05$), the number of cells – CD8+ increased statistically significantly only 1.40 times ($P < 0.05$).

2. The main indicator of the development of secondary immunodeficiency is recognized as a decrease in IRI by 2.01 times in the main group. To

assess the activity of the immune system, it was considered sufficient to compare the relative indices of immunocompetent cells and IRI.

3. No changes were observed in the B-link of the immune system, there was no significant difference, but in the main group there was a tendency for their growth. Cells – CD16+ significantly increase by 1.35 times in the main group of laboratory animals, which is a sign of increased activity of the immune system in relation to allogeneic and xenogenic cells. A significant decrease in the number of – CD95+ cells by 1.51 times in the main group was explained by a decrease in the readiness of lymphocytes for apoptosis, an increase in the likelihood of an increase in the number of tumor cells in the body.

4. When comparing the parameters of the biocorrected subgroup 1b with those of intact laboratory animals, we observe the following differences: absolute values of the absolute values of 9 studied parameters of the immune system relative to the control group; approximation of the relative number of immunocompetent cells to that of intact laboratory animals, the relative number of cells – CD4+ cells is almost the same before and after biocorrection with the biologically active additive «Lactopropolis-AWL» (P> 0.05) are far from normal. A large deviation of cells – CD20+ from the specified normative values. In the group of white outbred rats, the quantitative deficiency of the immune system was less pronounced than in the comparable group.

5. The immune system deficiency in the biocorrected group was relatively shallow, which indicated the immunostimulating effect of the biological product used, it was proved that its intake reduced the negative impact of acute exposure on the quantitative indicators of immune system cells.

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COMPARATIVE CORRELATION OF MARKERS OF INFLAMMATORY METAMORPHISM IN THE PERIPHERAL BLOOD IN DORSOPATHY OF DIFFERENT GENESIS

Abstract. A blood test for acute phase proteins and inflammatory markers is a comprehensive study of various proteins, the level of which in the blood increases during various inflammatory processes in the body. Dorsopathy is a common pathology accompanied by aseptic inflammation in the spine, but has not been studied for markers of inflammation. Purpose of the study: to study the indicators and comparative correlation of markers of inflammatory metamorphism in the peripheral blood of patients with chronic pain syndrome in dorsopathies of various origins. 320 patients with chronic pain syndrome with dorsopathies of various origins, who are being treated in the neurology department of the City Medical Association of Samarkand in the period from 2018 to 2021, were selected. Blood tests for acute phase proteins and inflammatory markers were used: fibrinogen, C-reactive protein, interleukin-1β. In patients with chronic pain syndrome in dorsopathies of compression-ischemic genesis, brucellosis, rheumatic and herpetic genesis, the detected concentrations of fibrinogen, C-reactive protein and interleukin – 1β in the blood serum indicated various indicators of the presence of an inflammatory process, provoking chronic pain, indicating an inflammatory nature, which determines the chronic course and nature of pain.

Keywords: inflammation markers, fibrinogen, C-reactive protein, interleukin-1β, dorsopathy.

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СРАВНИТЕЛЬНАЯ КОРРЕЛЯЦИЯ МАРКЕРОВ ВОСПАЛИТЕЛЬНОГО МЕТАМОРФИЗМА В ПЕРИФЕРИЧЕСКОЙ КРОВИ ПРИ ДОРСОПАТИЯХ РАЗЛИЧНОГО ГЕНЕЗА

Аннотация. Анализ крови на белки острой фазы и маркеры воспаления – это комплексное исследование различных белков, уровень которых в крови повышается при различных воспалительных процессах в организме. Дорсопатии – часто встречающаяся патология, сопровождающаяся асептическим воспалением в позвоночнике, однако не исследованная на предмет маркеров воспаления. Цель исследования: изучение показателей и сравнительная корреляция маркеров воспалительного метаморфизма в периферической крови больных с хроническим болевым синдромом при дорсопатиях различного генеза. Отобраны 320 больных с хроническим болевым синдромом при дорсопатиях различного генеза, находящихся на лечении в отделении неврологии Городского медицинского объединения г. Самарканда в период с 2018 по 2021год. Были применены исследования крови на белки острой фазы и маркеры воспаления: фибриноген, С-реактивный белок, интерлейкин –1β. У больных хроническим болевым синдромом при дорсопатиях компрессионно-ишемического генеза, бруцеллезного, ревматического и герпетического генезов, выявленные концентрации фибриногена, С-реактивного белка и интерлейкина – 1β в сыворотке крови указывали на различные показатели наличия воспалительного процесса, провоцирующие хроническую боль, указывающий на воспалительный характер, определяющий хроническое течение и характер боли.

Ключевые слова: маркеры воспаления, фибриноген, С-реактивный белок, интерлейкин –1β, дорсопатия.

Актуальность. Анализ крови на белки острой фазы и маркеры воспаления – это комплексное исследование различных белков, уровень которых в крови повышается при различных воспалительных процессах в организме [6]. Дорсопатии – часто встречающаяся патология, сопровождающаяся асептическим воспалением в позвоночнике, однако не исследованная на предмет маркеров воспаления [5; 9; 12].

Повышение фибриногена не только компонент свёртывающей системы крови, но и показатель острых и хронических воспалительных, иммунных и опухолевых явлений [1; 3]. Актуальные взгляды воспаления на развитие радикулопатий основаны на том, что процесс ограничивался одним или несколькими сегментами позвоночного столба, имея локальный характер [2; 7]. Повышение концентрации фибриногена свыше физиологической нормы при данных заболеваниях бывает умеренно выраженным и хорошо купируется препаратами НПВС [4; 8].

Цель исследования: изучение показателей и сравнительная корреляция маркеров воспалительного метаморфизма в периферической крови больных с хроническим болевым синдромом при дорсопатиях различного генеза.

Задачей поставленной работы явилось изучение концентрации фибриногена, С-реактивного белка и интерлейкина –1β в плазме крови у больных с хроническим болевым синдромом при дорсопатиях компрессионно-ишемического генеза, бруцеллезного, ревматического и герпетического генезов.

Материалы и методы исследования. Отобраны 320 больных с хроническим болевым синдромом при дорсопатиях различного генеза, находящихся на лечении в отделении неврологии городского медицинского объединения г. Самарканда в период с 2018 по 2021год.

Для дальнейшего научного исследования больные были распределены в следующие группы:

– 1-я группа: хроническая дорсопатия компрессионно-ишемического генеза (ДКИГ) – 82 больных;

– 2-я группа – дорсопатия при хроническом бруцеллезе (ДБрГ) – 84 больных;

– 3-я группа – дорсопатия ревматического генеза (ДРевГ) – 76 больных;

– 4-я группа – дорсопатия при хроническом герпесе (ДГерГ) – 78 больных;

– контрольную группу составили 40 условно здоровых людей признаков дорсопатий, соизмеримые по полу и возрасту с вышеперечисленными группами (были отобраны сотрудники городского медицинского объединения).

Исследования были проведены в рамках Хельсинской декларации Всемирной ассоциации «Этические принципы проведения научных и медицинских исследований с участием человека», с учетом поправок 2000 года. Вся информация о пациентах была собрана, проанализирована и письменно зафиксирована с согласия самих больных. Проведение научной работы было одобрено локальным этическим комитетом института согласно договорам о проведении совместных научных работ.

Все больные с ХБС находились в возрастном охвате лиц от 16 до 75 лет, при это преимущественно – 30–39 лет – 96 (30%), а также 50–59 лет – 67 (20,9%). Градация в разрезе пола из 320 пациентов: женщин – 205 (64,1%), мужчин – 113 (35,4%) (Таблица 1).

Таблица 1. – Градация в разрезе пола и возраста

Возраст (лет)	**Женщины (абс/%)**	**Мужчины (абс/%)**	**Всего (абс/%)**
1	***2***	***3***	***4***
До 19	13(4,1%)	11(3,4%)	24(7,5%)
20–29	44(13,7%)	13(4,1%)	57(17,8%)

1	*2*	*3*	*4*
30–39	59(18,4%)	37(11,6%)	96(30%)
40–49	30(9,4%)	23(7,2%)	53(16,6%)
50–59	44(13,7%)	23(7,2%)	67(20,9%)
60 и старше	17(5,3%)	6(1,9%)	23(7,2%)
Итого	207(64,7%)	113(35,3%)	320(100%)

Наибольший интерес вызвали дорсопатии различного генеза: дорсопатии компрессионно-ишемического генеза, дорсопатия при хроническом бруцеллезе, дорсопатия ревматического генеза, и дорсопатия при TORCH инфекции, а именно при герпесе.

В данной статье нашей целью явилось освещение полученных лабораторных исследований. Нами были проанализированы клинический и биохимический анализ крови, общий анализ мочи. 1 – **ревматические пробы**: а) ревмофактор (РФ) – исследовали венозную кровь методом иммунотурбидиметрии, положительны считался результат более 8МЕ/мл; б) С-рактивный белок (СРБ) – исследовали венозную кровь, где больного просили не принимать пищу в течение 12 часов перед исследованием, исключить физическое и эмоциональное перенапряжение за 30 минут до исследования, не курить в течение 30 минут до исследования. Показания больше 10 мг/л свидетельствует об остром воспалении, хроническом заболевании; в) антистрептолизин (АСЛО) – исследовали венозную кровь, где больного просили сдавать натощак, накануне исследований исключить алкоголь, интенсивные физические нагрузки и прием лекарственных препаратов. Показания выше 200 МЕ/мл считаются положительными [10].

2 – пробы для выявления **бруцеллёза**: а) реакция Хеддельсона – брали кровь натощак из пальца на предметное стекло, в него капали бруцеллезный диагностикум. Появлении реакции агглютинации считали положительной; б) реакция Райта – исследовали венозную кровь на наличие антител к антигену бруцеллёза. Показатели титра 100–200 говорили о положительном результате, при котором острый процесс возможно переходит в хроническую. 3 – анализ крови на TORCH инфекции, куда входили анализы на антитела к 4 инфекциям: герпес, токсоплазмоз, цитомегаловирус и вирус краснухи. Нами были отобраны больные с антителами к герпесу, так как по данным многих авторов, при данной патологии чаще всего наблюдается поражение чувствительных ганглиев и периферических нервов. Проверяли АТ к герпесу 1 и 2 типа IgG и Ig M. Положительный ответ на IgG означал хроническое носительство [11].

Для исследования эндотелина-1 применяли кровь, взятую натощак из локтевой вены (через 14 часов после еды). Кровь исследовали дважды, при поступлении и в конце проведенного лечения. Не позднее 2-х часов после забора крови путём центрифугирования (3000 оборотов в минуту) отделяли сыворотку и далее сразу же проводили исследование.

Определение концентрации фибриногена. Фибриноген в плазме крови определяли стандартно, модифицированном лабораторно-клиническим методом по A. Glauss, используя новую тест-систему «Мульти Тех-Фибриноген. Данный метод позволял определить концентрацию фибриногена в широком диапазоне, при котором нет этапа разведения, который мог повлиять на точность, правильность и разводимость. Суть метода заключалась в определении времени свертывания цитратной бедной тромбоцитами плазмы избытком тромбина. Для проведения исследования в пластиковую пробирку с цитратом натрия добавляли венозную кровь, далее две минуты инкубировали при 37 °С и только потом присоединяли 50 мл раствора тромбина. Время свертывания

исследуемой плазмы составлял от 5 до 100 секунд. Калибровка тест-системы выполнялась на коагулограммах с разным принципом регистрации полученного времени при образовании сгустка. Калибровочная кривая имела линейный характер в диапазоне 0,5–6 г/л [12].

С – реактивный белок (СРБ) является гликопротеином, относящимся к белкам воспалительного процесса, синтез которого увеличивается уже через 6 часов под воздействием противовоспалительных цитокинов: интерлейкина-1, интерлейкина-6 и фактора некроза опухолей – альфа, концентрация в крови повышается за двое суток почти в 100 раз. СРБ значится маркером воспалительной реакции принимая участие в реакциях гуморального и клеточного иммунитета. Значительные повышения наблюдается при вирусной или бактериальной инфекции, а также при некрозах тканей. Причинами повышения СРБ могут быть и аутоиммунные процессы (ревматоидные артриты, васкулиты спондилоартриты и т.д.), обострения хронических заболеваний и пр. Материал для исследования – кровь из вены, которую берут после 4-х часового голодания. Накануне сдачи крови исключается интенсивная физическая нагрузка, курение и прием спиртных напитков. При достижении реакцией конечной точки измеряли повышение абсорбции в результате преципитации. Калибровочная кривая имела линейный характер, и была выведена в пределах интервала данных значений по стандартам в антисывороткой к СРБ [13].

Интерлейкин-1β является провоспалительным цитокином с широким спектром действия, который несёт важную роль в развитии и регуляции неспецифической защиты и специфического иммунитета. Синтезируясь и выделяясь моноцитами и макрофагами, быстро включается в ответную защитную реакцию организма с патогенными агентами. В нашем исследовании определяли нтерлейкин-1β методом ИФА.

Обсуждение. Концентрацию фибриногена в плазме крови у больных с радикулопатиями компрессионно-ишемического генеза (I группа) не превышала 4,3 г/л, соответствующее физиологической норме.

У больных с хронической болью при дорсопатиях бруцеллёзного генеза (II группа) показатели фибриногена варьировали от 1,7 до 3,2 г/л, в среднем 2.45 г/л, что также соответствовало норме.

Однако в третьей группе больных с радикулопатиями ревматического генеза фибриноген повышался от 12 до 18 г/л, что в среднем составило 15 г/л.

Показатели фибриногена в плазме крови у больных с радикулопатиями герпетического генеза были несколько повышены, и составили 4,8–5,8 г/л, что в среднем составило в среднем 5,3 г/л.

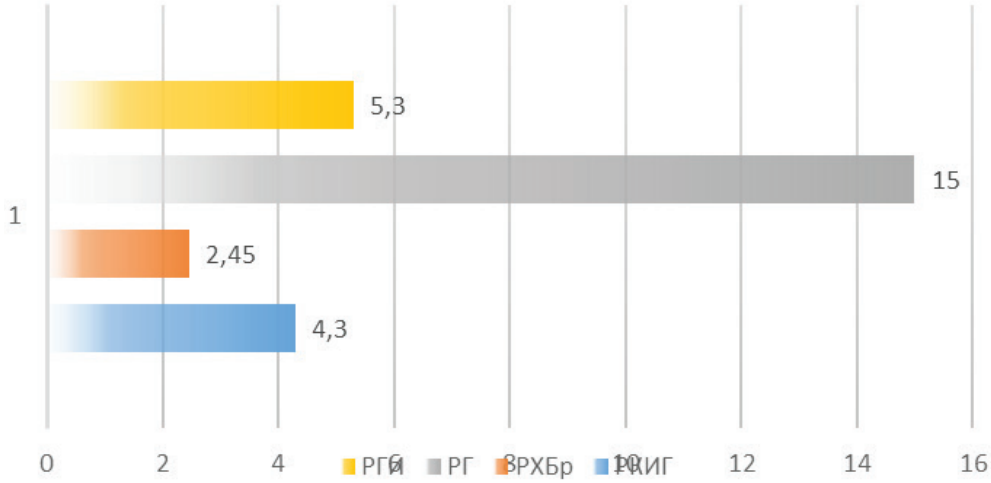


Рисунок 1. Концентрация фибриногена у больных с радикулопатиями различного генеза

Таким образом, на основании полученных данных наличие нативного фибриногена в плазме крови может быть выбрано в качестве дополнительного биохимического критерия для дифференциальной диагностики больных с хроническим болевым синдромом при дорсопатиях различного генеза.

