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КОЛОНКА ГЛАВНОГО РЕДАКТОРА

Dear Colleagues!

September has come. Autumn time. The work of the editorial board of the "Yakut Medical Journal" is a continuous cycle. The journal should be published quarterly on an approved schedule regardless of vacation period, long holidays and vacation days. No doubt, the editorial staff rests, goes on vacation, but this does not violate the work of the established mechanism, the result of which is the next issue. Here comes the third issue of the "Yakut Medical Journal".

In 2018-2019 the portfolio of materials submitted for publication in the "Yakut Medical Journal" is quite complete. The geography of the authors is wide. The subjects are diverse. Among the authors there are graduate students, applicants for academic degrees, the materials of which are accepted for publication in the first instance.

"Yakut Medical Journal" is a multidisciplinary publication. The editorial board adheres to the editorial policy developed in accordance with the Charter of the publication. One of the main principles of the journal's editorial policy is the principle of strict observance in each issue of its scientific profile. These are molecular genetics and biochemistry, cardiology, pediatrics, oncology, neurology. Materials on these topics are given priority in the publication.

The "Yakut Medical Journal" was established to more fully cover a wide range of health problems, prevention, revealing and treatment of widespread diseases of the Republic Sakha (Yakutia) population. Besides, its tasks surely include promoting the achievements of medical science and medical education not only in the republic, but also in the Russian Federation and the entire world community. Therefore, the "Yakut Medical Journal" is not limited to the publication of materials only in its scientific profile. Until now, the journal has had enough space for the publication of a wide range of scientific problems; it exists today, and will continue to be so.

I wish you, our authors, good health, success in research activities, interesting publications! And we thank our users for being with us, we are glad that papers of our journal are interesting for you!

See you in the next issues of our "Yakut Medical Journal"!

Editor-in-chief ***Anna Romanova***

ПЕРЕДОВАЯ СТАТЬЯ

A.N. Romanova, T.M. Klimova, A.G. Egorova, A.A. Kuzmina, I.S. Malogulova, N.S. Arkhipova

PREVALENCE AND TREATMENT OF ARTERIAL HYPERTENSION IN THE NATIVE RURAL POPULATION OF YAKUTIA

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The **objective** of the research was to study the prevalence and characteristics of treatment of arterial hypertension (AH) in the indigenous rural population of the Sakha (Yakutia) Republic.

Epidemiological research was conducted among the population (20 years and older) of 3 districts of the Sakha (Yakutia) Republic, and representatives of indigenous ethnic groups (Yakuts, Evens, and Evenks). The prevalence of AH among the surveyed population was 45.9% (95% CI: 42.5-49.3). There were no statistically significant differences in the frequency of hypertension in men and women (45.3 and 46.2%, respectively, p = 0.805). According to the survey, antihypertensive drugs (AHD) were taken by 51.2% of individuals with hypertension according to research criteria. Among women, the proportion of individuals using AHD was statistically significantly higher than among men (57.6 and 39.2%, respectively, p < 0.001). In 75.4% of cases, patients took one antihypertensive drug. In 52.8% of cases, drug therapy included angiotensin-converting enzyme inhibitors, in 42% of cases – calcium channel blockers, in 13.6% – β-blockers, 8.4% – angiotensin II receptor blockers, and in 3.1% – diuretics. The level of blood pressure corresponded to the "target" in 30.9% of those taking AHD.

Along with improving the diagnosis of hypertension and finding and eliminating risk factors, it is necessary to take measures to increase patient adherence to treatment and control blood pressure levels, as well as to conduct pharmacogenetic studies of the effectiveness of antihypertensive drugs.

Keywords: arterial hypertension, arterial hypertension, prevalence, antihypertensive drugs, treatment efficacy, Yakutia.

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Introduction. Arterial hypertension is a major risk factor for coronary heart disease, chronic renal failure, cerebral stroke and other cardiovascular diseases. According to WHO, in 2015, 22% of the world's population aged 18 years and older had elevated blood pressure [8]. While in high-income countries there is currently a decrease in the prevalence of AH, in low- and middle-income countries the number of AH patients continues to increase. This is caused not only by the aging of the population but also by the presence of such risk factors as overweight or obesity, decreased physical activity, stress, environmental degradation, etc.

In the Russian Federation, according to the multicenter study called Epidemiology of Cardiovascular Diseases in Various Regions of Russia (ECCD), the prevalence of hypertension among the population of 25–64 years old was 44%. The study showed variability in the prevalence rate depending on the region of the participant (from 37.8 to 56.1%) [1].

Sakha (Yakutia) Republic is the largest subject of the Russian Federation, characterized by unfavorable climatic conditions for living and working people. For the period from 2004 to 2018, the prevalence of diseases associated with high blood pressure increased among the adult population of the Republic from 65.0 to 108.4 per 1000 population [2, 5]. At the same time, official statistics probably do not fully reflect the entire situation. Additional research may help to make adjustments to ongoing prevention programs in the region.

The aim of the research was to study the prevalence and characteristics of treatment of hypertension in the indigenous rural population of the Sakha (Yakutia) Republic.

Materials and Methods. A screening survey was conducted in 2017-2018, among the population of 3 districts of the Sakha (Yakutia) Republic aged 20 years and older (Oymyakonsky, Gorny and Tattinsky), who were representatives of indigenous ethnic groups (Yakuts, Evens, and Evenki) The study was conducted subject to the voluntary informed consent of the participants. The survey program included: a survey using a special questionnaire, an anthropometric examination using a standardized method, a threefold measurement of blood pressure (BP), and venous blood sampling after fasting. The content of glucose, total cholesterol (cholesterol), triglycerides, high-density lipoprotein cholesterol (HDL cholesterol) was determined using the express analyzer CardioChek PA, USA. The concentration of low-density lipoprotein cholesterol (LDL cholesterol) was calculated using the Friedewald formula with a blood triglyceride level of less than 4.5 mmol/L. Arterial hypertension (AH) was established by the criteria of ESH/ESC, 2013 [9]. The group with hypertension also included individuals who took antihypertensive drugs (AHD) during the survey or stopped taking them less than 2 weeks before the survey, regardless of the measured blood pressure level. Effective treatment of hypertension was considered the achievement of target values of blood pressure on the back-

Table 1

Main Characteristics of the Surveyed Indigenous Population of the Sakha (Yakutia) Republic, 20 Years and Older

Indicator	20-43 years n=237	44-59 years n=310	60-74 years n=177	75 year and old n=53	p
Мужчины n=287					
SBP, mm Hg	120.0 (111.8-133.3)	130.0 (116.3-143.0)	141.0 (130.0-160.0)	130.0 (120.0-152.5)	<0.001
DBP, mm Hg	80.0 (70.3-84.3)	80.0 (73.3-90.0)	90.0 (80.0-100.0)	90.0 (80.0-92.5)	<0.001
Height, cm	168.0 (164.1-172.0)	167.0 (163.0-172.0)	162.0 (158.0-165.8)	160.0 (157.0-166.8)	<0.001
Body mass, kg	69.0 (62.0-79.8)	74.0 (64.0-81.0)	66.0 (62.0-76.0)	64.5 (55.8-73.8)	<0.001
Body mass index, kg/m^2	24.1 (21.9-27.3)	26.8 (23.7-29.3)	25.3 (23.1-29.2)	25.1 (22.1-26.7)	0.007
Waist circumference, cm	81.5 (76.3-94.0)	92.0 (84.0-99.8)	92.0 (84.0-97.5)	92.0 (88.0-97.0)	<0.001
Triglycerides, mmol/L	0.9 (0.6-1.2)	1.1 (0.8-1.8)	0.9 (0.6-1.3)	0.8 (0.6-1.4)	0.048
Total cholesterol, mmol/L	4.8 (4.1-5.8)	5.4 (4.3-6.2)	5.0 (4.2-5.7)	4.7 (3.7-5.6)	0.103
HDL cholesterol, mmol/L	1.4 (1.2-1.7)	1.4 (1.2-1.6)	1.5 (1.2-1.6)	1.1 (0.9-1.5)	0.032
LDL cholesterol, mmol/L	2.5 (1.9-3.1)	2.9 (2.2-3.4)	2.8 (2.2-3.7)	2.8 (2.2-3.7)	0.038
Atherogenic index, c.u.	2.4 (1.8-3.3)	2.8 (2.1-3.5)	2.4 (1.9-3.1)	2.7 (2.1-3.9)	0.106
Glucose, mmol/L	4.8 (4.5-5.3)	5.1 (4.6-5.6)	4.9 (4.3-5.5)	4.7 (3.9-5.0)	0.006
Women n=526					
SBP, mm Hg	120.0 (110.0-130.0)	134.0 (120.0-150.0)	140.0 (120.0-165.4)	150.0 (138.5-176.7)	<0.001
DBP, mm Hg	78.5 (70.0-84.2)	85.0 (80.0-94.0)	89.5 (80.0-100.0)	90.0 (80.0-100.0)	<0.001
Height, cm	158.0 (152.9-162.0)	154.0 (150.0-158.0)	150.0 (147.5-154.0)	146.0 (141.5-150.0)	<0.001
Body mass index, kg	61.9 (54.0-72.0)	67.0 (58.2-76.0)	63.0 (55.0-74.0)	58.0 (49.0-69.5)	<0.001
BMI, kg/m^2	24.9 (22.4-28.4)	27.9 (24.9-31.6)	27.9 (24.3-32.3)	27.6 (23.4-32.0)	<0.001
Waist circumference, cm	82.0 (74.0-93.8)	91.0 (83.0-100.0)	94.0 (83.5-103.0)	93.0 (84.3-101.0)	<0.001
Triglycerides, mmol/L	0.8 (0.6-1.1)	1.1 (0.8-1.5)	1.0 (0.7-1.4)	0.9 (0.7-1.1)	<0.001
Total cholesterol, mmol/L	4.6 (3.9-5.3)	5.7 (4.9-6.4)	5.4 (4.7-6.2)	5.4 (4.6-5.9)	<0.001
HDL cholesterol, mmol/L	1.6 (1.3-1.8)	1.5 (1.4-1.7)	1.4 (1.3-1.7)	1.5 (1.2-1.7)	0.253
LDL cholesterol, mmol/L	2.2 (1.8-2.8)	3.1 (2.5-3.8)	3.1 (2.6-3.8)	3.3 (2.5-4.0)	<0.001
Atherogenic index, c.u	2.2 (1.5-2.7)	2.8 (2.2-3.5)	2.7 (2.0-3.5)	2.6 (2.1-3.1)	<0.001
Glucose, mmol/L	4.6 (4.3-5.1)	4.9 (4.5-5.6)	4.6 (4.2-5.4)	4.5 (4.1-4.9)	<0.001

Note: p is the achieved level of statistical significance of differences when comparing age groups by gender (Kruskal–Wallis test).

ground of antihypertensive therapy [9].

Statistical data analysis was carried out in the IBM SPSS STATISTICS 22 package. When comparing groups depending on the type of data, Kruskal-Wallis criteria were used, as well as Pearson's chi-squared test (χ^2). The critical value of the level of statistical significance of differences (p) was taken to be 5%. Descriptive statistics of quantitative data are presented as median (Me) and interquartile range (Q1-Q2). AH prevalence rates are presented with a 95% confidence interval (95% CI).

Results and Discussion. During the epidemiological study in 3 districts of Yakutia, 813 men and women aged 20 years and older were examined. Men and women were comparable in age, the average age of the men surveyed was 49.3 (15.9) years, women – 50.9 (15.3) years (p = 0.138).

Analysis of the main anthropometric and metabolic indicators of the sample showed that, in general, the indigenous rural population is characterized by increased body weight, waist circumference, and a fairly favorable lipid profile (Table 1). At the same time, from the age of 44, the upper quartile of the distribution of systolic and diastolic blood pressures is in the range corresponding to the criterion of AH. These features were noted by us in previous studies [4, 6, 7].

Table 2

Prevalence of hypertension among the indigenous population of Yakutia, n (%)

Age, years	Men n=287	Women n=526	Both genders n=813	p
20-43	29 (26.6)	35 (21.3)	64 (23.4)	0.315
44-59	38 (41.80)	115 (52.5)	153 (49.4)	0.085
60-74	51 (71.80)	63 (59.4)	114 (64.4)	0.091
75 and older	12 (75.0)	30 (81.1)	42 (79.2)	0.616
All	130 (45.3)	243 (46.2)	373 (45.9)	0.805

Note: p is the achieved level of statistical significance of differences when comparing groups by gender (Pearson's test χ^2).

The prevalence of AH among the surveyed population was 45.9% (95% CI: 42.5-49.3). Among the male population, the figures were 45.3% (95% CI: 39.5-51.2), and among women 46.2% (95% CI: 41.9-51.5), respectively. With an increase in the age of the examined, the frequency of hypertension increased significantly (Table 2). There are no statistically significant differences in the prevalence of hypertension among men and women, both in general and in each age group separately. These data are close to the results of the ECCD study in 9 regions involving 15,300 people, where the prevalence of AH was on average 44%. The prevalence rates of hypertension in 8 regions were higher for men than for women. In the Tyumen Region, which also belongs to the northern territories, there are also no significant differences between women and men in the frequency of hypertension [1].

Evaluation of antihypertensive therapy was carried out according to the patients' self-reports, which makes possible the presence of a systematic error associated with a "memory error". Some patients could not specify all drugs that were taken in connection with high blood pressure. At the same time, it is closer to the actual practice of taking the drugs by the patients themselves. Conducting a future study with simultaneous evaluation of the doctor's prescriptions and patient self-report could help eliminate these shortcomings and objectively assess the patients' adherence to treatment, as well as the treatment tactics used by the medical staff.

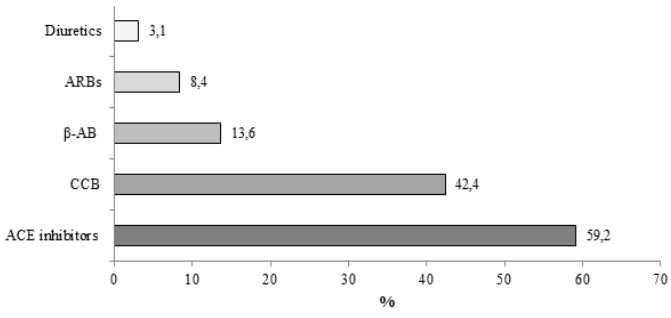

Fig. 1. Frequency of use of different groups of antihypertensive drugs: ACE inhibitors – inhibitors of the angiotensin-converting enzyme; CCB – calcium channel blockers; β-AB – beta blockers; ARBs – angiotensin II receptor blockers.

According to the survey, 191 people from among 373 persons diagnosed with AH by screening (51.2%) were taking AHD. Among women, the proportion of drug users was statistically significantly higher than among men (57.6 and 39.2%, respectively, p <0.001). According to the results of the ECCD study, on average in Russia 60.9% of women and 39.5% of men with hypertension took AHD [1]. Thus, the attitude of patients to the treatment of hypertension in Russia has common features, regardless of the region.

The most commonly used drugs were angiotensin-converting enzyme inhibitors (ACE inhibitors), which were used as monotherapy or were part of combination therapy in 59% of treatment cases. In 42% of cases, calcium channel blockers (CCB) were used, in 13.6% – β-blockers (β-АБ), 8.4% – angiotensin II receptor blockers (ARBs), 3.1% – diuretics (Fig. 1). According to the research of ECCD, ACE inhibitors were also the most frequently used drugs in other territories of the Russian Federation [1]. But in Yakutia, in contrast to the regions studied, the second in use are CCBs. The proportion of people receiving CCB was 18.8% in the Russian study, against 42% in Yakutia. The proportion of β-AB, diuretics and ARBs was significantly lower. The revealed features require additional studies, since the high frequency of prescribing CCBs may be due to their high efficiency in this ethnic group.

144 (75.4%) respondents taking AHD indicated using 1 drug. In 52.8% of cases, these were ACE inhibitors, in 31.9% – calcium antagonists, in 9% – β-AB. Of the 47 patients taking 2 or more drugs, 22 (46.8%) indicated that an ACE inhibitor was taken in combination with CCB. The second in frequency (14.9%) was a combination of an ACE inhibitor with β-AB. 6 respondents noted the use of 3 drugs, of which in 4 cases it was a combination of an ACE inhibitor + CCB + ARBs.

When measured in 59 out of 191 (30.9%) respondents taking AHD, the level of blood pressure corresponded to the "target". In women, the proportion of people with a normal level of blood pressure on the background of drug intake was slightly higher, but the differences did not reach a statistically significant level (32.1 and 27.5%, respectively, p = 0.535). According to the results of the ECCD study, the treatment efficiency was 53.5% among women and 41.4% among men, which is much higher than our data [1].

Thus, the results of the study showed a high incidence of hypertension among the indigenous population of Yakutia (45.9%). AHD was taken by 57.6% of women and 39.2% of men with hypertension according to the research criteria. At the same time, target blood pressure was achieved only in 30.9% of patients. Along with improving the diagnosis of hypertension, finding and eliminating risk factors, measures are needed to increase patient adherence to treatment and controlling blood pressure levels, as well as pharmacogenetic studies of the effectiveness of antihypertensive drugs in this ethnic group.

The work was carried out as part of the research project "The Contribution of Metabolic Syndrome to the Development of Coronary Artery Atherosclerosis in Yakutia's Residents" (Reg. No. 01-20-128-08-00).

Table 3

Range of used groups of antihypertensive drugs

Group of drugs	Drug intake n=191 (100%)		Monotherapy n=144 (75.4%)		Combined therapy n=47 (24.6%)	
	n	%	n	%	n	%
ACE inhibitors	76	39.8	76	52.8		
CCB	46	24.1	46	31.9		
β-АБ	13	6.8	13	9.0		
ARBs	5	2.6	5	3.5		
Alpha adrenomimetics	2	1.0	2	1.4		
Diuretics	2	1.0	2	1.4		
ACE inhibitors + CCB	22	11.5			22	46.8
ACE inhibitors + β-AB	7	3.7			7	14.9
CCB + β-AB	4	2.1			4	8.5
ACE inhibitors + AV + ARBs	4	2.1			4	8.5
CCB + ARBs	3	1.6			3	6.4
ACE inhibitors + ARBs	2	1.0			2	4.3
CCB + Diuretics	1	0.5			1	2.1
ARBs + Diuretics	1	0.5			1	2.1
β-AB + ARBs	1	0.5			1	2.1
ACE inhibitors + CCB + Diuretics	1	0.5			1	2.1
ACE inhibitors + β-AB + Diuretics	1	0.5			1	2.1

Note: ACE inhibitors – inhibitors of the angiotensin-converting enzyme; CCB – calcium channel blockers; β-AB – beta blockers; ARBs – angiotensin II receptor blockers.

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ORIGINAL RESEARCHES

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LIPOPROTEIN LIPASE GENE POLYMORPHISM rs320 AND METABOLIC SYNDROME IN NATIVE PEOPLE OF YAKUTIA

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The **aim** of the study was investigation the relationship of allelic variants and genotypes of the rs 320 polymorphism of the LPL gene with the metabolic syndrome and its components in adult population of the Yakut ethnic group. In the studied group, it was not possible to establish a direct connection between the allelic variants, the genotypes of the LPL rs320 gene with the metabolic syndrome and its components. However, it is important to note individuals with the TT genotype had somewhat higher level of triglycerides in the blood. It may be associated with a small sample size. We assume that the T allele is associated with low enzyme activity in this population, and plays a key role in the development of diseases associated with metabolic disorders.

Keywords: obesity, metabolic syndrome, multiple metabolic risk factors, population, genetics, rs320 polymorphism of the LPL gene, dyslipidemia, indigenous population, Yakutia, North.

One of the variants of the LPL gene, which encodes the enzyme lipoprotein lipase, is the replacement of thymine (T) by guanine (G) at position 495 in intron 8. The Hind III (rs320) polymorphism changes the recognition site of the Hind III restriction enzyme and affects the activity of the enzyme. In recent studies, it was shown that the polymorphism rs320 of the LPL gene has a significant effect on the structure of the precursor RNA [9]. The frequency of minor G allele in different world populations varies from 24 to 38%, the highest frequency is observed among the population of Saudi Arabia (37,6%) [3, 5]. The literature presents conflicting data on the role of Hind III (rs320) polymorphism in the development of diseases associated with lipid metabolism disorders. In some studies, the presence of a minor allele was associated with a lower risk of diseases associated with impaired lipid metabolism [4, 10, 12, 16], in other studies the presence of this polymorphism was a risk factor for the development of metabolic disorders and related diseases [7, 13].

In early studies the significant association between LPL rs320 with type 2 diabetes in the Yakut population has shown [1, 2, 3]. However, the mechanism of the influence of polymorphism on the development of metabolic disorders has not been studied enough. It is known that the inhabitants of the North from time immemorial adapted to a diet rich in fats. Currently, there is an intensive increase in the incidence of metabolic disorders in the Yakut population. In this regard, the study of the mechanisms of the influence of the LPL gene on the metabolism of indigenous peoples is a very interesting.

The purpose of this study was to estimate of the allele and genotype frequency of LPL gene rs 320 polymorphism and its association with metabolic parameters and components of the metabolic syndrome in the adult population of Yakut nationality living in Central Yakutia.

Materials and methods: The genotype frequency of the LPL gene rs320 was estimated among the unorganized population of the Central region (Gorny ulus, village Berdigestyakh) of the Sakha Republic (Yakutia). The research project was approved by the local bioethics committee of the Yakut Scientific Center for Complex Medical Problems (Protocol No. 39 dated June 26, 2014). Participation in the study was completely voluntary. Obtained clinically useful information was available to study participants. The initial participant's selection was based on household lists. The study included persons of the Yakut nationality (by self-determination) at the age of 18 and older, regardless of whether they have any somatic disease (n = 363).

Analyze of rs320 polymorphism was performed in 189 representatives (142 women and 47 men aged 18 years and older) who gave voluntary informational consent to conduct genetic studies. The average age was 52.7 (13.7) years. All participants were examined by a single program, including anthropometric examination by the standard method, analysis of body composition for bio-impedance analysis "Tanita" (Japan) SSC 330, twofold blood pressure measurement (BP), fasting venous blood sampling. The content of glucose, total cholesterol (cholesterol), triglycerides, high density lipoproteins (HDL cholesterol) was determined on the express analyzer Cardiochek PA, USA. The concentration of low-density lipoprotein cholesterol (LDL cholesterol)

was calculated using the Friedwald formula with a blood triglyceride level of less than 4.5 mmol/l.

Hypertriglyceridemia was established with triglycerides ≥1.7 mmol/l, hypoalphalesterolemia - at HDL cholesterol concentrations <1.0 mmol/l in men and <1.3 mmol/l in women; elevated blood pressure — with CAD ≥130 mmHg and/or DBP ≥85 mmHg; fasting hyperglycemia - with blood plasma glucose ≥5.6 mmol/l. Persons received specific medical treatment for these conditions were also referred to patients with metabolic disorders. Multiple metabolic disorders were established with 2 or more of the 4 above-mentioned risk factors. The following criteria were used to diagnose obesity: body mass index ≥30 kg/m2; the ratio of waist circumference to height ≥0.5; waist circumference by IDF criteria (IDF1) for European populations (more than 80 cm in women and 94 cm in men); IDF (IDF2) for Asian populations (more than 80 cm in women and 90 cm in men) [13].

LPL rs320 SNP was genotyped by the PCR-RFLP method. Amplification was performed with specially selected primers and ready-made commercial reaction mixtures on the T-100 amplifier (Bio-Rad). Next, the PCR products were subjected to Hind III restriction enzyme (New England Biolabs) according to the manufacturer's protocol. Restriction products were visualized using electrophoresis in a 3% agarose gel on the gel documentation system BDA digital system 20 (Biometra). Each reaction was carried out in triplicate.

The verification of the distribution of genotypes to the equilibrium state of Hardy-Weinberg was carried out using an online calculator at https://wpcalc.com/en/equilibrium-hardy-weinberg / [6]. Statistical data analysis was carried out in the IBM SPSS STATISTICS 22 package. The comparison of groups was performed using Mann-Whitney and Pearson χ2 criteria depending on the type of data. The critical value of the level of statistical significance of differences (p) was 5%.

Results and discussion. The distribution of genotypes, both in general among all examined, and in groups by age and sex, did not correspond to the Hardy-Weinberg equilibrium (Table 1). This is probably due to due to insufficient size of the studied group. However, an attempt to assess the relationship between lipid, anthropometric parameters and LPL rs320 was made as the part of exploratory research.

In the studied group, the T allele frequency was 68%, and the G allele - 32%. The TT genotype (58.7%) was the most common; GG (12%) was a rare genotype. The frequency of the heterozygous variant was 29%. Thus, homozygous genotypes were more common than heterozygous (table 1). These distributions are consistent with data from other European and Asian populations [3]. Table 2 presents the quartile distribution of some biochemical and anthropometric data depending on the genotype and allelic variants of the rs320 polymorphism. The triglycerides level in the blood of individuals with the TT genotype was slightly higher than that of GG homozygotes. The GT genotype was associated with lower diastolic pressure values compared to homozygotes. There were no statistically significant differences in the levels of other indicators.

Metabolic syndrome was observed in 27 studied patients (14.3%). The most common variant of the metabolic syndrome was a combination of central type of obesity, high blood pressure and dyslipidemia. The frequency of the metabolic syndrome and its components did not depend on the genotypes and allelic variants of the studied polymorphism (table 3). This result may be due to the limited number of observations with metabolic syndrome and lipid disorders. To date, the effect of rs320 polymorphism on the enzyme lipoprotein lipase activity and metabolic processes in the human body is not completely clear. Most studies have shown that allele G is associated with a low risk of developing metabolic syndrome, acute cardiovascular conditions (strokes, heart attacks), and a lower risk of developing hypertension [4, 10, 15]. But at the same time, there are works indicating that carriers of the GG genotype have a high risk of diabetic dyslipidemia and type 2 diabetes [11, 13]. There are studies that suggest the association of the genotype and nutrition in the form of greater sensitivity to the diet of carriers of the T allele, compared with carriers of G [7, 8, 15, 17].

Early studies in the Yakut population showed association of T alleles with an increased risk of type 2 diabetes [1, 2, 3]. Our data show that the TT genotype may be associated with low enzyme activity and an increase in triglyceride levels in the blood. Contradictory results of the different authors may be related to the fact that, the functioning of a gene is significantly affected by the lifestyle, physical activity of a person and the type of food, because the gene product associated with energy metabolism [1, 2]. The lower prevalence of diabetes and cardiovascular diseases among the indigenous people of the North in historical past is probably associated with a change in the energy balance of modern man.

Conclusion. In the studied indigenous population of Yakutia, we did not reveal an association of the rs320 polymorphism of the LPL gene and metabolic parameters, which may be due to limitations in the formation of the group. The allele and genotype frequency were close to those described for rs320 in other groups of the world's population. The obtained data and the analysis of literature suggest that the T allele carrier, associated with a low activity of the enzyme that hydrolyzes triglycerides in chylomicrons and LDL, may increase the risk of metabolic disorders under conditions of changes of energy balance.

Considering that this population is evolutionarily adapted to food rich in fats, study of the rate of utilization of dietary fats in individuals with different LPL rs320 genotypes could be of scientific interest.

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Table 1

Frequency distribution of alleles and genotypes of the rs 320 polymorphism of the *LPL* gene among the population

rs 320	n (%)	
Alleles		
G	78 (32)	
T	166 (68)	
Genotypes		
GG	23 (12.2)	χ^2= 12.47 p<0.001
GT	55 (29.1)	
TT	111 (58.7)	

Note: χ2 - Pearson Chi-square test; p - the achieved level of significance when checking compliance with the Hardy-Weinberg equilibrium distribution.