СРБ один из белков острой фазы воспаления с широким спектром биохимических и иммунохимических маркеров воспаления. Развитию хронического болевого синдрома при радикулопатии компрессионно-ишемического генеза способствуют дегенеративно-дистрофические процессы в позвоночнике и межпозвоночных дисках. Для развития боли на спинальные корешки воздействуют механические, биохимические и иммунологические факторы. В результате развивается асептическое аутоиммунное воспаление.

В нашей работе исследовался С-реактивный белок для оценки активности воспалительного процесса. В сыворотке крови здоровых людей СРБ выявляется в виде следов и составляет ниже 3 мг/л. При воспалении низкой интенсивности СРБ в сыворотке крови составляет до 7 мг/л. 7,1––50 мг/л – это показатель средней интенсивности воспалительного процесса. При тяжелом течении воспалительных и аутоиммунных заболеваний показатели СРБ превышают 50 мг/л.

Рисунок 2. Показатели С-реактивного белка в I группы

За день до сдачи крови больных попросили исключить интенсивную физическую нагрузку, воздержаться от курения и приема спиртных напитков. Кровь брали из вены утром натощак. Исследование провели всем 82 больным. Концентрацию СРБ определяли высокочувствительным количественным методом, с помощью набора реактивов фирмы «Thermo scientific».

В первой группе больных результаты показали, что у 12 (14,6%) пациентов – 3–6 мг/л; у 61 (74,4%) больного показатели СРБ были 7–12мг/л; у 9 (11%) больных – 13–16 мг/л. По современным представлениям, данное повышение концентрации СРБ в плазме крови у исследуемых больных указывал на субклинический воспалительный процесс. От отображал активность системного воспаления и иммунопатологических процессов в организме больных хроническим болевым синдромом при радикулопатии компрессионно-ишемического генеза.

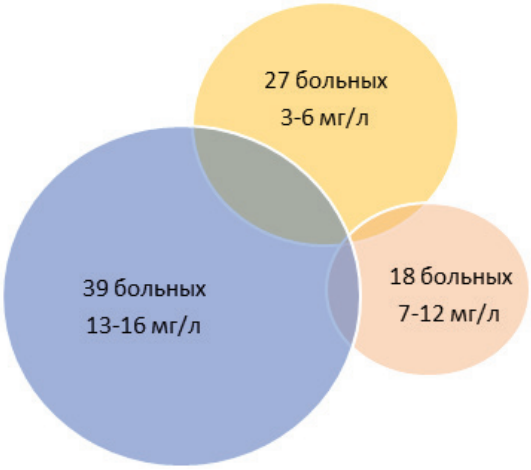


Рисунок 3. Показатели С-реактивного белка в II группы

Во второй группе больных исследование С-реактивного белка имело свои особенности. Нам известно, что возбудитель бруцеллёза располагается внутри клеточно, в результате чего происходит распознавание клеток рыхлой соединительной ткани и связывание их с рецепторами, сигналы которых способствуют запуску системы врожденного иммунитета. Находящиеся в клетке

экзогенные патогены способствуют синтезу и секрету в кровь провоспалительных цитокинов в рыхлой соединительной ткани (Симбирцев А. С., 2004). В ответ на синтез цитокинов гепатоциты индуцируют С-реактивный белок. У всех 84 больных II группы было проведено исследование С-реактивного белка, значения которых были следующими: у 28 (33,3%) больных – 3–6 мг/л; у 39 (46,4%) – 7–12 мг/л; у 17 (20,3%)– 13–19мг/л.

Показатели С-реактивного белка у больных III группы был специфическим и показательным, так как при заболеваниях ревматического генеза это исследование проводят обычно всем больным. При ревматическом процессе в ответ на попадание токсинов в кровь вырабатывается С-реактивный белок, который связываясь с ними обезвреживает их. В некоторых случаях С-реактивный белок нарастает активнее, чем симптоматика, и он является индикатором как развития заболевания, так и регресса заболевания. У всех больных 76 больных III группы было проведено исследование на показатели С-реактивного белка. Так у 8 (10,5%) больных – 3–6 мг/л; у 12 (15,8%) – 7–12 мг/л; у 56 (73,7%)– 13–19мг/л.

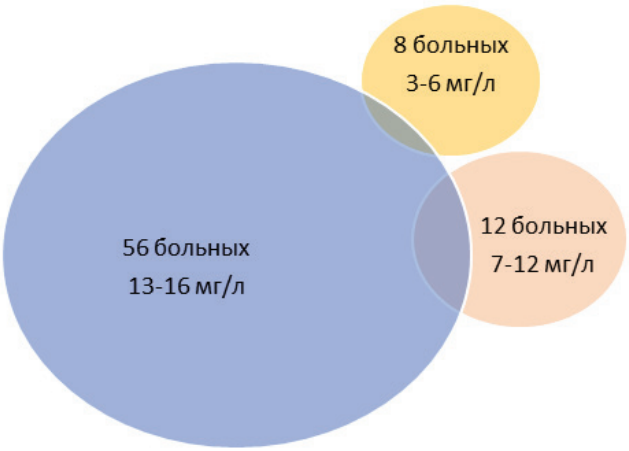


Рисунок 4. Показатели С-реактивного белка в III группы

У всех больных IV группы также была взята кровь на анализ С-реактивного белка, который по литературным данным не являлся специфичным, так как он является белком острой фазы воспаления и помогает в диагностике бактериальной инфекции. У всех больных 78 больных IV группы было проведено исследование на показатели С-реактивного белка. Так у 27 (34,6%) больных – 3–6 мг/л; у 50 (64,1%) – 7–12 мг/л; у 1 (1,3%)– 13–19мг/л.

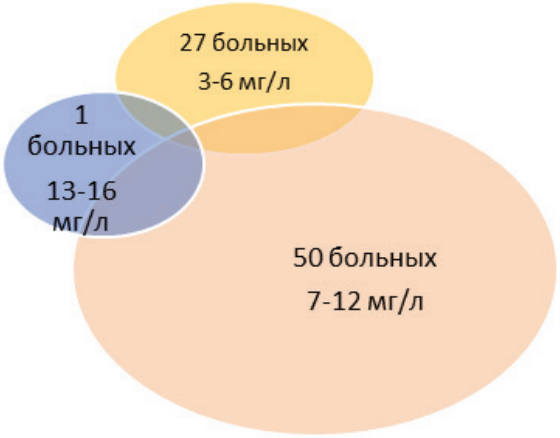


Рисунок 5. Показатели С-реактивного белка в IV группы

Подводя итоги проведенного исследования С-реактивного белка у больных с хроническим болевым синдромом нами были получены следующие результаты (Рисунок 6).

Таким образом, исследование концентрации СРБ в сыворотке крови больных хроническим болевым синдромом при дорсопатиях различного генеза является высокочувствительным количественным методом, который можно рассматривать как дополнительный диагностический признак в развитии хронического болевого синдрома. СРБ можно рассматривать как патогенетический фактор воспаления, приводящий к боли, а также и как фактор, стимулирующий продукцию провоспалительных цитокинов.

Интерлейкин –1β, секретируемый сывороточный цитокин, выделяется фагоцитирующими мононуклеарами, участвует в развитии как специфических, так и неспецифических защитных реакциях организма и активен в отношении множества клеток-мишеней, в том числе и при дорсопатиях.

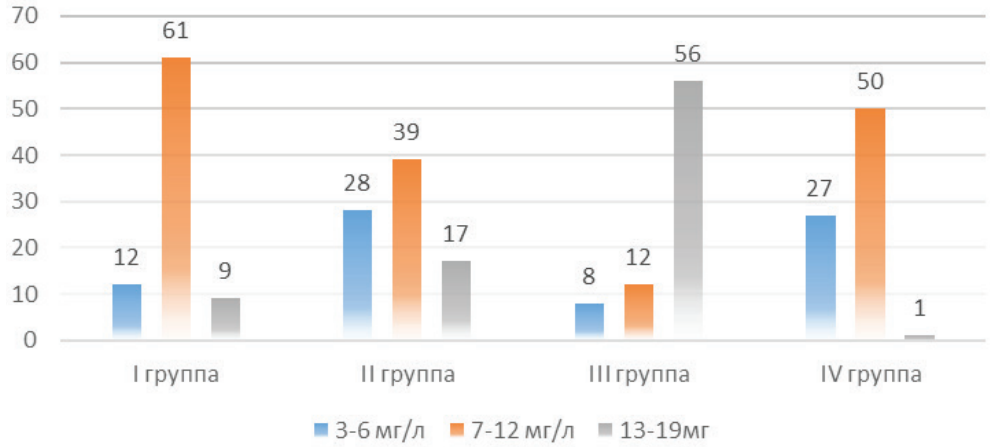


Рисунок 6. Показатели С-реактивного белка в плазме крови больных хроническим болевым синдромом при дорсопатиях различного генеза

Для проведения данного исследования нами было решено отобрать с каждой группы по 25 больных и для сравнения взять 10 человек контрольной группы. Нами были отобраны 25 больных из I группы больных для определения интерлейкина-1β методом ИФА с использованием стандартных наборов реактивов («Bender MedSystem 224/2», Австрия) по инструкции.

У больных с хронической болью при радикулопатии компрессионно-ишемического генеза были получены следующие результаты: у 11 (44%) больных была выявлена выраженная экспрессия интерлейкин –1β, которая составила 4,51 (4,47––4,55) пг/мл, у 5 (20%) 1,35 (1,29–1,41) – пг/мл, которая указывала на легкую степень воспалительной реакции и 9 (36%) – 0,56 (0,54–0,58) – результаты указывали на отсутствие воспалительных процессов (Табл. 2).

Таблица 2. – Содержание интерлейкина-1β в сыворотке крови у больных I группы

Обследованные больные	**11 (44%)**	**5 (20%)**	**9 (36%)**	**10 человек контрольной группы**
интерлейкин-1β пг/мл	4,51 (4,47–4,55)	1,35 (1,29–1,41)	0,56(0,54–0,58)	0,58 (0,55–0,61)

Для удобства корреляции полученных данных концентрации интерлейкина-1β (ИЛ-1β) в сыворотке крови больных II группы также были отобраны 25 больных. В результате были получены следующие показатели: у 2 (8%) больных 5,61 (5,60–5,62) пг/мл, у 15 (60%) – 2,35 (2,29––2,41) пг/мл, которая указывала на легкую степень воспалительной реакции и 8 (32%) 1,56(1,54–1,58) больных результаты указывали на слабую степень воспалительных процессов.

Таблица 3. – Содержание интерлейкина-1β в сыворотке крови у больных II группы

Обследованные больные	**2 (8%)**	**15 (60%)**	**9 (36%)**	**10 человек контрольной группы**
интерлейкин-1β пг/мл	5,61(5,60–5,62)	2,35 (2,29–2,41)	1,56 (1,54–1,58)	0,58 (0,55–0,61)

Содержание ИЛ-1β в сыворотке крови у больных III группы оказалось следующим: у 17 (68%) больных 7,65 (7,59–7,71) пг/мл, у 5 (20%) – 5,32 (5,26–5,38) пг/мл, которая указывала на выраженную степень воспалительной реакции и 3 (12%) 3,75 (3,72–3,78) больных результаты указывали на умеренную степень воспалительных процессов.

Таблица 4. – Содержание интерлейкина-1β в сыворотке крови у больных III группы

Обследованные больные	**17 (68%)**	**5 (20%)**	**3(12%)**	**10 человек контрольной группы**
интерлейкин-1β пг/мл	7,65(7,59–7,71)	5,32(5,26–5,38)	3,75(3,72–3,78)	0,58(0,55–0,61)

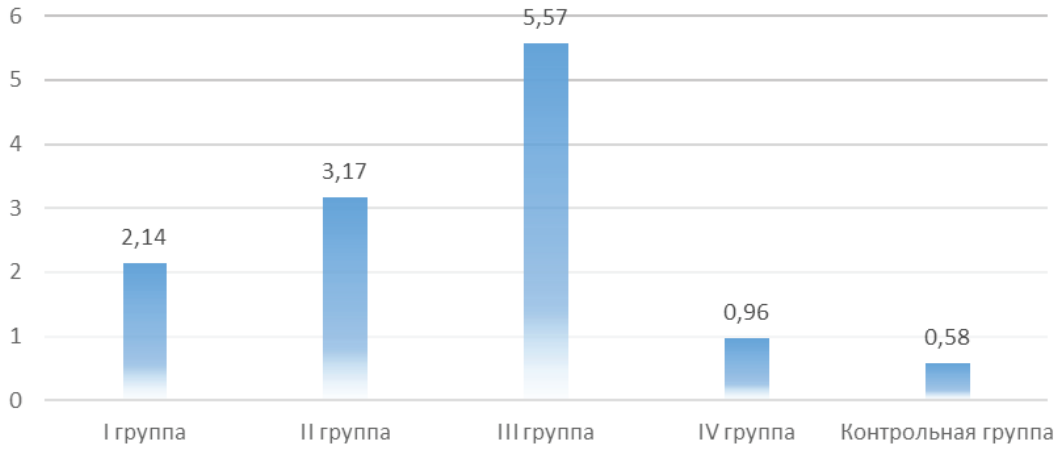
Концентрацию ИЛ-1β в сыворотке крови у 25 больных IV группы проверяли теми же методами и получили результаты: у 17 (68%) больных была выявлена не выраженная экспрессия интерлейкин –1β, которая составила 1,55 (1,49–1,61) пг/мл, у 4 (16%) – 0,75 (0,69–0,81) – пг/мл, которая указывала на низкую степень воспалительной реакции и 4 (16%) – 0,58 (0,56–0,60) больных результаты указывали на отсутствие воспалительных процессов.

Таблица 5. – Содержание интерлейкина-1β в сыворотке крови у больных IV группы

Обследованные больные	**17 (68%)**	**4 (16%)**	**4 (16%)**	**10 человек контрольной группы**
интерлейкин-1β пг/мл	1,55 (1,49–1,61)	0,75 (0,69–0,81)	0,58 (0,56–0,60)	0,58 (0,55–0,61)

Установленный уровень ИЛ-1β у больных с ХБС при РРГ был сопоставим со значениями, характерными для неспецифических и специфических инфекционных и неинфекционных воспалительных процессов (Л. М. Василец, Н. Е. Григориади и др., 2013; C. A. Dinarello 2009).

Как показано в таблицах выше, содержание ИЛ-1β в контрольной группе соответствует референтным значениям нормы для здоровых обследованных лиц, и согласуется с данными других авторов, использовавших аналогичные методы (Г. А. Зайцева, О. А. Вершинина и др., 2011; М. В. Киселевский, А. Р. Тугуз, 2003).