Table 2

Anthropometric and metabolic characteristics of the respondents depending on the allelic variant and the genotypes of the rs 320 polymorphism of the *LPL* gene

Genotypes						Аллель	
TT/GT		GT/GG		TT/GG		G/T	
Me (Q_1;Q_3)	p	Me (Q_1;Q_3)	p	Me (Q_1;Q_3)	p	Me (Q_1;Q_3)	p
Systolic blood pressure, mm Hg							
120 (110;130) 115 (100;129)	0.256	115 (100;129) 120 (107;138)	0.319	120 (110;130) 120 (107;138)	0.653	115 (100;130) 116 (110;130)	0.748
Diastolic blood pressure, mm Hg							
75 (70; 82) 70 (60; 80)	0.047	70 (60; 80) 80 (68; 90)	0.014	75 (70; 82) 80 (68; 90)	0.211	75 (63; 80) 75 (65; 80)	0.776
TC, mmol / l							
5.0 (4.2; 5.6) 4.7 (3.9; 5.7)	0.199	4.7 (3.9; 5.7) 4.9 (4.2; 5.6)	0.669	5.0 (4.2; 5.6) 4.9 (4.2; 5.6)	0.533	4.8 (4.1; 5.6) 4.9 (4.2; 5.7)	0.394
HDL-C, mmol / l							
1.7 (1.4;2.0) 1.8 (1.6;2.1)	0.096	1.8 (1.6; 2.1) 1.7 (1.4; 2.0)	0.308	1.7 (1.4; 2.0) 1.7 (1.4; 2.0)	0.959	1.8 (1.5; 2.0) 1.7 (1.5; 2.0)	0.439
TG, mmol / l							
0.9 (0.8; 1.2) 0.9 (0.6; 1.1)	0.265	0.9 (0.6; 1.1) 0.8(0.6; 1.0)	0.215	0.9 (0.8; 1.2) 0.8 (0.6; 1.0)	0.046	0.8 (0.6; 1.0) 0.8 (0.6; 1.2)	0.133
LDL-C, mmol / l							
2.8 (2.1; 3.4) 2.0 (2.5; 3.2)	0.112	2.0 (2.5; 3.2) 2.6 (2.2; 3.5)	0.338	2.8 (2.1; 3.4) 2.6 (2.2; 3.5)	0.924	2.5 (2.1; 3.2) 2.7 (2.1; 3.4)	0.450
Glucose, mmol / l							
4,7 (4,4; 5,1) 4,7 (4,4; 5,1)	0.853	4.7 (4.4; 5.1) 4.7 (4.2; 5.0)	0.541	4.7 (4.4; 5.1) 4.7 (4.2; 5.0)	0.368	4.7 (4.3; 5.1) 4.7 (4.4; 5.1)	0.260
Fat %							
18.4 (13.9; 26.5) 19.1 (12.8; 24.3)	0.903	19.1 (12.8; 24.3) 18.5 (14.5; 26)	0.938	18.4 (13.9; 26.5) 18.5 (14.5; 26)	0.946	19 (14.3;24.7)/19 (13.9;25.3)	0.973
BMI, kg / m2							
25.3 (22.7; 29.2) 24.7 (22.1; 27.5)	0.291	24.7 (22.1; 27.5) 25.1 (22.1; 28.5)	0.591	25.3 (22.7; 29.2) 25.1 (22.1; 28.5)	0.860	25.1 (22.1; 28.1) 25.1 (22.3; 28.4)	0.567
waist, sm							
91.9 (85.7; 101.8) 94.3 (83.2; 98.7)	0.802	94.3 (83.2; 98.7) 94.8 (83.8; 100.0)	0.967	91.9 (85.7; 101.8) 94.8 (83.8; 100.0)	0.791	93.3 (83.5; 99.3) 92.7 (85.4; 99.6)	0.824
Waist /growth							
0.58 (0.53; 0.65) 0.59 (0.54; 0.64)	0.99	0.59 (0.54; 0.64) 0.58 (0.53; 0.65)	0.697	0.58 (0.53; 0,65) 0.58 (0.53; 0.65)	0.755	0.8 (0.53; 0.64) 0.59 (0.53; 0.64)	0.862

Note: p - the achieved level of statistical significance of differences when comparing groups using the Mann-Whitney test; Me (Q1; Q3) - median (25-75%); BMI - body mass index, OT-waist circumference;

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Table 3

The frequency of the metabolic syndrome and its components depending on the allelic variant and the genotypes of the rs 320 polymorphism of the *LPL* gene

Factor	Genotypes n (%)			χ^2, p	Alleles n (%)		χ^2, p
	GG n=23	GT n=55	TT n=111		G n=78	T n=166	
Raised blood pressure							
Yes	13 (10.9)	36 (30.3)	70 (58.8)	χ^2=0.776 p=0.67	49 (31.6)	106 (68.4)	χ^2=0.003 p=0.955
No	9 (14.1)	16 (25)	39 (60.9)		25 (31.3)	55 (68.8)	
Reduced HDL cholesterol							
Yes	4 (28.6)	3 (21.4)	7 (50)	χ^2=3.845 p=0.146	7 (41.2)	10 (58.8)	χ^2=0.713 p=0.425
No	19 (10.9)	52 (29.7)	104 (59.4)		71 (31.3)	156 (68.7)	
Raised triglycerides							
Yes	4 (16)	4 (16)	17 (68)	χ^2=2.468 p=0.291	8 (27.6)	21 (72.4)	χ^2=0.290 p=0.590
No	19 (11.6)	51 (31.1)	94 (57.3)		70 (32.6)	145 (72.4)	
Raised fasting plasma glucose							
Yes	4 (16)	4 (16)	17 (68)	χ^2=2.315 p=0.314	8 (27.6)	21 (72.4)	χ^2=0.287 p=0.675
No	19 (11.9)	49 (30.6)	92 (57.5)		68 (32.5)	141 (67.5)	
Obesity							
Yes	11 (12.4)	25 (28.1)	53 (59.6)	χ^2=0.087 p=0.957	36 (31.6)	78 (68.4)	χ^2=0.002 p=1.0
No	6 (11.3)	16 (30.2)	31 (58. 6)		22 (31.9)	47 (68.1)	
Abdominal obesity IDF_1							
Yes	14 (10.9)	37 (28.7)	78 (60.5)	χ^2=0.23 p=0.891	51 (30.7)	115 (69.3)	χ^2=0.124 p=0.732
No	5 (12.8)	12 (30.8)	22 (56.4)		17 (33.3)	34 (66.6)	
Abdominal obesity IDF_2							
Yes	14 (11.6)	36 (29.8)	71 (58.7)	χ^2=0.129 0.938	50 (31.8)	107 (68.2)	χ^2=0.069 p=0.871
No	5 (10.6 %)	13 (27.7)	29 (61.7)		18 (30)	42 (70)	
Multiple metabolic risk factors							
Yes	7 (18.4)	9 (23.7)	89 (58.9)	χ^2=2.013 p=0.366	16 (34)	31 (66)	χ^2=0.45 p=0.734
No	16 (10.6)	46 (30.5)	89 (58.9)		62 (31.5)	135 (68.5)	
Metabolic syndrome							
Yes	4 (14.8)	6 (22.2)	17 (63)	χ^2=0.945 p=0.623	10 (30.3)	23 (69.7 %)	χ^2=0.019 p=1.0
No	15 (10.6)	43 (31.5)	83 (58.9)		58 (31.5)	126 (68.5)	

Note: $\chi 2$ * - Pearson Chi-square test, p – significance level

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DETERMINATION OF HLA ALLELES USING SINGLE NUCLEOTIDE POLYMORPHISM OF RS3104413 HLA-DQA1 GENE AMONG PATIENTS WITH TYPE 1 DIABETES OF THE REPUBLIC SAKHA (YAKUTIA)

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In this paper, we analyzed the polymorphism rs3104413 of the *HLA-DQA1* gene among patients with type 1 diabetes and a control sample of the population of the Republic of Sakha (Yakutia). Type 1 diabetes (diabetes mellitus type 1) among all forms of diabetes is no more than 10-15%, and type 1 diabetes is related to the most important medical and social problems associated with the often occurring childhood and adolescence, severe course, early disability and mortality. In the study of rs3104413 polymorphism, a significantly lower frequency of the C allele (47.1) was observed in the group of healthy individuals compared with the group of people with type 1 diabetes (78.3%). The calculation of the odds ratio showed that the frequency of the C allele in the group of people with type 1 diabetes was significantly higher (OR - 4.036; 95% CI: 2.71-6.02; p <0.001). The study revealed 6 haplotypes and genes. The haplotype DRB1 * 03: 01-DQA1 * 05: 01-DQB1 * 02: 01, DR3 / X, DRX / X was associated with the allele C of the rs3104413 polymorphism. The allele G of rs3104413 polymorphism was associated with the haplotype carrier DRB1 * 04: 01 – DQA1 * 03: 01-DQB1 * 03: 02 (DR4-DQ8) and DRB1 * 04: 01-DQA1 * 03: 01-DQB1 * 03: 01 (DR4-DQ7). Thus, the data obtained can be used as biological predictors of the development of type 1 diabetes in order to carry out timely personalized preventive measures.

Keywords: type 1 diabetes mellitus, HLA typing, *HLA-DQA1* gene, polymorphism.

Type 1 diabetes is a disease in which the body is not able to properly metabolize carbohydrates and to a lesser extent other components of food. This disease is caused by a lack of insulin, a hormone that is produced by the pancreas and that is required by the body to convert glucose from other food components into energy. The most severe form of diabetes is type 1 diabetes (type 1 diabetes mellitus). Despite the fact that its share among all forms of diabetes is no more than 10-15%, it is type 1 diabetes that is considered to be the most important medico-social problem of health care, since this disease often occurs in childhood and adolescence, characterized by severity, early disability and mortality [3].

According to modern data, a large number of genes are involved in the development of type 1 diabetes [3], more than half of the genetic risks are due to the participation of polymorphic variants of HLA genes located on the short arm of chromosome 6 (6p21). The main genetic contribution to the susceptibility to type 1 diabetes is made by genes of the HLA system encoding class II molecules of the main human histocompatibility complex, especially the DR and DQ genes of the HLA class, whose association with the development of type 1 diabetes has been shown in numerous publications for various population groups [1, 4].

In Russia, studies on the definition of HLA alleles using single nucleotide polymorphisms are not carried out. In this regard, today there is a need for research aimed at developing a regionally-adapted method for the HLA-typing of type 1 diabetes using single nucleotide polymorphisms (SNP).

Objective: to determine HLA alleles using single nucleotide polymorphism of rs3104413 *HLA-DQA1* gene and its association with type 1 diabetes.

Material and research methods: An experimental part of the work on the genotyping of the rs3104413 polymorphism, the *HLA-DQA1* gene, was carried out in the laboratory of hereditary pathology of the Department of Molecular Genetics of the Yakutsk Scientific Center for Complex Medical Problems (YSC CMP). DNA samples from the collection of the YSC CMP biomaterial are used for the study - a unique scientific installation "The Genome of Yakutia" (reg. No. US_507512). The sample of patients consisted of 92 patients of the Yakut Scientific Center for Complex Medical Problems, state autonomous institution of the Republic Sakha (Yakutia) "Republic Hospital №1 National Center of Medicine » and Endocrinology Department of Yakutsk Clinical Hospital, Yakutsk. The sample of patients included 92 patients with a diagnosis of type 1 diabetes, aged 4 to 56 years, living in the RS (Ya), Yakuts by ethnicity. By gender there were 44 (47.8%) male and 48 (52.2%) female. The average age of patients was 23.04 ± 0.27 years (from 4 to 56 years), the average age of male patients was 20.5 ± 2.3 years (from 5 to 40 years), and female - 25.11 ± 2 , 59 years old (from 4 to 56 years old). The control sample consisted of 210 Yakuts who did not suffer from type 1 diabetes. Ethnicity counted to the third generation. Ethnicity counted to third generation.

Amplification of the *HLA-DQA1* gene region containing the single nucleotide polymorphism rs3104413 was performed during real-time PCR using primer pairs and allele-specific probes for DNA amplification described in Serr I. et al. [6] Primers and probes were synthesized by the company Biotech-Industry (Lumiprobe) LLC (Moscow, Russia). The sequence of primers: Forward primer 5'-CAGCTGAGCACTGAGTAG-3 ', reverse primer 5'-GCAGTTGAGAAGTGAGAG-3'. Probes structure: FAM - Probe rs3104413 LPC [6FAM] CAGCCT [+ G] CT [+ C] TC [+ C] TA [+ T] TGG [BHQ1], HEX - Probe rs3104413 LPG [HEX] CAGCCT [+ G] CT

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Table 1

Temperature polymorphism amplification program rs3104413

Stages	Temperature, °C	Time	Cycles
First denaturation	95	10 s	1
Denaturation	95	30 s	50
Annealing	55	1 min	

[+ G] TC [+ C] TA [+ T] TGG [BHQ1].

Amplification was carried out according to the temperature program below (Table 1):

The fluorescence signal was measured at the second stage of the reaction (55 ° C - 1 min). The detection of fluorescence was carried out "at the end point" according to the protocol of the device "Real-time CFX 96 Touch" ("Biorad", USA). An example of the distribution of clouds of genotypes of PCR and detection of fluorescence "at the end point" is presented in Figure 1.

Statistical analysis of the results of the medical genetic study was conducted using the program: "Office Microsoft Excel 2010", "Statistics 8.0". The frequencies of alleles and rs3104413 genotypes were determined by direct counting. Results were considered significant when the “p” value was less than 0.05 (p <0.05).

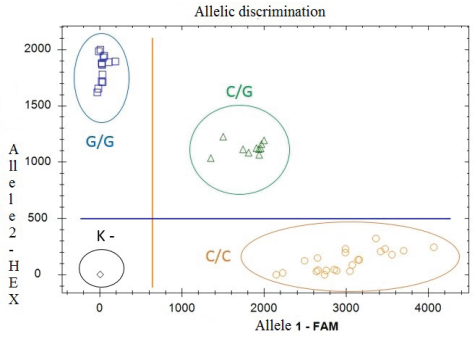

Figure 1. Distribution of genotype clouds of rs3104413 polymorphism of the *HLA-DQA1* gene. Note: “K–” - negative control, C / C - homozygous for ancestral allele C. C / G - heterozygote, G / G - homozygote for mutant allele G. Compliance with fluorescent dyes: allele C - FAM channel, allele G - channel HEX.

Genotyping of *HLA DRB1* and *DQB1* alleles was carried out with the commercial HISTOTYPE kits, the HLA alleles of *DRB1 * 03: 01 (DR3), DRB1 * 04: 01 (DR4), DQB1 * 02: 01 (DQ2), DQA1 * 05: 01* were progenotyped.

The amplification parameters were optimized for a total reaction volume of 10 μl. PCR was performed according to the manufacturer’s instructions in an MJ Mini Gradient Thermal Cycler (BioRad) thermal cycler (Table 2).

The results of the amplification were fractionated in 2% agarose gel, with ethidium bromide, at a voltage of 120-300 V, for 45-120 minutes. Documentation and visualization of PCR amplification was performed by photographing in UV light using a Vil-ber Lourmat gel-documenting instrument (Fig. 2).

The interpretation of the results of genotyping according to the HISTOTYPE kits (updated 01 / 2015_3.19.0 (6.2)) was carried out on the basis of the assessment chart: for HISTOTYPE, specific bands have sizes of 220, 200, 800, 150 and 235 bp. In all lanes without an allele-specific amplification, an internal control of 429 or 1070 bp should be clearly visible. Evaluation of the bands was carried out using a DNA marker “Step 100”

Table 2

Temperature polymorphism amplification program HISTOTYPE

Steps	Temperature, °C	Time	Кол-во циклов
First denaturation	96	5 min	1
Denaturation	96	20 s	5
Annealing and Elongation	68	1 min	
Denaturation	96	20 s	10
Annealing	64	50 s	
Elongation	72	45 s	
Denaturation	96	20 s	15
Annealing	61	50 s	
Elongation	72	45 s	
Final elongation	72	5 min	1

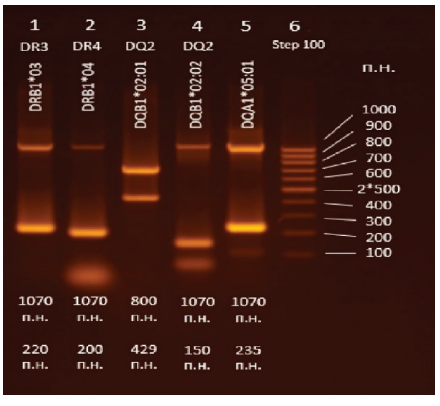

Figure 2. Electrophoregram of the *HLA DRB1* and *DQB1* amplification product on 2% agarose gel (*HLA DRB1* and *DQB1* genotyping using commercial HISTOTYPE kits). Note: b.p.. - base pair. 1 - *DRB1 * 03* (220 bp); 2, - *DRB1 * 04* (200 bp); 3 - *DQB1 * 02: 01* (800 bp); 4 - *DQB1 * 02: 02* (150 bp); 5 - *DQA1 * 05: 01* (235 bp). Internal control: 1070 b.p. (1, 2, 4, 5) and 429 bp (3). 6 - DNA marker "Step100".

(Biolabmix LLC, Novosibirsk, Russia).

Results and discussion. The results of the analysis of the frequency distribution of alleles and genotypes of the rs3104413 polymorphism among patients with type 1 diabetes and control sample are presented in table 3.

In the study of rs3104413 polymorphism, a significantly lower frequency of the C allele (47.1) was observed in the group of healthy individuals compared with the group of people with type 1 diabetes (78.3%). The calculation of the odds ratio showed that the frequency of the C allele in the group of people with type 1 diabetes was significantly higher (OR - 4.036; 95% CI: 2.71-6.02; p <0.001).

Analysis of the distribution of genotypes showed that the most common genotype of the studied polymorphism in the group of people with type 1 diabetes is C / C (69.6%), and in the group of people not suffering from type 1 diabetes is the homozygous genotype G / G (41.9%).

The calculated conjugacy coefficient of Pearson (C) allele C (0.278) shows the average strength of the connection between the carriage of the allele C and type 1 diabetes. The normalized value of the Pearson coefficient (C ') indicates the average relationship between the carriage of the allele C (0.393) and type 1 diabetes.

The analysis revealed 6 haplotypes and genes. The haplotype *DRB1 * 03: 01-DQA1 * 05: 01-DQB1 * 02: 01, DR3 / X, DRX / X* was associated with the allele C of the rs3104413 polymorphism. The allele G of rs3104413 polymorphism was associated with the haplotype carrier

Table 3

The frequency of occurrence of genotypes and alleles of the rs3104413 polymorphism in the group of patients with type 1 diabetes and control sample

Haplotypes, alleles	Patient with T1D (n = 92),abs. (%)	control sample (n = 210), abs.(%)	X^2	OR (95% CI) For alleles	Significance, p
C/C	64 (69.6)	76 (36.2)	32.099	4.036 (2.708-6.017)	<0.001*
C/G	16 (17.4)	46 (21.9)			
G/G	12 (13.0)	88 (41.9)			
C	144 (0.783)	198 (0.471)	49.184		<0.001**
G	40 (0.217)	222 (0.529)			

Note. The achieved level of significance when comparing the distribution of genotypes (*) and allele frequencies (**) in comparison groups 1 and 2 is the number of samples, X^2 with the Yeats amendment.

Table 4

Identification of HLA haplotypes and genotypes using single nucleotide polymorphism rs3104413

Haplotype by genes HLA	The number of people with this haplotype	Genotype, %			Allele *C*	Allele *G*
		C/C	*C/G*	*G/G*		
*DRB1*03:01-DQA1*05:01-DQB1*02:01*	16	87.5	12.5	0	0.938	0.063
*DRB1*04:01–DQA1*03:01-DQB1*03:02 (DR4-DQ8)*	20	0	40	60	0.200	0.800
DR3/4-DQ8	8	0	100	0	0.500	0.500
DR3/X	50	100	0	0	1.000	0.000
*DRB1*04:01-DQA1*03:01-DQB1*03:01 (DR4-DQ7)*	132	0	33.3	66.7	0.167	0.833
DRX/X	76	100	0	0	1.000	0.000

Note: DRX / X - the absence of both DR3 and DR4; DR3 / X - carrier variant 1 of type DR3 and type DR3, not related to DR4

*DRB1 * 04: 01 – DQA1 * 03: 01-DQB1 * 03: 02 (DR4-DQ8) and DRB1 * 04: 01-DQA1 * 03: 01-DQB1 * 03: 01 (DR4-DQ7)*. Table 4.

According to the literature, more than 90 percent of patients with type 1 diabetes are carriers of either *HLA-DR3, DQB1 * 0201 (DR3-DQ2), or DR4, DQB1 * 0302 (DR4-DQ8)*. About 30% of patients have the combined genotype DR3 / 4, which is associated with the greatest susceptibility to the disease [2]. Associated previously with a low risk of developing the disease is the haplotype *DRB1 * 04: 01-DQA1 * 03: 01-DQB1 * 03: 01 (DR4-DQ7*) [5].

Thus, the study of this rs3104413 polymorphism in determining the haplotype is insufficient and requires further research in combination with other SNPs.

Conclusion

The study revealed 6 haplotypes and genes. The haplotype *DRB1 * 03: 01-DQA1 * 05: 01-DQB1 * 02: 01, DR3 / X, DRX / X* was associated with the allele C of the rs3104413 polymorphism. The allele G of rs3104413 polymorphism was associated with the haplotype carrier *DRB1 * 04: 01 – DQA1 * 03: 01-DQB1 * 03: 02 (DR4-DQ8) and DRB1 * 04: 01-DQA1 * 03: 01-DQB1 * 03: 01 (DR4-DQ7)*.

There is a significantly low frequency of allele C (47.1) in the control sample compared with patients with type 1 diabetes (78.3%) in the rs3104413 polymorphism. The calculation of the odds ratio showed that the frequency of the C allele in the group of people with type 1 diabetes was significantly higher (OR - 4.036; 95% CI: 2.71-6.02; p <0.001).

Thus, the data obtained can be used as biological predictors of the development of type 1 diabetes in order to carry out timely personalized preventive measures.

The study was conducted in the framework of research on the study of the genetic structure and burden of hereditary pathology of populations of the Republic of Sakha (Yakutia).

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CORRELATION OF THE M235T POLYMORPHISM OF THE AGT GENE WITH ARTERIAL HYPERTENSION AND ITS RISK FACTORS IN THE INDIGENOUS PEOPLE OF THE ARCTIC TERRITORY OF YAKUTIA

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A case-control study was conducted for the indigenous population living in the Arctic territory of Yakutia to determine the association of the M235T polymorphism of the *AGT* gene with hypertension and its risk factors. A higher average blood pressure, elevated cholesterol and its fractions, a higher incidence of abdominal obesity in carriers of the mutant GG genotype were found both in the general population and separately for people with hypertension. The study shows the contribution of the G allele of the *AGT* gene to the development of hypertension, lipid disorders and abdominal obesity.

Keywords: *AGT* gene, polymorphism, arterial hypertension, risk factors, indigenous people, Yakutia.

Arterial hypertension is the leading risk factor for disability and premature mortality in the global population. As of 2010, 31.1% of the adult population of the world (1.39 billion people) was suffering from hypertension (30.7% of men and 28.8% of women) [10]. In Russia, according to an ESSE-RF epidemiological study, which was conducted in 12 regions, the prevalence of AH was 50.2% (51.1% in men, 49.7% in women) [2]. It is recognized that hypertension is a polygenic multifactorial disease, the genetic role of which has already been proven. Currently, more than 1.500 genetic polymorphisms associated with blood pressure have been identified, which contribute through various pathogenetic mechanisms [7]. A particularly important role belongs to the genes of the renin-angiotensin system (RAS) responsible for vascular tone. The most relevant polymorphisms of the RAS genes for hypertension are angiotensinogen gene polymorphisms (*AGT*). The results of various researches are ambiguous. Despite numerous studies, the degree and reliability of associations vary, for some loci the data are contradictory.

The **aim** of the study was to research the relationship of angiotensinogen (*AGT*) gene polymorphism with arterial hypertension and its risk factors in the indigenous people of the Arctic territory of Yakutia.

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Materials and research methods. The collection of material for the study was carried out in expeditionary conditions in the Arctic territory of Yakutia, including the places of compact residence of the indigenous peoples (Nizhnekolymsky, Verkhnekolymsky and Tomponsky districts). 348 people of the indigenous nationality were surveyed with the continuous method. The sample consisted of an adult population aged 20 to 70 years (225 women and 123 men). The response was 75%. The average age of respondents was 48.16 ± 0.52 years, 49.71 ± 0.63 in women and 44.98 ± 0.91 in men.

Inclusion criteria: representatives of indigenous people (Evens, Chukchi, Yukaghirs, Yakuts).

Exclusion criteria: representatives of non-indigenous nationalities.

The research program included the following sections: a survey on the questionnaire to assess the objective state; informed consent of the respondent to conduct research; anthropometric examination with hip and waist measurement; blood sampling for biochemical studies from the cubital vein in the morning on an empty stomach with a 12-hour abstinence from food. Blood sampling from the cubital vein for molecular genetic studies was carried out in a tube with EDTA. Genomic DNA was isolated from peripheral blood leukocytes by the method of phenol-chloroform extraction. Allelic variants of the *AGT* gene were tested using a polymerase chain reaction with real-time results (real-time PCR). Genotyping of the polymorphic *AGT* gene was performed with the usage of kits (Lytech R&D LLC, Moscow) on the «Real-time CFX96» amplifier (BioRad, USA) in accordance with the manufacturer's instructions. For quality control, 10% of randomly selected samples were subjected to repeated genotyping.

Biochemical methods of the research included blood lipid profile: total cholesterol (TC), LDL Cholesterol, HDL Cholesterol, TG, glucose test.

When judging the incidence of disorders of the blood lipid profile in a population, we used the Russian recommendations of the V revision of Society of cardiology of Russian Federation (VNOK), 2012, into account the European recommendations, 2011. Hypercholesterolemia (HCE) is the level of total cholesterol (TC) ≥ 5.0 mmol/l, the high LDL Cholesterol level≥3.0 mmol/l, the low HDL Cholesterol level ≤1.0 mmol/l in men; 1.2 mmol/l in women. Hypertriglyceridemia (HTG) is the TG level ≥1.7 mmol/l; a hyperglycemia on an empty stomach (a glucose in a blood plasma on an empty stomach ≥ 6.1 mmol/l) or glucose intolerance (a glucose in a blood plasma in 2 hours after glucose loading within ≥7.8 and ≤11.1 mmol/l).

Blood pressure (BP) was measured twice with an OMRON automatic tonometer (Japan) on the right hand in a sitting position with the calculation of the average BP. Hypertension is present at the 140/90 mmHg (2017 ACC/AHA Guideline).

The abdominal obesity (AO) is exposed to the value of the waist measurement (WM) ≥ 80 cm on women, ≥94 cm on men.

The study was conducted according to the Local Ethics Committee protocol YSC CMP on the respondent's informed consent to the processing of personal data and the study.

Statistical data processing was performed using standard methods of mathematical statistics using the SPSS software package (version 19.0). To define the characteristics, the arithmetic mean

(M) and the characteristic's standard error of the mean (m) were calculated. Intergroup differences were evaluated using analysis of variance or non-parametric criteria. When comparing the frequencies of genotypes, the standard χ2 criterion with the Yates correction was used. The relative risk (OR – odds ratio) of disease development at a certain genotype was calculated using the standard formula OR=a/b x d/c, where a and b is the number of patients with and without the mutant genotype, respectively, and d, c is the number of people in the control group with and without the mutant genotype. OR is indicated with a 95% confidence interval. Differences were considered statistically significant at p <0.05.

Results and discussion. In the total population of the indigenous people of the Arctic territory of Yakutia, the frequency distribution of the AA, AG and GG M235T genotypes of the *AGT* gene was 15.5% (n = 54), 45.1% (n = 157), 39.4% (n = 137), respectively, which corresponds to the Hardy-Weinberg equilibrium (χ2 = 0.18, p = 0.66), A alleles - 38.1% (n = 265), G - 61.9% (n = 431).

When comparing the mean values of lipids and glucose depending on a particular AGT gene genotype, we obtained statistically significant differences in all indicators in carriers of heterozygous AG and mutant homozygous GG genotypes. In GG carriers all values were higher: total cholesterol AG 4.93 ± 0. 06 and GG 5.12 ± 0.06, respectively, p = 0.037; HDL 1.32 ± 0.02 and 1.22 ± 0.02 (p = 0.003); LDL 3.12 ± 0.05 and 3.33 ± 0.05, (p = 0.005); TG 1.06 ± 0.02 and 1.21 ± 0.04 (p = 0.005). Our study confirms the contribution of the G allele to impaired lipid metabolism. On the contrary, their average glucose values are significantly lower compared with AG genotype carriers (4.83 ± 0.11 and 4.35 ± 0.08, respectively, p = 0.001). Significant differences were also obtained when comparing the mean values in individuals with homozygous AA and GG genotypes, namely, in TG values (1.03 ± 0.05 and 1.21 ± 0.04, p = 0.029), glucose (4.88 ± 0.14 and 4.35 ± 0.08, p = 0.001).

At analyzing the frequencies of lipid and carbohydrate disorders in respondents, it was found that all carriers of genotypes showed high numbers of hypercholesterolemia (HCE), especially atherogenic HCE, and GG genotype carriers showed the highest frequency of hypo-alpha-cholesterolemia (Hypo-α-CE). The frequencies of HCE, LDL HCE, Hypo-α-CE in the general population did not have significant differences between genotypes. Thus, in individuals with the AA genotype, the frequency of HCE was 46.3%, AG - 41.4%, GG - 49.6%. More than half of the respondents had the highest frequency of LDL HCE in individuals with AA genotype, 64.8% and GG genotype - 59.8%. The frequency of Hypo-α-CE was 33.3% in the AA genotype individuals, AG - 29.9%, GG - 43.1%. The frequency of HTG in the carriers of homozygous AA and GG genotypes significantly differed (5.5% and 17.5%, respectively, p = 0.033). Also significantly higher was the frequency of HG in heterozygous AG carriers compared with individuals with the mutant GG genotype (8.3% and 2.9%, respectively, p = 0.048).

We also conducted a study of the conjugation of AGT polymorphism with the presence of abdominal obesity. Carriers of the AG and GG genotypes (59.2% and 60.6%) had the largest statistically insignificant frequency of AO versus 46.3% of individuals with the AA genotype, thereby indicating a certain conjugacy of the G allele with the presence of AO.

Considering the high frequency of occurrence of AH in the population (53.3%), for further study, the general population of the indigenous people of the Arctic territory of Yakutia was divided into 2 groups. For the study, 2 groups were formed - "case" and "control": "case" - persons suffering from hypertension (175 people), "control" - people without hypertension (173 people). The average age of hypertensive patients was 53.07 ± 0.49 years, those without AH - 38.88 ± 0.60 years.

This case-control study was included to determine the association of *AGT* gene variants with AH and its risk factors.

The frequency of occurrence of M235T genotypes of the *AGT* gene among groups was compared. None of the data sets (Table 1) showed significant deviation from Hardy-Weinberg equilibrium (χ2 = 0.32, p = 0.24 for "case" and χ2 = 4.84, p = 0.02 for "control") and there was no significant difference in the frequencies of genotypes or alleles between hypertensive and normotonic patients, with the exception of the homozygous AA genotype (χ2 = 5.21, p = 0.001, OR = 0.39, 95% CI = 0.27-0.89) (Table 2).

We used 2 types of genetic models in order to verify the connection of the M235T polymorphism of the *AGT* gene with AH (Table 3). Analyzing the models, we found a link between AH and the mutant homozygous genotype GG and G allele in the recessive model. What is also confirmed by a number of foreign studies, in particular, the effect of the G allele and the GG genotype on the risk of developing essential hypertension [4,6,8,9,15,16]. In the Russian study, which included 514 patients, the association of the G allele with the risk of developing hypertension in men with an odds ratio of 1.95 (p = 0.003) was shown [1]. In contrast, in Colombia, Mongolia, the Caucasus, Lebanon, and India, no reliable association of AG and GG genotypes with AH was found [3,5,11,14,18]. It was assumed that the population is heterogeneous in these countries, polymorphism is associated with differences in populations.

Depending on the genotype, we analyzed the average level of systolic blood pressure (SBP) in hypertensive patients. In individuals with arterial hypertension, the average level of SBP in carriers of AA, AG and GG genotypes was 173.53 ± 3.62, 161.72 ± 1.40 and 159.72 ± 1.92 mmHg, respectively, there were significant differences in individuals with the AA genotype compared with others (p = 0.001). We did not detect any special differences in the mean values of SBP in normotonics.

Comparison of mean concentrations of blood lipids and glucose in individuals with and without hypertension was carried out, depending on whether the *AGT* gene is a member of a particular M235T

Table 1

Frequencies of genotypes and alleles of the M235T polymorphism of the *AGT* gene and correspondence to Hardy-Weinberg equilibrium (HWE)

Genotype	Case	HWE	χ^2	p	Control	HWE	χ2	p	Allele	Frequencies of alleles	
										Case	Control
AA	0.097	0.12	0.32	0.24	0.214	0.17	4.84	0.02	A	0.347	0.416
AC	0.497	0.45			0.405	0.49			C	0.653	0.584
CC	0.406	0.43			0.381	0.34					

Table 2

Frequency distribution of M235T genotypes of the AGT gene among persons with and without AH

Genotype	Frequencies of genotypes		χ2	p	OR	95%CI
	Case	Control				
AA	0.097	0.214	5.21	0.001	0.39	0.27-0.89
AG	0.497	0.405	1.71	нд	1.45	0.83-2.54
GG	0.406	0.381	0.13	нд	1.11	0.63-1.96

genotype (Table 4). For all respondents in the "case" values of lipid metabolism, except for HDL cholesterol, and glucose were higher compared to "control". Significant differences were found in the average concentrations of TG in all representatives, total cholesterol in the homozygous carriers of AA and GG genotypes, LDL cholesterol in carriers of the mutant GG genotype, glucose in individuals with the AA and AG genotype. The average concentrations of total cholesterol, atherogenic cholesterol and TG in hypertensive patients were higher with the GG genotype.

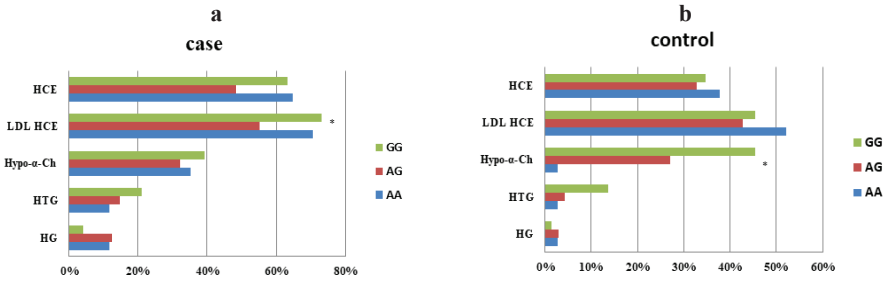
We determined the frequency of lipid and carbohydrate disorders for persons with and without AH, depending on genotype carriership (Fig. 1). In hypertensive patients, all values exceeded those of normotonics. When comparing certain types of lipid disorders and carbohydrate metabolism with respect to one or another genotype, individuals in the "case" and "control" identified significant differences in the frequency of LDL HCE in hypertensive patients of heterozygous and mutant homozygous genotypes, thereby proving the contribution of the G allele in the development of atherogenesis. In normotonics, significant differences were noted in the frequency of Hypo-α-cholesterol, where the highest frequency was observed in GG carriers. In many studies examining the association of the M235T *AGT* gene polymorphism with lipid disorders, no significant reliable links have been identified. Only a few studies confirm the fact that the G allele has a significant effect on increasing the concentration of total cholesterol and atherogenic cholesterol [12].