Рисуеки 7. Содержание интерлейкина-1β в сыворотке крови у больных с хроническим болевым синдромом при дорсопатиях

По полученным результатам в наших исследованиях выраженная экспрессия ИЛ-1β была выявлена в третьей группе у больных (табл. 3) с ХБС при РРГ и составила в среднем 5,57 пг/мл, что оказалось в 10 раз больше нормы. У больных второй группы с ХБС при РХБр показатели оказались в 5,5 раз выше нормы и показали в среднем 3,17 пг/мл. Далее по значимости полученных показателей была первая группа больных с ХБС при РКИГ значения которых были следующими 2,14 пг/мл и оказались повышенными почти в 4 раз. Значение содержания ИЛ-1β в сыворотке крови IV группы с ХБС при РГер показало среднее значение 0,96 пг/мл, что было повыше-

но в 2 раза, но однако указывало на снижение выработки данного цитокина при герпетической инфекции, по сравнению с другими группами.

Выводы. Исследование маркеров воспаления в сыворотке крови больных хроническим болевым синдромом при дорсопатиях различного генеза позволяют выявить признаки воспалительного процесса. Исследование нативного фибриногена в плазме крови может быть выбрано в качестве дополнительного биохимического критерия для дифференциальной диагностики больных с хроническим болевым синдромом при дорсопатиях различного генеза. При исследовании концентрации СРБ в сыворотке крови больных хроническим болевым синдромом при дорсопатиях различного генеза является высокочувствительным количественным методом, который можно рассматривать как дополнительный диагностический признак в развитии хронического болевого синдрома. Также СРБ можно рассматривать как патогенетический фактор воспаления, приводящий к боли, а также и как фактор, стимулирующий продукцию провоспалительных цитокинов. Выявленные концентрации интерлейкин – 1β в сыворотке крови указывали на различные показатели наличия воспалительного процесса, провоцирующие хроническую боль. Увеличение концентрация эндотелина-1 в сыворотке крови исследуемых больных можно рассматривать как свидетельство повреждения эндотелия периферических сосудов при дорсопатиях в зависимости от этиологии и патогенеза, которые также определяют и характер хронической боли.

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DERMATITIS IN CHILDREN: PREVALENCE, CLINICAL AND ALLERGOLOGICAL CHARACTERISTICS

Abstract. To assess the prevalence, clinical and allergological characteristics of atopic dermatitis (AD) among children.

Materials and methods. 5550 children aged 7–8 years old, living in the Tashkent region, Uzbekistan, took part in the study. The study included screening and clinical stages. At the screening stage, the prevalence of AD (ISAAC questionnaire) and risk factors (additional questionnaire) were studied. At the clinical stage, the diagnosis of AD was verified by allergists.

Results. The prevalence of AD was 10.5%. 62.3% of children had mild AD severity, 51.1% of children were sensitized. 25 (54.3%) children are sensitized to food allergens: 15 (32.6%) – to chicken eggs, 12 (26.08%) – to cow's milk. Sensitization to house dust mites prevailed in all regions of the Tashkent region. It was found that children living in Angren were significantly more likely to be sensitized to house dust mites ($p < 0.05$) compared to children living in Almalyk and Chirchik.

Conclusion. The prevalence of AD among children is 10.5%, most of the children have a mild severity of the disease, 51.1% of children are sensitized to one or more allergens.

Keywords: atopic dermatitis, children, allergic examination, prevalence, questionnaire.

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ДЕРМАТИТ У ДЕТЕЙ: РАСПРОСТРАНЕННОСТЬ, КЛИНИКО-АЛЛЕРГОЛОГИЧЕСКАЯ ХАРАКТЕРИСТИКА

Аннотация: Оценить распространенность, клинико-аллергологическую характеристику атопического дерматита (АтД) среди детей.

Материалы и методы. 5550 детей 7–8 лет, проживающих в Ташкентской области, Узбекистан, приняли участие в исследовании. Исследование включало скрининговый и клинический этапы.

Скрининговый этапе изучалась распространенность АтД (опросник ISAAC) и факторы риска (дополнительный опросник). На клиническом этапе диагноз АтД верифицировался аллергологами.

Результаты. Распространенность АтД составила 10,5%. 62,3% детей имели легкую степень тяжести АтД, 51,1% детей были сенсибилизированы. 25 (54,3%) детей сенсибилизированы к пищевым аллергенам: 15 (32,6%) – к куриному яйцу, 12 (26,08%) – к коровьему молоку. Сенсибилизация к клещам домашней пыли преобладала во всех регионах Ташкентской области. Установлено, что у детей проживающих Ангрене достоверно чаще отмечалась сенсибилизация к клещам домашней пыли ($p < 0,05$) по сравнению с детьми проживающих Алмалыке и Чирчике.

Заключение. Распространенность АтД среди детей – 10,5%, большая часть детей имеет легкую степень тяжести заболевания, 51,1% детей сенсибилизированы к одному или нескольким аллергенам.

Ключевые слова: атопический дерматит, аллергологическое обследование, распространенности, опросник.

Введение

Благодаря международному эпидемиологическому исследованию «International Study of Asthma and Allergies in Childhood» (ISAAC) хорошо изучены распространенность и факторы риска возникновения АтД среди детей школьного возраста. Так, распространенность АтД колеблется в зависимости от страны среди детей 6–7 лет от 0,7 до 18,4%, среди детей 13–14 лет – от 0,6 до 20,5% [1–4]. Факторами риска АтД, согласно исследованию ISAAC, являются отягощенный семейный аллергологический анамнез, пассивное курение, контакт с животными и антибиотикотерапия на первом году жизни ребенка [5–8]. Таким образом, существуют научно обоснованные данные об эпидемиологии АтД среди детей школьного возраста, в то время как распространенность и факторы риска АтД среди детей дошкольного возраста изучены недостаточно, поскольку международных эпидемиологических исследований среди этой возрастной группы не проводилось, и к настоящему времени опубликовано не большое количество работ, посвященных этому вопросу [9–12]. Отсутствие научно обоснованных данных о распространенности и факторах риска АтД у дошкольников не позволяет сформировать стратегии, направленные на его профилактику в раннем возрасте. В статье представлены результаты исследования распространенности, клинико-аллергологической характеристики и факторов риска АтД среди детей 7–8 и 13–14 лет.

Цель исследования

оценить распространенность, клинико-аллергологическую характеристику АтД среди детей.

Материалы и методы исследование

Нами было проведено анкетирование 5500 детей, в возрасте 7–8 лет и 13–14 лет, проживающих в промышленных регионах Ташкентской области (Республика Узбекистан). Основанием для проведения исследования в трёх регионах Ташкентской области послужило то, что в этих регионах расположены несколько промышленных объектов. Например, в Алмалыке располагается крупный промышленный холдинг АГМК (Алмалыкский горно-металлургический комбинат), где периодически происходит выброс цинка в воду. В Чирчике располагается крупный промышленный холдинг ООО «Узнефтегазмаш», который производит технологические оборудования для химической промышленности, там периодически происходит выброс паров хлора в атмосферу. В Ангрене располагается отрасль металлургической промышленности, где происходит выброс алюминия в почву в большом количестве. Для сравнения было проведено анкетирование

среди детей, проживающих в экологически более благоприятном регионе Ташкентской области (Кибрай). Например, в Алмалыке располагается крупный промышленный холдинг АГМК (Алмалыкский горно-металлургический комбинат), где периодически происходит выброс цинка в воду. В Чирчике располагается крупный промышленный холдинг ООО «Узнефтегазмаш», который производит технологические оборудования для химической промышленности, там периодически происходит выброс паров хлора в атмосферу. В Ангрене располагается отрасль металлургической промышленности, где происходит выброс алюминия в почву в большом количестве. Для сравнения было проведено анкетирование среди детей, проживающих в экологически более благоприятном регионе Ташкентской области (Кибрай).

Исследование проводилось в двух этапах: I – этап включал проведение анкетирования по адаптированной и модифицированной нами международной анкете ISAAC. Старшеклассники заполняли анкеты самостоятельно, за первоклассников анкеты заполняли родители. Планируя изучение распространенности симптомов АтД в регионах Ташкентской области, предполагали получить подтверждение истинной распространённости. Изучение распространенности АтД у школьников Ташкентской области проведено путем сплошного одномоментного исследования детей:

1. Дети, проживающие в г. Ангрен n=197
2. Дети, проживающие в г. Алмалык n=201
3. Дети, проживающие в г. Чирчик n=183
4. Дети, проживающие в г. Кибрай n=20

После 1 этапа исследования было отобрано 581 детей (10,5%) с большим количеством положительных ответов на вопросы анкетирования.

II этап обследования (клинико-функциональные и аллергологические исследования) проводился детям, которые дали положительные ответы на вопросы анкет.

Распространенность симптома – процент (%) положительно ответивших («Да») детей на вопрос анкеты от общего числа обследованных.

Результаты исследования

Изучение данных детей с подозрением на атопический дерматит показало, что на появление распространенной зудящейся сыпи в течение 12 месяцев жаловались 5,1% обследованных. Установлена зависимость распространенности АД от возраста детей. АД встречался в 2,2 раза чаще у младших школьников, чем у старших. При этом типичную локализацию сыпи в подколенных, локтевых сгибах, на коже лодыжек, вокруг шеи, глаз и ушей указали 4,8% опрошенных, из них у младших на 1,1 раза чаще, чем у старших школьников. У 5,5% детей АД протекал с периодами полной клинической ремиссии, когда сыпь исчезала полностью, и отсутствовали ночные пробуждения, вызванные зудом. Нарушение сна из-за сильного зуда реже 1 раза в неделю отмечено у 3,0%, а чаще 1 раза – у 1,2% опрошенных (табл. 1).

Таблица 1.– Распространенность симптомов атопического дерматита у школьников по данным анкетирования (%)

Симптомы заболевания	**Школьники**		**Всего n=581**
	7–8 лет (n=345)	**13–14 лет (n=236)**	
1	***2***	***3***	***4***
Частота симптомов АД (наличие зудящейся сыпи)			
В течение 6 месяцев жизни	8,9	5,9	7,7
В последние 12 месяцев	6,3	3,3	5,1
Типичная локализация сыпи	4,3	5,5	4,8
Полное исчезновение сыпи за последние 12 месяцев	7,5	2,5	5,5

1	*2*	*3*	*4*
Ночные симптомы: (нарушение сна из-за зудящейся сыпи)			
менее 1 ночи неделю	3,4	2,5	3,0
1 и более ночей неделю	2,0	1,6	1,2
Диагноз АД	4,3	2,9	3,7

** – p < 0,05 при сравнении между группами*

У 9,3% обследованных детей в анамнезе были симптомы АД. Среди них наибольший процент детей проживали в Ангрене (5,5%) (табл. 2). На нарушение сна из-за зудящей сыпи указали 3,5% учащихся проживающих в Ангрене, что в 1,8 раза чаще по сравнению со школьниками проживающими в Алмалыке и Чирчике (p <0,05). У 5,5% детей с АД, проживающих в Ангрене при обращении в медицинские учреждения были установлены такие диагнозы, как экзема, нейродермит. В Алмалыке и Чирчике таких детей было меньше (1,8 и 5,5 раза соответственно).

Таблица 2.– Частота симптомов атопического дерматита по данным, модифицированного опросника ISAAC в зависимости от региона,%

Признак	**Общее количество детей n=741**			
	Ангрен n=197	**Алмалык n=201**	**Чирчик (n=183)**	**Кибрай (n=20)**
Наличие зудящей сыпи когда-либо	7,6	6,9	4,3	1,25
Наличие зудящей сыпи за последний год	4,5	3,9	3,2	1,8
Нарушение ночного сна из-за зудящей сыпи	3,5	1,9*	2,1*	0,6
АД, диагностированный когда-либо	5,5	2,9*	1,0*	0,6*

** – p <0,05 при сравнении между группами*

Количество детей с легким, среднетяжелым и тяжелым течением АтД было – 131 (66,49%), 63 (31,9%) и 3 (1,52%) ребенок соответственно в Ангрене (табл. 3). Преобладание легкой степени тяжести АтД отмечено во всех регионах Ташкентской области.

Таблица 3.– Степень тяжести АтД у детей Ташкентской области

Степень тяжести	**Ангрен n=197**	**Алмалык n=201**	**Чирчик (n=183)**	**Кибрай(n=20)**	**p**
Легкая	131(66,49)	156(77,6)	155(84,6)	18(90)	> 0,05
Средняя	63(31,9)	44(21,8)	28(15,3)	2(10)	> 0,05
Тяжелая	3(1,52)	1(0,49)	–	–	> 0,05

Примечание: достоверность различий определялась между регионами

Из 90 детей 46(51,1%) были сенсибилизированы к одному или более аллергенам, из них 32(71,1%) моносенсибилизированы и 14(30,4%) – полисенсибилизированы. Нами установлено, что наиболее часто дети с АтД сенсибилизированы к клещам домашней пыли (40,0%; 13,3%; 26,6%), шерсти кошки (13,3%; 20,0%; 6,6%) и собаки – (20,0%; 13,3%; 13,3%) (табл. 4). Сенсибилизация к клещам домашней пыли преобладала во всех регионах. Установлено, что у детей проживающих Ангрене достоверно чаще отмечалась сенсибилизация к клещам домашней пыли (p <0,05) по сравнению с детьми проживающих Алмалыке и Чирчике.

У 25 (54,3%) детей выявлена сенсибилизация к пищевым аллергенам: у 15(32,6%) – к куриному яйцу, у 12(26,08%) – к коровьему молоку, у 6(13,04%) – к пшенице и у 4(8,6) – к рыбе.

Таблица 4. – Сенсибилизация при АтД у детей

Аллерген	Ангрен (n=15)	Алмалык (n=15)	Чирчик (n=15)	p
Ингаляционные				
Клещи домашней пыли	6 (40,0)	2 (13,3)	4 (26,6)	<0,05
Dermatophagoides pteronyssinus	4 (26,6)	3 (20,0)	2 (13,3)	>0,05
Dermatophagoides farinae	3 (20,0)	3 (20,0)	1 (6,6)	>0,05
Шерсть кошки	2 (13,3)	3 (20,0)	1 (6,6)	>0,05
Шерсть собаки	3 (20,0)	2 (13,3)	2 (13,3)	>0,05
Пыльца березы	1 (6,6)	2 (13,3)	1 (6,6)	>0,05
Смесь луговых трав	4 (26,6)	3 (20,0)	5 (33,3)	<0,05
Пыльца полыни	2 (13,3)	1 (6,6)	3 (20,0)	<0,05
Пищевые				
Коровье молоко	5 (33,3)	3 (40,0)	4 (26,6)	>0,05
Куриное яйцо	6 (40,0)	4 (26,6)	5(33,3)	>0,05
Пшеница	3 (20,0)	1 (6,6)	2 (13,3)	>0,05
Рыба	3 (20,0)	1 (6,6)	–	>0,05

Примечание: достоверность различий определялась между регионами

Согласно результатам нашего исследования, 51,1% детей с АтД имели сенсибилизацию к одному или более ингаляционным и/или пищевым аллергенам. Мы установили, что отягощенный по аллергическим заболеваниям семейный анамнез (62,5%), пассивное курение (34,1%) и нарушения питания на первом году жизни (21,7%) повышают риск развития АтД в школьном возрасте.