The study of conjugation of AGT polymorphism in the case and control with the presence of abdominal obesity revealed the highest incidence of AO in individuals with AH - carriers of AG and GG genotypes from 76.1% to 83.9%. In the control, the frequency of AO varied from 28.6% in carriers of the heterozygous genotype to 43.9% in homozygous GG carriers. Both in the group with AH and in the "control", the highest frequency of AO is associated with the G allele, thereby proving its contribution to the development of the metabolic syndrome. This was also confirmed by a number of foreign studies [13, 17].

Table 3

Frequency distribution of genotypes M235T of AGT gene among persons with and without AH according to the dominant and recessive model

Genotype	Frequencies of genotypes		χ2	p	OR	95%CI
	Case	Control				
AA+ AG	0.581	0.618	0.28	0.51	0.86	0.56-1.31
GG	0.418	0.382				
AA	0.095	0.214	9.58	0.001	0.39	0.21-0.72
AG+ GG	0.905	0.786				



1a. The frequency of disorders of lipid and carbohydrate metabolism in individuals with hypertension, depending on the genotypes M235T AGT, 1b. The frequency of disorders of lipid and carbohydrate metabolism in individuals without hypertension, depending on the genotypes M235T AGT. Note: *- p<0,05

Conclusion. Based on our findings, there is, indeed, a single genetic component in the implementation of hypertension and its risk factors for development, such as lipid disorders and abdominal obesity. Proof of this are higher average blood pressure, elevated cholesterol and its fractions, a higher incidence of abdominal obesity in carriers of the mutant GG genotype both in the general population of the indigenous people of the Arctic territory of Yakutia, and separately for people with arterial hypertension. Thus, the genetic mechanisms of hypertension in the group of patients with arterial hypertension are realized through the G allele, which programs obesity, increased pressure, and lipid metabolism disorders.

The research was conducted within research projects of YSC CMP "A contribution of a metabolic syndrome to development of atherosclerosis of coronary arteries in residents of Yakutia", R&D "De-

Table 4

Mean levels of lipid spectrum and blood glucose in hypertensive patients and those without hypertension depending on the M235T genotypes of the *AGT* gene (M±m)

Blood parameters	AA genotype			AG genotype			GG genotype		
	case	p	control	case	p	control	case	p	control
TC	5.16±0.11	<0.05	4.74±0.16	4.98±0.08	>0.05	4.78±0.10	5.29±0.07	<0.01	4.74±0.09
LDL	3.30±0.08	>0.05	3.06±0.12	3.17±0.06	>0.05	2.98±0.08	3.47±0.06	<0.01	3.04±0.08
HDL	1.32±0.06	>0.05	1.26±0.05	1.29±0.02	<0.05	1.40±0.04	1.22±0.02	>0.05	1.23±0.03
TG	1.17±0.08	<0.02	0.90±0.06	1.14±0.03	<0.01	0.87±0.04	1.29±0.05	<0.05	1.05±0.06
glucose	5.37±0.24	<0.01	4.43±0.14	5.10±0.15	<0.01	4.15±0.10	4.40±0.10	>0.05	4.24±0.10

velopment of new technologies of treatment and risk prediction of hypertension and insult in the Republic of Sakha (Yakutia)" (Government contract No. 1133).

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EXPRESSION OF SOME MOLECULAR AND BIOLOGICAL MARKERS IN DIFFERENT PERIODS OF PROGRESSION AFTER RADICAL SURGICAL TREATMENT OF ESOPHAGEAL CANCER

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30 patients with stage II and III of squamous cell carcinoma of the esophagus after surgical treatment were analyzed retrospectively. Prognostic significance of the expression of immunohistochemical markers p53, bcl-2, ki-67 and E-cadherin and tumor proliferative activity were studied. A significant decrease in the frequency of tumors expressing p53, as well as an increase in the number of tumors expressing bcl-2, was detected in the group of patients with an increase in the event-free period for up to 365-540 days. The mean numbers of bcl-2 positive cells in groups with progression from 181 to 364 days and from 365 to 540 days were 2.3 and 2.8 times higher than in patients with progression in 180 days and earlier. The ki-67 index in the latter was significantly higher than in groups with progression within 181-364 and 365-540 days.

An increased proliferative activity was registered only in patients with progression in 180 days and earlier. The E-cadherin expression in the group with progression in 365-540 days was significantly higher than in patients with progression in < 180 and 181-364 days.

Keywords: esophageal cancer, immunohistochemical markers, proliferative activity, p53, bcl-2, ki-67, E-cadherin, progression.

Esophageal cancer is one of the most aggressive malignant diseases of the gastrointestinal tract significantly affecting the quality of life of the patient with high rates of poor outcome [3, 10]. Tumors of epithelial origin, mainly squamous cell carcinoma and adenocarcinoma, are the most common. According to the International Agency for Research on Cancer (IARC), EC incidence and mortality in 2008 were 49.2 and 34.3, respectively, per 100 000 per year [12].

High expression of p53 mutant protein is known to predict poor survival in cancer of the stomach, lung, and other cancers [4]. However, the predictor role of p53 for EC remains a debatable [14]. In 2015, British journal of cancer published a meta-analysis review of 11 large-scale studies on the role of p53 in EC over the past 20 years, in order to identify potential biomarkers that are sensitive and predictive in EC. As a result, only three studies including 268 patients showed a connection between the poor prognosis and high expression of p53. The results of other studies contained conflicting data, most of which showed that the prognostic role of this marker was not obvious [13].

Among other markers considered to be oncogenes, the bcl-2 gene involved in the negative apoptosis regulation can be marked. Some authors regard high expression of bcl-2 as a negative prognostic factor due to the fact that it contributes to the survival of tumor cells [6, 8]. Other researchers showed high expression of bcl-2 to be a prognostically favorable factor [5, 9].

Analysis of proliferative activity (PA) of a tumor is the most important characteristic of cancer, which allows characterizing its biological behavior. It is estimated by the ki-67 index, as only dividing cells detect antibodies to ki-67 [7].

Disorders of intercellular adhesion associated with pathological changes in the membrane protein E-cadherin are one of the factors contributing to the metastasis and progression of malignant tumors [1]. Studies of E-cadherin expression in lung, bladder and gastric cancers showed the significance of its determination. Studies have shown that E-cadherin has the properties of a tumor growth suppressor and its invasion [2]. An imbalance in the cadherin system, in particular inhibition of E-cadherin expression and overexpression of N-cadherin, is considered an important component of the epithelial-mesenchymal transition process.

Thus, these IHC markers allow characterization of the processes of adhesion, apoptosis and proliferation of tumor cells, which seems significant for assessing the potential of tumor progression. That is why we selected these markers and studied their expression in EC cells

in different periods of the disease progression after radical surgical treatment.

The purpose of the study was a comparative assessment of the expression of p53, bcl-2, ki-67, E-cadherin IHC markers in the tumor tissue of EC patients at different progression periods after surgical treatment.

Material and methods. The study included 30 patients diagnosed with stage II (n=15) and III (n=15) middle and lower thoracic esophageal squamous cell carcinoma undergoing treatment in Rostov Research Institute of Oncology. All patients received Lewis surgery with standard bizonal lymph node dissection. No special antitumor therapy was performed until progression was detected. Median age of patients was 57.83 years. All patients developed progression within 1.5 years (up to 540 days). Depending on the time to progression, the patients were divided into 3 groups: up to 180 days; from 181 to 364; from 365 to 540 days. In 11 of 30 cases (36.7%), progression occurred within 180 days; in 9 (30%) - from 181 to 364; in 10 (33.3%) - from 365 to 540 days. The median event-free survival was 9 months.

The IHC study was performed on 3-4 μm sections from paraffin blocks prepared using the Thermo Scientific Microm HM 325 rotary microtome (Great Britain). Automated immunohistochemical staining was carried out in the Thermo Scientific 480S IHC stainer. The following monoclonal antibodies were used for the study: to p53 (clone DO-7, DAKO, 1:100 dilution), bcl-2 (clone Sp 66, DAKO, 1:100 dilution), ki-67 (clone H3060, Spring Biosience, 1:200 dilution), E-cadherin (clone EP700Y, Thermo scientific, 1:100 dilution). Dewaxing and dehydration stages were performed according to the standard scheme. The PT-LinkThermo was used for antigen unmasking. The Reveal Polyvalent HRP-DAB Detection System (Spring Bioscience) was used for imaging. The cut-off point for positive tumor assessment was 25% for both nuclear staining for p53 and cytoplasm staining for bcl-2. Proliferative activity (PA) was calculated by counting the proportion of positively stained cells to the ki-67 marker per 100 tumor cells. The ki-67 index was determined by the formula: proliferative activity = the number of positively stained cells to the tumor marker ki-67 x 100/total number of cells. Statistical analysis of the results was processed using the Statistica 8.0 program [9], and the Student's t-test was calculated.

Results and discussion. The results were expressed in a comparative analysis of the frequency of expression and average values of indicators depending on the time to EC progression. An increased time interval to disease progression was accompanied by an increase in the frequency of expression of bcl-2+ and a decrease in p53+ (table 1). No correlation was observed between the disease stage and event-free period.

Table 1 demonstrates that longer relapse-free survival was accompanied by decreased rates of tumors expressing p53, with their minimal number (1.5 times lower compared with patients who did not survive six months without progression) in patients with the longest event-free period (365-540 days).

decrease in the proportion of p53 positive tumor cells was detected as the time to progression increased. With an increase in the time to progression to 540 days, the number of p53 positive cells was 2.2 times lower than in patients with progression within 180 days from the surgery, and 1.5 times lower than in cancer progression from 181 to 364 days. The differences were statistically significant in all cases ($p<0.05$).

While expression of p53+ positive cells decreased significantly with longer time to progression, expression of bcl-2 showed the opposite tendency. The average number of bcl-2 positive cells in tumors was 2.3 times higher in progression

Table 1

Frequency of expression of IHC markers (p53 and bcl-2) depending on the time to progression, absolute count (%)

Time to progression, days	Markers (IHC)			
	p53+	p53-	bcl-2+	bcl-2-
< 180	9 (81.8)	2 (18.2)	7 (63.6)	4 (36.4)
from 181 to 364	6 (75)	2 (25)	6 (75)	2 (25)
from 365 to 540	6 (54.5)	5 (45.5)	10 (90.9)	1 (9.1)

In these patients, the maximum rate of positive bcl-2 expression was found – 1.4 ($p<0.05$) and 1.2 ($p<0.05$) times higher than in groups with progression-free periods of <180 and 181-364 days, respectively (Table 1, Figure 1).

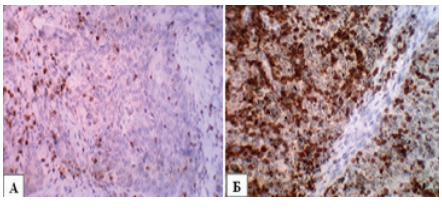

Fig. 1. Squamous cell carcinoma of the esophagus: А - 360 days to progression. Low expression of bcl-2; Б - 540 days to progression. High expression of bcl-2. 400x magnification

Table 2 presents the results of a comparative analysis of average expression of IHC markers. A statistically significant

from 181 to 364 days, compared to patients with progression within 180 days. When progression-free period lasted for up to 540 days, the value increased by up to 2.8 times (differences were statistically significant, $p<0.05$).

The maximal index of proliferation of tumor cells determined by ki-67+ was detected in tumors with the shortest time to progression. It was 3.1 and 2.5 times higher, compared to the values in groups with progression in 181-364 and 365-540 days.

No statistically significant differences in proliferation indices determined by ki-67+ cell proportion were observed in patients with progression within 181-364 and 365-540 days. Therefore, this indicator can be considered as a marker of early (up to six months after surgery) progression of esophageal cancer.

Assessment of the proliferative potential of tumors in the same patients also re-

Table 2

Expression of studied markers in patients with different periods to progression, %

Time to progression, days	Expression of IHC markers			
	p53	bcl-2	ki-67	E-cadherin
< 180	60.9±7.4	21.4±3.9	49.7±8.6	65.5±4.6
from 181 to 364	41.9±6.6°↓	48.9±4.6°↑	15.9±4.8°↓	66.3±8.8
from 365 to 540	28.2±4.2°↓	59.5±4.8°↑	19.7±4.9°↓	89.1±4.9°↑°°↑

Note. ° – differences from values < 180 days; °°– differences from values 181–364 days. Differences were statistically significant in both cases ($p<0.05$).

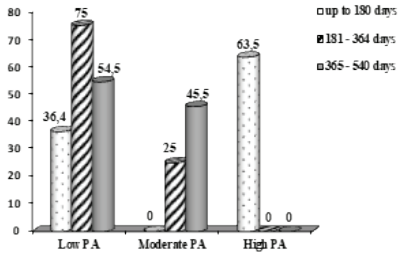

Figure 2. Proliferative activity of tumors (percentage) in dependence on time to progression in patients with stage II-III EC. The Y axis - %.

vealed a number of differences (Figure 2).

Tumors with high PA were found only in patients with an early period before progression (up to 180 days), while such activity was not detected in tumors of patients with progression from 181–364 and 365–540 days.

Tumors with low PA were most often observed in the group with progression in 181-364 days, and tumors with moderate PA were found in the group of 365–540 days. The number of tumors with moderate PA in the 365–540 day group was 1.8 times ($p<0.05$) higher than in the 181–364 day group. It should be noted that tumors with moderate PA were not detected in the group with progression in <180 days.

Patients in groups with progression within <180 and 181-364 days did not show statistically significant differences in the average values of E-cadherin expression. However, when the time to progression increased to 365–540 days, this indicator became 1.4 and 1.3 times higher, respectively (the differences were statistically significant, $p<0.05$); table 2, figure 3).

Conclusions. Immunohistochemical analysis allowed identification of some differences in occurrence rates and expression of molecular and biological markers p53, bcl-2, ki-67 and E-cadherin associated with the processes of proliferation, adhesion and apoptosis of tumor cells at different periods to the progression of esophageal cancer (<180 days; from 181 to 364; from 365 to 540 days). The results showed that the most favorable outcome of surgical treatment for esophageal cancer was characterized by

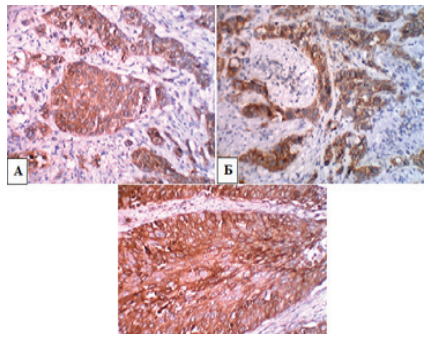

Fig. 3. Squamous cell carcinoma of the esophagus. Days to progression: А – 180, Б - 364 days, В – 540. Expression of E-cadherin. 400x magnification.

high expression of bcl-2 and E-cadherin with low proliferative activity of the tumor and low expression of p53, suggesting the potential use of these markers as prognostic ones along with well-known clinical prognosis factors.

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GENETIC DIVERSITY IN YAKUT POPULATION BY LOCI ASSOCIATED WITH BODY MASS INDEX AND OBESITY

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Obesity is one of the main risk factor for the development of socially important diseases, determining the life quality and human longevity. According to the World Health Organization (WHO) overweight and obesity are dramatically increased all over the world. This problem is particularly acute in industrialized countries, where it is becoming a non-infectious pandemic. Thus, it is critically important to focus our research efforts on studying of the genetic basis of the obesity spread in modern human populations. Genetic markers that are related to obesity and quantitative characters as body mass index (BMI), blood lipid levels and others have been identified as a result of number of studies. In the present study the variability of the GWAS-identified SNP allele frequencies associated with BMI and obesity was studied. The results of our study were compared with data on 20 populations from the international project "1000 Genomes". Genetic markers that make the greatest contribution to the genetic differentiation of populations were identified.

Keywords: human populations, polymorphism, obesity, body mass index.

Obesity is a complex, largely preventable disease that, together with overweightness, affects more than a third of the world's population today. This phenotype is known to increase the morbidity of many socially significant diseases. In particular, overweightness and obesity can contribute to the development of type 2 diabetes even in the absence of other metabolic disorders (hypertension, dyslipidemia, insulin resistance) [29]. Overweightness is a recognized risk factor for cardiovascular diseases and ischemic stroke that are responsible for the majority of deaths in the modern world. Obesity is also associated with oncological diseases. About 6% of cancer diseases (4% in men, 7% in women) have been shown to be associated with obesity [27]. More recently, evidence has been obtained that overweightness and obesity increase the risk of developing cancer of the gallbladder, prostate, ovarian epithelium, liver, as well as leukemia. [11, 21-23, 26].

Obesity is associated with anatomical as well as functional changes in the human brain. Studies of elderly people have shown that the body mass index (BMI) is negatively correlated with the brain volume and is associated with atrophy of the frontal lobes, hippocampus and thalamus. [10]. Moreover, obesity in children and adolescents is associated with a smaller amount of gray matter in the orbitofrontal cortex [28]. Overweightness in middle-aged patients increases the risk of developing Alzheimer's disease and vascular dementia by 35% and 33%, respectively; an even higher risk of these diseases is observed in obesity [9]. Thus, the influence of overweightness and obesity on human health is significant, especially in combination with other concomitant diseases.

As is known, this phenotype has a genetic nature. According to studies of twins, the coefficient of obesity heritability has been found about 40% [12]. Over the past decade, many scientific papers on the association of candidate genes with obesity have been published, but the results of these studies are largely contradictory [19]. This is probably due to the influence of adaptive, ethnic, economic and sociocultural factors. In particular, the indigenous populations of the Siberia and the Far East in the period of adaptation to low atmospheric temperatures acquired special anatomical features contributing to a decrease in heat transfer (constitution with a developed musculoskeletal mass, high body density, etc.) [1]. The Republic of Sakha (Yakutia) is one of the arctic and subarctic regions of the Russian Federation. According to the 2017 data of the Ministry of Health of the Russian Federation, the frequency of obesity in the Yakut population is 593.0 per 100 thousand people [5]. It should be noted that the relatively high prevalence of obesity among individuals living in the Republic of Sakha (Yakutia) can be associated not only with their adaptive properties, but also with changes in the traditional lifestyle and characteristic features of modern nutrition.

The aim of this work is to investigate the genetic markers associated with obesity and BMI as part of the genome-wide association study (GWAS), to study the variability of these markers in the population sample of Yakuts in comparison with world populations using the methods of the statistical analysis of the data obtained.

Materials and methods. The study was conducted on a population sample of Yakuts. The sample included 95 non-admixed and unrelated individuals: 30 men (mean age of 27.56±18.61 years) and 65 women (mean age of 31.02±16.49 years). This sample was collected the Byadi village, the Republic of Sakha (Ya-

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kutia). Additionally, the study included the results of genotyping of 20 populations from the "1000 Genomes" project (Esan, Gambian, Luhya, Mende, Yoruba, Peruvian, Bengali, Chinese Dai in Xishuangbanna, Han Chinese in Bejing, Southern Han Chinese, Japanese, Kinh, Finnish, British, Iberian, Toscani, Gujarati Indian, Indian Telugu, Punjabi, Sri Lankan Tamil).

Genetic markers were selected from the GWAS catalog, where they have shown statistically significant associations with BMI and/or obesity in two or more studies. Thus, 58 single nucleotide polymorphisms (SNPs) were studied, genotyping of which was conducted using the MALDI-TOF mass spectrometry method [3]. 7 out of 58 SNPs (rs10968576, rs13130484, rs11671664, rs12566985, rs17381664, rs2287019 and rs657452) demonstrated a low genotyping efficiency (less than 70%) and were excluded from the analysis.

To verify the Hardy-Weinberg equilibrium in the obtained distribution of genotypes and allele frequencies, the χ criterion was used. The expected heterozygosity reflecting the percentage of heterozygotes in the population sample was estimated. To study genetic diversity, we calculated the values of expected heterozygosity, but not observed one, because in small samples the frequencies of genotypes and the observed heterozygosity, for random reasons, can significantly deviate from the general values [2]. Genetic differentiation of the populations under study was calculated using analysis of molecular variance (AMOVA). To study genetic relationships, we used the principal components method. Statistical processing of the results was carried out using the software packages «Arlequin 3.5» and «Statistica 7.0».

Results and discussion. In this work, an analysis of the genetic diversity of the Yakut population was conducted. The frequencies of the ancestral alleles of the Yakut population sample, the average values of expected heterozygosity (He) and genetic differentiation (Fst) for the studied polymorphic variants in the 21 populations are presented in Table 1. The deviation of the conformity of the distribution of genotype frequencies with the Hardy-Weinberg equilibrium in Yakuts was shown for 2 out of 51 studied SNPs: rs2207139 located in the intergenic region and rs7903146 of the *TCF7L2* gene. Statistically significant deviations ($p<0.05$) from the Hardy-Weinberg equilibrium probably reflect specific features of population-genetic processes, among which may be such a factor as the functional significance of SNPs. In general, the population sample of Yakuts is characterized by a significant genetic variability: the frequencies of ancestral alleles range from 0.00 for the rs13021737 locus to 1.00 for the rs11847697 locus located in the intergenic region and the rs13107325 locus of the SLC39A8 gene. The frequency of the ancestral allele of the rs13021737 locus in the populations from the "1000 Genomes" project varies in the range from 0.05 in Luhya to 0.21 in Toscani; rs11847697 – from 0.56 in Yoruba to 1.00 in Han Chinese from Bejing, Southern Han Chinese, Kinh, and Japanese; rs13107325 – from 0.89 in Toscani to 1.00 in 15 out of 20 population samples from the "1000 Genomes" project. Thus, the indices of the variability of the ancestral allele frequencies of the SNP data in Yakuts correspond to those in the world populations.

The average level of genetic diversity in the population sample of Yakuts for 51 SNPs was 0.340, this index corresponds to the average level of genetic diversity in 21 population samples for all studied SNPs – 0.328. The highest genetic diversity were shown for the loci rs2112347 of the gene *LOC441087* and rs7141420 of the gene *NRXN3*, the lowest – for the loci rs6804842 of the gene *RARB* and rs9540493 located in the intergenic region. These genetic markers are characterized by an average level of between-population genetic diversity (from 2% to 6,2%), which corresponds to the level of genetic differences between populations for different genetic markers, according to the results of other studies [8]. The greatest contribution to the genetic differentiation of populations is made by the rs1167827 loci of the *HIP1* gene, where the Fst index is equal 45.9%, which significantly exceeds the average Fst in the studied populations (9.8%). This locus is associated with BMI in several studies; the *HIP1* gene product is involved in clathrin-mediated endocytosis in cells and is associated with the development of prostate cancer and Huntington's disease [15, 17, 18]. The rs10182181 and rs11847697 markers located in the intergenic region are also characterized by high values of Fst. According to the GWAS catalog, the 10182181 marker was shown to be associated with obesity and BMI, rs11847697 – with BMI [7, 13, 14, 16]. According to the HaploReg v4.1 online resource, the rs10182181 marker is closely linked to an rs11676272 allelic variant of the *ADCY3* gene (r2=0,97; D'=0,99) [20]. The product of this gene is known to be widely expressed in various tissues, whereas the polymorphic variants of the *ADCY3* gene are associated with obesity [6, 25]. Epigenetic studies have shown the significance of the methylation of the CpG sites of the *ADCY3* gene in the molecular mechanisms of obesity development. The smallest genetic differences between populations have been found for the rs13021737 and rs1800437 loci, where Fst comprises 1.9%.

Fig. 1 presents an analysis of the genetic relationships of world populations according to frequencies of the ancestral alleles of genetic markers associated with obesity and BMI. The first 2 main components account for 68.4% of the total variability of allele frequencies in the analyzed population samples. The position of the studied populations in the space of the principal components reflects their geographical localization, i.e. geographically close populations get into one cluster (African, East Asian, West European clusters and Hindustan cluster), which corresponds to the results obtained in previous works [4]. The population sample of Yakuts is located in the space of the principal components together with the East Asian populations, which characterizes its genetic proximity to this cluster. Yakuts, as well as population samples of Chinese, Japanese and Kinh, belong to the Mongoloid race.

The first main component is likely to correspond to the contribution of several climatic and geographical factors: a correlation of the values of this component with absolute latitude ($R=-0.596$, $p=0.004$) and longitude ($R=-0.636$, $p=0.002$) and temperature indices (average annual temperature ($R = 0.556$, $p = 0.009$), temperature of the coldest ($R = 0.642$, $p = 0.002$) and warm ($R = 0.438$, $p = 0.047$) months and temperature variation ($R = -0.607$, $p = 0.004$)) was found for 51 SNPs. The second main component reflects a change in the absolute longitude index ($R=0.599$, $p=0.004$).

Conclusion. Currently, obesity has become one of the most important medical and social problems, due to its progressive spread and severity of complications. Genetic predisposition is one of the important factors in the pathogenesis of obesity. In this work, we identified high genetic diversity and differentiation in the 21 world populations according to the studied genetic markers associated with obesity and body mass index. The Yakut population is characterized by a significant intrapopulation genetic variability (0.340). We found a correlation between allele frequencies for 51 SNPs and changes in climatic and geographical conditions. The analysis of the main

Genetic diversity and differentiation of population samples for 51 SNPs studied

SNP	Ancestral allele	Frequencies of ancestral alleles (Yakuts)	He (21 populations)	Fst	SNP	Ancestral allele	Frequencies of ancestral alleles (Yakuts)	He (21 populations)	Fst
rs10182181	G	0.147	0.387	0.222	rs2568958	G	0.053	0.368	0.126
rs10938397	A	0.870	0.410	0.037	rs3101336	T	0.053	0.368	0.126
rs1121980	A	0.324	0.434	0.052	rs3810291	G	0.598	0.371	0.185
rs1167827	G	0.089	0.276	0.459	rs3817334	C	0.665	0.409	0.057
rs11847697	C	1.000	0.246	0.219	rs571312	C	0.768	0.372	0.042
rs12429545	G	0.711	0.257	0.088	rs633715	T	0.582	0.248	0.049
rs12446632	G	0.979	0.135	0.036	rs6567160	T	0.768	0.345	0.023
rs12463617	A	0.165	0.259	0.029	rs6804842	A	0.363	0.468	0.062
rs12940622	A	0.371	0.443	0.065	rs6864049	G	0.702	0.379	0.072
rs13021737	A	0.000	0.205	0.019	rs7138803	G	0.737	0.369	0.048
rs13107325	C	1.000	0.116	0.076	rs7141420	T	0.418	0.476	0.036
rs13191362	A	0.953	0.115	0.047	rs7164727	C	0.847	0.406	0.167
rs1421085	T	0.697	0.305	0.118	rs7195386	C	0.694	0.373	0.165
rs1514175	A	0.541	0.436	0.083	rs7498665	G	0.263	0.328	0.099
rs1516725	C	0.989	0.193	0.024	rs7531118	T	0.555	0.335	0.160
rs1558902	T	0.654	0.306	0.120	rs7647305	T	0.228	0.322	0.105
rs16851483	G	0.815	0.228	0.117	rs7903146	T	0.043	0.293	0.097
rs17094222	T	0.769	0.274	0.096	rs8050136	A	0.326	0.399	0.061
rs17782313	T	0.761	0.356	0.025	rs887912	C	0.984	0.201	0.119
rs1800437	G	0.823	0.268	0.019	rs9540493	A	0.750	0.447	0.061
rs2030323	A	0.255	0.328	0.145	rs9568867	G	0.707	0.245	0.087
rs2033529	A	0.648	0.284	0.046	rs9641123	G	0.744	0.337	0.124
rs2112347	G	0.451	0.488	0.020	rs9816226	T	0.989	0.230	0.041
rs2206277	C	0.640	0.323	0.040	rs987237	A	0.747	0.280	0.047
rs2207139	A	0.686	0.273	0.061	rs9941349	C	0.676	0.364	0.070
rs2531995	C	0.633	0.375	0.139	Среднее	-	-	0.328	0.098

He (21th population) – the values of the average expected heterozygosity in the 51 populations (the Yakut population and 20 populations from the project "1000 Genomes"), Fst – the values of genetic differentiation of populations.

components showed the genetic affinity of the Yakut population to the East Asian population samples. Genetic markers that better characterize genetic differences between the studied populations, in particular, rs1167827 of the *HIP1* gene and rs10182181 and rs11847697 located in the intergenic region, were identified.

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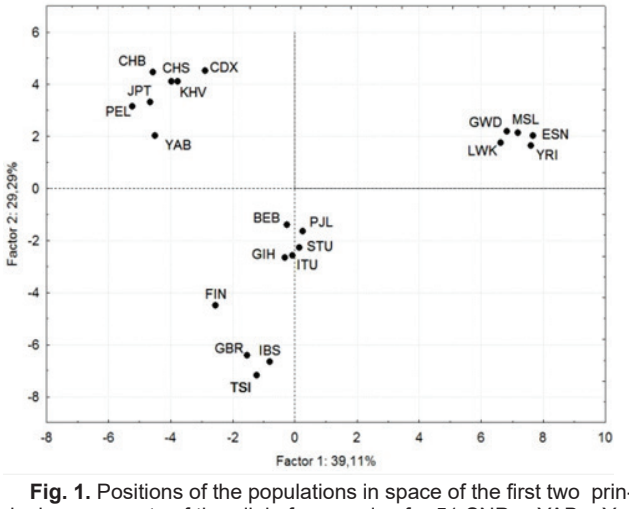

Fig. 1. Positions of the populations in space of the first two principal components of the allele frequencies for 51 SNPs.: YAB – Yakut, ESN – Esan, GWD – Gambian, LWK – Luhya, MSL – Mende, YRI – Yoruba, PEL – Peruvian, BEB – Bengali, CDX – Chinese Dai in Xishuangbanna, CHB – Han Chinese in Bejing, CHS – Southern Han Chinese, JPT – Japanese, KHV – Kinh, FIN – Finnish, GBR – British, IBS – Iberian, TSI – Toscani, GIH – Gujarati Indian, ITU – Indian Telugu, PJL – Punjabi, STU – Sri Lankan Tamil.

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LIPID SPECTRUM FEATURES AND RELATIONSHIP BETWEEN SPECIFIC CLASSES OF LIPIDS AND SEX HORMONE LEVELS IN ASIAN NORTH MEN

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We studied lipid spectrum features in indigenous and non-indigenous residents of Asian North in Russia against the levels of dehydroepiandrosterone sulfate (DHEA-S) and testosterone. Materials and methods: We compared the main parameters of lipid and sex hormone metabolism in indigenous and non-indigenous men inhabitants of Asian North with those of relatively healthy men in Western Siberia (comparison group). Results: lipid profile of indigenous men featured lipoprotein spectrum shifted towards high-density lipoprotein cholesterol compared with lipid profile of non-indigenous population and comparison group. Atherogenicity coefficient in indigenous people lied within permissible values. We revealed that low-density lipoprotein cholesterol level and atherogenic coefficient positively correlated with chronological age, and high-density lipoprotein cholesterol level positively correlated with DHEA-S both in native and non-indigenous residents of Asian North. DHEA-S level in non-indigenous population was found to negatively correlate with triglycerides and atherogenic coefficient. This group of men was characterized by high levels of total cholesterol, triglycerides, low-density lipoprotein cholesterol and high atherogenic coefficient.

Keywords: lipid profile, sex hormones, indigenous and non-indigenous residents, Asian North, Arctic zone of the Russian Federation.

Introduction. For the last decade, economic development of the Arctic zone of the Russian Federation (AZRF) has been considered a priority of state policy as exploration and development of huge reserves of natural gas and oil in the Arctic will help to achieve sustainable economic growth and improve life quality not only of AZRF residents but nationwide.

Some researchers often distinguish between European and Asian North of Russia based on climatic factors and geographical location [4, 7, 8]. It is not unlikely that these factors as well as food patterns, nationality, age, degree of physical fitness and activity, ecological situation and heredity determine the current demographic situation in these regions. In particular, it is known that total primary incidence by ICD-10 (A00–T98) per 100.000 population in Yamal-Nenets Autonomous District (Asian North of Russia) in 2007-2016 was higher than in Murmansk Region (European North of Russia) [3]. The same ratio was for arterial hypertension incidence.

The prevalence of major circulatory diseases in non-indigenous population of AZRF and a high risk of cardiovascular pathology are caused by the negative impact of extreme climatogeographic factors, such as cold, wind, dry air, contrasting photoperiodism, intense cosmic radiation, geomagnetic fluctuations and increasing anthropogenic pollution of some areas.

Many authors also attribute the growth of cardiovascular diseases (CVD) incidence in extreme AZRF conditions to unfavorable lipid profile [5, 9, 11, 21]. Individual characteristics of lipid metabolism are influenced by numerous factors: nutrition, degree of physical fitness and activity, ecological situation, heredity, age, nationality, place of residence. For instance, the residents of the eastern part of the southern Arkhangelsk region (61-62° N) had higher levels of low-density lipoprotein cholesterol (LDL-C) and phospholipids compared with those in western part of the region [17]. Studying the representatives of indigenous and non-indigenous residents living in the same area can be expected to reveal group-specific features of lipid metabolism that are not associated with the influence of AZRF climatic factors.

It is common knowledge that LDL-C plays a leading role in atherogenesis. Under oxidative stress, LDL-C modifies and increases its atherogenic properties. The levels of oxidized LDL-C significantly increase with age [22]. Sex hormone levels also change with age. Men aged 60-69 residing in European North had 1/3 of dehydroepiandrosterone sulfate (DHEA-S) levels in young group (up to 29) [25]. There was no positive correlation between DHEA-S and lipid levels. Some epidemiological studies of men, however, found a link between low levels of DHEA and DHEA-S with increased CVD risk [19, 20], while another study shows no correlation [23]. SCORE-based cardiovascular risk in European North miners was significantly higher than in group of men living in Western Siberia [25]. Cardiovascular risk of northerners increased from low to very high values with chronological age.

The relevance of this study is also related to emerging reports that differences in lipid profile of indigenous and non-indigenous northerners tend to erase, which may be due to changes in the lifestyle of the former [2].

Objective: to identify the features of lipid spectrum in indigenous and non-indigenous Asian North residents living at the same latitude and to assess the relationship between specific indicators of lipid metabolism and the levels of DHEA-S and testosterone.

Materials and methods. The study was conducted among men of Samburg village (67° N, 78° E), Yamal-Nenets Autonomous District, in spring (March–April). The study involved informed consent enrollment of indigenous population (group 1, men (n=18) with the mean age of 38.06±2.92) and non-indigenous population (group 2, men (n=19) with the mean age of 43.79±2.68, polar experience of 23.75±5.22). The indigenous population included forest and tundra Nenets who preserved a traditional food pattern, engaged in reindeer husbandry, fishing and hunting. Representatives of non-indigenous population were engaged in physical labor, preferred European food patterns. Both groups had comparable physical activity (1.4–1.6). The comparison group consisted of apparently healthy men of the same age (group 3, men (n=14) with the mean age of 42.86±3.45) living in Novosibirsk (55° N, 82° E, Western Siberia).

This study approved by the Ethics committees of FRC ICG SB RAS and FRC FTM was performed in accordance with the requirements of "Ethical principles for medical research involving human subjects" and "Rules for clinical practice in the Russian Federation".

Blood was sampled from ulnar vein on an empty stomach after night fasting. The levels of the following components were determined: total cholesterol (TC), very low-density lipoprotein cholesterol (VLDL-C), LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides (TGs), DHEA-S, and testosterone. Atherogenic coefficient (AC) was also calculated.

Levels of TC and TG, as well as HDL-C and LDL-C were determined using Thermo Fisher Scientific (USA) and DiaSyS (Germany) kits, respectively. Measurements were carried out using automatic biochemical analyzer AU 480 Beckman Coulter (USA). Levels of DHEA-S and testosterone were measured using "Steroid ELISA-DHEA-sulfate" and "Steroid ELISA-testosterone" tests (Russia) for ELISA. The results were read using a microplate reader Stat Fax-2100 (Awareness Technology Inc., USA).

Data were statistically processed using Statistica v. 10 package (Stat Soft Inc., USA). Mann-Whitney U–test was used to compare two independent groups by the same parameter. Nonparametric Spearman's rank correlation coefficient (r) was used to assess the correlation between individual characteristics. The data are presented as M±m, where "M" is the arithmetic mean and "m" is the mean error. Differences were considered statistically significant at $p<0.05$.

1. **Results and discussion.** Table 1 shows the levels of lipids, sex hormones and AC in study groups. Except for HDL-C, group 1 men had significantly lower lipid levels compared to group 2.

Group 1 had 2.3-, 2.8- and 1.2-times higher levels of TG, LDL-C and TC, respectively, compared to group 2. This affected AC value that was 2.1-times lower than in group 2. HDL-C levels in group 1 was 1.4-times higher than in group 2. TG levels in group 1 was 1.3-times lower than in group 3. Characteristics of lipid metabolism were identified in the study of first- and second-generation young Caucasians born in the North and indigenous students of Magadan Region (the Evens, the Koryaks, the Chukchis) [1]. The characteristics reflect ethnic differences in metabolic processes shaped by long-term adaptation to North conditions. In the indigenous group, TC, TG, LDL-C levels were lower and the concentration of HDL-C was higher than in the group of Caucasians born in the North.

Levels of TG, TC, LDL-C and AC value in group 2 study exceeded the permissi-

Table 1

Lipid and sex hormone levels in serum of male representatives of indigenous and non-indigenous population of AZRF (M±m)

Parameter	Group			p
	indigenous	non-indigenous	comparison	
	1	2	3	
Age, years	38.06±2.92	43.79±2.68	42.86±3.45	–
TC, mM/l	4.76±0.24	5.70±0.35	4.41±0.26	1-2=0.034 2-3=0.006
TG, mM/l	0.82±0.06	1.86±0.32	1.40±0.22	1-2=0.002 1-3=0.010
VLDL-C, mM/l	0.24±0.04	0.66±0.15	–	1-2=0.011
LDL-C, mM/l	3.06±0.23	3.67±0.31	2.49±0.17	1-3=0.050 2-3=0.002
HDL-C, mM/l	1.32±0.07	0.97±0.07	0.92±0.07	1-2=0.001 1-3=0.001
AC	2.30±0.23	4.91±0.57	4.28±0.59	1-2=0.001 1-3=0.002
DHEA-S, μg/ml	2.33±0.19	2.14±0.17	1.84±0.15	1-3=0.050
Testosterone, nM/l	23.04±1.74	18.88±1.99	18.43±2.10	1-3=0.034

ble values, which indicated lipid metabolism disorder, hypertriglyceridemia and hypercholesterolemia. Notably, group 2 lipid profile did not differ from that identified by Z.N. Krivoshapkina and colleagues [14] when studying non-indigenous residents of Yakutia with more than 20 years of polar experience. TC and LDL-C levels of group 2 exceeded those of group 3 with normal lipid parameters, with the exception of AC (**Table 1**).

Lipoprotein lipase is known to bind endothelium capillary and hydrolyzes TG in chylomicrons (CM) and VLDL-C with latter transforming into HDL-C. There could be the following reasons of hypertriglyceridemia: increased formation of VLDL in liver; disorders of TG hydrolysis in CM and VLDL-C and their transformation into remnants; and blockade of receptor absorption by the cells of CM and VLDL-C remnants [16].

Lipoprotein spectrum shift towards HDL-C in group 1 can be considered as a manifestation of reasonable and economical metabolic background described earlier as a "northern" or "polar" type of metabolism [6, 12, 13]. Normolipidemia in group 1 can be explained by liver capability of active esterification of TC, intensive biosynthesis of bile acids and transportation of sterols to bile [10].

It is generally accepted that increased LDL-C level is a key factor of cardiovascular pathology. In one of the studies [24], LDL-C level was predictive of cardiovascular risk in patients with type 2 diabetes. In persons with diabetes and insulin resistance, as well as in elderly patients, the prognostic value of this parameter is higher. The average level of LDL-C may slightly differ in different populations due to both genetic characteristics and environmental factors.

The content of sex hormones in groups 1 and 2 did not differ (**Table 1**). However, DHEA-S and testosterone levels in group 1 were higher than in group 3. Sex hormone levels in all groups were within reference values.

Thus, significant differences of lipid metabolism were found when comparing two groups of men of similar age and the same class of physical activity living in the same geographical area of Asian North located at the same northern latitude. Group 1 had more favorable lipid profile as evidenced by lower levels of TC, TG, LDL-C and higher levels of HDL-C compared to those of group 2. AC, which is considered as a prognostic indicator of atherogenesis and predisposition to cardiovascular pathology, did not exceed 2.30 in group 1. Group 2 had increased levels of TC, TG, LDL-C, LDL-C and AC, which suggests lipid metabolism disorder and enable us to classify these men to those at risk of cardiovascular pathology. This is confirmed by more pronounced deviations of lipid profile in non-indigenous people suffering from coronary heart disease compared with the indigenous population with the same pathology [15]. The differences between group 1 and 2 appear to be related to lifestyle and diet, which reflect ethnicity.

Correlations between studied parameters were investigated to understand the features of hormonal and metabolic relationships (**Table 2**). The analysis showed a number of correlations between lipid metabolism indicators inherent in all three groups: a) strong positive correlation between TC and LDL-C levels; b) positive correlation between TG and AC levels with average and strong correlation in groups 1, and 2 and 3, respectively; c) negative correlation between HDL-C and AC levels. Group 1 had an average correlation, while groups 2 and 3 had a strong correlation. The identified relationships reflect strong positive correlations between proatherogenic lipid fractions and negative correlations between the anti-atherogenic fraction and AC.

Of great interest were significant correlations identified in groups of men living in the same geographical area of the Asian North. Positive correlations between DHEA-S and HDL-C levels, the level of LDL-C and age, AC index and calendar age of men were common for men in groups 1 and 2. Only group 1 had correlations between LDL-C and TG levels and between LDL-C and AC.

Group 2 demonstrated a positive correlation between TC level and age, VLDL-C and TG levels, LDL-C and HDL-C levels, VLDL-C level and AC, negative correlation between HDL-C and TG levels, DHEA-S and TG levels, VLDL-C and HDL-C levels, DHEA-S level and AC. This group featured correlations between more atherogenic lipid fraction – LDL-C and AC, TG – compared with group 1 (LDL-C).

Negative correlations between DHEA-S and AC, as well as DHEA-SC and TG, observed in group 2 only, suggest the active DHEA-S participation in lipid metabolism regulation among non-indigenous population of the Asian North. It can be assumed that increased DHEA-S will reduce AC and TG levels. There is evidence of DHEA presence in HDL-C and LDL-C particles of healthy young and middle-aged volunteers [18]. Levels of DHEA and DHEA-S in LDL-C particles progressively decreased with age and were almost undetectable in persons over 65. The same *in vitro* model study demonstrated that DHEA increased LDL-C resistance to oxidation. LDL-C oxidation inhibition potential of DHEA were higher than that of vitamin E [18]. Our study revealed significant correlations

Table 2

Relationship between lipid profile indicators and sex hormone levels / age in indigenous and non-indigenous population of Asian North (r; p)

Parameter	Group		
	indigenous	non-indigenous	comparison
TC – Age	–	0.54; 0.021	–
TC – TG	–	–	0.71; 0.005
TC – LDL-C	0.83; 0.0005	0.81; 0.0005	0.99; 0.0005
TC – AC	–	–	0.73; 0.003
TC – Testosterone	–	–	-0.58; 0.031
TG – VLDL-C	–	0.85; 0.0005	–
TG – LDL-C	0.51; 0.031	–	0.73; 0.003
TG – HDL-C	–	-0.75; 0.0003	-0.63; 0.015
TG – AC	0.66; 0.004	0.92; 0.0005	0.79; 0.001
TG – DHEA-S	–	-0.47; 0.044	–
HDL-C – VLDL-C	–	-0.74; 0.001	–
HDL-C – AC	-0.61; 0.015	-0.81; 0.0005	-0.82; 0.0005
HDL-C – DHEA-S	0.68; 0.005	0.48; 0.046	–
LDL-C – Age	0.52; 0.028	0.81; 0.0005	–
LDL-C – HDL-C	–	0.52; 0.026	–
LDL-C – AC	0.72; 0.001	–	0.80; 0.001
LDL-C – Testosterone	–	–	-0.59; 0.026
AC – Age	0.55; 0.022	0.47; 0.045	–
AC – VLDL-C	–	0.81; 0.0005	–
AC – DHEA-S	–	-0.62; 0.005	–

between DHEA-S and lipid metabolism indicators (HDL-C and TG) in groups 1 and 2 only, which indicates characteristic relationships between lipid metabolism indicators and DHEA-S level in men living in the Asian North.

Group 3 demonstrated positive correlations between TC and TG levels, TC level and AC, TG and LDL-C levels, LDL-C level and AC and negative correlations between cholesterol and testosterone levels, TG and HDL-C levels, LDL-C and testosterone levels. These correlations indicate unfavorable lipid profile and moderate cardiovascular risk. Group 3 featured important role of testosterone in lipid metabolism. The identified correlations between TC, LDL-C and TG levels may predetermine increased AC.

Lipid profiles and sex hormone levels in men differentiate them by risk of diseases accompanied by lipid metabolism disorder. The first group of men can be considered favorable as lipid metabolism indicators are within normative values. This is possibly due to high sex hormone level and features of traditional food patterns. It should not be however forgotten that this group had correlations between LDL-C, TG and AC. Due to hypertriglyceridemia, hypercholesterolemia and increased AC, group 2 can be classified into a high risk group. Correlation analysis demonstrated the role of age, LDL-C and DHEA-S in atherogenic disease risk. Such lipid spectrum changes can be considered as a "fee" for living in extreme climatic conditions. Group 3 can be characterized to have moderate risk of atherogenic diseases. Complex interactions between pro- and anti-atherogenic lipid fractions and testosterone involvement in regulation of TC and LDL-C levels only increased AC.

Conclusion. Comparative study revealed some features of lipid profile and sex hormones in indigenous and non-indigenous men of the same age who live in the same climatogeographic area of the Asian North, but have different food patterns. Indigenous men had optimal content of TC, TG, and VLDL-C but their lipid spectrum was shifted towards HDL-C compared with lipid profile of non-indigenous men. AC also indicates more favourable lipid profile of indigenous people. It can be assumed that the favorable lipid profile of the indigenous people induced by traditional way of life and food patterns will preserve their health and prevent diseases of civilization, including CVD.

Non-indigenous men had increased TC, TG, LDL-C levels and AC (4.91), which suggests unfavorable lipid profile and classifies these men into a high cardiovascular disease risk group.

Lipid profile correlations were identified that are "united" by living conditions of the same geographical area and are characteristic for Asian North residents. Calendar age was found to correlate with LDL-C, AC (for indigenous and non-indigenous residents), and TC (for non-indigenous residents). Northerners (indigenous and non-indigenous) also featured a positive correlation between DHEA-S with HDL-C with only non-indigenous men having negative correlations between DHEA-S, AC, and TG. These correlations indicate significant positive contribution of DHEA-S to lipid metabolism regulation in indigenous northerners, and a possible negative impact of DHEA-S in non-indigenous northerners, taking into account the known age dynamics of this hormone.

Average positive correlations between TG and TC levels, TG and LDL-C levels, as well as between TC level and AC was a distinctive feature of the comparison group. Testosterone levels negatively correlated with TC and LDL-C levels in this group. The analysis of lipid profile and relationships between its indicators in men from Western Siberia allows us to classify them into a group of moderate atherogenic disease risk.

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PATENT DUCTUS ARTERIOSUS ASSOCIATION WITH THE CONGENITAL HEART DISEASE IN THE NEWBORNS OF THE REPUBLIC OF SAKHA (YAKUTIA)

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Long-term persistence of the ductus arteriosus is considered as a variant of pathology. Therefore, the identification of the most significant factors in the persistence of the ductus arteriosus is the basis for prevention. The aim of the study was to determine the factors associated with the persistence of the ductus arteriosus in newborns with congenital heart defects. This kind of study is performed for the first time in the Republic of Sakha (Yakutia). The article represents retrospective clinical study. The database included 1.824 cases of children with congenital heart defects. The most common association of the patent ductus arteriosus with congenital heart defects was found among the newborns with a gestation period of less than 32 weeks. It was determined that the prevalence of association of congenital heart disease with a patent arterial duct considerably increased depending on the severity of the heart failure.

Keywords: birth defects, heart, patent ductus arteriosus, children, Yakutia.

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Introduction. Congenital heart defects (CHDs) represent heterogenic groups of diseases, including comorbities, isolated and combined anomaly of multifactorial etiology. The problem of blood circulation defects is significant as it causes high mortality rate, especially during the first year of life, and disability afterwards. It is determined that CHDs are related to the disturbances of embryogenesis in the 2nd-8th week of gestation as result of genetic factors, environment and mother’s physical condition [3,5,7].

Long-term persistence of the ductus arteriosus is considered as a variant of pathology. However, the prevalence of patent (open) ductus arteriosus among the indigenous population of the North is still undetermined as there are no distinct criteria from what period of gestation the ductus arteriosus is considered to be a defect of development [1,3]. There are single publications of such kind concerning Caucasian population. It is hypothetically believed, that it should be closed during the first two weeks of life. Under such criteria, the prevalence of the isolated anomaly is 0.14-0.3 per 1000 live-born children, 7% among all CHDs and 3% among all the critical defects [6]. Persistence of the ductus arteriosus significantly depends on the term of pregnancy, besides that there are factors caused by mother, as intrauterine hypoxia, nonsteroidal anti-inflammatory drugs use and others [2,4]. The list of some other factors, which can be associated with the long-term persistence of the patent ductus arteriosus among the children with CHDs is not enough studied in the Republic of Sakha (Yakutia).

Objective The objective is to deter-

mine the association of the patent ductus arteriosus with CHDs in newborns of the Republic of Sakha (Yakutia) by the method of logit and regression analysis. This kind of investigation is performed for the first time in the Republic of Sakha (Yakutia).

Materials and methods: A retrospective clinical research work was performed on the base of the Perinatal centre of the Republican hospital No1, National centre of medicine. A research work is based on 1,824 clinical results of medical tests, taken from the medical records of the patients with a diagnosed "Congenital heart disease" (CHD). The time distance of the medical records is registered two times, thus from 2001 to 2003 and from 2013 to 2015. The CHD is recorded according to Q20-Q28 (ICD-10, chapter XVII: Congenital malformations, deformations and chromosomal abnormalities). The delivery case reports (#010u) and patient's discharge statistic card (#066/u-02) were the initial documentations for analysis.

All the newborns had experienced ultrasound examination (Doppler echocardiography) of the heart to evaluate the anatomical structure and cardiovascular function. The selection is based on the cases with bypass through interatrial septum according to the results of ultrasound investigation. The functioning activity of the arterial duct was evaluated by colour Doppler test to define additional flow in the vessel projection, i.e. pulmonary trunk. The research was performed from 2001 to 2003 on the base of ATL-HDI-3000 Philips, from 2013 to 2015 on the base of EPIQ-7 Philips.

Logit and regression analysis is performed to define the association of patent ductus arteriosus with CHD.

When $p<0.05$ the intergroup accuracy was considered significant. The initial data were accumulated in the database by means of Microsoft® Excel software, all the statistic operations were conducted by means of SPSS® Statistics software (IBM®, USA).

Results. The association of patent ductus arteriosus with CHD was revealed in 386 cases, 21.2%. No significant differences between gender association of patent ductus arteriosus was revealed, prevalence of patent ductus arteriosus was 21.8% in boys, and 20.4% ($p=0.436$) in girls.

Most commonly the association of patent ductus arteriosus with CHD was noticed in newborns with the period of gestation less than 32 weeks, rarely in groups of newborns with 32-37 weeks of gestation ($p<0.001$) (Table 1).

The association of patent ductus arteriosus with CHD differed not only by

Table 1

The distribution of patent ductus arteriosus cases in children with CHD according to the weeks of gestation

Gestation period	Absolute number of cases	Prevalence, %
Less than 32 weeks	78	30.3
32-37 weeks	119	16.4
38 weeks and more	189	22.6

Table 2

The prevalence of patent ductus arteriosus association with other CHDs

CHD case	Absolute number of cases	Prevalence
CHD without heart failure (HF): isolated interatrial septum defect, mild or in association with patent ductus arteriosus less than 0.2 cm.	73	7.2
CHD with HF of 1st class, NYHA classification 1: moderate interatrial septum defect or in association with patent ductus arteriosus less than 0.2 cm.	24	13.0
CHD with HF of 1st and 2nd class and more, NYHA classification of the 1st and 2nd class and more, NYHA classification 2 and more: non-complicated (simple) CHD + complicated (complex) CHD	289	46.0

Table 3

Association of patent ductus arteriosus with CHDs according to nosologies

CHD group	Absolute number of cases	Prevalence, %
Non-complicated (simple) CHDs	347	19.8
Complicated (complex) CHDs, including:	33	51.3
atrioventricular canal, complete	2	33.3
Anomalous pulmonary veins drainage, total	2	40.0
Pulmonary artery atresia Ebstein's anomaly,	5	71.4
tricuspid valve anomaly	3	50.0
Tricuspid valve atresia	0	0
Double-outlet right ventricle	2	50.0
Obstructive heart defects, coarctation of the aorta, interrupted aortic arch	1	100.0
Pulmonary artery stenosis	2	33.3
Transposition of great vessels	3	60.0
Fallot's tetrad	10	58.9
Abdominal aortic aneurysm	0	0
Complex CHD	3	60.0

Table 4

Factors associated with patent ductus arteriosus in newborns with CHD

Indicator	Corrected OS	95% DI for corrected OS	
Body weight	1.00	1.00	1.00
Sex: male female	 1.00 0.85	0.66	1.10
Gestation, weeks	0.89	0.84	0.95
CHD groups: group 1 group 2 group 3	 1.00 1.83 12.36	 1.11 9.12	 3.01 16.76
Complex CHD: no yes	 1.00 1.44	 0.89	 2.36

groups of defects depending on the presence / absence of impaired heart failure, but also nosological groups of defects. It is estimated that the prevalence of CHD association with patent ductus arteriosus considerably increased depending on the expression of the heart failure ($p<0.0001$), see tabe2.

Complicated (complex) CHDs more often were associated with patent ductus arteriosus (51.3% as against 19.8%, $p<0.0001$), see table 3.

According to the logit and regression analysis with the correction of the gestation, it was determined (see table 4) that CHD with heart failure of 1st degree (NYHA classification 1) moderate interatrial septum defect or in association with patent ductus arteriosus less than 0.2 cm and CHD with HF of 1st and 2nd class and more (NYHA classification of the 1st and 2nd class and more), NYHA classification 2 and more were significantly associated with patent ductus arteriosus. Moreover, there is no significant association of patent ductus arteriosus with complex congenital malformation.

Conclusion: According to the logit and regression analysis, the association of the patent ductus arteriosus with other CHDs is most common for newborns with the gestation period of less than 32 weeks. The association of CHD with the patent ductus arteriosus differed not only groups of defects depending on the prevalence of the heart failure, but also the nosologic groups of defects. The prevalence of CHD association with patent ductus arteriosus depending on the heart failure expression is revealed. The patent ductus arteriosus was also associated with complex heart defects.

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DIAGNOSTIC AND TREATMENT METHODS

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THE RISK STRATIFICATION OF THE VENOUS THROMBOEMBOLIC COMPLICATIONS IN ONCOCOLOPROCTOLOGY

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The article is devoted to the problem of the venous thromboembolic complications stratification in cases of the colorectal cancer. We performed prospective, randomized, blind study in colorectal surgery department. We analyzed the TEC risk factors due to up-to-date recommendations of the 100 consecutive patients with operable colorectal cancer. The doctors didn't know about the study (blind) to decrease the ability for study aggravation. After all, 100 cases were get numbers and randomized by the method of random number for 2 groups: Main group (n50) – the TEC stratification performed by our method; control group (n50) – the TEC level got from history of the patients.

The underestimation of the risk level of these complications was revealed. The reason of this risk underestimation was the absence of some risk factors evaluation connected with the patients' comorbidity and surgery. The authors of the article described method of the thromboembolism risk stratification by new soft for PC with ability to evaluate the risk objectively, unified and with mathematical accuracy with minimal effort.

It was found out the patients suffering from colorectal surgery has extremely high risk of the thromboembolic complications.

Keywords: colorectal cancer, thromboembolic complications, thromboembolism of the pulmonary artery, stratification.

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Introduction. The problem of the venous thromboembolic complications (VTEC) of the oncological surgical patients is still urgent. The risk of VTEC at this case is 10 till 40% without prophylaxis and fatal in about 10% cases [11]. The VTEC is situated on the second place in the structure of mortality and take place approximately in 20% [2]. The recent investigations has shown high risk of VTEC in cases of colorectal cancer [1, 3, 7].

The multifactorial analysis has shown that the risk of lethal outcome, shock or thromboembolism of the pulmonary artery (TEPA) increased in 3 times during 30 days in case of cancer [14]. Obviously, the best method of TEC care is primary prophylaxis. The primary TEC prophylaxis is based on risk stratification and prophylaxis with accordance to risk level – physical, pharmacological (drug) or surgical methods. Nowadays, the most popular stratification scheme is method of Ch. Samama proposed in 1999 [15]. But, this scheme is based on only one factor evaluation that has most serious impact to thromboembolism. However, the TEPA risk is defined by summation of the risk factors connected with comorbid status and type of surgical intervention. Currently, we have a waste majority of the individual TEC evaluation with the point grading system of every risk factor [4, 9, 12].

But unfortunately these methods are quite complicated and that's why can't be useful in real clinical practice.

Objective – to improve the TEC prophylaxis for the patients with colorectal cancer.

The design of research. We performed prospective, randomized, blind study in colorectal surgery department. We analyzed the TEC risk factors due to up-to-date recommendations of the 100 consecutive patients with operable colorectal cancer. The doctors didn't know about the study (blind) to decrease the ability for study aggravation. After all, 100 cases were get numbers and randomized by the method of random number for 2 groups: Main group (n50) – the TEC stratification performed by our method; Control group (n50) – the TEC level got from history of the patients.

Materials and methods. We invented software "The program for automatic evaluation of the thromboembolic complications and its prophylaxis" (Russian state registration certificate for software for IBM PC №2015619184, from 26.08.2015). This software has interface of dialogue window with ability for a doctor to point the risk factors of TEC: the age (41-60, 61-74, 75 and more), risk factors connected with the patient (29 factors) and with the surgery (9 factors). The software automatically calculates the level of TEC risk (low, moderate, high and extremely-high) with the accordance to the quality and quantity risk factors individually to every patient due to up-to-date stratification models [4, 12]. Besides, our software offers the prophylaxis program individually with the accordance to the TEC risk level [6]. The software also has ability to calculate the prophylactic and cure dose of the most actual anticoagulants in appliance with the patients' weight. After all, the doctor has ability to print the protocol of stratification and put it into the history case. This protocol reflects all risk factors and overall risk level for every patient to protect doctor in a case of judicial trial.

Results and discussion. Both groups weren't statistically differing by the age. The age of patients has a great impact to TEPA stratification: 41-60 years – 1 points, 61-74 years – 2 points, 75 and more – 3 points. First group average age was 63,32±7,58 years (31 - 81 years), the second group - 64,21±5,62 (34 – 80 years). It's necessary to stress that both groups has more than 70% patients with the age more than 61 years and more than 20% among them was in a group of the maximal risk by the age – more than 75 years and only 2 (4%) patients of the first group and 1 patient (2%) of the second group wasn't in a high TEC risk because of the age less than 40 years.

All patients had colorectal cancer. But the localization of the tumor doesn't matter due to our program and correspond to 2 points.

All patients were passed through the radical surgery with the duration more than 45 minutes that is also risk factor with 2 points.

Moreover, the patients of the both group had risk factors: varicose of the leg veins – n=8 (16%) of the main group and n=11 (22%) of the second group, the leg puffiness – n=10 (20%) and 12 (24%) accordingly, obesity – n=11 (22%) and 8 (16%) accordingly, chronic obstructive disease n=7 (14%) and n=5 (10%). Furthermore, the coexistence of 4 and more factors was in 92% for the 1 group and 86% for the second. Thus, all patients of both groups had extremely high risk of TEC (more than 5 points).

Nonetheless, all patients of both groups got TEC prophylaxis only in a level of compression therapy and early activation of the patients after the surgery (no more than 72 hours). This prophylaxis program corresponds to the moderate level of TEC risk. And only one case of the main group and 2 cases of the control group correspond to the level of the high TEC risk because of the decompensated varicose disease of the leg veins that's why patients were consulted by angiosurgeon, ultrasound investigation performed and after all anticoagulants in prophylactic dosage were used in perioperative period.

Thus, the main group patients had average risk level 6,69±1,2 points (from 5 till 10 points). If we took as a basis that control group had prophylaxis of TEC due to recommendations for the moderate risk level with no more than 2 points of TEC risk factors, we found statistically true difference (p=0,023) between the patients of the main and control group because of the underestimation of the TEC risk by doctors without software. Some authors shown us in their investigation that this underestimation of the TEC risk is worldwide tendency [8, 13]

In spite of this, we didn't get manifested TEC in both groups. Though, some researchers shown [5, 10] that even fatal TEPA can occur in remote period after the surgery and discharge form the hospital.

Our software is very simple in usage – to fill the forms surgeon need no more than 1 min. The possibility to print the protocol of stratification let us to get objective calculation of the TEC risk score and protect the doctor from some juridical problems.

Conclusions. "The program for automatic evaluation of the thromboembolic complications and its prophylaxis" gives us opportunity to evaluate objectively the risk of thromboembolical complications;

Patients suffering from colorectal cancer and passed through the radical surgery have extremely high risk of TEC.

The accuracy of the TEC stratification by our method corresponds to modern recommendations and surgeon could be protected from some legal problems;

Our method allows optimizing and unifies the prophylactic of the TEC program.

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CLINICAL AND EPIDEMIOLOGICAL ASPECTS OF CHRONIC MYELOPROLIFERATIVE DISEASES IN THE REPUBLIC SAKHA (YAKUTIA)

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Chronic myeloproliferative diseases are characterized by excessive proliferation of myeloid cell lines and a high risk of thrombotic complications. The **purpose** of the research was to analyze the clinical features and epidemiology of chronic myeloproliferative diseases in the Republic Sakha (Yakutia). We carried out a retrospective analysis of medical records of patients followed-up by hematologists of Yakutsk from 1995 to 2018. The study included 104 patients, 39 of them were diagnosed with ET (27 women and 12 men), 40 had PV (21 women and 19 men), and 25 had PMF (11 women and 14 men). The diagnosis was established based on the current diagnostic criteria of the World Health Society (WHO).

The results of study demonstrated an increase of disease incidence in 2015-2016, prevalence of thrombotic complications among people younger than 60 years and the prevalence of the latent onset of the disease. The average time from thrombosis onset to disease diagnosis was 1 year. Arterial thrombosis such as acute disorders of cerebral circulation and myocardial infarction occurred more often.

It is necessary to carry out a molecular genetic study to identify driver mutations. During follow up 19.4% of patients have developed re-thrombosis.

Keywords: chronic myeloproliferative diseases, thrombosis, cardiovascular risk.

Introductio. Chronic myeloproliferative diseases (CMPD) result from malignant transformation of pluripotent stem cell followed by clonal proliferation of one or more myeloid cell lines (erythroid, myeloid, megakaryocytic) that differentiate into mature forms. Mutations of genes *JAK2*, *MPL* and *CALR,* leading to hyperactivation of the JAK-STAT signaling pathway, play a key role in developing CMPD [11, 13]. Polycythemia vera (PV) is characterized by proliferation of three myeloid cell lines, while in essential thrombocythemia (ET) hyperplasia of the megakaryocytic line with thrombocytosis are mainly observed. In case of primary myelofibrosis (PMF) abnormal megakaryocytes produce cytokines leading to the development of bone marrow fibrosis and extramedullary hematopoiesis [7].