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Section 2. Pharmaceutical sciences

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MAIN PROBLEMS IN THE PHARMACEUTICAL DEVELOPMENT AND MANUFACTURE OF DRUGS ON THE BASIS OF IN SITU SYSTEMS

Abstract. *In situ* systems are one of the most promising modern delivery systems. Their use in clinical practice can solve the problems of patient compliance, as well as increase the bioavailability of active ingredients, However, the global scientific community needs to make efforts to solve the key problems that stop the development of the technology of these targeted delivery systems.

Keywords: *in situ* systems, *in situ* gelling, implants, drug design, target delivery system.

Introduction. According to an analysis of the database of medical publications PubMed [1–5], *in situ* systems are one of the most dynamically developing area in drug design. *In situ* systems show high potential and clear advantages over classical drugs in *in vitro, in silico* and *in vivo* trials [2; 3]. However, the number of registered and industrially produced drugs based on them is still insignificant [4; 5].

Despite sufficient accumulated clinical experience, drug design *in situ* systems remains more scientifically oriented and often does not go beyond scaling.

More and more *in situ* systems with proven efficacy are registered as medical devices and cosmetics, which no longer allows them to be considered as targeted drug delivery systems. In order to form a strategy for solving this problem, it is necessary to determine the causes of this phenomenon.

The purpose of this work is to consider the main problems both in the field of pharmaceutical development and the introduction of in situ systems into clinical practice and the industrial production of drugs based on them.

The first reason is the conservatism in the consumer preferences of patients in terms of medicines and the relative freedom for perfumes and cosmetics. Patient confidence in medications and routes of administration that have been marketed for years, despite obvious shortcomings, is a major reason for the slow pace of innovation in treatment regimens.

One such example is the use of eye drops in ophthalmic practice. Despite the fact that dozens of studies have shown the problems associated with the use of eye drops, this dosage form continues to be the most popular and widely used in ophthalmology.

When a patient instills eye drops, a high percentage of errors are allowed, which lead to a significant loss of dose, and, accordingly, can lead to ineffectiveness of the therapy. Using classic eye dropper bottles, the risks of cross-microbial contamination are increased (by some researchers, these risks are

estimated as comparable or even greater compared to applying the drug by a patient with a finger – as for contact lenses, eye films, gels, etc.). Leakage of eye drops from the lacrimal sac occurs even when instilled by medical personnel. the dose of eye drops is measured using the dropper of the package, which in itself cannot provide absolute accuracy. dosing accuracy for such dosage forms is extremely conditional.

At the same time, in the form of eye drops, not only drugs are produced that have a local effect on the cornea – for example, containing hyaluronic acid or carbomer – for the treatment of dry eye syndrome, but also drugs containing active ingredients with a pronounced pharmacological effect – adrenoblockers, adrenomimetics, M-anticholinergics and others, for which dosing accuracy will be the property that determines the effectiveness of pharmacotherapy.

An alternative to classic eye drops are in situ ophthalmic systems – with a reduced risk of leakage, a prolonged effect, which reduces both the frequency of use and the likelihood of errors with each instillation. However, despite all the significant advantages, such systems not only have not yet replaced the classic eye drops in treatment regimens, but are also present on the pharmaceutical market in extremely limited quantities.

The solution to this problem may be to conduct international campaigns to educate patients in the field of in situ systems – to increase their level of awareness and the possibility of choosing alternative effective treatments.

In the sphere of perfumery and cosmetic products, unlike most dosage forms, consumer awareness of the benefits of new systems is carried out through well-established marketing strategies. On the one hand, this explains the reason for the registration of some targeted in situ delivery systems as cosmetics.

Medical devices are mainly intended for manipulation by medical personnel. Since the global practice includes a streamlined process of continuous education of doctors and medical personnel, informing about new effective targeted delivery systems that would not only increase the effectiveness of therapy and patient adherence, but also facilitate medical manipulations, occurs quite quickly and in a timely manner. The publication of a large number of review articles intended for professionals in this field, the holding of thematic conferences and congresses, trainings, master classes and webinars, contributes to the fact that doctors and medical staff demonstrate a much greater commitment to the use of new delivery systems in therapy than patients.

The main reason hindering the introduction of in situ systems into clinical practice is the insufficiency of the regulatory framework for registration and standardization of such drugs.

It is obvious that registration of such systems only in the initial or final form ("before" or "after" the phase transition) is an incorrect approach, leading to the appearance on the market of ineffective or low-quality drugs that discredit delivery systems in general.

Standardization of in situ systems should be a two-step process, and include both traditional quality measures related to the aggregate state of the system or route of administration (e.g., viscosity, pH, isoosmoticity) and specific quality indicators that are important to control during the screening step (e.g., time film formation, strength of the gel structure, mucoadhesion, film elasticity, gas permeability, etc.). the phase transition process is separately standardized and studied depending on the factors initiating it. Thus, for thermoreversible systems, the most important parameter of the phase transition is the temperature of gelation, for ion-selective polymers, the ionic composition, etc. These characteristics help the researcher to predict the targeting of the in vivo delivery system even at the drug design level. The study of the parameters that determine the phase transition is complicated by the actual lack of simple and accessible validated models. Most researchers still use in vivo and ex vivo methods that cannot be sufficiently reproducible and experimentally controlled. As an alternative, biorelevant in vitro reproducible models should be proposed, but the modern scientific community is just beginning

to deal with the issues of their construction. Models of the vitreous body have been developed to assess the phase transition and the formation of in situ implants, the nasal cavity – to develop intranasal in situ gels, but their implementation in drug design and validation is still a matter for future research.

There are certain prospects for the introduction of modern 3D printing technologies for modeling in vitro systems. This method would provide standard models commercially available to many research laboratories – and would facilitate harmonization of in situ system evaluation parameters.

The third, but no less important problem among others, limiting the introduction of in situ systems into production, is the stability of the above indicators. Thus, recent studies have shown that some thermoreversible matrices based on poloxamer 407, which provide a phase transition during development in an acceptable temperature range, lose this property during long-term storage, due to which the gelation temperature drops to room values that do not correspond to the tasks research. To stabilize this parameter, various technological methods can be proposed, in particular, in recent studies, the range of excipients introduced into the composition of thermoreversing matrices that stabilize the phase transition temperature has been determined.

However, this circumstance indicates the need to fix at the regulatory level, to conduct long-term technological tests for the developed systems, since the complexity and sensitivity of the phase transition parameters can often make them unstable, inefficient and reduce or even completely eliminate their targeting.

Conclusion. *In situ* systems are one of the most promising modern delivery systems. Their use in clinical practice can solve the problems of patient compliance, as well as increase the bioavailability of active ingredients, However, the global scientific community needs to make efforts to solve the key problems that stop the development of the technology of these targeted delivery systems.

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REPURPOSING OF KNOWN DRUGS AS POTENTIAL THERAPEUTICS FOR CANCER IMMUNOTHERAPY FOR PATIENTS WITH SOLID TUMORS

Abstract. For several decades treatment of advanced cancer has been challenged by lack of reliable therapeutic options. Patients with metastatic tumors that were not surgically resectable had to depend on chemotherapy, which is commonly associated with severe adverse events as well as high rates of relapse. As the understanding of immune system and immune surveillance grew, the idea of utilizing immune cells to eliminate cancer gained significance and various strategies to activate immune response were developed.

Tumor cells form immune escape and subsequently obtain unlimited proliferation ability due to the abnormal immune surveillance mediated by immune checkpoints. Negative immune checkpoints, such as programmed cell death protein 1 (PD-1), are regulators of human immune system that downregulate T-cell activation and hinder the ability of the immune system to attack cancer cells. FDA-approved monoclonal antibodies (mAbs) against negative immune checkpoints have revealed remarkable clinical success in different malignancies. However, there are currently no small molecules clinically approved based on targeting immune checkpoints. The aim of this project is to identify FDA-approved drugs that can be potentially used to target immune checkpoints and inhibit their function. The approach will be based on a computational study by investigating the ability of a library of known drugs to interact with the crystal structure of PD-1. This work would potentially enable the development of small molecules for early cancer diagnosis and personalized cancer immunotherapy.

Keywords: Immune Checkpoints, PD-1/PD-L1, Target, Small Molecule Inhibitors, Cancer Immunotherapy.

1. Introduction

Immune checkpoint molecules work as protective factors for the body's immune system [1]. However, when immune checkpoint molecules are overexpressed or overactivated, immune function is inhibited. The PD-1/PD-L1 signaling pathway was discovered relatively early. In the tumor microenvironment, activated T cells express high levels of PD-1 [2]. Upregulated PD-L1 prevents excessive activation of T cells, maintains the immune system's tolerance to self-antigens, and reduces the immune response against the surrounding normal tissue after combining with PD-1 on T cells via protein–protein interactions. Therefore, blocking the interaction of PD-1 and PD-L1 can reverse immunosuppressive conditions and improve the killing of tumor cells by the body's

immune cells. In recent years, anti-PD-L1 monoclonal antibodies have shown positive responses in clinical trials for a variety of malignancies, including melanoma, metastatic non-small-cell lung cancer, bladder cancer, and skin Merkel cell carcinoma [3; 4].

However, antibody drugs are associated with several disadvantage, such as immunogenicity issues and the poor permeability of tumor tissues, which lead to the overall low response rate of PD-1/ PD-L1 antibody drugs [5]. Tumor cells continually activate the PD-1/ PD-L1 signaling pathway by overexpressing PD-L1 to trigger multiple immune suppression mechanisms. From this perspective, this binding can also be interrupted by inhibiting the expression of PD-L1 or promoting its degradation. Increasing research is devoted to intervening in the PD-1/PD-L1 signaling pathway by applying small molecule compounds such as peptides and peptidomimetics to address this problem. Currently, these small molecular compounds are in the preclinical research stage. However, in some cases, malignant cells prohibit immune responses against tumors by upregulating immunosuppressive molecules or downregulating immune-activated molecules, thereby achieving immune escape and immortalization [6; 7]. PD-1/PD-L1 has been the most studied negative regulatory immune checkpoint-related axis in recent years and plays a prominent role in tumor immune escape [8; 9].

The purpose of my research paper is to focus on identifying FDA-approved drugs that can be potentially used to target immune checkpoints and inhibit their function. It would serve as starting points to designing more efficient inhibitors. The approach will be based on a computational study by investigating the ability of a library of known drugs to interact with the crystal structure of PD-1. This work would potentially enable the development of small molecules for early cancer diagnosis and personalized cancer immunotherapy.

2. Literature Review

For several decades treatment of advanced cancer has been challenged by lack of reliable therapeutic options. Patients with metastatic tumors that were not surgically resectable had to depend on chemotherapy, which is commonly associated with severe adverse events as well as high rates of relapse. As the understanding of immune system and immune surveillance grew, the idea of utilizing immune cells to eliminate cancer gained significance and various strategies to activate immune response were developed [10; 11; 12]. However, the first generation of immunotherapies were limited by low response rates and high incidence of serious adverse events [13]. The search for dependable targets for the modulation of immune responses led to the discovery of checkpoints of T-cell activation and development of monoclonal antibodies targeting the checkpoints [14–20]. The impact of CTLA-4 and PD-1 blockers on cancer research and their success in cancer treatment is acknowledged by researchers as well as clinicians worldwide and rightfully the Nobel Prize in Physiology or Medicine for 2018 was awarded to Professor James Allison, MD Anderson Cancer Center, USA and Professor Tasuku Honjo, Kyoto University, Japan for their research on CTLA-4 and PD-1 respectively [21; 22].

For T cells, several regulatory mechanisms are induced during initial antigen-mediated activation, which involves peptide–MHC engagement of the T cell receptor (TCR) and positive costimulatory signals such as interactions between CD28 on T cells and CD80 and/or CD86 on antigen-presenting cells (APCs). Early during the activation process, negative regulators are induced to counteract the activation programme. Cytotoxic T lymphocyte antigen 4 (CTLA4) is one of the first negative regulators to be induced, and it directly competes with CD28 for the ligands CD80 and CD86. Programmed cell death protein 1 (PD1) is also expressed during T cell activation and counters positive signals through the TCR and CD28 by engaging its ligands programmed cell death 1 ligand 1 (PDL1) and/or PDL2 (referred to collectively here as PD1 ligands) [23–26]. These 'coinhibitory' receptors function as breaks for the adaptive immune response, serving as immune

checkpoints that effector T cells must pass in order to exert their full functions.

3. Methodology

3.1 Availability of PD-1 Binding Sites

In the first experiment, Geometric method was used to determine available binding sites of PD-1. The website https://proteins.plus/ was used to determine all the binding sites of PD-1. The PDB code of PD-1, which is "3RRQ," was entered into the "PDB-code" section. Then, "Go!" was pressed, leading to the "ProteinsPlus – Structure-Based Modeling Support Server," which displayed an PD-1 model on the left and a list of options on the right. In the list of options to the right, "DoGSiteScorer Binding site detection" was selected. "DoGSiteScorer" was then selected and a list of options for settings appeared. The settings were set to as follows: for the "Analysis detail" section, "Pocket(s)" was chosen; for the "Binding site prediction granularity" section, "and druggability" was chosen; for the "Ligands" section, it was left blank; for the "Chain" section, "A" was chosen. After that, "calculate" was selected.

3.2 Virtual Screening of Potential Inhibitors of PD-1

In the second experiment, virtual screening was used to narrow to a smaller number of compounds that can potentially bind and inhibit PD-1. Virtual screening was based on pharmacophore maps, which are a presentation of a map of the interactions between two compounds. First, http://pocketquery.csb.pitt.edu/ was used to determine the strength of the interaction between the compound tested and PD-1. After landing on the Pocket Query web page, "Search" was clicked and then "3BIK" was put into the "ID" section. The computer key "Enter" was clicked, yielding a list of clusters. For each cluster, the "export" button was clicked and then the "send to ZincPharmer" button was clicked. After landing in ZincPharmer for each cluster, the "Viewer" tab was clicked and then the "Receptor Residues" was made invisible. After that, the "Pharmacophore" tab was selected. Within the "Pharmacophore" tab, different cluster groups were enabled and/or disabled, then the "submit query" button was selected to yield the number of hits found.

3.3 Evaluation of Selected Compounds Binding to PD-1

In the third experiment, the molecular docking approach can identify the degree of binding of each of the compounds from PocketQuery to PD-1. http://www.swissdock.ch/docking# was used to perform this procedure. On the SwissDock website, there are three sections to be filled: Target Selection, Ligand Selection and Description. For the "Target Selection" section, "upload file (max 5MB)" was selected. Then, the PDB file, the PDB code for PD-1 was uploaded to SwissDock. For the "Ligand Selection" section, the ZINC code for each compound was inputted into the text box. Then, yielding a new page containing all the ZINC AC hits found. The ligand that corresponded to the ZINC code was selected, and then the "Dock 1 selected ligand" button was clicked. Finally, in the "Description" section, the ZINC code for each compound was entered under the "Job Name (required)" section. Then, an E-mail address was inputted under the "E-mail address (optional)" section. "Start Docking" was selected. After a few hours, messages containing the link to each output of SwissDock were sent to the inputted E-mail address.