The main clinical problem of patients with CMPD, leading to disablement and death, is thrombotic complications [5]. In large international studies, it was shown that thrombosis is observed in 23.4% of patients with PV and 12% of patients with ET [12]. Arterial thrombosis, especially in cerebrovascular system, is more common than venous one. Mortality of patients with CMPD because of cerebrovascular diseases is 1.5 times higher than in general population [4]. Venous thrombosis is less common, but affects patient survival and development of microcirculatory disorders causing decrease in quality of life. Thrombotic complications are less common in patients with PMF, which can be explained by transformation into secondary acute myeloid leukemia and lower survival rates [7].

Disease manifestation can have a long-term latent course without obvious signs of myeloproliferation, which complicates early disease diagnosis and increases the risk of complications.

Objective: to analyze the clinical and epidemiological features of CMPD in the Republic Sakha (Yakutia).

Materials and methods. We carried out a retrospective analysis of medical records of patients followed-up by hematologists of Yakutsk from 1995 to 2018. The study included 104 patients, 39 of them were diagnosed with ET (27 women and 12 men), 40 had PV (21 women and 19 men), and 25 had PMF (11 women and 14 men). The diagnosis was established based on the current diagnostic criteria of the World Health Society (WHO) [14]. The epidemiological, clinical, laboratory, therapy data obtained during outpatient consultation. Primary incidence was calculated as ratio of newly diagnosed patients` number to average region population number per 100 thousand populations. Complete blood cells (hemoglobin, platelet, leukocyte counts and number of blast cells) and spleen size were recorded at the time of diagnosis. Analysis of correlation of risk factors with incidence of thrombosis was performed using a four-field contingency table (table 1) and a χ-square test with Yeats correction ($p_{\chi 2}$). Results were considered significant at $p < 0.05$.

χ-square test with Yeats correction

$$\chi^2 = \sum_{i=1}^{r}\sum_{j=1}^{c}\frac{(|O_{ij} - E_{ij}| - 0,5)^2}{E_{ij}}$$

calculated by formula:

where Oij is the actual number of observations ij, Eij is the expected number of observations.

Results and discussion. According to literature review CMPD are mainly found in the elderly. The median age of patients at the moment of disease manifestation in our study was 50 years in ET (from 38 to 77 years), PV – 56 years (from 21 to 80 years) and PFM – 60 years (from 28 to 80 years). The median time of follow-up was 48 months (from 2 months to 23 years). In Republic of Sakha (Yakutia), the primary incidence of ET in different years ranged from 0 to 0,83, PV – from 0 to 0,73, and PMF – from 0 to 0,52 per 100 thousand population per year (fig. 1). The primary incidence of CMPD reached its maximum in 2015-2016 years, which is most likely due improvement of diagnosis with molecular genetic testing. According to foreign researchers' data, the primary incidence of ET is 0,38-1,7, PV – 0,68-2,6, and PMF – 0,1-1 per 100 thousand population per year [8], in Russian Federation there are no large epidemiological studies.

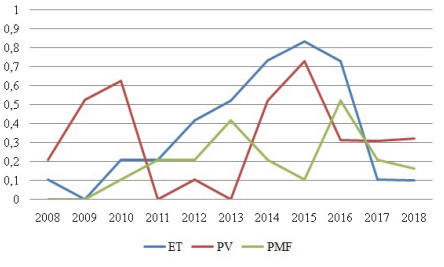
At the moment of diagnosis in patients with ET isolated thrombocytosis was the most common sign. Patients with PV demonstrated the signs of three-lineage hyperplasia and in PMF patients – leukocytosis with thrombocytosis. Splenomegaly was more common in patients with PMF (table 2).

Table 1

Four-field contingency table

	Patients with thrombosis	Patients without thrombosis	Total
Presence of risk factor	A	B	A + B
Absence of risk factor	C	D	C + D
Total	A + C	B + D	A + B + C + D

Thrombotic complications were recorded in 42,5% of patients with PV (17/40), 30,8% of patients with ET (12/39) and 28,0% (7/25) with PMF (table 3). According to the literature, thrombosis is more common among patients with PV [6, 15], which is associated with an extreme increase in the number of blood cells, hematocrit, and increased blood viscosity. In 58,3% (21/36) cases thrombosis was the first clinical symptom of disease. On average, the time from thrombosis to diagnosis of disease was 1 year. CMPD often has a latent manifestation. Polycythemia or thrombocytosis can be masked by increased plasma volume and/or hypersplenism, which causes difficulties in interpreting laboratory data, and



Morbidity of CMPD in Republic of Sakha (Yakutia) 2008-2018 years

Table 2

Clinical characteristics of patients at diagnosis

	ET	PV	PMF
Men, % (abs.)	30.8 (12)	47.5 (19)	56 (14)
Women, % (abs.)	69.2 (27)	52.5 (21)	44 (11)
Median age (from min to max)	50 лет (от 38 до 77 лет)	56 лет (от 21 до 80 лет)	60 лет (от 28 до 80 лет)
Average erythrocytes count, $M \pm m_м$*	4.7±0.9	6.6±1.4	5.1±1.4
Average hemoglobin count, $M \pm m_м$	135±19.6	171±25.2	127±30.5
Average hematocrit, $M \pm m_м$	46.5±4.6	51.3±7.7	41.7±42.6
Average leukocytes count, $M \pm m_м$	9.4±2.7	14.1±13.3	31.4±9.0
Average thrombocytes count, $M \pm m_м$	1113±442.2	711.8±445.3	881.5±615.2
Splenomegaly, % (абс.)	38.5 (15)	47.5 (19)	60 (15)

*$M \pm m_м$ – mean value ± standard deviation

Table 3

Prevalence of thrombotic complications in patients with CMPD, % (abs.)

Localization	ET (n=39)	PV (n=40)	PMF (n=25)
Arterial, total	25.6 (10)	30.0 (12)	16.0 (4)
Cerebral blood flow acute disturbances	12.8 (5)	22.5 (9)	12.0 (3)
Myocardial infarction	12.8 (5)	7.5 (3)	4.0 (1)
Venous, total	6.0 (2)	12.5 (5)	12.0 (3)
Deep vein thrombosis	6.0 (2)	10.0 (4)	4.0 (1)
Splanchnic vein thrombosis	-	2.5 (1)	8 (2)

the clinical picture is represented only by thrombosis [6].

Arterial thrombosis (30,0 and 25,6%) prevailed among thrombotic complications in patients with PV and ET — acute disorders of cerebral circulation and myocardial infarction, less frequently seen venous thrombosis (12,5 and 6%). In patients with PMF, arterial thrombosis was observed in 16% of cases, and venous in 12%. The median time between the diagnosis of the disease and the development of thrombosis was 3 years (from 0 to 30 years). Recurrent thrombotic complications were observed in 19,4% (7/36). The predominance of arterial thrombosis over venous thrombosis is explained by the direct participation in the pathogenesis of clot formation of the vascular endothelium. Damage to the vascular wall caused by hyperviscosity syndrome and the production of proteolytic enzymes by activated neutrophils, morphological and functional changes of blood cells and procoagulant state of plasma represent a multicomponent mechanism of clot formation. A number of publications report a higher thrombogenic potential of platelets in patients with *JAK2*V617F mutation [9].

The analysis of risk factors for thrombotic complications included both major factors (age over 60 years, history of cardiovascular risks) and additional (thrombocytosis more than $1000*10^9$/l and leukocytosis more than $11*10^9$/l) [3]. The contribution of different factors to pathogenesis of thrombosis is widely discussed in literature, and a number of scales have been proposed for risk stratification. Most authors agree that statistically significant risk factors for thrombotic complications are age over 60 years and history of thrombosis [2]. Among additional risk factors, some authors pay special attention to leukocytosis. It was demonstrated that activated leukocytes synthesize prothrombotic substances that cause functional changes in the endothelium, stimulate platelet activity, and they contribute to generation of thrombin and development of thrombosis [15].

Statistically significant differences in the group of patients with thrombosis and without thrombosis were revealed only by the presence of cardiovascular risk factors ($p < 0.05$) (table 4). There were no statistically significant differences in incidence of thrombosis in groups of people older than 60 years and younger. Thrombotic complications in people of working age have a high social significance, since they can lead to disability and a decrease in quality of life.

During follow-up molecular genetic testing was performed in 20,2% of patients (21/104), of which in 15,4% of patients (16/104) mutation of *JAK2* gene was fond and in 3,8% (4/104) mutation of *CALR* gene. Among patients with *JAK2*V617F mutation, thrombotic complications were observed in 62,5% of cases.

First-line therapy with interferon was prescribed to 42,5% of patients (17/40) with PV, 51,3% (20/39) with ET and 24% (6/25) with PMF. Hydroxyurea was administered to 30% (12/40) of patients with PV, 23,1% (9/39) with ET, and 44% (11/25) with PMV. In other cases, patients receive antiplatelet and vascular therapy. 6 patients are currently receiving targeted therapy with Ruxolitinib with positive effect. During therapy with Ruxolitinib, thrombotic complications were not observed in patients.

Conclusion. In the Republic Sakha (Yakutia) for the research period (1995-2018) the primary incidence of ET per 100 thousand population per year was 0 – 0.83, PV – 0 - 0.73, and PMF – 0 – 0.52, reaching maximum values in 2015-2016. Thrombotic complications, which are a serious clinical problem, are observed in patients with CMPD in 28-42.5% of cases. In a half of the cases, thrombosis was a first clinical symptom of myeloproliferative disease. A statistically significant risk factor for thrombosis is the presence of cardiovascular risks, which determines the need for a comprehensive approach to the treatment of this group of patients.

Table 4

Prevalence of thrombosis risk factors in patients with and without thrombosis, % (n)

Risk factor	Patients with chronic myeloproliferative diseases	
	without thrombosis (n=68)	with thrombosis (n=36)
Age 60 and older	51.5 (35)	47.2 (17)
Cardiovascular risk factors	19.1 (13)	38.6 (15)
Thrombocytosis>$1000*10^9$/l	30.9 (21)	19.4 (7)
Leukocytosis >$11*10^9$/l	27.9 (19)	33.3 (12)

* $p_{\chi 2}$ – χ-square test with Yeats correction

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THE INCIDENCE OF DYSPLASTIC CHANGES IN CERVIX UTERI AMONG WOMEN OF DIFFERENT AGE GROUPS

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The article presents an analysis of the incidence of dysplasia degrees and cervical cancer (CC) in women of different age groups based on cytological studies from 2016 to 2018 inclusive. The frequency of incidence of CIN 1, CIN 2, CIN 3 and CC was determined, which is inversely dependent on the dysplasia degree in all age groups of women. While the incidence of CIN 2, CIN 3 and CC was decreasing, CIN 1 increased between 2016 and 2018. Women 26-35 years had the highest incidence of CIN 1, CIN 2 and CIN 3; also CIN 2 was detected in women 36-45 years, as in the first group; women of 46-55 years had a sharp rise in CC - it is 2.5 times higher than in previous two groups. The peak incidence of CC was in patients aged 56 years and older.

Keywords: screening, oncocytology, diagnosis, dysplasia, cervical cancer.

Relevance. According to various authors, cervical pathology makes up from 10 to 15% of all gynecological diseases [3]. Occurrence and development of the causes and mechanisms of cervix uteri pathological processes are rather complex and understudied process [2]. As is known, dysplastic changes in the cervix uteri epithelium are considered as precancerous states [6], there is evidence that one of the main conditions for the development of dysplasia and CC is the persistence of the human papillomavirus (HPV) [8,9].The state of local immunity, as a regeneration process control agent [1], has great importance in the development of dysplastic processes in the cervix uteri, as well as a hormonal state, since cell developing and differentiation in the stratified squamous epithelium of the cervix uteri is hormone-dependent. Because of the hormonal status in women depends on age, it determines the usefulness of studying the features of dysplastic changes in cervix uteri in different age groups, irrespective of the

HPV detection in patients. In addition, the frequency of epithelial dysplasia increases with age [6]. However, the greatest pathogenic effect of HPV manifests in young women, and it realizes in the development of cervical intraepithelial neoplasia (CIN) of severe degree [9], which requires careful study of age-related features of pathomorphological dysplasia presentation. Dysplasia is a morphological concept, so diagnosis is made only on the basis of cytological and histological data [6].Cells with dyskaryosis are cytologically detected in dysplasia of cervical smear. Depending on the severity of changes in the nucleo-cytoplasmic ratio and other structural features (shape, nuclei, content, and distribution of chromatin, inclusions in the cytoplasm) there are 3 degrees of CIN: CIN 1 (mild dysplasia), CIN 2 (moderate dysplasia) and CIN 3 (severe dysplasia) [7]. Cytological picture of CIN 1 is represented by relatively mature cells with relatively large nuclei. These cells are located separately or in the two-dimensional assembly of unchanged squamous epithelial cells. Cells retain signs of cytoplasmic differentiation characteristic of the surface and intermediate layers of the flat epithelium. Nuclei – slightly hyperchromic, with the same type of uniform granular structure of chromatin, nucleoli are absent. Signs of infection with the human papillomavirus (HPV) are often occurred . In CIN 2 the shape and size of cells resemble cells of immature squamous metaplasia, but with larger nuclei. The cytoplasm has a sharp contour (a distinction of squamous cell differentiation). Nuclear-cytoplasmic ratio is increased. There is hyperchromia of the nuclei, the granular structure of chromatin, and nucleoli are not visible. Sometimes signs of HPV infection are found. In cytological preparations with CIN 3 signs of atypia are more intensive. Sharp contours of the cytoplasm are visible in cells, making them relate to the squamous epithelium cells. Nuclear-cytoplasmic ratio strongly increased. Severe atypia is particularly visible in the nucleus: lumpy chromatin, nuclear membrane are irregular, nucleoli are absent. There are remote signs of HPV infection [5].

Purpose of research. To determine the features of the occurrence of dysplastic changes in cervix uteri in women of different age groups, we decided to analyze the frequency of incidence of CIN 1, CIN 2, CIN 3 and CC in cytological smears of women of different age groups who were examined from 2016 to 2018 inclusive; to identify the frequency and dynamics of CIN 1, CIN 2, CIN 3 and CC depending on the year of examination and age of women.

Materials and methods of research: The analysis of cytologic material of a cervix of 7600 women aged from 18 up to 88 years with the preventive and diagnostic purpose, during 2017 – 2018 is carried out to laboratory of a pathomorphology, histology and cytology of Clinic of Medical institute of NEFU.

The material of the study was smears from the mucosa of the cervix uteri and the cervical canal. Cytological diagnosis was carried out by staining, the method of Romanovskiy - Giemsa. Cytological diagnosis – degree CIN (cervical cancer) is made in accordance with the clinicopathologic classification of Y. V.Bokhman (1976). The incidence of CIN 1, CIN 2, CIN 3 (CC) in smears was expressed in percentage of the total number of women with dysplasia.

Results and discussion. The total number of patients with dysplastic changes in the cervix uteri of different degrees was 931 people. Of them, 128 women (13.7% of the total) went through cytological examination in 2016, 322 women (34.6 %) in 2017, and 481 women (51.6%) in 2018. Cytological material was studied in women according to the age groups, the distribution was as follows: women under 25 years - 144 people (15.5%), 26-35 years – 222 people (23.8%), 36-45 years – 212 women (22.7%), 46 – 55 years – 192 women (20.6%), 56 years and older – 161 women (17.3%).The CIN incidence of varying degrees is analyzed, as well as CC in the cytological smears of all women who underwent examination from 2016 to 2018 inclusive. It is clear that the highest rate is in CIN 1, which was registered in 578 women and amounted to 62.1% of all women studied, CIN 2 was found in 241 women (25.9%), and CIN3 was diagnosed in 97 women, which amounted to 10.4% of all cervical dysplasia in the examined group (pic.1,2).Cervical cancer was cytologically detected in 15 cases and amounted to 1.6% of the total number of examined women (pic.5).It should be noted that the high frequency of CIN 1 incidence is detected in the inflammation of the cervix when a cytological study reveals reparative atypical cells – equivalents of dysplasia. These phenomena often disappear after anti-inflammatory treatment, elimination of the viral agent [4].

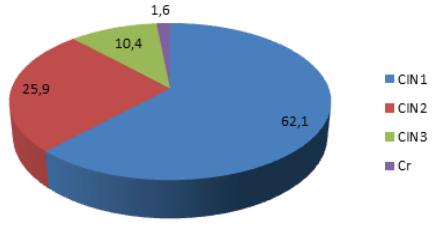

Fig. 1. The distribution of the incidence rate of the dysplasia of different degree for the period 2016-2018

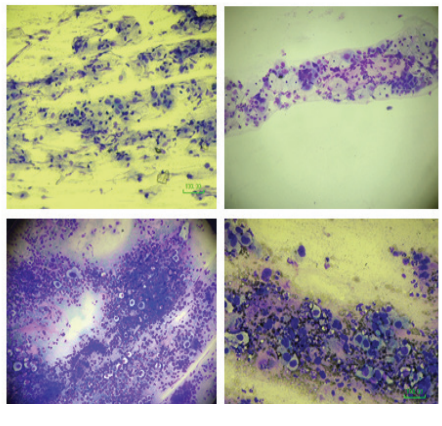

Fig. 2 A – Cells with signs of mild dysplasia (CIN 1), B – cells with signs of moderate dysplasia (CIN 2), C, D– severe dysplasia (CIN 3), X200

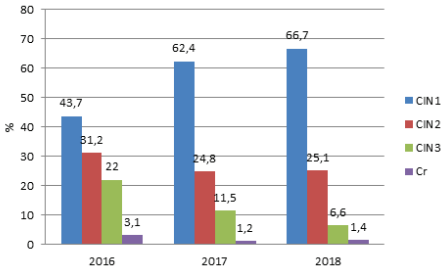

Fig. 3. Dynamics of incidence of dysplasia of different degrees for the period 2016-2018

As Fig.3 shows analysis of the frequency of CIN 1, CIN 2, CIN 3 incidence and CC over a three-year period (from 2016 to 2018 inclusive), depending on the year of the examination, CIN 1 is increasing from year to year while CIN 2 and CIN 3 are reducing. The frequency of CIN 1 incidence in 2018 increased by 52.6% compared to 2016, while the CIN 2 incidence decreased by 24.3%, and the CIN 3 incidence decreased 3.3 times. The incidence of CC decreased 2.2 times in the studied smears during a three-year period. It indicates a positive dynamics in the development of dysplasia. The growth of CIN1 can be

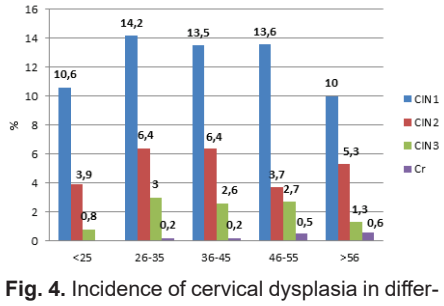

Fig. 4. Incidence of cervical dysplasia in different age groups

explained by reactive epithelial changes in various inflammatory diseases. Reduction of CIN2 and CIN3, CC can be associated with constant monitoring of patients and the development of dysplasia in the dynamics and effectiveness of the treatment.

In studying the incidence of cervical dysplasia depending on age, our analysis showed that the most frequently diagnosed cervical pathology in all age groups was CIN 1(pic.4).The maximum frequency of CIN 1(14.2%) incidence was observed in women of 26-35 age group, the minimum value of this indicator (10%) was in the group of 56 years and older. The maximum frequency of CIN 2 (6.4%) incidence was observed in the same population in two groups (26-35 years and 36-45 years). Both groups represent women of childbearing age. The minimum frequency of CIN 2 (3.7%) incidence was in the group of women 46-55 years. The highest incidence of CIN3 was observed in women aged 26-35 years and was 3%. The minimum incidence of CIN3 (0.8%) was in women under 25 years. The obtained data is indicating the maximum number of women who became ill at fertile age, and it is an alarming fact since this group of patients is not only a reproductive considerable part of the female population but also an active social group. Cervical cancer was detected cytologically in 15 cases and amounted to 1.6% of the total number of women examined. The maximum incidence of CC was observed in of 56 years and older age group-6 cases (0.6%). It should be noted that the incidence of CC increases depending on the age of patients. The rate is 2.5 and 3 times higher in women of 46-55 years and 56 and older age groups than in women 26-45 years age group (in women under 25 years, CC was not detected).The study confirms that the progression of the severity of dysplasia is going many decades [10]. Also, when the severity of dysplasia increases -the risk of its progression increases and the chance of regression decreases.

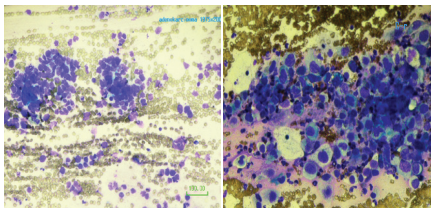

Fig. 5. A - adenocarcinoma of the cervix uteri, B - squamous cell carcinoma of the cervix uteri, X200

Conclusion. The frequency of CIN 1, CIN 2, CIN 3 and CC incidence in smears of cervix uteri and the cervical canal was inversely dependent on the degree of dysplasia in all age groups of women who were examined from 2016 to 2018.The incidence rate of CIN 1 increased from 2016 to 2018, while CIN 2 and CIN 3 and CC have been decreasing the rates. Analysis of the nature of CIN 1, CIN 2, CIN 3 and CC incidence, depending on age revealed that women of 26-35 years had the highest incidence of CIN 1, CIN 2 and CIN 3, women of 36-45 years had CIN 2 with the same frequency as in the previous group, and women of 46-55 years had a sharp increase in CC by 2.5 times, compared with the previous two groups, but patients of 56 years and older had the peak incidence of CC.

Regular cytological examination of cervix uteri leads not only to decrease in the number of newly diagnosed patients from year to year but also to absence or slowdown of negative dynamics and possible regression of existing pathological changes in cervix uteri. Prevention, early detection and effective treatment of malignant tumors is one of the most important part of modern medicine. The need of regular preventive examinations of women with the necessary cytological examination, clinical examination, and treatment of patients with background CC diseases is appears based on the data analysis of the incidence of dysplasia and CC. Such an arrangement should be optimized according to the age of women. Our results require special studies on developing the lines of approach on the main problems associated with the detection, prevention, and treatment of early forms of CC. However, at present, we recommend paying more attention to women born in 1980-1990 (age group 26-35 years), who most often had dysplasia of all degrees, including severe degree, women of 1960 (age group 46-55 years and older), who had a sharp increase of CC.

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THE STRUCTURED SPOT OF BLOOD PRESSURE FROM THE PERSPECTIVE OF THE "GOLDEN RATIO" PROPORTION

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The analysis of blood pressure indicators for residents of the Republic (Yakutia) from the position of the golden ratio using the structural spot of blood pressure (SSBP) - the ratio of DBP / SBP with a value close to the value of the golden ratio (ZP) - 0.618 (harmonious ratio) was performed. Existing blood pressure standards (120/80 mmHg) are not always acceptable for all categories of the population, especially for older people. Therefore, each person needs an individual approach. It has been established that SSBP opens up new possibilities in terms of the proportion of the golden ratio in predicting the stability of the course of blood pressure during functional studies in patients with arterial hypertension.

Keywords: Yakutia, blood pressure, arterial hypertension, golden ratio.

Introduction. In recent decades, essential arterial hypertension (EH) and coronary heart disease (CHD) have firmly taken the leading place in the structure of cardiovascular and overall population morbidity. Arterial hypertension (AH) is significant because it is the most important risk factor for cardiovascular diseases, mainly affecting the statistics of complications, disability and high mortality in the world community. More than half of the deaths in the Russian Federation are due to circulatory system diseases. According to the statistics of the general morbidity rate of the adult population in 2017, the index of hypertensive heart and kidney disease was 264.3 per 100,000 of the total population [10].

In recent years, the prevalence statistics of AH in the territory of the Sakha (Yakutia) Republic continues to grow. Therefore, in 2016-2017, the prevalence of AH was 43.7 and 44.82%, respectively. According to the latest statistics, the number of deaths from circulatory system diseases from January to December 2018 in Yakutia was 355.0 per 100,000, and 325.6 from January to February 2019 [5, 19].

According to the synergetics theory, the human body is a multi-level hierarchically organized complex system. Different levels interact with each other in different ways and thereby determine the state of dynamic equilibrium [6,15].

The state of dynamic equilibrium supports the functioning of the organism, and a change of this state as a result of external influences or diseases leads to disturbances in hierarchical interactions. These disorders are either quickly compensated or lead to the development of the pathological process [3].

Thus, the circulatory system can also be viewed as a multi-level hierarchically complex system and at the level of its constituent subsystems that determine the balance of the body. One of the displays of such structural and functional balance is a correspondence with the “Golden ratio” rule [17,18].

The rule of the golden ratio has been known to mankind for a long time and has found application both in science and art. Pythagoras introduced the concept of the gold division into science. The “golden ratio” is known as proportions: the division of the AC interval into two parts, so that the length of the bigger part AB is to the length of the smaller part BC in the same way as the length of the whole interval to the length of AB (AB: BC = AC: AB). The golden ratio is made if the whole is to the one part as 1:0.618, and most to the lesser as 0.618:0.382 [17, 18]. Also, the concept of the “golden ratio” is described by the proportions found by using the value that is the universal quotient of dividing a larger number by the next smaller number in the gold series of Fibonacci numbers (1, 1, 2, 3, 5, 8, 13, 21, 34, 55, 89 etc.; that is 89:55 = 1.618 ...) [17,18].

In recent years, scientists have actively studied the relationship of the golden ratio with the heart function and hemodynamic indices. V.D. Tsvetkov was the first to show the role of the golden ratio and Fibonacci numbers in the organization of the cardiac systems, he found that the golden numbers are the guarantors of the optimal heart activity, the most economical in terms of energy and living matter [7, 18]. Moreover, it was researched that the ratio of heart rate variability to the diastolic interval was 1.618, which is the golden ratio [8, 21]. Similar studies were conducted to find out whether diastolic and systolic blood pressure is consistent with this ratio [22].

Deviations from ideal indices (1.618 or 0.618) among healthy people are considered to be no more than 5–8%, even with the changes of hemodynamic indices by 1.5–2 times [1].

In 1998 V.V. Shkarin and E.V. Gurvich studied the clinical value of diastolic (DBP) and systolic (SBP) blood pressure (BP) ratio. This ratio has the term "structured spot of blood pressure" (SSBP). Currently, it is known that SSBP is approaching the value of the “golden ratio” proportion - 0.618. Regardless of BP indicators, SSBP aims for a constant value [3, 4].

V.G. Bochkov developed a universal table of the quality zones of the systems

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functioning, depending on the value of indices similar to SSBP for any biological system, applicable for BP, too [4].

The purpose of this study was to assess and analyze the structured spot of blood pressure in residents of Yakutia from the perspective of the "golden ratio".

Materials and methods. The study used the existing database of biomedical expeditions of the Yakut Science Centre of Complex Medical Problems from 2008-2018, including data on 1959 people. Blood pressure data of 12 regions of the Republic of Sakha (Yakutia) was analyzed. Districts were divided by socio-economic zones: Northern (Arctic) - Anabarsky, Verkhnekolymsky, Srednekolymsky; Eastern - Ust-Maysky, Oymyakonsky (Tomtor, 2018), Oymyakonsky (Ust-Nera, 2008); Western – Vilyuysky; Southern - Lensky, Aldansky; Central - Megino-Kangalasky, Ust-Aldansky, Yakutsk.

The body mass index (BMI) was calculated by the formula: BMI = body weight in (kg) / height (m)^2 [16]. For overweight took the values were > 25 and < 30 kg / m^2. Obesity was recorded with a BMI ≥ 30 kg / m^2 (according to European recommendations of the III revision, 2003). During the classification of blood pressure levels of mm Hg. data from VNOK (2009) [2] was used, so the optimal was <120 and <80 mm Hg, normal 120–129 and / or 80–84 mm Hg, high normal 130-1139 / or 85–89 mm Hg; Grade 1 hypertension corresponded to 140–159 and / or 90–99 mm Hg, grade 2 hypertension - 160–179 and / or 100–109 mm Hg, 3rd degree hypertension - ≥ 180 and / or ≥110 mm Hg. For the assessment of blood pressure indices, the "structured spot of blood pressure" (SSBP) and the ratio of DBP/SBP was used. It is now known that SSBP is approaching the value of the golden proportion of the RFP - 0.618 (harmonious ratio). The values of blood pressure with SSBP in the range from 0.564 to 0.673 among healthy people were considered stable. In patients with arterial hypertension (AH), "disharmony" ranged from 0.549 to 0.687 (the deviation of GP from up to 8% - 11%).The greatest differences from the GR proportion, "imbalance or disbalance" (12% and above), which are characteristic of unstable states: borderline arterial hypertension, severe forms of AH, possibly crisis forms of AH [3].

Statistical processing of the results was performed using the SPSS application package (version 17) and Microsoft Office Excel 2003.The accuracy of differences between average indices was assessed using Student's t-test, Wilcoxon–Mann–Whitney (Z) and Kolmogorov–Smirnov nonparametric test. Differences were considered statistically significant at p <0.05.

Research results. According to the blood pressure data of the studied population, the structured spot of blood pressure was calculated as the clinical value. At the moment, it has been shown that SSBP is approaching the value of the proportion of the golden ratio = 0.618 [4].

The results of anthropometric indices close to the golden proportion (GP) in terms of blood pressure and SSBP are presented in Table 1. With the indices of SSBP equal to (0.615-0.618), the residents of Tomtor village, Oymyakonsky District had the shortest height (1,547 ± 0,03), and the residents of Yakutsk are the tallest 1,731 ± 0.06 m (p <0.05). The body weight of the residents of the Srednekolymsky District corresponded to 81.10 + 7.24 kg and was the highest indicator in the compared groups, and the residents of the Megino-Kangalasky district had the smallest weight - 61.42 + 7.36 kg (p <0.05). Body mass index (BMI) showed as overweight almost in all groups. Obesity was observed in residents of the Verkhne- and Srednekolymsky districts (30.83 + 3.06, 31.59 + 4.32 respectively), as well as in the Oymyakonsky District, Ust–Nera village (32.89 + 3.00) (Table 1).

The results of the obtained blood pressure (BP) data and SSBP in the surveyed residents by district are presented in Table 2. The average indices of blood pressure and SSBP in the districts were SBP 129.94 + 0.544 mm Hg, DBP 81.10 +, 297 mm Hg. at a harmonious SSBP of 0.629 + 0.00. A SSBP close to the golden proportion (0.618) was found in the residents of Anabarsky (0.615 + 0.00) and Ust-Aldansky (0.619 + 0.00) districts, where blood pressure corresponded to SBP 135.45 ± 2.29 mm Hg. and 134.05 + 1.59, DBP 82.13 ± 0.82 and 81.92 + 0.76 mm Hg respectively (Table 2).

With age, there is a tendency of increased blood pressure and decreased SSBP, while significant differences in pressure and SSBP have been observed since the age of 30. High pressure, exceeding normal values, begins at the age of 50 and reaches the highest value in the age group of 80-89 years old (Table 3). It should be noted that from the surveyed population, only 1.61-3.23% of the population had a harmonious (0.615) SSBP indices, close to the GP (0.618) (Table 3).

The surveyed population was divided into 2 groups: the 1st group included res-

Table 1

Anthropometric measurements and BMI among the examined residents with the SSBP indices close to the Golden proportion (0,615-0,618)

DISTRICT	Height, m	Weight kg	BMI	SBP, mm Hg	DBP, mm Hg	SSBP
Anabarsky n=16 (13.11%)	1.62 ±0.05	74.41 ±8.30	29.35 ±3.59	130.0 0±.00	80.0 0±.00	0.615 0±.00
Lensky n=13 (9.15%)	1.61 ±.04	68.25 6±.30	26.25 ±2.49	128.1 3±.65	78.84 2±.19	0.616 ±0.00
Megino-Kangalasky n=12 (6.15%)	1.53 ±0.04	61.42±7.36	26.31± 2.69	130.00 ±5.73	80.00 ±3.44	0.615 ±0.00
Oymyakonsky 2018 (Tomtor village) n=3 (1.62%)	1.55 ±0.03	62.33 ±11.43	26.14 5±.14	121.67 ±10.97	75.00 ±6.58	0.617 ±0.00
Srednekolymsky n=4 (8.51%)	1.67 ±0.02	81.10 ±7.24	31.59 ±4.32	130.75 ±12.43	80.50 ±7.52	0.616 ±0.00
Ust-Aldansky n=16 (4.97%)	1.61 ±0.05	68.68 ±4.65	26.49 ±1.61	132.50 ±8.90	81.56 ±5.46	0.616 ±0.00
Ust-Maysky n=8 (5.63%)	1.59 ±0.04	73.87 ±9.23	29.25 ±4.11	129.12 ±14.47	79.38 ±8.77	0.615 ±0.00
Vilyuysky n=4 (5%)	1.59 ±0.05	63.25 ±13.73	25.026 ±4.84	125.75 ±15.64	77.50 ±9.35	0.617 ±0.00
Verkhnekolymsky n=7 (8.05%)	1.65 ±0.05	83.57 ±9.53	30.83 ±3.06	119.14 ±6.48	73.57 ±3.85	0.618 ±0.00
Yakutsk n=13 (3.54%)	1.73 ±0.06	83.23 ±7.45	27.79 ±2.10	130.00 ±0.00	80.00 ±0.00	0.615 ±0.00
Aldansky n=15 (8.93%)	1.67 ±0.05	77.13 ±8.40	27.60 ±2.53	133.33 ±6.56	82.00 ±3.94	0.615 ±0.00
Oymyakonsky 2008 (Ust-Nera village) n=7 (6.94%)	1.59 ±0.48	83.80 ±5.19	32.89 ±3.00	121.57 ±6.67	75.00 ±3.97	0.617 ±0.00

Table 2

The indices of BP and SSBP by districts

Districts	n	SBP, mm Hg	DBP, mm Hg	SSBP
Anabarsky	122	135.45±2.29	82.13±0.82	0.615+0.00
Lensky	142	137.64+2.19	81.77+0.86	0.604+0.00
Megino-Kangalasky	195	117.79+1.44	73.59+0.81	0.627+0.00
Oymyakonsky 2018 (Tomtor Village)	185	144.52+2.02	90.19+1.02	0.632+0.01
Srednekolymsky	47	126.32+2.54	78.50+1.62	0.625+0.01
Ust-Aldansky	322	134.05+1.59	81.92+0.76	0.619+0.00
Ust-Maysky	142	132.26+1.97	85.34+1.25	0.648+0.00
Vilyuysky	80	130.76+2.34	82.71+1.57	0.634+0.00
Verkhnekolymsky	87	129.57+2.77	77.53+1.26	0.605+0.06
Yakutsk	367	123.30+0.96	77.99+0.70	0.632+0.00
Aldansky	168	125.80+1.10	82.05+0.71	0.653+0.00
Oymyakonsky 2008 (Ust-Nera village)	101	125.13+2.00	80.96+1.17	0.649+0.00
Overall	1959	129.94+0.54	81.10+0.29	0.629+0.00

idents who did not have high blood pressure, the 2 group included people diagnosed with arterial hypertension. When comparing the average indices of SSBP by districts in the 1st group with harmonious SSBP, residents of the Verkhnekolymsky district amounted to mean 0.609 ± 0.05, and disharmonious SSBP was found among residents of Yakutsk 0.631 ± 0.06. In group 2, harmonious SSBP (0.614 ± 0.07) was observed in the residents of Tomtor village, Oymyakonsky District and Megino-Kangalasky (0.609 ± 0.05) District. Residents of Lensky District turned out to have a disharmonious SSBP (0.566 ± 0.07).

When analyzing data by districts, harmonious SSBP was observed among the population of Ust-Aldansky, Anabarsky and Lensky districts, and when comparing across SSBP zones, harmonious indices were found among residents of the Arctic (Table 4). Within the zone by districts, a significant difference was found in the Northern (Arctic) zone - between Anabarsky and Verkhnekolymsky districts - p <0.04 (according to Kolmogorov). The eastern zone - between Ust–Maysky and Oymyakonsky (Ust-Nera, 2008) districts - p <0.05. Southern zone - a significant difference was observed between Lensky and Aldansky, p <0.001, the Central zone - Magino-Kangalassky district and Yakutsk, p <0.001. Also, the difference in SSBP indices between the zones was significant: between the Northern and Eastern, Northern and Western (p <0.02), Western and Southern, (p <0.001), Southern and Central zones (p <0.02) (Table 4).

Results of the comparative analysis of the groups 1 and 2 are presented in table 5. Indices of blood pressure of the 1st group were within the limits of the permissible rate, harmonious SSBP was detected in 70 people, which amounted to 3.57% (Table 5). In group 2, blood pressure was higher than normal - SBP144.36 ± 0.88 and DBP 89.15 ± 0.51, however, it should be noted that disharmonic SSBP was 0.619 ± 0.00, which is very close to the golden proportion (0.618). Thus it is possible to confirm the statement of K. Nishi that the main indicator of health is the ratio of upper (SBP) and lower (DBP) pressure, which is 7/11 (or quite close to this value within 6/11 - 8/11), as it is approaching the golden ratio (0.618). Meanwhile, in group 2, harmonious SSBP (0.615) was indicated in only 1.84% of people. Harmonious SSBP in group 1 was significantly different from all other indices of SSBP and blood pressure of group 2 (χ 2 = 0.000, p = 0.001) (Table 5).

Table 3

The indices of BP and SSBP in relation to age

Age	N	SBP, mm Hg	DBP, mm Hg	SSBP	with SSBP (0,615) in %	P<0,05
20-29	247	112.07+3.83	73.29+2.35	0.635+0.00	3.23	-
30-39	360	118.32+0.84	76.13+0.57	0.644+0.00	2.5	+
40-49	417	125.79+0.95	80.73+0.63	0.643+0.00	2.63	+
50+59	574	135.88+0.98	84.83+0.54	0.629+0.00	2.09	+
60-69	249	147.32+1.69	87.43+0.87	0.599+0.00	1.61	+
70-79	75	153.28+3.03	86.40+1.31	0.572+0.00	2.66	+
80-89	19	154.42+6.04	84.742.99	0.555+0.02	-	+
90 + y. o.	1	160	80	0.500	-	-

In the study of SSBP, depending on the classifications of blood pressure, the following results were obtained. Out of the total number of people studied, hypotonia was detected in 75 people (3.84%) with an average BP of 94.06 / 61.75 mm Hg, SSBP was disharmonious. 578 people (29.57%) had optimal pressure, BP was 108.65 / 70.4 mm Hg, SSBP was disharmonious. Normal blood pressure was observed in 401 people (20.51%), blood pressure was 123.56 / 81.35 mm Hg, and SSBP was disharmonious. High normal blood pressure was present in 262 people (13.40%), blood pressure was 131.97 / 90.59 mm Hg, SSBP was disbalanced. Moderate hypertension was detected in 378 people (19.34%), blood pressure was 145.61 / 90.47 mm Hg, SSBP was disharmonious. Hypertension of moderate severity occurred in 169 people (8.44%), blood pressure ranged 165.70 / 94.87 mm Hg, SSBP was disbalanced. 92 people (4.71%) appeared to have severe hypertension, BP 192.33 / 103.04 mm Hg, SSBP was disbalanced (Table 6). Unbalanced SSBP (0.542) occurred in all classifications of blood pressure, however, the highest incidence was observed in people with moderate (16.57%) and severe hypertension (64.13%). Harmonious SSBP (0.615) is observed only in residents with high normal pressure. SSBP was disharmonious in all classifications of blood pressure and the largest numbers had residents with hypotension (50.67%) (Table 6). With an increased blood pressure and BMI, a decrease in SSBP and remoteness from the golden proportion (0.618) was observed, and a strong inverse correlation was noted between them (r = -0.854, p <0.05) (Table 6).

When the heart is working in the vessels, hydrodynamic pressure is created, which is caused by the resistance of the vessel walls. For an adult, a conventionally normal blood pressure is: the maximum (systolic) -100 - 140 mm Hg. and the minimum (diastolic) - 70 - 90 mm Hg.

Thus, the range of possible BP in humans is 0–100–140 mm Hg. We divide this range in relation of 1.61:1, we get 100 / 1.618 = 61.8 mm Hg. 140 / 1.618 = 86.5 mm Hg., which is very close to the parameters of diastolic pressure. With

Table 4

The indices of SSBP by districts, divided by the socio-economic zones

Socio-economic division of districts by zones	Group 1 (without AH)	Group 2 (with AH)	Total amount
Northern (Arctic)			
Anabarsky	0.654±0.03 n=64	0.573±0.05 n=58	0.615±0.04 n=122
Verkhnekolymsky	0.609±0.05 n=60	0.598±0.08 n=27	0.606±0.06 n=87
Srednekolymsky			0.625±0.05 n=47
TOTAL			0.615±0.05
Eastern			
Ust-Maysky	0.655±0.04 n=72	0.641±0.07 n=71	0.648±0.06 n=143
Oymyakonsky 2018	0.674±0.05 n=55	0.614±0.07n =130	0.632±0.07 n=186
Oymyakonsky 2008	0.662±0.03 n=55	0.641±0.04 n=56	0.650±0.04 n=101
TOTAL			0.643±0.04
Western			
Vilyuysky	0.642±0.05 n=52	0.621±0.06 n=28	0.635±0.06 n=80
TOTAL			0.635±0.06
Southern			
Lensky	0.642±0.04 n=71	0.566±0.07 n=71	0.604±0.07 n=142
Aldansky	0 . 6 5 7 ± 0 . 0 3 n=117	0.644±0.05 n=48	0.653±0.04 n=165
TOTAL			0.628±0.05
Central			
Megino-Kangalasky	0.637±0.03 n=30	0.609±0.05 n=65	0.628±0.04 n=195
Ust-Aldansky	0.646±0.03 n=170	0.588±0.06 n=152	0.619±0.06 n=322
Yakutsk	0.631±0.06 n=251	0.633±0.06 n=116	0.632±0.06 n=367
TOTAL			0.626±0.05n=1959

Table 5

The indices of BP and SSBP among the examined residents without AH and with AH

	Indices	SBR, mm HG	DBR, mm HG.	SSBR	%
Group 2 (without AH)	Stable disharmony (0.564-0.673) n=732	116.24±0.53	74.14±0.03	0.638±0.00	37.37
	Lower disbalance (from 0.564 and lower) n=96	118.57±1.85	63.45±0.81	0.537±0.00	4.9
	Higher disbalance (from 0.673 and higher) n=232	116.81±1.05	82.79±0.35	0.709±0.00	11.84
	Harmonious. close to GP (0.618) n=70	126.13±1.27	77.60±0.62	0.619±0.00	3.57
Group 2 (with AH)	Stable disharmony (0.549-0.687) n=535	144.36±0.88	89.15±0.51	0.619±0.00	27.31
	Lower disbalance (from 0.549 and lower) n=152	170.70±1.56	86.01±0.95	0.505±0.00	7.76
	Higher disbalance (from 0.687 and higher) n=106	134.46±1.37	96.24±0.98	0.716±0.00	5.41
	Harmonious. close to GP n=36	131.11±1.95	80.69±1.19	0.615±0.00	1.84
	Total n=1959				100%

hypertensive disease or with increased physical exertion, blood pressure rises. The maximum possible systolic pressure in humans can reach 230 mm Hg. The limiting value of blood pressure differs from normal systolic by 1.618 times: 140 * 1.618 = 226.5 mm Hg. From this we can conclude that the ratio of blood pressure with the golden proportion is obvious.

It is believed that the fluctuations of the upper pressure are harmful to the body. However, as it was written above, Professor Katsuzo Nishi (2006), lived in the early 20th century, the ratio between upper and lower pressure and vice versa considered to be especially dangerous disruptions. He considered the "golden ratio" of blood pressure, which is 7/11 (or rather close to this value within (6/11 - 8/11)), as an indicator of health, which should be aligned with. With this ratio, practically any figures of upper and lower pressure are absolutely not dangerous for a person, even 274/174 mm Hg (0.635). But if this "golden ratio" is violated, for example, at the level of BP of 127/95 mm Hg (0.748), there is a significant health hazard. And, of course, the greater the difference between the ratio of upper/lower pressure and the "golden ratio" is, the higher the risk of developing cardiovascular diseases. It should be noted that this formula is applicable only to people over 20 years of age [9].

O.V. Tatarinova (2014) in a result of a 7-year prospective observation of residents of Yakutia over 60 years old with a minimal risk of death, revealed that in both sexes, the SBP was 148.3 ± 24.2 and the DBP was 87.4 + 11.7, BMI - 26.7 ± 5.1. Let's make the calculation from the point of view of the Nishi's golden proportion: 87.4 x11 = 961.4 / 148.3 = 6.48, which is an indicator of health in the "golden ratio", SSBP turned out to be disharmonious - 0.589. Our obtained results upon the age gradient above 60 years old correspond with the data of O.V. Tatarinova (Table 3) [14].

M.A. Karpenko et al. (2010) researched the clinical value of quantitative analysis of ECG and BP using the "golden ratio" method and found that if the ECG and blood pressure values deviate from the optimal values by more than 15%, the probability of having CHD in the examined patients is 85% [6].

It is interesting how according to a large-scale HOT study (Hypertension Optimal Treatment), which included the study of 18,790 patients with hypertension, the optimal blood pressure in terms of the lowest risk of death due to cardiovascular causes, is considered to be BP = 138.8 / 86.5 mm Hg. The calculation of

Table 6

The indices of SSBP in relation to the qualification of BP

Classification of BP	SBP, mm Hg	DBP, mm Hg	SSBP	SSBP (0,542)	SSBP (0,615) harmonious	SSBP (0,667)
Hypotonia lower than 100/60 n=75	94.06 ±2.30	61.75 ±1.70	0.657 ±0.01	(1.33%) n=1	-	(50.67%) n=38
Optimal BP 100-119/60-79 n=578	108.65 ±1.37	70.40 ±1.91	0.649 ±0.02	(14.19%) n=82	-	(5.53%) n=32
The norm 120-129/80-84 n=401	123.56 2±.39	81.35 ±2.43	0.659 ±0.02	(1.74%) n=7	-	(53.87%) n=216
High normal BP 130-139/85-89 n=262	131.97 ±1.21	90.59 ±16.73	0.688 ±0.13	(262%) n=5	(35.87%) n=94	(8.6%) n=22
Moderate hypertension (1st degree AH) 140-159/90-99 n=378	145.61 1±.30	90.47 ±1.88	0.622 ±0.01	(2.91%) n=11	-	(6.08%) n=23
Hypertension of intermediate severity (2nd degree AH) 160-179/100-109 n=169	165.70 ±1.59	94.87 ±3.07	0.573 ±0.02	(16.57%) n=28	-	(1.18%) n=2
Severe hypertension (3rd degree hypertension) Higher than 180/ Higher than 110 n=92	192.33 ±5.07	103.04 ±4.53	0.537 0±.02	(64.13%) n=54	(1.08%) n=1	(3.26%) N=3
TOTAL=1955				193 (9.87%)	95 (4.85%)	336 (17.19)

SSBP from these data gives the number of 0.6231, absolutely identical to the average value of SSBP, which was obtained from the study of a group of healthy individuals, and according to Nishi, the ratio of blood pressure was 6.85. The lowest risk of developing cardiovascular complications was found at BP = 138.5 / 82.6 mm Hg. SSBP in this case is equal to 0.5942, which is also included in the range of SSBP ± 1s [3].

Thus, the existing norms of blood pressure (according to WHO: 120/80 mm Hg) do not apply to all people, especially the elderly. Therefore, an individual approach is necessary for each patient, taking into account the proportion of the “golden ratio”. Analysis of the values of the structural constant of blood pressure opens up new possibilities in terms of predicting the stability of arterial hypertension, and determination of the structured spot of blood pressure will be appropriate during functional studies in patients with arterial hypertension and coronary heart disease.

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STUDY OF THE LACTATE LEVEL IN THE BLOOD SERUM OF ATHLETES TRAINING IN THE CONDITIONS OF THE FAR NORTH

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The article presents the results of studies of the lactate level, physical performance and lipid peroxidation in highly skilled athletes in the Far North. We examined 85 men of Yakut nationality, including 60 highly qualified athletes (candidates for masters of sports (kmc) and masters of sports (ms)), aged 17 to 21 years old, the first group consisted of free-style wrestlers -30 people, the second - boxers 30 people.

The control group consisted of young students engaged in physical exercises at least twice a week. It was shown that the level of lactate depended on the level of physical performance of athletes and the accumulation of lipid peroxidation products. The highest values of lactic acid were noted at the recovery stage.

Keywords: lactate, lipid peroxidation, physical performance, athletes, Far North.

Introduction. The level of lactate (lactic acid) in the blood serum, and the intensity of free-radical processes in the body are one of the criteria characterizing the fitness of athletes and show their tolerance to physical exertion [3, 4, 6]. With intense physical exertion, active forms of oxygen are formed leading to a significant increase in lipid peroxidation (LPO), which has a negative effect on muscle activity [5]. In conditions of high energy production in anaerobic mode, lactate is a carrier of energy from those places in which it is impossible to transform energy, due to increased acidity, to those places in which it can be transformed into energy (heart, respiratory muscles, slowly contracting muscle fibers, others muscle groups). Lactate plays a special role in maintaining the body's ability to perform strenuous physical work.

It has been established, that with intense physical exertion in the muscles a large amount of lactic acid is formed, which inhibits their contractility and causes muscle fatigue [3, 5]. The importance of individual metabolites of anaerobic glycolysis, lactate (lactic acid), is currently being widely studied.

Material and research methods. A survey of 85 men of Yakut nationality was conducted, of which 60 athletes of high qualification (candidates for masters of sports (cms) and masters of sports (ms)), aged 17 to 21 years old. The first group consisted of free-style wrestlers -30 people, the second – boxers (30 people). The control group consisted of 25 young students, of the same age, engaged in physical education at least twice a week. All examined according to the results of an in-depth medical examination were practically healthy.

The research material was heparinized blood and serum. Blood was taken - in the morning on an empty stomach from the cubital vein. The study was approved by the decision of the local Ethics Committee at the Yakutsk Research Center for Complex Medical Problems.

The intensity of lipid peroxidation was determined by spectrophotometric method [8]. The level of lactate in the blood serum was determined during ongoing examinations in a state of relative rest, on a semi-automatic analyzer "Screen Master" (Italy).

The overall physical performance of the PWC170 was determined using a Neurosoft bicycle ergometer (Ivanovo). The subjects performed two loads of moderate intensity with a pedaling frequency of 60 rpm on a bicycle ergometer, separated by a 3-minute rest interval. Each load lasted 5 minutes [2].

Statistical processing of the obtained data was carried out using the package of applied statistical programs STATIS-

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TICA 6.0. We used standard methods of variation statistics: calculation of average values, standard errors, 95% confidence interval. Statistical data processing was carried out by the non-parametric Kolmogorov-Smirnov method. The probability of validity of the null hypothesis was taken at p <0.05.

Results and discussion. According to our data, the lactate content in both groups of martial arts athletes in the blood serum is at the upper limit of the norm and has no significant differences (p> 0.05). The highest values of lactic acid were noted at the recovery stage, in the first group of athletes higher in 1.47 and the second -1.40 times (p <0.01), respectively, compared with the control group (Fig. 1).

The increase in the level of lactate in both groups of athletes in the blood serum is due to the high rate of oxygen utilization and developing hypoxia in the working muscles. Since the high muscle demand for energy substrates in conditions of oxygen deficiency is satisfied due to anaerobic oxidation of glucose. The accumulation of lactate stimulates proteolysis and supplies glycogenic amino acids for the increasing energy needs of athletes. Fights of fighters, and fights of boxers are characterized by work of submaximal power. With submaximal power in the body, although to a lesser extent, anaerobic processes in the release of energy prevail over aerobic ones. As a result of intense glycolysis in the muscles, a large amount of lactic acid accumulates in the blood. According to published data, the level of lactate in the skin extract after exercise in untrained people rises 2 to 3 times compared with the results before exercise. For novice athletes, this indicator increased by 1.5-2 times. The quantitative content of lactate in the skin extract in professional athletes before and after physical activity remained unchanged [6]. It was also shown, that it saliva the lactate content increases by 2–3 times after prolonged training [6]. The results of the study revealed significant increases in the concentration of lactate in the blood of athletes in response to competitive loads (at p≤0.01). In this case, the maximum concentration of lactate after competitive fights for mas-wrestling was recorded in the region of 10-12 mmol / l, which corresponds to the level of anaerobic (An1) physical activity [1].

In the athletes physical performance considered low at PWC_{170} 870 ± 41 kgm, lower than average –1160 ± 31, average - 1305 ± 22 and good - 1614 ± 82 kgm.

Correlation analysis showed that there is a positive relationship between

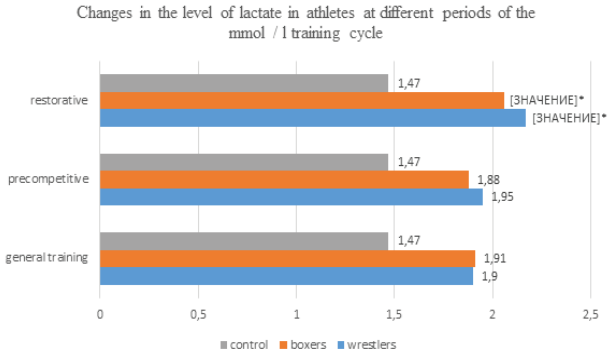

Fig. 1. Note: * p <0.01 compared with the control group

the PWC170 value and the lactate level (p <0.01). It is known that the concentration of lactic acid (lactate) in venous blood is an indicator of anaerobic performance.

A low level of lactate was observed in martial arts athletes, with low working capacity, with an increase in the level of training and working capacity of athletes, the lactate content increased 1.1, 1.3 and 1.4 times (Fig. 2). In wrestlers with excellent physical performance after the maximum load was fulfill, the lactate content was 1.1 times higher than in in the athletes with average and good physical performance, which is consistent with the literature data [7]. A comparative analysis of the level of lipid peroxidation products at rest, before the test load showed that athletes with low working capacity and with working capacity lower than the average concentration of thiobarbituric-active products (TBA - AP) (was 1.87 and 1.96 times higher (p < 0.01), compared with athletes with good performance. High aerobic performance among athletes with good working capacity is explained by the fact that aerobic performance is most manifested under those loads where it is possible to fully satisfy the oxygen demand and where a steady level of oxygen consumption is maintained for a long time.

Anaerobic performance, in which it is not possible to provide the working muscles with an adequate amount of oxygen, plays a decisive role in short-term high-intensity exercises.

Conclusion. Thus, a higher concentration of lactate in athletes, compared with a group of people engaged in physical education at least twice a week, indicates that during physical exertion, anaerobic glycolytic processes are significantly accelerated. A comparative analysis of the data we cited among athletes of the martial arts group showed that these processes are more intense in wrestlers. Possibilities of anaerobic oxidation in athletes with medium and good performance are higher than in athletes with low performance and lower than average groups, as evidenced by higher rates of lactate. Despite the higher level of lactic acid in the blood serum, the body of these athletes is characterized by greater resistance to work in conditions of oxygen deficiency, which indicates the fitness of their body.

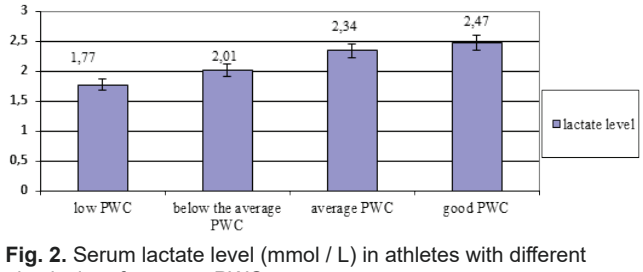

Fig. 2. Serum lactate level (mmol / L) in athletes with different physical performance PWC

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DNA DIAGNOSTICS IN CLINICAL PRACTICE APPLIED TO TRANSLATIONAL MEDICINE

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The review presents examples of the translation of genomic studies into practical medicine of two common European hereditary diseases - autosomal recessive cystic fibrosis and autosomal dominant Huntington's chorea. With the development of genetic technologies in the Republic Sakha (Yakutia), translational medicine is becoming a reality, and it is necessary to outline the approaches and problems in this field of research using the examples of type 1 spinocerebellar ataxia and type 1A autosomal recessive deafness which are frequent in the republic.

Keywords: translational medicine, hereditary diseases, DNA diagnostics, patient.

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Introduction. So-called translational studies are becoming increasingly more developed as of lately. Translational medicine is a modern multidisciplinary science that will have a leading role in the development of genomic medicine. Translational medicine can be considered as a process involving the transfer of discoveries made as a result of fundamental research in biomedicine into medical practice in order to improve diagnosis and treatment [11, 38].

The National Institutes of Health (USA) proposed the following definition of translational medicine: "translational research includes two areas of translation, the first of which is to bring the results of discoveries made in laboratories and preclinical studies to the stage of clinical research and human studies; the second area of translation is associated with research aimed at increasing the efficiency of introducing advanced technologies into wide medical practice"[22]. In accordance with this definition, translational studies are part of a unidirectional continuum in which research results move from the experimenter's laboratory table to the patient's bed and to society as a whole [17].

In turn, translational genomic research can be included in translational medicine. Translational genomic research is centered around the development of evidence-based guidelines [32]. The whole process includes at least three phases. The first phase is fundamental genomic research carried out by qualified specialists in specialized molecular genetic laboratories at research centers or universities. The second phase is the translation of the discoveries and achievements of genomic research and the development of approaches to the application of the results of genetic research in practical medicine, the assessment of their effectiveness and safety, as a rule, is done with the help of clinical trials conducted in specialized medical centers associated with research institutions [36]. The third phase is the conclusive step for the implementation of translational genomic research into the healthcare system, and, very importantly, this process also includes the revision and development of legal and bioethical norms, taking the application of genomic technologies in practice into account. The final stage establishes adequate recommendations for the optimal, safe and efficient use of new medical technologies in order to improve public health [12].

In this review, we **aim** to display examples of the translation of genomic studies into practical medicine of two common European hereditary diseases - autosomal recessive cystic fibrosis (CF) and autosomal dominant Huntington's chorea (HC). With the development of genetic technologies in the Republic of Sakha (Yakutia), translational medicine is becoming a reality, and it is necessary to outline the approaches and problems in this field of research using the examples of type 1 spinocerebellar ataxia (SCA1) and type 1A autosomal recessive deafness (DFNB1A) which are frequent in the republic.

Cystic fibrosis (CF). In European populations, cystic fibrosis occurs with a frequency of 1: 2500, while in Asian populations it is equal to 1: 90,000. If a frequent monogenic disease acquires social significance, a need for a number of measures to prevent the hereditary disease from spreading appears. A spectrum of more than 1900 different mutations of the *CFTR* gene has been described in 25394 patients from 23 European countries [40]. A permanent European Cystic Fibrosis Society Patient Register (ECFSPR) has been created that collects, quantifies and compares data on CF patients living in Europe and neighboring countries who agree to be included in the registry. This is done in order to better understand CF, develop new European standards for care and treatment, conduct research and treatment (https://www.ecfs.eu/projects) [45]. The CF gene is mapped on the long arm of chromosome 7 (7q31.1) in 1985. At the end of 1989, the CF gene itself was identified. The protein product of this gene was characterized, which was called the "Cystic Fibrosis Transmembrane conductance Regulator" (*CFTR)* and the most frequent mutation was revealed — a deletion of phenylalanine at the 508 position of the amino acid sequence of the protein (delF508), leading to the disease [28,29]. In addition to deletions, many other mutations have been detected in the CFTR gene. Unlike delF508, the vast majority of them are represented by sporadic cases, that is, they are quite rare. By the end of 2006, more than 1,500 point mutations, several deletions and duplications were identified in the *CFTR* gene.

The neonatal screening protocol for CF in the Russian Federation includes 4 stages: determination of immunoreactive trypsin (IRT1), re-determination of immunoreactive trypsin (IRT), sweat test and DNA diagnostics, and only the first three stages are mandatory in the national protocol and are provided by the state. Therefore, DNA diagnostics in many cases are limited. The availability of DNA diagnostics is limited by the high cost and the small number of laboratories capable of conducting this analysis [9,14]. DNA testing of CF is carried out using diagnostic panels, for example, in the "RCMG" a panel is used that includes the most frequent mutations in the world: F508del, CFTRdele2.3 (21kb), 3849 + 10kbC> T, W1282X, 2143delT, 2184insA, 1677delTA , N1303K, G542X, R334W, E92K, L138ins, 394delTT, 3821delT, S1196X, 2789 + 5G> A, G85E, 2183AA> G, 604insA, 621 + 1G> T, R117H, R347P, R553X, 3667insTCA17, 557171TCA17, 55717TCA17, 55717TCA17, 55717TCA17, 55717 -1G> A, 2184delA. Thus, using a specially designed panel that includes 28 mutations, it is possible to detect only about 82.5% of the mutant alleles in the total sample of examined CF patients. Almost 20% of patients with CF need an additional examination to detect rarer mutations or polymorphisms, including the ones which require the usage of the sequencing method, which is not yet routinely used in the Russian Federation [14].

Huntington's chorea (HC) is a progressive autosomal dominant neuromuscular disease characterized by the development of choreic hyperkinesis and dementia. Symptoms of the disease are caused by atrophy of the putamen and the caudate nucleus in the brain of patients, associated with premature selective death of neurons. In most Russian populations, the prevalence of HC is 1 in 10,000. Significant differences are noted in relation to the age of onset and severity of the disease. Moreover, even within individual families, pronounced clinical heterogeneity is observed. When HC is inherited on the paternal side, the effect of anticipation is sometimes manifested — an increase in the severity and a decrease in the age of onset of the disease in a number of generations [6].

The *IT15* gene, in which dynamic mutations lead to the development of HC, is expressed in many types of cells and encodes a protein with a molecular mass of 348 kDa, called huntingtin. In the *IT15* coding region, at a distance of 18 codons downstream from the start of the translation, a polymorphic trinucleotide repeat (CAG)n is localized. The number of CAG repeats in the *IT15* gene normally varies from 9 to 37, while the mutant alleles of patients with HC carry 36 to 121 triplets. An inverse correlation was found between the length of the CAG repeat and the age of onset of the disease and a direct correlation with the rate of progression of clinical symptoms. The change in the length of the repeat during transmission to the offspring explains the majority of cases of anticipation [25].

Mutant alleles in the range of 36–40 triplets are characterized by incomplete penetrance. A significant number of patients with HC with a similar number of repetitions on the mutant allele have been described, and at the same time, clinically healthy individuals older than 70 can be found in the same pedigrees. Alleles with a number of CAG repeats ≥ 40 are always associated with the development of the disease. The study of the state of CAG repeats by PCR in high-risk families allows direct molecular diagnostics of the disease at any stage of ontogenesis, including the pre-symptomatic period [7]. At the same time, it is important to note that genetic counseling in families with HC (as in the case of other diseases with late manifestation) is fraught with ethical difficulties. Given the dominant type of inheritance, the risk of obtaining a mutant gene for children and siblings of a patient with HC is 50%. Naturally, the exclusion of carriage, of course, should have a positive impact on the mental state of people at risk. On the other hand, given the lack of effective methods of treatment for HC, the identification of an allele in a patient with expansion is almost the same as a death sentence. At present, it is customary to conduct a pre-symptomatic examination exclusively of adults from the risk group when they directly seek advice. A serious argument in favor of a pre-symptomatic examination of relatives of patients is the possibility of preventing the disease in high-risk families by conducting prenatal diagnosis. But if we are talking about prenatal DNA testing as a method of preventing hereditary diseases with late onset, which include HC, we cannot ignore the complex moral and ethical aspects that inevitably arise during prenatal medical and genetic counseling [18, 43].