3.4 Identification of the Best Compound as Inhibitor of PD-1

In the fourth experiment, SwissADME was used to evaluate how five of the selected compounds based on the most negative ΔG fared with Lipinski's rule. To start, http://www.swissadme.ch/_was inputted into the search engine. Then, the SMILES code for each of the selected compounds is entered into the "Enter a list of SMILES here" section. Finally, "Run!" was clicked. Then, a detailed report about each compound was generated. The molecular weight, number of H-bond acceptors, number of H-bond donors, and Log $P_{o/w}$ (LogP) were recorded to determine if any aspect of Lipinski's Rule of Five is violated.

4. Results and Discussion

4.1 Availability of PD-1 Binding Sites

In the first experiment, three methods were used to determine the available binding sites for PD-1. It would ensure that PD-1 has binding sites for identified inhibitors to bind. The Geometric method determines the binding sites based on the size and shape of PD-1. The website https://proteins.plus/ was used because it incorporates the Geometric method when determining the binding sites to PD-1. Fig. 1 shows the binding sites of PD-1 determined using the Geometric method, and Table 1 shows the surface area and volume of binding sites.

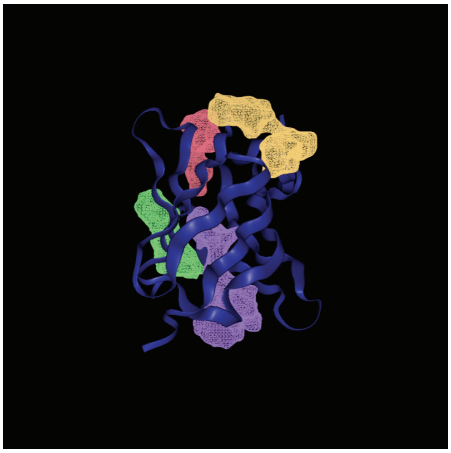


Figure 1. The binding sites of PD-1 determined using the Geometric method

Table 1. – The Surface Area and Volume of Binding Sites Determined by the Geometric Method

Name of binding site	Displayed color	Surface area(Å²)	Volume (Å³)
P_0		593.75	238.78
P_1		319.8	209.79
P_2		326.88	153.92
P_3		329.38	127.74

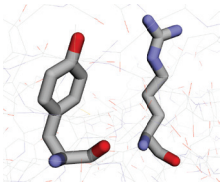
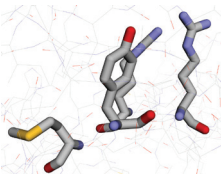
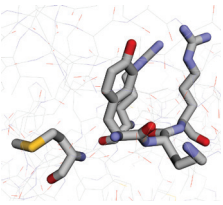
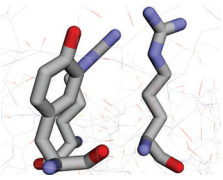
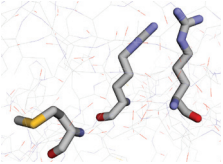
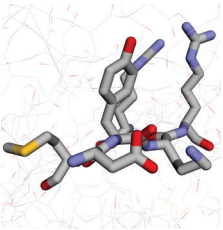
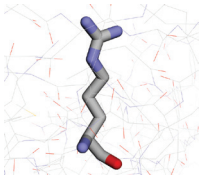
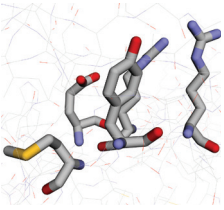
From these results, there are 4 available binding sites. It is notable that the binding site with the greatest surface area and volume is P_0, which has a surface area of 593.75Å^2 and a volume of 238.78 Å^3. The binding site with the smallest surface area is P_1, with 319.8Å^2. The binding site with the smallest volume is P_3, with 127.74Å^3. From the experimental results, we can conclude that PD-1 has numerous binding sites. It means that there are likely many opportunities to inhibit this protein, be it competitively or noncompetitively. However, there are only a very limited amount of inhibitors approved by the FDA.

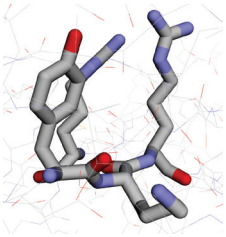
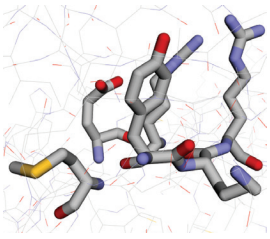
4.2 Virtual Screening of Potential Inhibitors of PD-1

In the second experiment, http://pocketquery.csb.pitt.edu/ was first used to show the strength of the interaction between the antibody and PD-1, and that strength is represented by a score. PocketQuery determines the strength of interaction by virtual screening and matching the compounds that may bind to PD-1 through pharmacophore maps. A pharmacophore map is a 3D representation of features that are critical for a ligand to interact with the target receptor of a specific binding site. The strongest interaction has a score of 1, with decreasing strengths leading to lower scores. Virtual screening was completed and ten clusters of chain A with the highest scores were selected. The scores, along with the models, amino acids, and sizes are showcased in (Table 2).

Table 2 shows that the first Chain A, consisting of TYR123 and ARG 125, has the highest score of 0.81099. This indicates the antibody and PD-1 have the strongest interaction. In comparison, the last Chain A consisting of GLU58, ARG 113, MET 115, TYR123 and ARG 125 has the lowest score of 0.680281. This indicates the antibody and PD-1 have the weakest interaction.

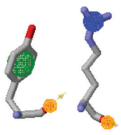
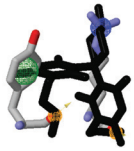
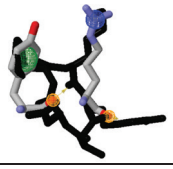
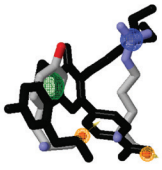
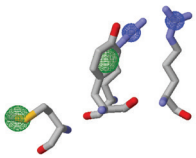
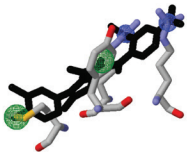
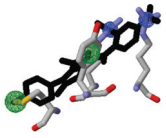
Table 2. – The Results of Virtual Screening of Potential Inhibitors of PD-1

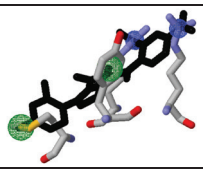
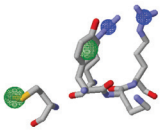
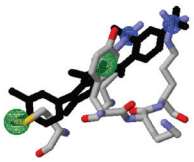
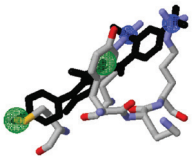
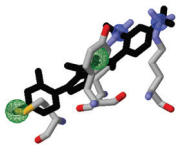
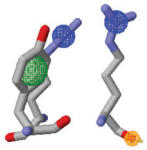
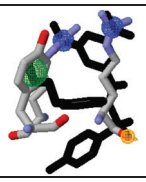
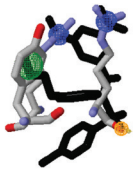
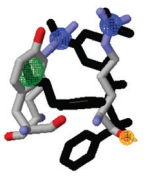
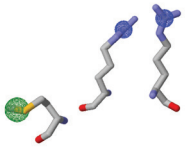
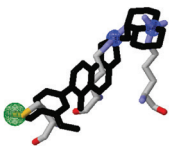
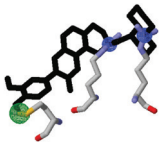
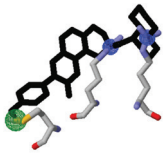
Chain	Size	Amino Acid	Score	Model
1	*2*	*3*	*4*	*5*
A	2	TYR123 ARG 125	0.81099	
A	4	ARG 113 MET 115 TYR123 ARG 125	0.740154	
A	5	ARG 113 MET 115 TYR123 LYS124 ARG 125	0.722176	
A	3	ARG 113 TYR123 ARG 125	0.705746	
A	3	ARG 113 MET 115 ARG 125	0.705299	
A	6	ARG 113 MET 115 ASP 122 TYR123 LYS124 ARG 125	0.701324	
A	1	ARG 125	0.693793	
A	5	GLU58 ARG 113 MET 115 TYR123 ARG 125	0.680281	

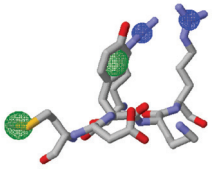
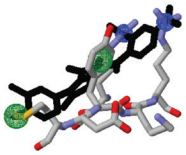
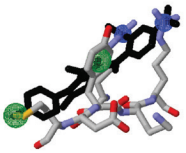
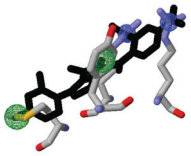
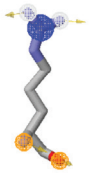
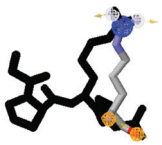
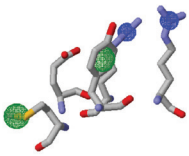
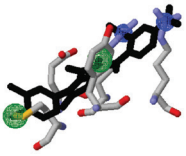
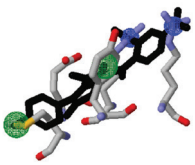
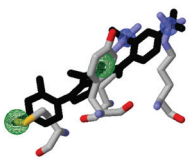
1	*2*	*3*	*4*	*5*
A	4	ARG 113 TYR123 LYS124 ARG 125	0.677142	
A	6	GLU58 ARG 113 MET 115 TYR123 LYS124 ARG 125	0.667507	

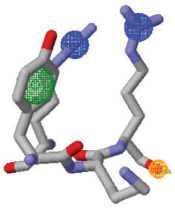
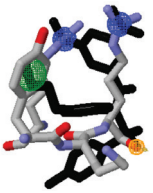
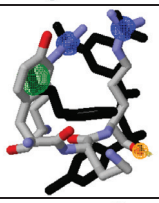
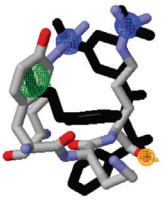
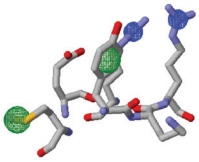
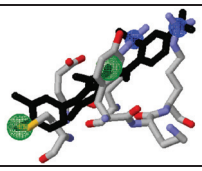
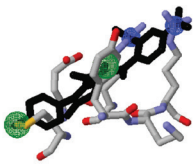
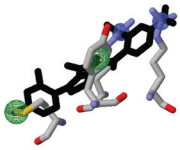
Each cluster will now be focused on individually to determine the hits that have the lowest RMSD scores, which indicate the hit that has the greatest overlap with the binding site of PD-1. The results are displayed in the table below. The structure in black represents the paired compound while the structure in gray represents the cluster. Table 3 shows each compound's RMSD score, name of hit, and model.

Table 3.– The RMSD Scores and the Model of 30 Selected Hits

Cluster Score + Model	**Name of Hit**	**RMSD Score**	**Model**
1	*2*	*3*	*4*
0.81099 	ZINC16267039	0.409	
	ZINC71788370	0.425	
	ZINC35326858	0.447	
0.740154 	ZINC02101516	0.183	
	ZINC02101503	0.184	

1	*2*	*3*	*4*
	ZINC02101649	0.188	
0.722176 	ZINC02101516	0.183	
	ZINC02101503	0.184	
	ZINC02101649	0.188	
0.705746 	ZINC40967643	0.189	
	ZINC40967646	0.190	
	ZINC40967640	0.190	
0.705299 	ZINC20762311	0.029	
	ZINC20761644	0.029	
	ZINC20762875	0.033	

1	*2*	*3*	*4*
0.701324 	ZINC02101516	0.183	
	ZINC02101503	0.184	
	ZINC02101649	0.188	
0.693793 	ZINC17020760	0.332	
	ZINC04899739	0.335	
	ZINC13541443	0.358	
0.680281 	ZINC02101516	0.183	
	ZINC02101503	0.184	
	ZINC02101649	0.188	

1	*2*	*3*	*4*
0.677142 	ZINC40967643	0.189	
	ZINC40967646	0.190	
	ZINC40967640	0.190	
0.667507 	ZINC02101516	0.183	
	ZINC02101503	0.184	
	ZINC02101649	0.188	

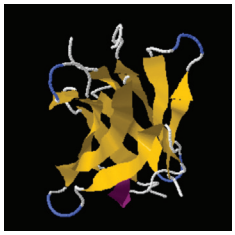
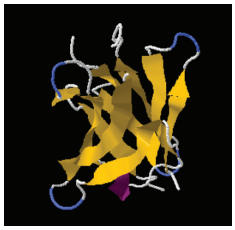
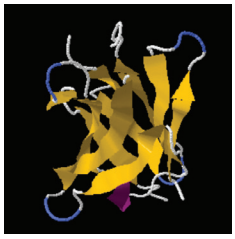
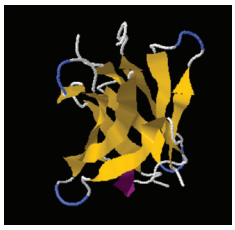
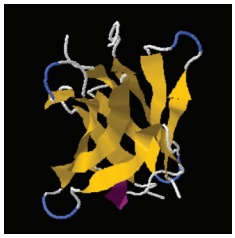
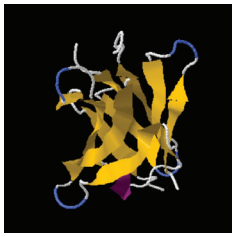
According to Table 3, the hits ZINC20762311 and ZINC20761644 from the cluster with a score of 0.705299 both have the lowest RMSD scores of 0.029. This represents an almost perfect overlap between the binding site and the hits. In contrast, the hit ZINC35326858 from the cluster with a score of 0.81099 has the highest RMSD score of 0.447. This means that the overlap is the least identical between the hit and PD-1.

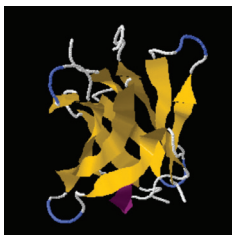
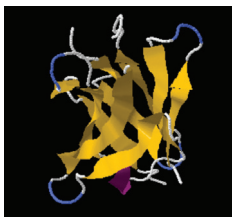
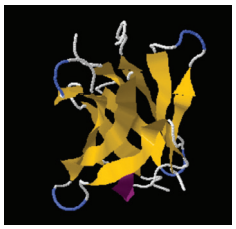
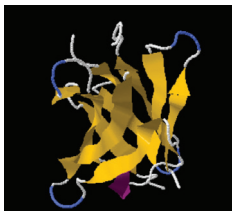
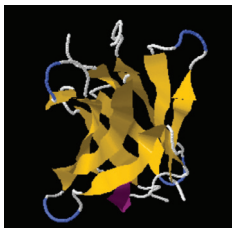
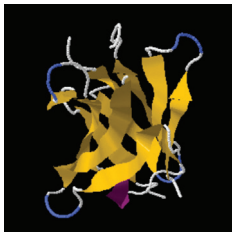
4.3 Evaluation of Selected Compounds Binding to PD-1

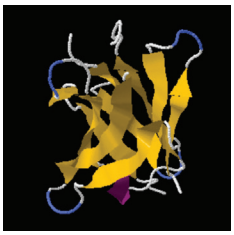
In the third experiment, the SwissDock server (http://www.swissdock.ch/docking#) was incorporated to determine which of the 15 identified compounds is best able to bind to PD-1. SwissDock takes each of the 15 compounds and PD-1 and allows them to freely interact with each other. From this, SwissDock identifies the degree of interaction in all available binding sites. The output that SwissDock provides is the number of clusters, which indicates the number of binding sites; the number of elements, which indicates the number of positions the compound can interact with a specific binding site; the Full Fitness and Gibbs Free Energy (ΔG), which both quantify the favorability of the interaction. ΔG will be focused on instead of Full Fitness as it is more universally used by the scientific community. A more negative ΔG indicates a more favorable

interaction between the compound and PD-1. The results gathered are displayed in Table 4. It shows the models and estimated Δ*G* values for the 15 selected compounds.

Table 4.– Models and Estimated Δ*G* values for the 18 Selected Compounds

ZINC ID	Number of Clusters	Estimated ΔG(kcal/mol)	Model
1	*2*	*3*	*4*
ZINC16267039	31	–5.93	
ZINC71788370	29	–5.45	
ZINC35326858	30	–5.55	
ZINC02101516	32	–6.36	
ZINC02101503	33	–6.21	
ZINC02101649	33	–5.44	

1	*2*	*3*	*4*
ZINC40967643	33	–6.43	
ZINC40967646	31	–5.88	
ZINC40967640	30	–6.14	
ZINC20762311	31	–6.58	
ZINC20761644	32	–6.94	
ZINC20762875	31	–6.67	
ZINC17020760	36	–6.18	

1	*2*	*3*	*4*
ZINC04899739	30	–6.39	
ZINC13541443	31	–6.02	

From the results, the compound named ZINC20761644 has the most negative estimated Δ*G* of –6.94 kcal/mol. This suggests that ZINC20761644 binds to PD-1 the most favorably. The compound named ZINC02101649 has the lowest estimated Δ*G* of –5.44 kcal/mol. This suggests that ZINC02101649 binds to PD-1 the least favorably. From this, we can conclude that we do have compounds that are capable of binding to PD-1 and the most promising prospect is ZINC20761644. Furthermore, the range of clusters between the 15 compounds is 29 to 36.

4.4 Identification of the Best Compound as Inhibitor of PD-1

From the previous experiment, each compounds' affinity to the binding site of PD-1 was quantified using **ΔG**. From the results, the five compounds with the most negative Δ*G* are selected for the last experiment because they bind to PD-1 the best. In this experiment, each compound's adherence to Lipinski's Rule of Five will be evaluated to determine the best compound to bind to PD-1. Lipinski's Rule of Five is used to evaluate a drug's viability in terms of absorption and permeation. The four requirements of Lipinski's Rule of Five are as follows: no more than five hydrogen bond donors, no more than ten hydrogen bond acceptors, calculated LogP of no greater than five and molecular mass of fewer than 500 daltons. Specifically, LogP determines the range of aqueous character and the lipid character, with a score having a positive relationship with the former and a negative relationship with the latter. Each compound is screened in the SwissADME server, which generates all the data needed to determine the conformity to Lipinski's Rule of Five. In Table 5, each component of Lipinski's Rule of Five is quantified by SwissADME and the conformity to Lipinski's Rule of Five is determined.

Table 5.– Analysis of Five Selected Compounds by SwissADME

ZINC Code	**Molecular weight (g/mol)**	**Number of H-bond Acceptors**	**Number of H-bond Donors**	**Log $P_{o/w}$ (iLOGP)**	**Conformity to Lipinski's Rule of Five**
ZINC20761644	492.61	5	2	4.89	Yes
ZINC20762875	462.58	4	2	4.68	Yes
ZINC20762311	492.61	4	1	2.80	Yes
ZINC40967643	497.52	7	0	2.83	Yes
ZINC04899739	272.32	3	4	0.36	Yes

According to table 5, all five compounds adhere to Lipinski's Rule of Five. In this case, logically, the compound with the most negative estimated Δ*G* would serve as the best inhibitor for PD-1 because it has most favorable interactions with PD-1. The compound that would be the best inhibitor for PD-1. Therefore, it is ZINC20761644, and it has a Δ*G* of –6.94 kcal/mol.

5. Conclusion

In this research paper, the purpose was to identify new inhibitors of PD-1 that would serve as starting points to making more efficient inhibitors. These inhibitors would serve as therapeutics to prevent or cure cancer. The approach used was a series of computational studies. First, three methods were used to determine if there are sufficient binding sites for compounds to bind and inhibit PD-1. Then, a list of inhibitors was gathered through virtual screening in the PocketQuery and ZINCPharmer servers. Finally, the compound that would serve best as the inhibitor to PD-1 on the basis of energy of interaction and adherence to Lipinski's Rule was identified using SwissDock and SwissADME servers. The outcome from this computational study is a compound known as ZINC20761644. From all the compounds favorable interactions with PD-1. Furthermore, ZINC20761644 satisfies Lipinski's Rule of Five, screened, ZINC20761644 has the most negative Δ*G* of – 6.94 kcal/mol, indicating that it has the most signifying that it has the chemical and physical properties for it to serve as a therapeutic for human use.

The next step of this project is to test ZINC20761644 in a laboratory environment. Due to the COVID-19 pandemic, physical testing was not possible. However, physical testing is nevertheless an important part of validating the results obtained in this previous series of experiments as well as to further assess ZINC20761644 as a viable therapeutic for human use.

6. Acknowledgements

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7. Conflict of Interest

The authors declare no conflict of interest

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PHARMACOECONOMICS AND THE PATIENTS' COMPLIANCE AS AN ESSENTIAL PART OF SUCCESSFUL THERAPY OF IRON DEFICIENCY ANEMIA

Abstract. This article is devoted to pharmacoeconomics and patients' compliance to the therapy of iron deficiency anemia. These directions are relatively young in science and their importance often remains underestimated by most specialists. Pharmacoeconomics' main goal is to determine the most optimal medicine for treating the disease's cost-effectiveness ratio. Therefore, this review presents the main facts that determine the therapeutic efficacy of specific iron preparations and their clinical and economic analysis results. It also provides the statistical and theoretical substantiation of the significance of research and control of patients' compliance in the treatment of iron deficiency anemia.

Keywords: compliance; iron deficiency anemia; pharmacoeconomics; iron preparations.

Introduction

Iron deficiency is the most common form in the world of microelement deficiencies. Iron deficiency ranks first among the 38 most common human diseases, affecting more than 3 billion people on Earth [1; 2]. This is the only form of micronutrient deficiency present in both developing and developed countries [3]. The clinically pronounced form of iron deficiency in the body is iron deficiency anemia (IDA).

IDA is a polyethyologic disease, the occurrence of which is associated with iron deficiency in the body due to violation of its intake, absorption or increased losses, characterized by microcytosis and hypochrome anemia [4]. Treatment of IDA with iron compounds (IC) is a complex and multifaceted field that requires knowledge of several nuances that must be taken into account when prescribing and monitoring therapy to achieve the optimal clinical effect.

Clinical efficacy of IC

Practice shows that the most common causes of ineffective treatment of IDA IC are the use of too low doses of the drug, short duration of therapy, impaired absorption, and treatment of chronic posthemorrhagic anemia without elimination of the source of blood loss [5]. Moreover, if the last two factors do not depend on the drug used, the rest are primarily determined by the drug's characteristics.

As a rule, the doctor chooses IC for the prescription to the patient, considering his own experience, information about the medicine, obtained at training cycles or exhibitions, from medical journals or the Internet, as well as material capabilities of the patient, that is, the possibility of purchasing the medicine for the entire course of treatment.

For many years, IDA therapy has included divalent iron drugs, mainly in iron sulfate. Iron sulfate preparations were considered the "gold standard" of IDA therapy, as they have the highest absorption capacity [6]. In this regard, it is no coincidence that most salt ICs have this very active substance on their basis. Gluconate, chloride and iron fumarate have a less pronounced ability to absorb [5; 7].

However, the world experience in the treatment of IDA has shown that the use of divalent iron preparations in doses of 5–8 mg/kg of body weight per day leads to the development of side effects of IDA in the majority of patients, which may be the basis for drug withdrawal, dose reduction and treatment breaks [3,4]. In this connection, a trend to change IC with a divalent gland to less toxic IC with the trivalent gland has started to be observed in the world today [8]. The appearance of ICs based on the hydroxide polymaltose complex (HPC) has forced specialists to change the tactics and plan of IDA therapy.

Distinctive properties of IC with trivalent iron are high molecular weight, presence of trivalent iron hydroxide nucleus consisting of 260 atoms, high iron content in the nucleus (about 27%), and the presence of polymaltic shell instead of protein [7; 8]. These characteristics make the iron in these preparations very similar in structure and valence to the natural iron compound molecule in the body – serum ferritin.

In general, randomized studies on the side effects of IDA treatment with IC (II) and IC (III) have shown their equal effectiveness in the less pronounced toxicity of the latter for the GIT [7; 8; 9].

Pharmacoeconomic issues in the treatment of IDA

A global health problem in most countries, regardless of their political and economic situation, is the need to continuously increase spending to provide health care to the population. This phenomenon has its peculiarities for the health care system in different countries. The main reasons for the cost increase in the health care system are socio-demographic, economic and medical factors [10].

One of the problems of domestic health care, which is the main prerequisite for the development of pharmacoeconomics, is generic drugs. The determining factor in this problem is precisely the cost and effectiveness of drugs. The economic factor is the leading one for the majority of the population. Among a wide range of drugs, including IC, the least affordable are original drugs, while their generics are cheaper because of the lower cost of their creation and clinical trials. However, manufacturers of these generics often extrapolate data on the original drugs' efficacy, which is not always justified [10; 11].

Clinical and economic analyses are the solution to these problems because they are based on evidence-based medicine and comparative clinical trials. The data obtained with their help allows us to assess the importance of drugs for reasonable health care and determine the cost of additional benefits they possess [9; 12].

First of all, the results of clinical and economic studies should be addressed to practicing doctors and their patients. In this case, the pharmaco-economic analysis data will allow choosing the optimal cost/efficiency ratio scheme of medication treatment, conduct treatment taking into account the quality of life of patients, reduce the length of stay in hospital and reduce the frequency of disability. All of this will lead to a decrease in all other costs, including non-material suffering and patients' psycho-emotional problems [9; 10; 11].

IDA treatment is a significant clinical and economic problem, as IC treatment is long-term and numerous drugs are quite expensive. Besides, the treatment of severe IDA forms requires regular laboratory control to assess the dynamics, which also requires economic costs. Therefore, pharmacoeconomic analysis is of great interest [12].

If we consider the price of 1 package, 1 tablet, 1 ml of the preparation and 100 mg of IC most used by physicians in the treatment of IDA in Russia, then after assessing the amount of the active ingredient in these drugs, the attitude to the drugs themselves changes. If to recalculate for elemental iron, in IC (II), its content is several times less [7; 9].

In particular, the comparison of IC Maltofer and Actiferrin in the form of droplets, specially designed for children of the first months of life, has shown that the iron content of 1 ml of Maltofer droplets is equal the iron content of 6 ml of Actiferrin droplets. The calculation of the drug price, in turn, showed that Maltofer is cheaper rather than Actiferrin. Similar calculations for

tablet IC showed that 1 tablet of Maltofer equals 3 tablets of Phenulse or 3 capsules of Ferro-Folgam. The IC price is higher: instead of two tablets per day, Maltofer has to use up to 6 tablets with constant monitoring of their intake, which is very inconvenient [9; 12].

Pharmacoeconomic analysis results showed that it was more advantageous to use IC (III) for complete clinical and laboratory treatment of IDA. The higher cost of IC treatment (II) is the need for repeated treatment and an increase in the number of visits to the doctor due to the refusal of treatment or because of the side effects of taking IC [7; 9; 12].

The lower cost of using IC (III) is explained by the fact that their treatment leads to a positive result within the standard time frame, i.e., after 3–6 months after therapy. IC (II) may increase treatment time due to periodic drug withdrawal, more side effects and low tolerance. The results of the cost-benefit analysis of IDA treatment showed that the cost of treatment increases due to the consequences of discontinuing IC (II) [6; 79].

Cost analysis showed that despite the high price of IC (III) packing, the cost of 100 mg of iron in all drugs is approximately comparable. Simultaneously, the cost of eliminating possible consequences, which can potentially appear in case of refusal from therapy, can be several times higher than the cost of used IC for the treatment of IDA [12].

Pharmacoeconomic analysis results show the necessity to use those ICs in the treatment of IDA, allowing the patient to get the best treatment. In this regard, doctors should be aware of the benefits of IC not only from a material point of view but also in terms of the quality of treatment, rapid improvement in the patient's quality of life, and the absence of complications. Doctors must be fully aware of the economic component of the issue and explain to patients the benefits of IDA treatment with specific ICs.

Patients' compliance for IC therapy

The study of patients' attitudes to the prescribed therapy and the degree of compliance is a relatively new scientific research area. This area's development is due to the doctor-patient interaction paradigm's significant role, the transition from the paternalistic model to the partnership, and the patient's awareness of their active role in therapy. Doctors must understand the actual situation from avoiding mistakes in the form of unreasonable prescription of large doses and intensification of therapy, leading to an overdose. Finally, the economic factor plays a significant role since significant damage to the health care economy can be caused by patients' neglect of prescriptions [13].

Compliance is the patient's precise fulfillment of all medical recommendations and prescriptions within the framework of prevention, treatment, and rehabilitation. WHO offers a more complex definition: "the extent to which the patient's behavior concerning the use of a drug, the implementation of recommendations on nutrition or lifestyle changes to the prescriptions and instructions of the doctor" [14].

According to WHO, 5 groups of factors causing noncomplliance are identified: social and economical (a financial situation, low cultural level, old age), systemic (doctor-patient relations, education of paramedics, possibilities of the health care system, duration of medical cosnutation), related to the disease (degree of severity of symptoms, comorbidity, stage of disease progression, availability of effective therapy), caused by the therapy (complexity of the regime, duration of treatment, unwanted reactions to drugs, the ineffectiveness of the prescribed therapy), due to the patient's peculiarities (forgetfulness, knowledge about the disease, fear of unwanted side effects, premature termination of treatment). Along with the presented factors, one should not underestimate patients' distinct mental characteristics, often due to a system of their views and perceptions, including those established in a certain community and territory [13; 15].

Insufficient compliance is a widespread phenomenon and a problem for health care systems in many countries. According to WHO, in developed countries, only 50% of patients with chronic diseases have long been in strict compliance with medical recom-

mendations; in developing countries, the rate is even lower [14; 15].

Even in a country like Germany, where there is a high level of commitment to society, patients' non-compliance is relevant. According to the ABDA (Federal Union of Pharmacy Associations), more than 50% of all prescription drugs are not taken following medical guidelines. In order to prevent non-compliance, in Germany, the implementation of medical prescriptions is monitored. A database on prescriptions has been created, which currently covers 80% of patients for whom drugs are paid by health insurance [13; 14; 15].

The direct consequence of non-compliance with the doctor's recommendations is the lack or insufficient effectiveness of treatment, deterioration of the patient's condition, development of complications, more frequent relapses, development of drug resistance, exacerbation of the underlying disease, adverse drug effects and increased risk of complications. All of the above affects the health of patients and causes significant damage to the health budget.

In the United States, losses due to non-complications are estimated at $100–300 billion annually. Over 5% of all hospitalizations in the country are due to inadequate compliance. In large European countries, additional losses due to non-compliance in patients are estimated at 10 billion euros annually. According to reports of the European Federation of Pharmaceutical Industry Associations, patient non-compensation costs the European governments' budget almost 125 billion euros and contributes to the premature death of about 200 thousand Europeans every year [15; 16].