Therefore, as shown by the practice of DNA diagnosis of HC in different countries, a very small number of burdened families agree to prenatal diagnosis. For example, in Portugal, over 5 years of research, 158 families burdened with HC conducted 338 genetic tests, of which 234 were for diagnosis, 96 for pre-symptomatic and only 4 for prenatal DNA testing [34]. In Canada, 1061 pre-symptomatic DNA tests of HC and 636 diagnostic tests were performed over 14 years, of which 15 burdened families agreed to prenatal testing [37]. In Greece, DNA testing of HC was performed in 461 people with clinical symptoms and 256 people for pre-symptomatic diagnosis. Mutation (allele extension) was confirmed in 278 individuals. Prenatal diagnosis was carried out in 6 cases [27]. The authors note that the main reasons for rejecting prenatal diagnosis are the hope of developing treatment for HC and the reluctance to terminate the pregnancy for psychological reasons [24].

Spinocerebellar ataxia of the 1st type belongs to the group of neurodegenerative diseases with late manifestation. Inheritance is characterized by a high degree of penetrance, the phenomenon of anticipation. The mutation of the *SCA1* gene located on the short arm of the 6th

chromosome consists in an uncontrolled increase in the number of trinucleotide CAG repeats in the coding region of the gene. The clinical manifestations of the disease are very diverse, the main ones are: a slow progressive loss of coordination of movements and speech, the presence of the cerebellar-pyramidal syndrome, various degrees of damage to the cerebellum and its pathways [8].

In the 1970s Pierre-Marie cerebellar ataxia was first differentiated from the clinical forms of Vilyui encephalomyelitis (VE), previously this disease was attributed to one of the forms of chronic VE [3]. A comprehensive study of hereditary cerebellar ataxia (HCA) in Yakutia was launched in 1992 during the implementation of the scientific program "Biology of Vilyuisky Encephalomyelitis". Molecular genetic studies of HCA were carried out as part of the scientific project "Identification of genes and genetic mechanisms that cause hereditary neurological diseases", developed by the Department of Neurogenetics of the National Institute of Neurological Disorders and Stroke (NINDS / NIH) in the USA. In 1993, the research work of Dr. H. Orr et al. for the isolation of the Spinocerebellar ataxia type 1 *(SCA1)* gene was accomplished [23]. In 1994, the first work on the molecular genetic study of HCA in the Yakut population was published. A. Lunkes et al. (1994) revealed an allelic association of highly informative markers D6S274 and D6S89 flanking the SCA1 locus on chromosome 6 with HCA disease. The association was absolute in the case of D6S274 microsatellite, while for D6S89 allelic substitution was recorded only in two families, which gave rise to the assumption of historical recombination and date of the spread of the disease in the Yakut population [19]. In 1996, the results of a joint project by Yakut and American researchers were published, in which hereditary cerebellar ataxia, common in Yakutia, was identified as Spinocerebellar ataxia type 1 (SCA1). In these studies, the Siberian site of disease accumulation is defined as the largest known in the world, prone to further increase [41].

The molecular genetic methods of DNA testing of SCA1 were introduced in 1999 in the medical practice of the medical and genetic consultation of the Republican Hospital No. 1 - the National Center of Medicine of the Ministry of Health of the Republic of Sakha (Yakutia) and acquired the status of routine clinical analyzes, despite the absence of relevant instructions and orders for DNA diagnostics of hereditary diseases in clinical diagnostic laboratories. For the first time, DNA testing and prenatal DNA diagnostics work algorithms and bioethical rules for medical and genetic counseling for patients from burdened families were developed [2,4].

Hereditary deafness. Studies have shown that about 50-60% of congenital hearing loss are hereditary. The most common of the hereditary forms is sensorineural hearing loss, which is caused by mutations in the *GJB2* gene encoding the connexin 26 protein, currently there are more than 150 of them [21]. This form of hereditary hearing loss is detected in 1 out of 2,000 newborns, which is twice as often as cystic fibrosis and five times as often as phenylketonuria. Usually the parents of a deaf child have normal hearing, because they are heterozygous carriers of the mutation [5].

Around the world, the spectrum of the main pathological mutations that cause hearing impairment is wide and diverse. So, in various ethnic groups: Europeans, Indians, Jews, Arabs, Bedouins, Pakistanis, etc., the mutation c.35delG was found, among Ashkenazi Jews, the mutation c.167delT is the most common, in Asian populations - the mutation c.235delC [26,35]. Among Yakuts, the population frequency of c35delG is extremely low (0.2%), which may indicate the non-specificity of this deletion for the Yakut population or be single cases of crossbreeding [1]. In the Yakut population, the main cause of congenital hearing loss is a mutation in the donor site of splicing of c.-23+1G>A gene *GJB2 (Cx26)* and, according to the international OMIM catalog (Online Mendelian Inheritance in Men), is classified as an allelic variant of autosomal recessive deafness type 1A (ARD1A) [44].

According to N.A. Barashkov (2011), the prevalence of ARD1A is 16.2 per 100,000 of the Yakut population, and the frequency of heterozygous carriage of the mutation c.-23+1G>A varies from 3.8 to 11.7% among the indigenous population of Yakutia (Evens, Evenks, Dolgans, Yakuts). The results of the study of the *GJB2 (Cx26*) mutation gene splicing site indicate the existence of the world's largest "endemic focus" of c.-23+1G>A accumulation in Eastern Siberia [20].

The high frequency of deafness mutations c.35delG (22.3%) in patients of Caucasian origin in the Republic of Sakha (Yakutia) suggests the possibility of direct DNA diagnostics, differential and prenatal diagnosis, as well as screening of hereditary forms of deafness among wide groups of people, because approximately 50% of the inhabitants of Yakutia are Caucasians [31].

According to V.G. Pshennikova (2017), the proportion of pathogenic variants of the *GJB2* gene was 51.10% of the number of chromosomes studied in 393 unrelated patients. Among them, the three most common (allelic frequency >1%) pathogenic variants were identified: c.-23+1G>A (42.3%), c.35delG (5.9%) and c.109G>A (1,9%). When distributing unrelated patients by ethnicity: among the Yakut patients, the most frequent pathogenic variant is c.-23+1G>A (51.8%), the second most frequent is c.109G>A (2.4%), and the third is c.35delG (1.6%). Among Russian patients, c.35delG (22.3%) and c.-23+1G>A (5.3%) were most frequently encountered [13]. Given the identified spectrum and frequency features of pathogenic variants in the *GJB2* gene in patients with hereditary hearing impairment in Yakutia, a routine DNA diagnostic algorithm for autosomal recessive deafness type 1A was developed. The algorithm is based on a sequential search for the most common variants of the *GJB2* gene (c.-23+1G>A, c.35delG and c.109G>A), followed by resequencing of the protein-non-coding (exon1) and protein-coding regions (exon 2) of the *GJB2* gene, as well as the search for an extended deletion of c.del (GJB6-D13S1830), which allows to detect up to 99% of pathogenic variants responsible for ARD1A in Yakutia [15].

DNA testing of hearing impaired/deaf people involves many organizational and ethical issues. When communicating with deaf people, it must be borne in mind that they are members of a socially isolated community of the "world of the deaf" with their own language, culture and habits [39]. The number of assorted marriages among the deaf is growing, sometimes spouses may express a desire to have a deaf child, despite the unfairness of such a decision in relation to the child.

In any case, comparing themselves to hearing people, most deaf people consider themselves to be flawed and socially deprived [42]. The use of DNA testing to detect mutations responsible for the development of deafness can pose a risk of psychological stress and exacerbate the sense of inferiority in the individual. Therefore, it is necessary to create special conditions for genetic counseling and obtaining informed consent among the deaf [10].

Conclusion. It is impossible to overestimate the importance of translational medicine for solving practical problems of healthcare, because such an approach has already led to the transfer of the role and place of a practical doctor to a different plane, where they operate with fun-

damentally new technologies. Moreover, the ever-increasing distance between practical health care and the accumulating information in the field of fundamental biomedicine dictates the need for direct professional contact between clinicians and research scientists. Moreover, this kind of contact is required to cover not only biological and medical sciences, but also a number of related disciplines that generate facts of strategic importance, which, in turn, need active transfer (translation) to the field of medical practice, and, accordingly, to the real and effective care for a particular patient [16].

According to P. Lunt (2010), the common features of the organization of clinical molecular genetic laboratories are:

- limited contingent for which the diagnosis is intended, these are mainly families burdened by a hereditary disease and their relatives;
- mandatory patient follow-up with counseling and psychological assistance by a trained clinical geneticist;
- a small amount of conductible research; higher price of both the means invested in the laboratory and the cost of analyzes;
- the difficulty of interpreting the results of the study, the long duration of waiting for the results of the analysis;
- the existence of moral and ethical aspects of genomic analyzes [33].

Molecular genetic studies of hereditary diseases in Yakutia open up great opportunities in the field of translational medicine, namely the introduction of the results of scientific research into medical practice in the form of routine DNA diagnostics. On the other hand, modern personalized medicine using genomic technology requires the mandatory consideration of the bioethical, psychological and social aspects of translational medicine.

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HEALTHY LIFESTYLE. PREVENTION

L.D. Starostina

COMPARATIVE ANALYSIS OF HEALTH-SAVING BEHAVIOUR OF STUDENTS OF COMPREHENSIVE SCHOOLS AND UNIVERSITY IN YAKUTSK

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This research compares the behaviour components defining the attitude of the person to his health at comprehensive schools and university in Yakutsk. So, distinctions in value-required, cognitive, emotional and behavioural components have been found. Individual peculiarities, consciousness and attitude to health-saving behaviour have been revealed. Health-saving set and readiness for actions in this area are insufficiently generated in both groups. We should rely on youth high aspirations to self-assertion and self-development when we work with them in the field of health-saving consciousness and behavior.

Keywords: *healthy lifestyle, health-saving behavior, teenage age, student's age, attitude to health, consciousness.*

Introduction. Formation of health-saving behaviour is an important part of education. The researchers mark close interrelation between health, health-saving behaviour and potential development of the person. Many scientists have been studying the attitude to health, formation factors of health-saving behaviour at the teenager age. For instance, R.A. Berezovskaya's researched the problem of the attitude to health and developed the questionnaire for assessment of health-saving behaviour [2]. Ya.V.Ushakova devoted her works to self-saving behaviour, health control of the youth and its formation factors [8, 12, 13]. N.N.Avdeeva, I.I.Ashmarina, G.B.Stepanova researched the human potential of students and factors, promoting its realisation [1]. Youth health as object of social policy was considered by I.V.Zhuravleva, N.V.Lakomova [3]. G.Y. Kozina studied the youth attitude to healthy lifestyle factors [4, 6]. L.G.Rozenfild has described major risk factors of health disorders of students and Y.G.Mironova – self-saving behaviour of student's youth [7, 9]. Researches on the yielded subjects were made also among teenagers [5, 11].

Formation of health-saving behaviour and responsibility for your health should

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be an integral part of educational process at schools and universities [14]. In modern life this period is frequently interfaced to untimely food intake, non-regular sleep, insufficient stay in the open air, low motor activity, absence of harden procedures, smoking, etc. Successful strategy realisation of youth healthy lifestyle values at the university is frequently circumscribed by insufficient material base, absence of health-saving technologies adapted for the region, methods of diagnostics, medical-rehabilitation actions, and also the irresponsible attitude of the majority of youth to the health [10]. The objective situation assessment and search of key parts of the impact, considering different stages of formation of health-saving sets is necessary to overcome these obstacles.

Considering all this, the aim of our research is a comparative analysis of health-saving behaviour of students at comprehensive schools and university in Yakutsk, to define all possible ways of formation of healthy lifestyle sets.

Material and methods. Research was made among students of North-Eastern federal university named after M.K.Ammosov and pupils of comprehensive schools of Yakutsk. The following methods were used to get psychological information: «Personal differential» (adapted version of scientific research institute by V.I.Bekhterev); R.L.Berezovskoy's questionnaire «Attitude to health [2]. 124 respondents have taken part in our research, 64 students at the age from 18 to 21 years old and 60 schoolchildren at the age of 14-15 years old. Both groups were comparable by girls and boys share (p=0,687).

The statistical analysis of the data has been executed in package IBM SPSS STATISTICS 22. Mann-Whitney U-test and Pearson's test χ^2 were used for groups comparison. Critical value of level of the statistical importance of distinctions (p) was taken equal to 5 %.

Results and discussion. Let's consider the list of predominant requirements for values system among schoolchildren and students by scales "Attitude to health" R.A.Berezovskaya (Table). In the list of leading values, "Health" takes the first position among girls that can be explained by future motherhood sets whereas among boys "Health" is on the fourth position after social values (p <0,001). Comparing predominant requirements for values system of it is possible to notice that at school age girls do not reflect yet about health (but among females -students the yielded value is on the first place that can be caused by their reproductive behaviour). Prevalence of value «Family well-being» among girls-students (in comparison with schoolgirls), also confirms the assumption of their sets for the future home life. Average values of "Career" among students and schoolgirls are identical, however at females-students, "Career" is only on the fifth position, unlike schoolgirls where this value occupies one of leading places. Actualisation of the yielded value at schoolgirls can be probably explained by school exams period, and with the plans to continue education.

Predominant values and attitude to health

Schoolchildren	Students
Predominant requirements for system of values	
1) health 2) independence 3) career	1) Friends 2) health 3) happy family
Block «What I do for health preservation»	
Preventive procedures and diet	Baths and saunas
Block «What prevents me from healthy lifestyle»	
Other causes (are not specified)	Financial possibilities, absence of conditions, shortage of time
Actions at deterioration of health state	
I go to polyclinic I do not pay attention	I consult to my friends, relatives

Value "Health" among schoolboys is on the first place while at students it concedes values "Friends". It is possible to assume that in student's years, young men are more adhered to friends (fellow-students), they like to spend their free time together.

Thus, predominant requirements in the system of values are: at schoolboys – health, independence, career; at students – friends, health, happy family. Thus value «Recognition of people» at students takes higher places in hierarchy of values, than at schoolboys (p <0,001) that speaks about the importance of a social recognition at student's age.

Both schoolboys and students bind success in life first of all to diligence, abilities, necessary communications, thus the important factor defining working capacity and persistence – "Health", does not undertake them in attention. At females (students and schoolchildren) the interrelation of the personal qualities promoting vital successes, has similar allocation, except for scales "Health" and "Prosperity". Here as well as in the previous comparison, value "Health" at schoolgirls takes lower places, than at students (p <0,001).

The analysis of the role of various information resources in the field of health has shown that the most important canal of reception of the information about health for students are: doctors, further on decreasing: television and the Internet, friends and people, special literature, periodic printed editions. Thus, if girls-students prefer opinion of real doctors, schoolgirls prefer Internet resources. Schoolboys besides doctors trust the literature, and students trust their friends' advices.

According to students, the factors negatively influencing on health are: wrong lifestyle and nutrition, insufficient health care, bad ecology and medicine. Thus the most significant factor is "lifestyle", "food", "lack of health care", "quality of health services" and "ecology". Schoolboys showed the following - "lifestyle", "ecology", "quality of medical services", "food". Thus schoolgirls equally evolve the importance for health of "lifestyle" and "food", and schoolboys mark "ecology" and " lifestyle".

Refusal of bad habits, overweight control, sleep regime, physical exercises were considered to be significant ways of health maintenance among girls-students. The rating differed a little at students-boys, and has been presented in the following sequence: physical exercises, avoiding bad habits, sports, sleep regime. According to schoolgirls, the most important ways of health preservation are bad habits refusal, physical exercises, diet and healthy nutrition. Among boys — bad habits avoiding, regular physical exercises, sleep and wakefulness regime, various sports sections. The analysis of the actions made by youth for health preservation has shown that students visit baths and saunas much more often, than schoolboys (p <0,001), and schoolboys have preventive procedures more often and keep to a diet (p <0,001) (table).

Students have specified the causes

of insufficient healthcare: time lack, absence of necessity, unprofitable, absence of conditions, employment. Thus females-students, first of all, mark a lack of time and cost-based, then absence of will power, absence of necessity and conditions. Accordingly, male-students: absence of necessity and shortage of time, unprofitable, not to stint themselves in everything. The causes of insufficient health care s also are "absence of necessity" as they consider themselves healthy and do not wish to apply any efforts on health conservation, referring to employment and "absence of time".

At deterioration of physical state of health students consult to their friends and relatives more often, self-medicate, try not to pay attention to illness, and only in severe case they visit medical institution. Schoolboys more often, than students go to doctors, or also do not pay attention to the state.

The information concerning features of individual peculiarities, consciousness and attitudes has been received by method "Personal differential" (scientific research institute by V.I. Bekhterev). Results of diagnostics have shown that 68% of students have high values by self-esteem scale to themselves as a personality, average values at 28%, that is, students take over themselves as positive, socially-desirable characters. 71% of students and 60% of schoolboys showed mean level of strong-willed ability. Thus 21% of schoolboys have low indexes on will power. Low values speak about insufficient self-control, inability to keep to the taken over line of behaviour, dependence on choronomic circumstances and assessments. Students have realistic enough representations about a role of strong-willed regulation in healthy lifestyle, than schoolboys.

We may assume that student's life period has more social activity than at school which is expressed in change of a social situation of development, social status and environment. Thus, extrovert indexes (activity, sociability, impulsiveness) were higher at student's age, than in school. Level of aspiration by self-esteem scale was higher at student's age. Discrepancy between indexes was more expressed by activity scale that testified that, both groups would like to be more awake and sociable «in ideal». This fact can specify in occurrence of problems in interaction with a social environment.

Conclusion. Thus, the analysis of health-saving behaviour of schoolchildren and students has shown the presence of peculiarities determined by respondents' age, gender, social situation of development, self-assessment level. However it is possible to assert that for school and student's youth health issues are more "abstraction" rather than a necessary reality. Even if health is proclaimed as a part of students' value (especially among girls), nevertheless, is poorly presented in individual consciousness. That is the concept "health" is not included into sphere of personal senses of the individual at this age. The comparative analysis has allowed revealing existence of distinctions concerning students and schoolchildren to health on the following points: dominant requirements; actions for health preservation; causes preventing healthy lifestyle; actions at health deterioration.

Students and schoolchildren can't adhere to the taken over line of behaviour with healthy lifestyle, owing to insufficient development of self-control and dependence on circumstances and assessments. However students understand a role of strong-willed regulation for healthy lifestyle more. The student's period is marked by bigger social activity than at school which is expressed in change of a social situation of development, social status and environment. Level of aspiration by self-esteem scale also raises at student's age that speaks well for that the youth would like to be more awake and sociable «in ideal». All features set forth above specify in the big readiness of students to acceptance of values and observance of norms of healthy lifestyle, in comparison with schoolchildren, but health-saving and readiness for actions in this area are insufficiently generated in both groups. At work with youth in the field of formation consciousness and behaviour it is necessary to lean against high claims of youth to self-affirmation and requirement for self-development. We should rely on youth high aspirations to self-assertion and self-development when we work with them in the field of health-saving consciousness and behavior.

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REGIONAL CHARACTERISTICS OF PERMANENT TEETH ERUPTION IN VOLGOGRAD SCHOOLCHILDREN

The physical development assessing, reflecting the formation of morphological and functional properties of the organism is the most important part of the children health studying. One of the criteria for a child's biological development is tooth maturity. Dental maturity as a criterion of biological age is determined by the timing of the milk and permanent teeth eruption. At the same time, the overwhelming majority of hygienic work on the assessment of regional characteristics of children's physical development contains information on morphofunctional indicators: length and body weight, chest circumference, muscular strength of the hand, lung capacity, but very rarely provide information about "dental age". Analysis of the results of assessing the morphofunctional state of schoolchildren using the local standard is preferable for preventive medicine, including for developing priority health measures for this category of the population.

The **objective** of the investigation was to identify the characteristics of the permanent teeth eruption in the Volgograd schoolchildren, to compare the obtained data with the dynamics of anthropometric indicators (height, body weight), taking into account gender differences; to analyze the differences in the indicator "permanent teeth eruption" in different regions of the country (according to literary sources). The number and timing of the permanent teeth eruption in Volgograd schoolchildren from 7 to 17 years old were estimated. The differences in number and timing of the permanent teeth eruption in comparison with similar indicators in regions with other climate, socio-economic, ethnic and ecological peculiarities were identified. The relationship between the timing of the permanent teeth eruption and dynamics of somatometric parameters was established. The necessity of the permanent teeth eruption standards development and the usage of this indicator in assessing the physical development of schoolchildren are justified.

Conclusions: it is necessary to include standards for the permanent teeth eruption in regional standards for the physical development of children and adolescents. During preventive medical examinations of minors, it is necessary to indicate not only the sexual development formula of the child, but also the terms of the permanent teeth eruption. According to the teething indicators in different regions of the country, differing in climatic-geographical, socio-economic, ethnic and ecological characteristics, it is necessary to develop standards and further studying the characteristics of the eruption process for each region in Russia.

Keywords: physical development, dental maturity, permanent teeth eruption, somatometric indicators, morphofunctional status.

Introduction. The physical development assessing, reflecting the formation of morphological and functional properties of the organism is the most important part of the children health studying. There are various methods and scientific approaches in assessing the physical development of children and adolescents [12].

The main method of studying the physical development of children and adolescents is a comprehensive assessment in hygienic practice, firstly approved by the Civil Code of the RF SEC in 1996. Modern techniques, rules for examining and assessing the physical development of a child, as well as organized groups of children and adolescents of school age, is described in the manual for medical workers "Assessment of the physical development of children and adolescents in educational organizations" ed. by V.R.Kuchma [8]. Comprehensive assessment supposes assessing the morphofunctional status of the child (the balance development) and the level of biological development. One of the criteria for a child's biological development is tooth maturity. Dental maturity as a criterion of biological age is determined by the timing of the milk and permanent teeth eruption; biological age for school children can be determined by dental maturity before the age of 14 [1, 10]. During assessing the studied indicators from the point of their informational significance as criteria of biological age, a statistically strong direct connection of the level of biological development with signs of puberty and the connection of the average degree - with the number of permanent teeth erupted, which characterizes them as leading informational criteria in school-age children [3, 9]. At the same time, the overwhelming majority of hygienic work on the assessment of regional characteristics of children's physical development contains information on morphofunctional indicators: length and body weight, chest circumference, muscular strength of the hand, lung capacity, but very rarely provide information about "dental age" [1]. Generally, in assessing the indicators of a child's biological development (development of secondary sexual characteristics, number of permanent teeth), the authors, as a rule, use all-Russian data.

The main question is to develop and use of regional standards for assessing the physical development of children and adolescents. According to many authors, the objective assessment of physical development is possible in the presence of "standards" in a particular region, characterized by a certain ethnic composition, climate, geographical and socio-economic conditions [4, 5, 12]. The use of other regions standards is undesirable due to differences in these indicators. Standards of physical development of children and adolescents require regular (at least 1 in 10-15 years) updates [4, 5].

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Analysis of the results of assessing the morphofunctional state of schoolchildren using the local standard is preferable for preventive medicine, including for developing priority health measures for this category of the population [2].

Objective of the study: to identify the characteristics of the permanent teeth eruption in the Volgograd schoolchildren, to compare the obtained data with the dynamics of anthropometric indicators (height, body weight), taking into account gender differences; to analyze the differences in the indicator "permanent teeth eruption" in different regions of the country (according to literary sources).

Material and methods. The dentists of the children's dental treatment-and-prophylactic institutions of Volgograd carried out the study and the "dental age" assessing, including the number and timing of the permanent teeth eruption in Volgograd schoolchildren during 2015-2017 (epy patient examination was carried out in such health care facilities as: APHCI "Children's dental clinic №2", APHCI "Dental clinic №11", APHCI "Dental clinic №12", APHCI "Volzhski city dental clinic"). In total about 2,000 schoolchildren were examined, including 965 girls and 999 boys aged from 7 to 17 years. During the same period, about 3,000 schoolchildren from 7 to 17 years old were examined (1,388 boys and 1,602 girls) in order to study the morphofunctional state of children and adolescents living in Volgograd. Somatometric indicators were studied: height and body weight. The measurements were carried out according to generally accepted methods in the first half of the day. Standing body height was measured by using an wooden height meter with an accuracy of 0.5 cm. Body weight was measured with the help of lever medical scales such as Fairbanks with an accuracy of 50 g. The calculation of the main statistics - the mean value, the standard deviation, as well as the construction of regression dependencies of height and weight; analysis of the number and timing of the permanent teeth eruption in boys and girls within the age group from 7 to 17 years was carried out using the statistical package Statistica V 6. Linear pairwise correlation analysis of somatometric signs and the number and timing of the permanent teeth eruption in boys and girls conducted using MS Excel 2007.

Results and discussion. Analysis of the permanent teeth eruption in Volgograd children and adolescents of school age showed that this stage covers the period from 6-7 to 15 years. According to some authors, the period of permanent teeth eruption is 9 years and includes two phases of active eruption (from 7 to 8 years and from 10 to 13 years) and two periods of relative rest: the first is after the first molars and incisors eruption (8 years old in girls and 8–9 years old in boys), the second is after the all permanent teeth eruption (except the third molars). In girls, it began at age 13, in boys at age 14 [3].

It was determined that the first phase of the examined schoolchildren of both sex groups was at the age of 7 years, and the most significant increase in the number of permanent teeth (intensive period of teething or the second phase) was at the age of 11 years in Volgograd boys and girls. And it is 2 years ahead of the average terms in Russia [10, 11].

To our minds, the important thing is the question of the relationship between the results of the "teething" indicator and the dynamics of the somatometric parameters of the physical development of children and adolescents in the Volgograd oblast. We conducted a comparative analysis of the intensity and timing of the permanent teeth eruption in Volgograd schoolchildren with dynamic characteristics of height and body weight.

It was indicated that the first growth jump in boys took place at 10 years (+7.0 cm). The age of pubertal growth jump was at 13-14 years (+7.0). The assessment of the corresponding indicator in girls showed that the first growth jump was also at 10 years (+7.9 cm), the second - at 12 years (+8.5 cm). Analysis of the indicator "body weight" revealed the fact of a sharp increase in the indicator "body weight" in boys from the age of 12 and older: the difference between 11-year-old and 12-year-old boys is almost 8 kg. Girls have a sharp increase in body weight from the age of 13.

A comparative analysis of the dynamics of changes in mass-growth parameters and their comparison with the permanent teeth eruption data in schoolchildren showed that these processes are multidirectional. It WAS revealed that the second stage of the most significant increase in the number of permanent teeth corresponds to the age of 11 years in Volgograd boys and girls, i.e. a year later in comparison with growth jumps (Fig. 1) and falls on the age period between two growth jumps. The inverse relationship was determined in comparison the "dental age" with the weight gain indicators in Volgograd schoolchildren (Fig. 2). Thus, the greatest increase in the "body mass" indicator is 12 years for boys and 13 years for girls, which is 1-2 years later than the "jump" for the permanent teeth eruption (Fig. 2).

According to the results of the Linear pairwise correlation analysis (the Pearson correlation coefficient was determined using MS Excel), a close positive relationship was indicated between the timing and intensity of the permanent teeth eruption and changes in height and body weight. Correlation coefficients, respectively, were 0,95 and 0,92 for boys, and 0,97 and 0,95 for girls. This confirms the fact of a close biological connection in children of this age group (7–17 years old) between mass and growth changes and changes in the dental system. At the same time, children with low and below average somatometric parameters are more likely to have late teething, which coincides with the data of Zolotareva L.A. [6].

The comparative analysis of the period of "rest" among adolescents living in different regions of the country is worth studying. The data of V.A. Petrov [7] (Pri-

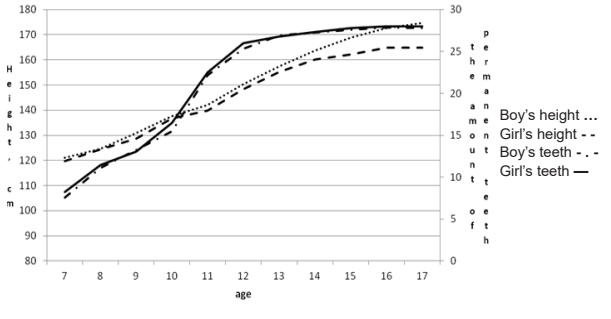

Fig. 1. Dynamic characteristics of indicators of body height and "dental age" in children of Volgograd

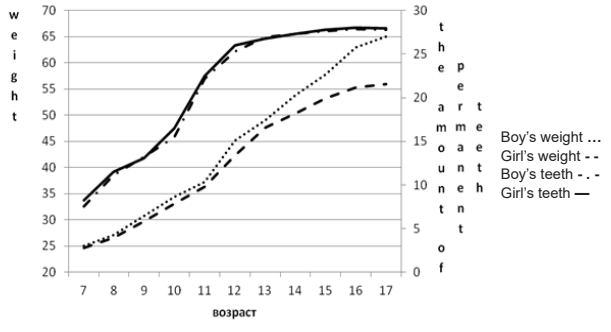

Fig. 2 Dynamic characteristics of indicators of body mass and "dental age" in children of Volgograd.

morsky Krai) and S.Yu. Kasyugi et al. [7] (Nizhny Novgorod) indicate the onset of the second period of “rest” in girls from the age of 13, in boys - from the age of 14. According to our data, the second “rest period” in Volgograd boys and girls begins at the age of 12 (the least statistically significant increase). It was also found that in the Volgograd oblast, the period of the most intense dentition occurs in boys and girls at 11 years old (in Primorsky Krai, it begins at 10 years in both boys and girls, in the Nizhny Novgorod oblast: in boys at 11 12 years old, in girls 10-11 years old). It is possible that the revealed differences are due to climate, nutritional, ethnic, and ecological peculiarities of living, which requires further scientific study and confirmation [6].

of the eruption process for each region in Russia.

Comparative data on the number of permanent teeth in different regions (M±δ)

Age	Nizhny Novgorod		Primorsky Krai		Volgograd oblast	
	boys	girls	boys	girls	boys	girls
6	-	-	-	-	2.62±2.19	3.06±2.29
7	7.7±2.6	8.5±2.6	7±3	9±3	7.53±2.94	8.21±3.22
8	10.6±1.8	11.4±2.4	12±2	12±3	11.12±2.09	11.48±1.98
9	12.9±2.6	13.8±3.1	14±2	15±3	13.24±2.54	13.07±2.22
10	14.6±3.9	16.8±4.4	18±3	19±3	15.49±3.19	16.47±4.39
11	18.8±5.2	20.0±4.7	20±4	21±3	22.15±4.29	22.48±4.08
12	23.5±4.1	24.5±3.8	24±3	25±2	25.29±3.11	25.97±2.36
13	25.6±3.2	26.7±2.0	27±1	28	26.90±1.65	26.78±1.64
14	27.3±1.4	27.5±1.2	28	28	27.29±1.69	27.35±1.25
15	27.6±0.8	27.7±0.9	28	28	27.62±1.15	27.83±0.63
16	-	±	28	28	27.84±0.72	28±0.00
17	-	±	28	28	27.82±1.16	27.97±0.30

Conclusions:

1. It is necessary to include standards for the permanent teeth eruption in regional standards for the physical development of children and adolescents. During preventive medical examinations of minors, it is necessary to indicate not only the sexual development formula of the child, but also the terms of the permanent teeth eruption.