Thus, patient compliance research is a trend that is developing quite rapidly. Its results are interesting and significant for healthcare professionals of different profiles. The importance of patient compliance in the treatment of IDA is due to many factors. The main ones are the long duration of therapy, the high cost of IC, the prevalence of side effects of IC that cause pain to patients during therapy, and the underestimation by patients of the severity of the disease and its consequences. In this regard, the study of this aspect of IDA therapy is relevant for regions with a high prevalence of pathology, as it may contribute to the development of new methods of control over the treatment of patients.

Conclusion

Iron deficiency anemia is fully a non-contagious epidemic for modern society, which causes significant damage to the health of the most vulnerable groups in society, children and pregnant women. The high prevalence of iron deficiency anemia makes it necessary to re-evaluate its correction methods when patients' characteristics and the peculiarities of the attitude towards therapy in the whole population come to the fore. Analysis of the literature has shown that the issues of competent pharmacoeconomics and strict compliance of patients to the therapy with iron preparations are an essential part of the treatment, determining in many cases, its positive outcome.

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Section 3. Physiology

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COMPARATIVE CHARACTERISTICS OF THE PSYCHOPHYSIOLOGY INDICATORS OF YOUNG SWIMMERS (CADETS AND JUNIORS)

Abstract. Since temperament is a genetically programmed form of human behavior, its properties are clearly manifested against the background of the physical activity of athletes, since temperament is considered as a type of higher nervous activity (I. P. Pavlov). nervous system, i.e. choleric type corresponds to a strong unbalanced nervous system, sanguine type (balanced) – to a strong balanced mobile nervous system, phlegmatic type (inert) – to a strong balanced inert nervous system, melancholic type (weak, inhibitory) – to a weak nervous system.

Keywords: athletes, swimmers, juniors and cadets, neurophysiological status, psychophysiological features, type of higher nervous activity.

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СРАВНИТЕЛЬНАЯ ХАРАКТЕРИСТИКА ПОКАЗАТЕЛЕЙ ПСИХОФИЗИОЛОГИИ ЮНЫХ ПЛОВЦОВ (КАДЕТОВ И ЮНИОРОВ)

Аннотация. Поскольку темперамент является генетически запрограммированной формой поведения человека, его свойства ярко проявляются в на фоне физической активности спортсменов, поскольку темперамент рассматривается как тип высшей нервной деятельности (И. П. Павлов) [2; 3; 5; 6; 10]. Физиологическое обоснование различных типов поведения (темпераментов), взаимосвязаны с типологическими особенностями свойств нервной системы, т.е. холерический тип соответствует сильной неуравновешенной нервной системе, сангвинистический тип (уравновешенный) – сильной уравновешенной подвижной нервной системе, флегматический тип (инертный) – сильной уравновешенной инертной нервной системе, меланхолический тип (слабый, тормозной) – слабой нервной системе [11; 14].

Ключевые слова: спортсмены пловцы, юниоры и кадеты, нейрофизиологический статус, психофизиологических особенность, тип высшей нервной деятельности.

Актуальность. Изучение и оценка психофизиологических особенностей спортсменов в ходе подготовки к выступлениям на спортивной арене имеет важную роль [1; 4; 6; 7; 15]. Так учебно-тренировочный процесс напрямую зависит от динамических особенностей психики спортсмена, занимающегося плаванием, такие качества как сообразительность и медлительность, инертность и ряд других особенностей в большей степени зависят от типа темперамента [8; 9; 12; 13].

Цель исследования. Изучение и оценка психофизиологических особенностей спортсменов пловцов.

Материалы и результаты исследования. Для выполнения поставленных нами задач были определены типы темперамента исследуемых групп спортсменов-пловцов (Рис. 1–2), а также проведена оценка нервной системы при помощи теппинг-теста (Рис. 3–4).

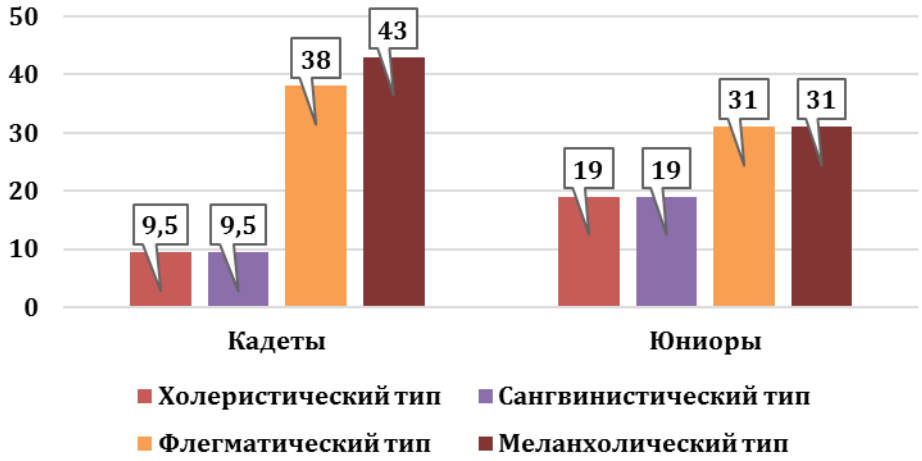

Рисунок 1. Результаты определения типов темперамента спортсменов пловцов мужского пола, в%

Для определения типов темперамента нами был использован опросник Г. Айзенка (опросник FPQ), где обработка полученных данных сопоставлялась с «ключом» ответов в баллах, а интерпретацию полученных результатов проводили по шкалам экстра- и интраверсии, нейротизма и психотизма.

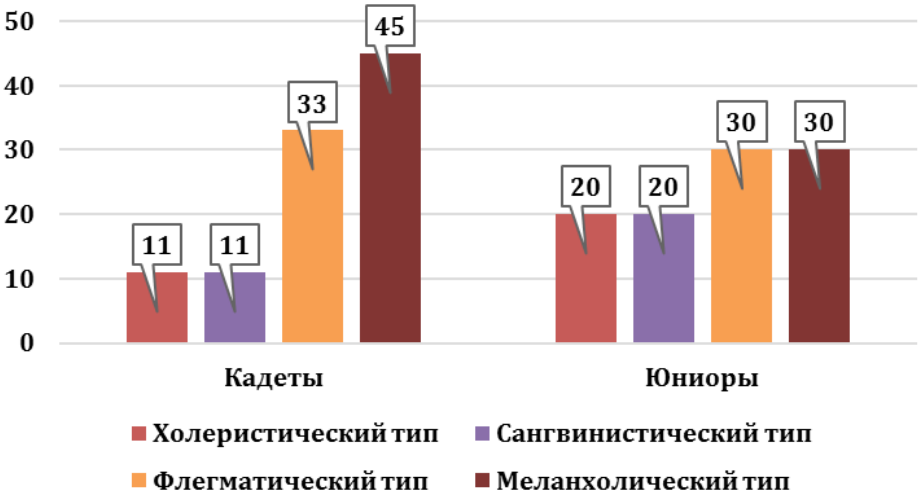

Рисунок 2. Результаты определения типов темперамента спортсменов пловцов женского пола, в%

При анализе полученных результатов опроса спортсменов пловцов было установлено, что среди кадетов и юниоров как мужского пола, так и женского (Рисунок 1. и 2) сангвинистический и холеристический типы темперамента составили одинаковые значения (кадеты – 10%, юниоры 20%). Флегматический и меланхолический типы темперамента в юниорских группах обоих полов составили 30% от общего числа исследуемых, тогда как среди кадетов обоих полов – 40%.

Спортсмены обладающие флегматическим типом темперамента как правило обладает уравновешенным и сильным типом нервной деятельности, так как в следствии малой возбудимости спортсмен может сохранить спокойствие, при этом быть высоко активным, что в совокупности даёт высокие показатели таких качеств как выносливость, терпеливость, выдержка и самообладание. Поэтому следующим этапом нашего исследования заключалось в оценке функционального состояния нервной системы.

Для исследования лабильности (подвижности) нервной системы спортсменов нами был проведен «Теппинг – тест», где показатель лабильности равен количеству нервных импульсов в единицу времени, который характеризует скоростные функции ткани. Лабильность определяется измерением максимальной частоты движения кисти и является показателемфункционального состояниядвигательной активности.

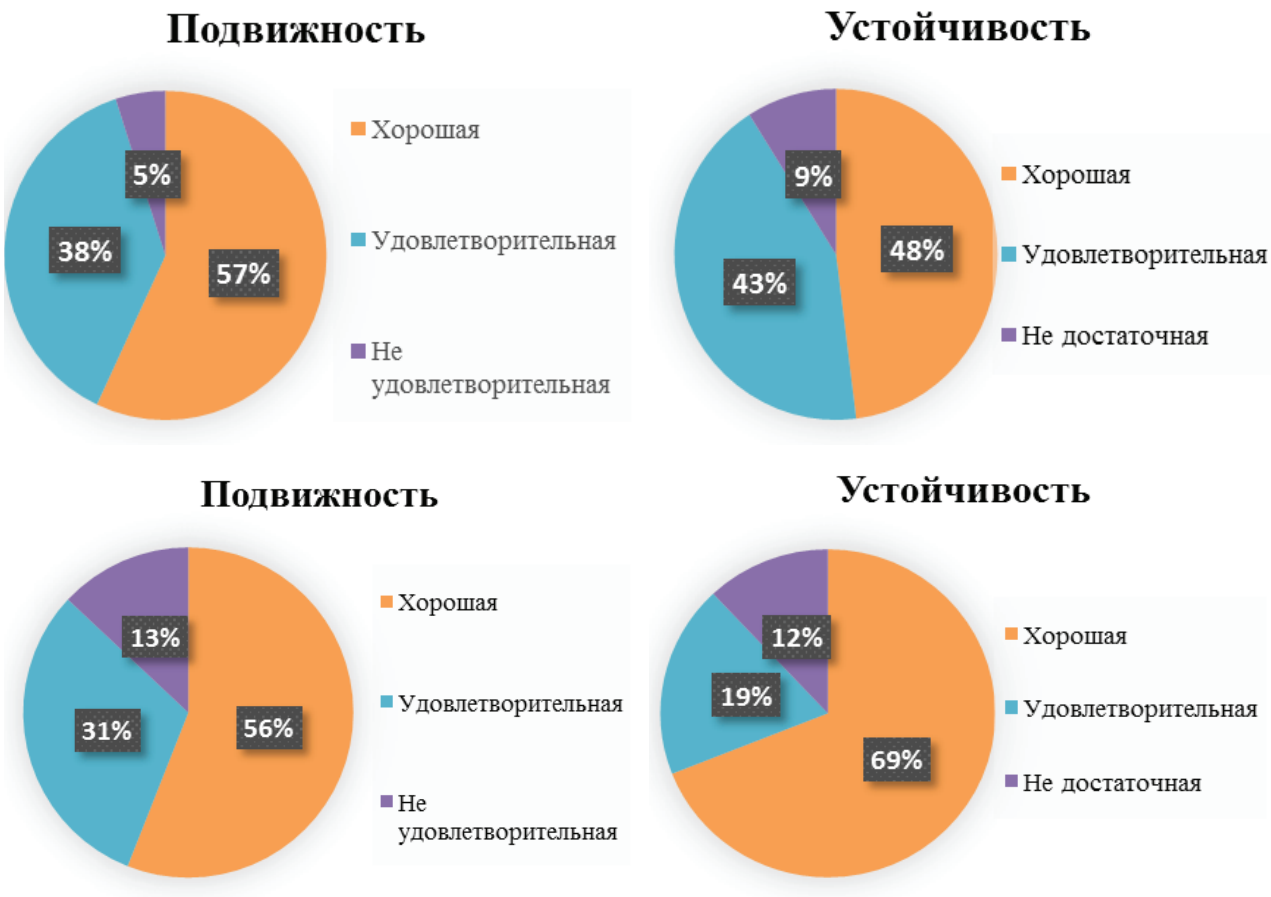

Рисунок 3. Показатели оценки функционального состояния нервной системы спортсменов пловцов мужского пола (кадетов и юниоров), в%

Функциональное состояние двигательной сферы спортсмена в сочетании с устойчивостью даёт возможность дать оценку утомлению организма в следствии выполнения мышечной работы

и процесса фазовых изменений в коре больших полушарий. которые характеризуются не адекватными сильными и слабыми реакциями, что проявляется снижением работоспособности, чувства усталости, снижением мышечной силы и нарушением координации.

Установлено, что среди пловцов кадетов и юниоров женского пола (рисунок 4) результаты теппинг-теста у 46% оценивается как «хорошо», у 40% «удовлетворительно», у 11% «не удовлетворительно», что говорит о высоком уровне тренированности.

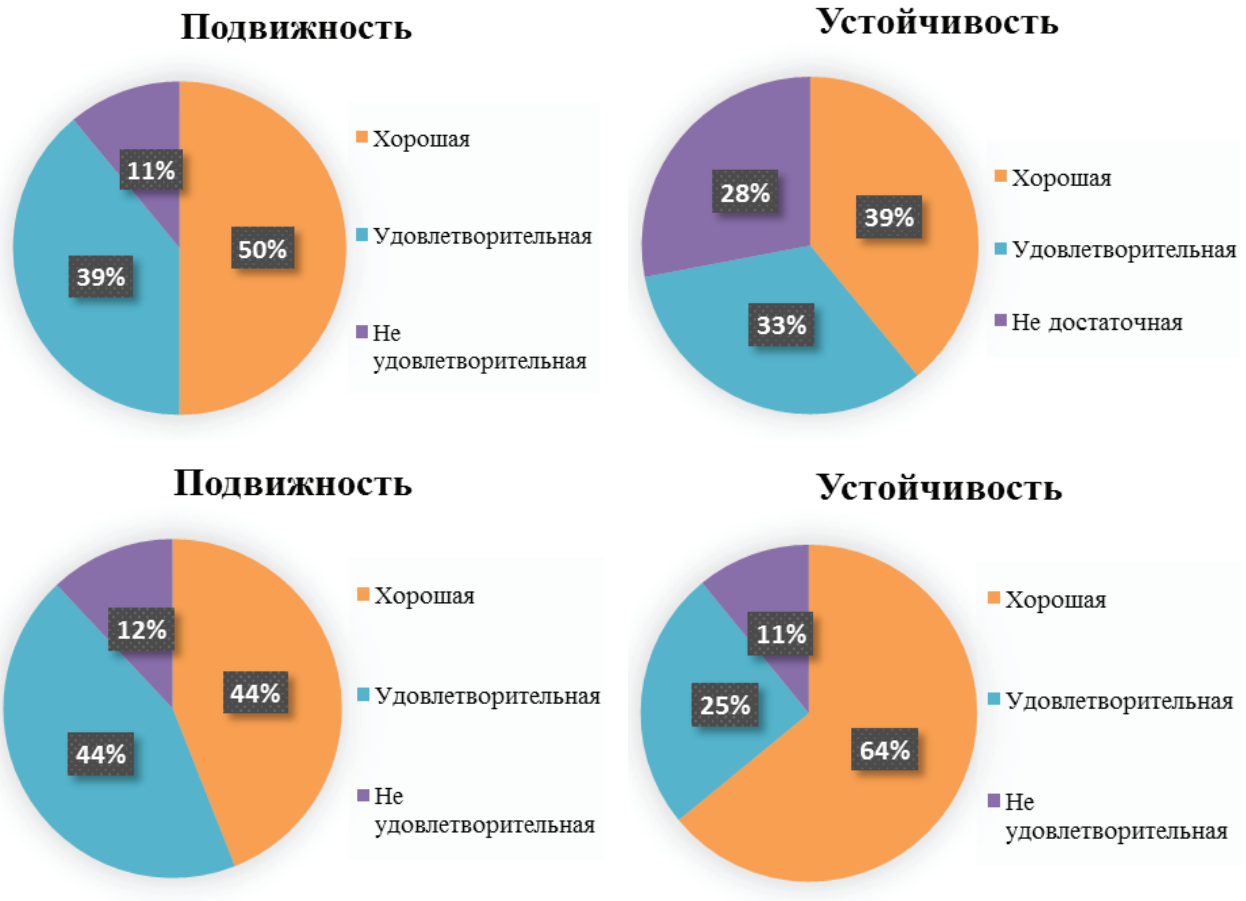

Рисунок 4. Показатели оценки функционального состояния нервной системы спортсменов пловцов женского пола (кадетов и юниоров), в%

На основе полученных данных в ходе исследования на юных спортсменах, занимающихся плаванием можно судить о том, что данный вид спорта- специфичен, оказывая особое влияние на развитие психофенотипа спортсмена, за счет длительности и упорства спортивных тренировок, максимально напрягая физические и психические силы юного спортсмена.

Вывод. Таким образом, можно предположить, что включая упражнения на развитие психофизиологических показателей в тренировочный процесс спортсменов-пловцов поспособствует повышению уровня мастерства комплексным воздействием на разные уровни процесса в спортивной подготовке.

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ANALYSIS OF THE BODY COMPOSITION OF JUNIOR AND CADET ATHLETES AND CYCLISTS

Abstract. One of the methods that determine the adequacy of physical activity is the determination of the component composition of body weight. Body composition parameters include body fat, lean mass, and skeletal mass, which are needed to compare the data of the athletes we study, which differ in age and body type. Changes in indicators of the body composition of athletes during physical activity are closely related to the functional indicators of systems that determine performance.

Keywords: junior athletes and cadets, component composition of body mass, working capacity.

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АНАЛИЗ СОСТАВА ТЕЛА СПОРТСМЕНОВ ЮНИОРОВ И КАДЕТОВ ЛЕГКОАТЛЕТОВ И ВЕЛОГОНЩИКОВ

Аннотация. Одним из методов, определяющих адекватность физических нагрузок – это определение компонентного состава массы тела. Параметры состава тела включают показатели жировой, мышечной и скелетной массы, которые необходимы для сопоставления данных исследуемых нами спортсменов, различающихся по возрасту и телосложению. Изменения показателей состава тела спортсменов при физических нагрузках тесно взаимосвязаны с функциональными показателями систем, определяющих работоспособность.

Ключевые слова: спортсмены-юниоры и кадеты, компонентного состава массы тела, работоспособность.

Актуальность**.** В спортивной науке и практике активно изучается проблемы селекции одаренной молодёжи, однако вопросы отбора детей в спорт, в частности в легкую атлетику и велоспорт недостаточно изучены [1; 4; 6; 7; 10]. Для решения проблем селекции одаренной молодежи и грамотной ориентации в спортивные секции, при прогнозировании успешности спортсменов, необходимо основываться на современных методах спортивной генетики, которые позволяют найти правильное решение на основе фенотипических и генетических маркерах, отражающих наследственную предрасположенность будущего спортсмена [2; 3; 5]. В процессе изучения и анализа этих маркеров становится возможным индивидуализировать и оптимизировать тренировочный процесс. для достижения максимального эффекта от тренировки. Одним из методов, определяющих адекватность физических нагрузок – это определение компонентного состава массы тела. [8; 9; 11; 14]. Параметры состава тела включают показатели жировой, мышечной и скелетной массы, которые необходимы для сопоставления данных исследуемых нами спортсменов, различающихся по возрасту и телосложению

[12; 13]. Изменения показателей состава тела спортсменов при физических нагрузках тесно взаимосвязаны с функциональными показателями систем, определяющих работоспособность [1; 4; 6; 7; 15]. К важным композиционным особенностям легкоатлетов-бегунов и велогонщиков определяемых при помощи дополнительных антропометрических обследований, калиперометрии, биоимпедансометрии и воздушной плетизмографии, следует отнести рост, длину туловища, массу **тела**, а также соотношение мышечной, костной и жировой тканей.

Цель исследования. Изучить показатели мышечного, костного и жирового компонентов тела у исследуемых спортсменов юниоров и кадетов легкоатлетов и велосипедистов.

Материалы и результаты исследования. Нами были изучены показатели мышечного, костного и жирового компонентов тела у исследуемых спортсменов (таблица 1–4), методом предложенный Я. Матейко, где нахождение жирового, мышечного и костного компонентов массы **тела** происходит по специальным формулам с учетом антропометрических данных и метода калиперометрии.

Таблица 1.– Результаты показателей состава тела спортсменов легкоатлетов, M±m

Показатель	**Кадеты (12–14 лет), n=36**	**Юниоры (15–17 лет), n=27**
Жировой компонент,%	11,7±3,8	10,3±2,6
Мышечный компонент,%	48,3±4,2	49,3±5,8
Костный компонент,%	14,3±3,4	13,2±2,8

Согласно полученным данным по составу тела в группе легкоатлетов-кадетов жировой компонент не значительно выше, чем у юниоров. По результатам анализа мышечного компонента наблюдается обратная картина, у спортсменов-кадетов данный показатель незначительно ниже, чем у легкоатлетов-юниоров, тогда как каостный компонент в группе кадетов выше, чем в группе юниоров.

Таблица 2.– Результаты показателей состава тела спортсменов легкоатлеток, M±m

Показатель	**Кадеты (12–14 лет), n=36**	**Юниоры (15–17 лет), n=27**
Жировой компонент,%	12,3±2,6	10,7±3,2
Мышечный компонент,%	47,4±3,9	48,6±4,5
Костный компонент,%	15,6±4,4	14,6±3,7

Согласно полученным данным по составу тела в группе легкоатлеток-кадеток жировой компонент не значительно выше, чем у юниорок. По результатам анализа мышечного компонента наблюдается обратная картина, у спортсменок-кадеток данный показатель незначительно ниже, чем у легкоатлеток-юниорок, тогда как костный компонент в группе кадеток выше, чем в группе юниорок.

Таблица 3.– Результаты показателей состава тела спортсменов велогонщиков, M±m

Показатель	**Кадеты (12–14 лет), n=34**	**Юниоры (15–17 лет), n=24**
Жировой компонент,%	9,2±3,5	8,8±3,1
Мышечный компонент,%	48±2,8	50±6,4
Костный компонент,%	15±3,3	14,3±4,7

Согласно полученным данным у велогонщиков кадетов показатель мышечного компонента ниже чем в группе юниоров, однако показатели жирового и костного компонента тела в данной группе выше в сравнении с юниорами.

Таблица 4.– Результаты показателей состава тела спортсменов велогонщиц, M±m

Показатель	Кадеты (12–14 лет), n=34	Юниоры (15–17 лет), n=24
Жировой компонент,%	9,4±3,8	6,3±5,2
Мышечный компонент,%	51±3,8	48±6,1
Костный компонент,%	14,2±4,7	13,8±5,2

Согласно полученным данным у велогонщиц кадеток показатель мышечного компонента ниже чем в группе юниорок, однако показатели жирового и костного компонента тела в данной группе выше в сравнении с юниорками.

В ходе проведенных исследований были выявлены отличия в компонентном составе тела спортсменов легкоатлетов и велогонщиков обоих полов. У кадетов легкоатлетов и велогонщиков обоих полов более высокое содержание жирового компонента по отношению к спортсменам в группе юниоров. По уровню мышечного компонента в группах кадетов легкоатлетов и велогонщиков обоих полов показатель ниже по сравнению с юниорами. Анализируя показатели костного компонента, аналогичная картина.

Таким образом, у исследуемых групп спортсменов установлены морфологические и метаболические особенности, которые сформировались под влиянием регулярной физической активности.

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Section 4. General biology

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CORNELIAN CHERRY (CORNUS MAS L.) HISTORY OF INTRODUCTION TO CULTURE

Abstract. Cornelian cherry or male — Cornus mas L. is a deciduous shrub or small tree from the family of dogwood (Cornaceae) with a height of 3–5 (up to 10) m. The article presents data on the results of studies of cornelian cherry (Cornus mas L.). This fruit plant is very ancient, valuable food, medicinal, soil-protective and decorative, undemanding to growing conditions, almost not damaged by pests and not affected by diseases.

Key words: Families, fruit, flower, reproduction, fever, active substances, medicine.

The stem of old trees reach a diameter of 25, in rare cases even 45 cm, covered with gray cracked cortex. The lateral shoots extending from the main stem are directed upwards almost vertically. The leaves are opposite, ovate or elliptical, up to 10 cm long, with an elongated and pointed tip, with arcuate lateral veins, whole-cut, with petioles. The leaves on both sides are covered with pressed bristles, which easily break off and get on human skin, cause unpleasant itching.

The flowers are bright yellow, collected in 5–9, in umbellate inflorescences with a diameter of about 1 cm, surrounded by wrappers of 4 filmy leaflets. Inflorescences are located on shortened shoots. The flowers are regular, 4-membered, bisexual, but in some flowers the stamens are sterile. The calyx is grayish. Corolla with lanceolate-triangular petals 2–2.5 mm long. A pistil with a lower ovary and a green column. The flowers are pollinated by bees and other insects.

Fruits are large cylindrical or pear-shaped, rarely almost spherical drupes up to 3.5 cm long and up to 2 cm in diameter, with juicy pulp of sweet and sour, slightly astringent taste. When fully ripe and after frosts, the astringency decreases. The color of fruits in different individuals (as well as their shape and size) varies greatly, it can be pink, red or dark red in different shades. Each drupe contains 1–2 oblong bones (seeds). The red color of the fruits gave the basis to the name of the plant ("dogwood" in Turkic "red") [1, 2]. Blooms early in spring — in March-April, before the leaves bloom. The fruits ripen in August-September. Individuals live up to 250 years.Wild dogwood species are common in the mountains of the Caucasus, Asia Minor, and Southern Europe. It grows in the undergrowth of deciduous forests, on their edges and clearings in the lower and middle belts. It is also found on the territory of the Russian regions of the North Caucasus. The extent to which it is widespread there can be judged by the size of fruit preparations — in the 50s. in the last century, up to 3 thousand were

harvested in Dagestan alone. tons of this product annually [2,3].

Cornelian cherry has long been growed near houses and in gardens, even varieties that differ in large fruitfulness have been bred. In Uzbekistan, the cornelian culture as a "Conservation and development of Biodiversity" in Republic online scientific and practical conference fruit plant has not been widely distributed. In many places in Russia, the Caucasus and the Astrakhan region, you can find its planting. It is also planted in protective forest strips in the Rostov region, Krasnodar and Stavropol territories. Up to the Eagle, you can find individual cornelian plants in plantings. Propagated by seeds that germinate unfriendly, and young seedlings grow very slowly, which makes it difficult to breed cornelian [4].

Cornelain cherry is a well-known food plant. Its fruits contain up to 10% sugars (mainly glucose and fructose), 2–3.5% acids (mainly malic), pectin, tannins and coloring substances, essential oil, vitamins C (up to 120 mg) and R. In terms of ascorbic acid content, dogwood fruits surpass such well-known vitamin-bearing fruits as citrus fruits. There is a lot of fatty oil in the seeds [2].

Cornelian fruits are eaten fresh and boiled, jam, jam and compote are prepared from them, processed into pastilles, marmalade, syrup, alcoholic and soft drinks. Fresh and dry fruits are used as a seasoning for meat dishes, marinades and sauces are prepared from them. Caucasian peoples make pita bread from dogwood fruits — cakes made from dried fruit pulp, as well as turshu — boiled juice.

Cornelian juice is popular in Georgia. He was loved by Sergei Yesenin, who wrote, addressing the Caucasus: "You teach my Russian verse to flow with cornelian juice." Fruits are raw materials for the confectionery and canning industry. For home use, they can be stored for several months in a cool place, sprinkled with granulated sugar. The seeds of the fruit serve as a good substitute for coffee [3]. Cornelian has not only food use. It is decorative, used to create hedges. It is valued as an early spring honey plant that gives nectar and pollen. The bark and leaves were used for tanning and coloring the skin. Cornelian wood is very strong and heavy, has a beautiful pattern, so it is appreciated for artistic crafts. Previously, weaving shuttles, buttons and even watch wheels were made of it. And in Dagestan there were masters who made a name for themselves by making wonderful dogwood canes. Branches are used as handles of various tools and agricultural implements. Note in passing that the Latin name Cornus, which means "horn", dogwood received precisely for hard wood with thin annual rings, really remotely similar to horn [5]. In ancient medicine, dogwood fruits and the bark of the aboveground part of the shrub were used as a wound healing and antidote. At the Republican online Scientific and Practical Conference "Conservation and development of Biodiversity", burnt bark or crushed dogwood fruits were applied to the surface of the wounds. According to Avicenna, the squeezed juice was applied inside or in the form of a medicinal dressing applied to the bite site of poisonous snakes (vipers). Cornelian was known in ancient Greece, and it was salted like olives. In ancient times, even before Galen, dogwood was used as an astringent. Later this property was confirmed by the Salerno School. In the folk medicine of Armenia, dogwood seeds, powdered and boiled in water, as well as a drink made from roasted seeds, like coffee, are given for diarrhea. In the Caucasus, juice from fresh leaves is used as eye drops. From a decoction of dogwood leaves and barley flour, a plaster mask is prepared for the treatment of abscesses. A thick decoction of fruits is spread on wet gauze and put on the forehead for headaches. In Karachay-Cherkessia, a decoction of dogwood roots is taken orally for rheumatism, and a decoction of fruit seeds for diarrhea.

Chinese traditional medicine recommends fruits as a restorative and tonic for tuberculosis, pain in the lumbar region, frequent urination, tinnitus [6]. In America, the roots and bark of dogwood branches are used as a substitute for quinine as an antimalarial

agent. Juice, jam and fruit compote in folk medicine are recommended for anemia, liver diseases, gout, diabetes mellitus, as a concoction, choleretic and diuretic. Water extracts from fruits and leaves are used as an antipyretic and diuretic. For the treatment of the same diseases, you can use a decoction and an infusion of dogwood. Water extracts from dogwood bark are a good tonic and stimulant.

For medicinal purposes, dogwood fruits, leaves, shoots, bark, roots are used. According to research, the fruits have an anti-scurvy, antidiabetic, antipyretic, anti-inflammatory, bactericidal, antimalarial, bile and diuretic, tonic effect. They treat gastrointestinal diseases, dysentery, typhus, anemia. They help with measles, flu, scarlet fever, rickets, sore throat, diarrhea, tuberculosis, cirrhosis of the liver and other diseases.

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