2. According to the teething indicators in different regions of the country, differing in climatic-geographical, socio-economic, ethnic and ecological characteristics, it is necessary to develop standards and further studying the characteristics

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O.N. IVANOVA

RECURRENT STOMATITIS IN CHILDREN

This article is devoted to the actual problem of recurrent aphthous stomatitis in children. The authors studied the features of the course of recurrent aphthous stomatitis in children and the effectiveness of the use of Imudon in the treatment of this disease.

We surveyed 100 children with recurrent aphthous stomatitis, within a year at the age of 7 to 12 years on the basis of the Consultative Clinic RH №1- National center of medicine (Yakutsk). All children were examined by a pediatrician and profile specialists: an endocrinologist, a hematologist, an otolaryngologist, and a dentist. General blood and urine tests, biochemical studies (CRP, ASLO), blood sugar levels, a study of the level of immunocompetent cells in peripheral blood and the level of immunoglobulins A, M, G were examined in all children. Then a group of 50 children with recurrent stomatitis was identified, all of them except of local therapy (cauterization of ulcers by the stomatofit) received treatment with Imudon (the group under study). A group of children (50 people) received only local treatment (the control group). All children showed a decrease in immunity, changes in the general blood test. In the treatment of recurrent stomatitis, in addition to local treatment, treatment with Imudon is recommended, which leads to a reduction in clinical symptoms, normalization of immune status indicators and a general blood test.

Keywords: stomatitis, aphthae, children, immunity, ulcers, therapy, Imudon.

Stomatitis is a disease of the oral mucosa. Pathogens are more often streptococci. Stomatitis is most often caused by a failure of the immune system or a number of diseases of various organs (diabetes mellitus, kidney disease, blood deficiency disease, vitamin deficiency).

In children, aphthous form of stomatitis is more common. Aphthae appear as small white or yellowish plaques of various sizes, surrounded by a red rim, on the mucous membrane of the cheeks, gums, lips or tongue. Characterize by a sharp pain when eating and symptoms of intoxication. Their outcome is often favorable, after 6-8 days the process subsides, aphthae heal, erosion epithelialized. Sometimes stomatitis becomes chronic and tends to recur.

As a result of treatment with antiseptic agents of the oral cavity, aphthae heal, but new ones appear. The process can last for years, affecting the patient's quality of life; children try to eat liquid food in order not to injure the oral mucosa. In the process of the disease, children lose weight, are stunted in growth and psychomotor development [1,2].

Objective: To study the peculiarities of the course of recurrent aphthous stomatitis in children and the effectiveness of the use of Imudon in the treatment of this disease.

Materials and methods. We surveyed 100 children with recurrent aphthous stomatitis for a year, aged from 7 to 12 years based on the Consultative Clinic RH №1- National center of medicine. All children were examined by a pediatrician and profile specialists: an endocrinologist, a hematologist, an otolaryngologist, and a dentist. General blood and urine tests, biochemical studies (CRP, ASLO), blood sugar levels, a study of the level of immunocompetent cells in peripheral blood and the level of immunoglobulins A, M, G were examined in all children. Then a group of 50 children with recurrent stomatitis was identified, all of them except of local therapy (cauterization of ulcers by the stomatofit) received treatment with Imudon (the group under study). A group of children (50 people) received only local treatment (the control group).

All the data obtained were subjected to thorough statistical processing: the numerical data were calculated as the arithmetic mean and standard error of the mean M ± m; differences were considered significant at $p < 0.05$. Comparisons of mean values were performed by single-factor analysis of variance using Student's t-test to assess the equality of the averages of the Fisher's F-test to assess the equality of the variance. The relationship between the parameters was estimated using linear and rank correlation coefficients.

Results. A survey of 100 children with recurrent stomatitis by specialists revealed that 15 (15%) people had iron deficiency anemia, 70 (70%) children had chronic tonsillitis, 50 (50%) children had caries.

Then we decided to study the main symptoms in children with recurrent stomatitis: 90 children (90%) had a burning sensation and soreness of the oral mucosa when eating, 65 children (65%) had a weight loss of 1 to 3 kg during the year, 30 % growth retardation, 60 (60%) decrease in appetite, 90% weakness, fatigue.

All patients with recurrent stomatitis had a general blood count.

According to the results of a general blood test in patients with stomatitis, the level of erythrocytes, platelets, hemoglobin and erythrocytes is reduced (Figure 1).

All patients with recurrent stomatitis were examined for their immune status. The following results were obtained: a decrease in the content of CD4 + lymphocytes, that is, activated T-cells, a decrease in the number of natural killer cells (CD16 +), T-helper cells (CD4 +), cytotoxic T-lymphocytes (CD8 +), and an increase in IgM (Table 1).

Table 1

Indicators of the immune status in children of RS (Ya) in children with recurrent stomatitis and healthy children, M±m

Indicator	Children with recurrent stomatitis (n = 100)	Health children(n = 2000)
CD3+	18.1 ± 1.03*	27.2±1.04
CD4+	16.2 ± 0.5*	28.3±0.6
CD8+	15.9 ± 0.8*	24.1±2.5
CD16+	10.1 ± 1.2*	22.0±1.01
IRI	0.7 ± 0.6	1.08±0.02
IgA	1.1 ± 0.1*	2.9±0.6
IgG	18.2 ± 0.7	17.1±0.09
IgM	1.0 ± 0.08*	2.2±0.09
CD25+	13.9 ± 1.2*	24.6±0.7
CIK	186.2 ± 1.5<0.05*	70±0.07

Note. In the Tables 1-2 *p < 0.05 between standards and indicators in each group

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Table 2

Indicators of the immune status in children with recurrent stomatitis of the examined and control groups after therapy, M±m

Indicator	Children of the examined group after therapy (n = 50)	Children of the control group (n = 50)
CD3+	27.1 ± 1.1	22.1 ± 1.03
CD4+	21.6 ± 0.9	18.9 ± 0.5
CD8+	18.2 ± 0.2	16.9 ± 0.8
CD16+	20.3 ± 1.0	13.1 ± 1.2*
IRI	1.9 ± 0.1	0.7 ± 0.6
IgA	2.6 ± 0.1	1.8 ± 0.1*
IgG	18.9 ± 0.2	18.2 ± 0.7
IgM	2.4 ± 0.2	1.2 ± 0.08*
CD25+	20.1 ± 1.2	13.9 ± 1.2
CIK	172.1 ± 1.0	186.2 ± 1.5<0.05

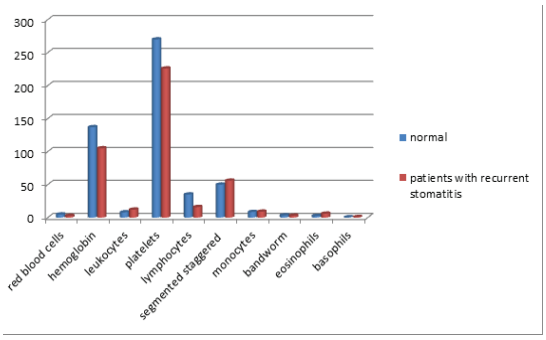

Fig. 1. General blood count in patients with recurrent stomatitis compared with normal values

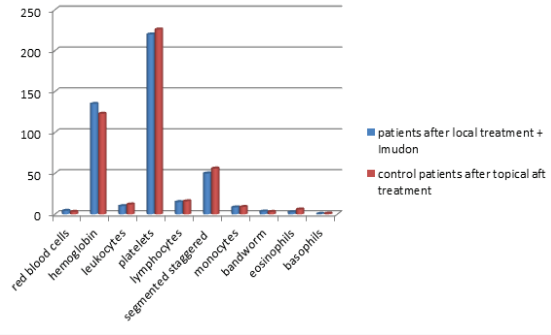

Fig. 2. Dynamics of changes in the general blood count in children with recurrent stomatitis of the examined and control groups after the treatment

Standards of immune status indicators were developed by the team of the Immunology Laboratory of the Medical Institute in 2018 based on a survey of 2,000 healthy children aged 5 to 10 years (Table 1).

Treatment of recurrent stomatitis was carried out jointly with the dentist. Within 1 month, 50 children of the examined group with recurrent stomatitis received the drug Imudon 1 tablet 3 times a day. Patients from the control group of 50 children received only antiseptic treatment with stomatofit, cauterization of aphthae.

During the therapy and after the treatment, the aphthasis did not appear in the examined group in children during the month, the symptoms of the children in the control group remained the same.

Thus, as a result of the treatment carried out in the examined group of children (local antiseptic treatment and imudon), there was a positive dynamics of clinical manifestations in comparison with children of the control group who received only local antiseptic treatment.

In the examined group of children, there was a positive trend in the indicators of the general blood test (Figure 2).

All children were examined for immune status in the control and survey groups. It was revealed that the immune indices improved in the group of children with recurrent stomatitis after therapy (local treatment and imudon): an increase in cellular and humoral immunity: the level of normal killer CD16 + and the level of IgA, IgM (Table 2). These changes are significantly higher than the immune status in children of the control group who received only topical antiseptic treatment of stomatitis.

Thus, there is a positive dynamics of indicators of immune status, clinical manifestations of recurrent stomatitis of children of the examined group as a result of the treatment.

Conclusion. In the treatment of recurrent stomatitis, in addition to local antiseptic treatment, treatment with Imudon is recommended, which leads to a reduction in clinical symptoms, normalization of immune status indicators and a general blood test.

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HYGIENE, SANITATION, EPIDEMIOLOGY AND MEDICAL ECOLOGY

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COMPREHENSIVE INDICATIVE ANALYSIS OF THE PERFORMANCE AND QUALITY OF ACID-FAST BACTERIA DETECTION BY PRIMARY CARE FACILITIES IN THE SAKHA REPUBLIC (YAKUTIA)

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The study takes a look at the work of clinical laboratory service performing microscopic diagnosis of tuberculosis in the Sakha Republic (Yakutia). We analyzed results of Ziehl-Neelsen microscopic detection of tuberculosis (TB) in clinical diagnostic laboratories of primary care facilities in 2005, and over the period from 2012 to 2016.

Analysis was based on national-level and industry sectoral reports, and annual reports of laboratories performing microscopic diagnosis of TB. Data from the following statistical forms were studied: Form 30, Form 33, Form '7-ТБ', Register '03-ТБ/у', Register '4-ТБ/у' for the years 2005, and 2012-2016.

Keywords: Mycobacterium tuberculosis, clinical diagnostic laboratory, acid-fast bacilli, Ziehl-Neelsen microscopy, primary care.

Introduction. Today's epidemiological situation with tuberculosis (TB) in Russia, and in the world, is demanding fast and effective detection and control of the causative agent, to prevent its spread. Microscopic method based on acid-fast biological properties of Mycobacterium tuberculosis is one of the detection methods that are both fast and inexpensive [9].

Detection of acid-fast bacilli (AFB) in diagnostic specimens is significant in terms of identifying infectious TB cases, which present the biggest epidemiological risk. As is recognized, these patients can infect 20-30 or even more persons a year, on average [1, 5, 9].

In this view, intensifying the detection of cases by microscopic methods is considered more and more as an urgent task for laboratory services within all medical and preventive healthcare facilities, irrespective of their departmental affiliation or forms of ownership [9].

One of the viable focus areas in raising the effectiveness of anti-TB measures is the application of indicative approach to state monitoring and management system. Monitoring trends in indicators can be useful in terms of more effective management of prevention and treatment practices, and to assess the performance of anti-TB measures. Based on indicative approach, improved epidemiological monitoring and quality assessment systems in TB care system have been developed and implemented at a regional level [7].

Aim. Analyze performance and quality of AFB detection by means of Ziehl-Neelsen staining-based microscopic examination performed in laboratories of primary care facilities in the Sakha Republic (Yakutia).

Material and methods. We analyzed the work of laboratory service performing microscopic diagnosis of TB in Yakutia. Analysis was based on national-level and industry sectoral reports, and annual reports of laboratories performing microscopic diagnosis of TB.

Data from the following statistical forms were analyzed: Form 30, Form 33, Form '7-ТБ', Register '03-ТБ/у', Register '4-ТБ/у' for the years 2005, and 2012-2016.

Statistical data processing was performed using commonly available software (Microsoft Excel), and StatSoft Statistica 6, and was based on mean values (M±m), and statistical significance measure for observed statistical differences (P).

Results and discussion. As of January 1, 2017, 209 clinical laboratories of all levels were functioning in the Sakha Republic (Yakutia).

Of 209 laboratories, Ziehl-Neelsen microscopic tests for AFB were performed by 144 (68.9%) labs. Due to substandard resources, 60 (28.7%) labs were not licensed to work with RG3 and RG4 biological agents, and were not performing tests for AFB.

Based on WHO recommendations for primary care facilities, the key performance quality indicators for Ziehl-Neelsen (ZN) microscopy are AFB detection rate in diagnostic specimens, multiplicity of tests performed, population coverage (%) with tests, and proportion of new TB cases with positive ZN sputum microscopy detected in primary care laboratories. Based on these criteria, we assessed performance for ZN microscopic tests conducted in clinical diagnostic laboratories of primary care facilities over the period from 2012 to 2016.

As is seen in Table 1, over the specified period, number of tests performed and number of individuals tested for AFB in primary care laboratories had remained practically at the same level, with minor variations ranging from 79 258 (2012) to 79 544 (2016) tests/year, and from 30 760 (2012) to 30 174 (2016) patients/year. Proportion of AFB-positive patients had been declining each year (WHO reference level: 1%), with 0.3% in 2016, compared to 0.5% in 2012. Multiplicity of tests (WHO reference value: 3.0) remained stably at 2.6. Population coverage (WHO reference level: 5%) ranged from 3.4% to 3.1%.

It can be said, that AFB detection rate, multiplicity of ZN tests, and population coverage with ZN testing in primary care

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laboratories had been below the reference WHO levels over the period from 2012 to 2016, and showed a trend to decline.

Therefore, with the aim to comprehensively assess performance of microscopies for AFB, we analyzed some aspects in generating the values for indicative statistics.

The first indicator, *AFB detection rate*, is used to describe the percent of smear-positive TB patients among patients suspected for TB and tested in primary care laboratories. Indicative value is calculated based on ratio of smear-positive patient number to total number of persons tested for TB (% of infectious TB patients identified by microscopy). Calculation is made using the formula:

$$\frac{\text{Number of smear-positive patients}}{\text{Number of patients with suspicion tested for TB}} \times 100$$

This indicator is used to assess performance of primary level laboratories in detecting TB cases. It is in correlation with TB prevalence level in a region. Reference value for AFB detection rate should be 1%.

Data in Table 1 show that in the Sakha Republic, the reference value for AFB detection rate is achieved only in specialized TB service facilities. Considering the existing estimated TB incidence in Russia, primary level laboratories could be able to detect, respectively, 1-2% and 2-3% of TB cases in cities and in rural areas, per every 100 individuals tested [6].

Reaching these proportions will demand rigorous adherence to requirements: appropriate patient referral for AFB-test; adequate multiplicity of tests performed; adequate quality of diagnostic specimens.

The second indicator, *multiplicity of tests*, is calculated using the formula:

$$\frac{\text{Number of samples tested}}{\text{Number of patients with suspicion tested for TB}} \times 100$$

WHO recommends collecting three samples from each patient suspected for TB to perform sputum microscopy. Ideally, an average number of slides (samples) observed to diagnose 1 patient should be 3 or close to 3. Too many (>3) or too few (<2) samples would be considered as noncompliance to sputum collection procedure [6]. But taking into consideration the new recommendations, cancel of further diagnostic tests of specimens is allowed, if AFB are detected in the first sputum sample. Optimal multiplicity for sputum tests per 1 patient, performed with diagnostic purpose, could be 2.7.

The third indicator describing the performance of primary-level facilities is *population coverage with microscopy*, calculated using the formula:

$$\frac{\text{Number of patients with suspicion tested for TB}}{\text{Total population of an area}} \times 100$$

Reference level for this indicator is 5%. This level is achievable with adequate patient classification to social and medical risk groups for TB.

The forth indicator, a significant one, is the *proportion of smear-positive patients with TB detected in primary-level laboratories among all notified new smear-positive TB cases*.

With well-organized workflow, the majority of infectious TB cases identified by sputum microscopy should be detected by primary-level facilities. Recommended detection level is estimated as no less than 50-70%. This indicator is calculated using the formula:

$$\frac{\text{Number of smear-positive TB patients detected by primary-level facilities}}{\text{Number of all notified new smear-positive TB cases}} \times 100$$

To analyze this indicator, results of microbiological examinations were studied in newly identified patients within annual cohorts of pulmonary TB cases in Sakha Republic for the years 2005, and 2012-2016.

Over the study period, there was a decline trend in number of new cases of pulmonary TB, with a decrease by 15.3%, on average (from 577 in 2005 to 489 in 2016). Among new pulmonary TB cases, diagnosis of infectious TB (i.e. case identification and notification) by means of microscopy (ZN, fluorescence) decreased by 5% (from 34.0% in 2005 to 32.3% in 2016) (Table 2).

There was a noticeable increase in AFB detection rate by microscopies performed in primary-level facilities. In 2005, proportion of AFB+ results in primary-level facilities was 18.4%, but during the period from 2012 to 2016, there was a statistically reliable increase by a factor of 2.4 ($p<0.05$), and in 2016, the proportion was 44.3%.

In the Far-East Federal District, the proportions of new infectious (smear-positive) TB cases detected by microscopy were lower, compared to Sakha Republic (Table 3): 32.2 (2012); 30.2 (2013); 31.5 (2014); 32.8 (2015); 30.2% (2016). In Russian Federation, the proportions were almost the same as in Sakha Republic: 33.8 (2012); 34.2 (2013); 34.0 (2014); 34.1 (2015); 33.8% (2016) [2,3,4,8].

For the last 5 years, the proportion of AFB-positive cases detected by primary-level facilities, among all notified AFB+ cases, was stably above 40% (except 39.8% in 2015), which was meaningfully higher, compared to Far-East Federal District and Russian Federation (2.3 and 2.4 times ($p<0.05$), respectively).

Hence, taking into consideration the increase in microscopic detections by primary-level facilities in Sakha Republic, observed over the study period, an appropriate reference level for this indicator would be no less than 60%.

Conclusion. All reference indicators discussed are suitable for estimation of the performance, quality of work, and work-

Table 1

Number and quality of ZN microscopies for AFB in clinical diagnostic laboratories of primary care facilities in 2012-2016

Indicators	Years				
	2012	2013	2014	2015	2016
Number of tests, total	79258	83501	79305	80034	79544
Of them, AFB+	322	228	226	187	162
Detection % (WHO reference: 1%)	0.4	0.3	0.3	0.2	0.2
Patients tested	30760	32584	30797	29920	30174
Of them, AFB+	149	126	110	101	87
Detection % (WHO reference: 1%)	0.5	0.4	0.4	0.3	0.3
Test multiplicity (WHO reference: 3.0)	2.6	2.6	2.6	2.7	2.6
Population coverage % (WHO reference: 5%)	3.2	3.4	3.2	2.8	3.1

flow management of primary-level laboratories performing ZN microscopy for AFB.

The indicators are easy to calculate, and are currently included in official statistical recording and reporting forms.

In conclusion, present-day reality is demanding further dedicated managerial efforts to continue actively using microscopic method in case detection, in particular, pulmonary TB cases, and especially, among social and medical risk groups. In view of this, more emphasis is put on comprehensive indicative approach to estimation and continuous monitoring of workflow organization and quality of microscopic tests performed, for the purposes of TB detection.

Table 2

AFB detection among new cases of pulmonary TB, Sakha Republic, 2005, 2012-2016

Year	Total number	Of them AFB+ (microscopy)		Of them, AFB+ (microscopy in primary care)	
		n	%	n	%
2005	577	196	34,0	36	18,4
2012	576	215	37,3	88	40,9
2013	591	199	33,7	81	40,7
2014	558	212	38,1	94	44,3
2015	517	171	33,1	68	39,8
2016	489	158	32,3	70	44,3
Trend over 2005-2016	- 15,3%	- 19,4%	- 5%	+1.9 times	+2.4 times

Table 3

Proportion of new cases of pulmonary TB with positive microscopy, Sakha Republic, Far-East Federal District, Russian Federation, 2012-2016

Indicator	Years				
	2012	2013	2014	2015	2016
Notified with AFB+ microscopy: Yakutia: (M±m) = 34.9±1.2 Far-East: (M±m) = 31.4±0.5 Russia: (M±m)=34.0±0.1	37.3 32.2 33.8	33.7 30.2 34.2	38.1 31.5 34.0	33.1 32.8 34.1	32.4 30.2 33.8
Of them. proportion of AFB+ detected in primary care facilities: Yakutia: (M±m) = 42.0±0.9 Far-East: (M±m) =17.9±0.5 Russia: (M±m) =17.5±0.3	40.9 19.2 18.3	40.7 18.7 17.9	44.3 16.1 16.8	39.8 17.2 17.5	44.3 18.1 16.8
Increase in Yakutia, compared to Far-East Federal District and Russia: by a factor of 2.3 and 2.4.					

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ACTUAL TOPIC

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METABOLIC SYNDROME AMONG YAKUTIA'S INDIGENOUS FEMALE POPULATION

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ABSTRACT

The aim of the study was to assess the prevalence and structure of metabolic syndrome among the indigenous female population (n=628) of the Republic of Sakha (Yakutia). The screening survey was conducted among the female population of 2 districts of the Republic of Sakha (Yakutia) at the age of 20 and older (Oimyakonsky, Gorny, Tattinsky). IDF metabolic syndrome was established in 142 women, thus prevalence was at 22.6%. The most common variant of the clinical manifestations of metabolic syndrome was a combination of abdominal obesity with high blood pressure and dyslipidemia (in 62.7% of cases). The dynamics of the frequency of metabolic disorders in different age groups suggests that abdominal obesity is the main pathogenetic factor contributing to the development of a chain of metabolic disorders in a given population.

Keywords: metabolic syndrome, Yakutia, abdominal obesity, diabetes mellitus, fasting hyperglycemia.

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Introduction. Metabolic syndrome is a complex of pathological conditions characterized by abdominal obesity, insulin resistance, hypertension, and hyperlipidemia. The syndrome contributes to the development of diseases such as diabetes mellitus type 2, coronary heart disease, stroke, and other disorders. The prevalence of metabolic syndrome has increased markedly over the past decades worldwide [5]. The main reasons for this are the changes in nutrition and a decrease in physical activity [6].

In the Sakha (Yakutia) Republic, changes in the socio-economic structure of the population in the 20th century changed the structure of diseases and their prevalence. Epidemiological transition is accompanied by an increase in the number of non-communicable diseases, including cardiovascular and type 2 diabetes. According to the state statistics bodies, the incidence of type 2 diabetes among the adult population of the republic increased from 2004 to 2017. from 14 to 40.3 per 1000 population, diseases of the circulatory system from 164.8 to 236.2 per 1000 population. Undoubtedly, this also entails an increase in longevity, but on the whole, indicates a significant burden on society. Effective control of risk factors for these diseases is possible with an objective assessment of the epidemiological situation.

In this regard, the purpose of the study was to assess the prevalence and structure of the metabolic syndrome among the indigenous female population of the Sakha (Yakutia) Republic.

Materials and Methods. A screening survey was conducted in 2017 among the female population of 2 districts of the Republic of Sakha (Yakutia) aged 20 and over (Oymyakonsky, Gorny, Tattinsky), representatives of indigenous ethnic groups (Yakuts, Evens, Evenks). The study was conducted subject to the voluntary informed consent of the participants. The examination program included: anthropometric examination by the standard method, triple measurement of blood pressure (BP), fasting venous blood sampling. The content of glucose, total cholesterol (cholesterol), triglycerides, high-density lipoproteins (HDL cholesterol) was determined on the express analyzer Cardiochek PA, USA. The concentration of low-density lipoprotein cholesterol (LDL cholesterol) was calculated using the Friedwald formula with a blood triglyceride level of less than 4.5 mmol/L. Hypertriglyceridemia was established with a triglyceride content of ≥ 1.7 mmol/L, hypercholesterolemia – at a concentration of HDL cholesterol < 1.0 mmol/L in men and < 1.3 mmol/L in women; elevated blood pressure – with systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mm Hg; fasting hyperglycemia (FHG) – when the plasma glucose level is ≥ 5.6 mmol/L, or when an established diagnosis of diabetes mellitus (DM). Persons receiving specific medical treatment for these conditions were also referred to as persons with these disorders. As criteria for metabolic syndrome, IDF 2006 criteria were used, according to which MS was established in the presence of abdominal obesity (waist circumference more than 80 cm) and 2 or more of the 4 above-mentioned risk factors [6].

Statistical data analysis was performed in the IBM SPSS STATISTICS 22 package. When comparing groups depending on the type of data, Kruskal-Wallis and Pearson χ^2 criteria were used. The critical value of the level of statistical significance of differences (p) was taken to be 5%. Descriptive statistics of quantitative data are presented as median (Me) and interquartile range

(Q1-Q2). Frequencies are presented with a 95% confidence interval (95% CI). In calculating the age-standardized prevalence rate, MS used the age structure of the world population (WHO World Standard) [4].

The work was carried out as part of the research "The Contribution of Metabolic Syndrome to the Development of Atherosclerosis of the Coronary Arteries in Yakutia Residents Reg. No. 01-20-128-08-00 Modern Conditions" (Registration Number AAAA-A17-117021310139-5, 17.6344.2017/8.9.).

Results and Discussion. During the epidemiological study, 628 women 20 years and older were examined. The average age of participants was 47.4 (standard deviation 15.1) years. The proportion of women 50–59 years old was 28%, 20-39 years old – 32.7%, 40-49 years old – 19.4%, 60 and older – 19.6%.

Table 1 presents the main anthropometric and metabolic characteristics of the women examined. The dynamics of indicators in the age groups corresponded to the natural changes associated with the age of the subjects. The growth of women of young age groups was statistically significantly higher than that of older women, which reflects acceleration processes. The median value of body mass index from 40-49 years was in the range of "increased" body weight. The median waist circumference, ranging from 30-39 years, met the criteria for abdominal obesity. From 40-49 years for dap and 50-59 years for CAD, the values of blood pressure corresponding to the upper quartile of the distribution were in the range of "arterial hypertension" according to the criteria of Moscow Society of Obstetrician Gynecologists (www.moag.pro). The cholesterol content was elevated from 40-49 years old, while the proportion of HDL cholesterol was maintained at a fairly high level in all age groups. Low triglyceride levels are noteworthy. Thus, in general, the metabolic profile of women of Yakutia of indigenous nationality is characterized by the following features: increased body mass index, abdominal obesity, a fairly favorable lipid profile, and normal blood glucose. These results are consistent with data previously obtained in epidemiological studies among the Yakut population [1].

The frequency of metabolic syndrome and its components, depending on the age of the examined, is presented in table 2. If we consider the frequency of metabolic disorders in the whole group, abdominal obesity was detected in 444 women and its prevalence was 70.7% (95% CI: 66.9 -74.2). In 283 women, the blood pressure level was rated as "elevated", prevalence rates were 45.1% (95% CI: 41.2-49.0). Reduced HDL cholesterol levels were found in 162 patients, which was 25.8% (95% CI: 22.5-29.4). Hypertriglyceridemia occurred in 63 women, respectively, the prevalence was 10.0% (95% CI: 7.9-12.7). Fasting hyperglycemia or an earlier diagnosis of diabetes was found in 72 women, 11.5% (95% CI: 9.2-14.3). The frequency of all these disorders increased significantly from the age of 40-49 years.

IDF metabolic syndrome was established in 142 women, the prevalence was respectively 22.6% (95% CI: 19.5-26.1). The highest frequency of MS was observed at the age of 50-69 years. The age-standardized MS prevalence rate by IDF criteria among the female indigenous population of Yakutia was 21.2% (95% CI: 17.7-24.7). The study of the prevalence of MS among various groups of the population of Yakutia was also carried out by other authors. Thus, the prevalence of MS according to IDF criteria, among indigenous women in Yakutsk 60 years and older was 34.8%, which is comparable

Table 1

The main anthropometric and metabolic characteristics of the female indigenous population of Yakutia, Me (Q_1-Q_3)

Indicator	20 years and older N=628	20-29 years n=91	30-39 years n=114	40-49 years n=122	50-59 years n=178	60-69 years n=72	70 years and older n=51	p
SBP, mm Hg	120.0 (110.0-140.0)	108.2 (100.0-115.0)	110.0 (100.0-120.3)	119.0 (107.5-135.3)	130.0 (113.8-150.0)	140.0 (120.0-160.0)	140.0 (125.0-170.0)	<0.001
DBP, mm Hg	80.0 (70.0-90.0)	72.3 (65.0-80.0)	79.5 (70.0-84.0)	80.0 (70.0-90.0)	82.7 (75.3-99.3)	81.5 (71.8-95.3)	90.0 (80.0-100.0)	<0.001
Height, cm	155.5 (151.0-160.0)	158.8 (155.0-163.2)	158.0 (155.0-163.0)	157.0 (154.0-161.0)	154.3 (151.0-158.5)	151.0 (147.6-154.2)	148.0 (143.0-151.0)	<0.001
Body mass, kg	61.8 (53.3-72.0)	54.2 (49.2-61.3)	58.5 (53.3-68.0)	64.0 (55.4-75.0)	65.0 (56.9-75.8)	64.0 (54.8-74.8)	61.0 (48.5-68.0)	<0.001
Body mass index, kg/m^2	25.3 (22.2-29.7)	21.7 (19.4-24.2)	23.5 (21.2-26.6)	26.2 (23.2-30.1)	27.3 (24.1-31.2)	27.3 (24.2-32.9)	27.1 (22.5-31.4)	<0.001
Waist circumference, cm	87.0 (78.0-97.2)	75.0 (70.0-84.0)	80.0 (71.8-85.5)	85.0 (79.0-97.1)	93.9 (85.0-102.0)	95.4 (86.3-106.5)	92.0 (84.0-102.0)	<0.001
Cholesterol mmol/L	5.2 (4.4-5.9)	4.2 (3.6-4.9)	4.8 (4.1-5.5)	5.2 (4.6-5.7)	5.7 (5.1-6.3)	5.4 (4.7-6.2)	5.3 (4.6-6.1)	<0.001
HDL mmol/L	1.6 (1.3-1.9)	1.7 (1.3-2.1)	1.6 (1.3-1.9)	1.6 (1.3-2.0)	1.6 (1.3-1.9)	1.5 (1.2-1.7)	1.4 (1.1-1.7)	<0.001
LDL mmol/L	2.9 (2.2-3.6)	1.9 (1.5-2.4)	2.5 (2.0-3.2)	3.0 (2.4-3.4)	3.2 (2.7-3.9)	3.3 (2.5-4.0)	3.4 (2.8-4.1)	0.003
VLDL mmol/L	0.4 (0.3-0.6)	0.3 (0.3-0.5)	0.4 (0.3-0.5)	0.5 (0.3-0.7)	0.5 (0.4-0.7)	0.4 (0.3-0.6)	0.4 (0.3-0.6)	<0.001
Triglycerides mmol/L	0.9 (0.7-1.2)	0.8 (0.6-1.0)	0.8 (0.6-1.0)	0.9 (0.7-1.3)	1.0 (0.8-1.4)	1.0 (0.8-1.4)	0.9 (0.7-1.2)	<0.001
Glucose mmol/L	4.4 (4.0-5.0)	4.3 (3.9-4.9)	4.1 (3.9-4.6)	4.4 (4.0-5.2)	4.5 (4.1-5.1)	4.4 (4.0-5.2)	4.3 (4.1-4.7)	<0.001

Note: p-value is an achieved level of significance of differences when comparing groups by age (Kruskal–Wallis test).

Table 2

Prevalence of metabolic syndrome and its components among the female indigenous population of Yakutia

Age	Возраст						Total n=628
	20-29 years n=91	30-39 years n=114	40-49 years n=122	50-59 years n=178	60-69 years n=72	70-79 years n=51	
Triglycerides ≥ 1.7 mmol/L							
n	4	6	14	28	8	3	63
% (95%ДИ)	4.4 (0.6-11.9)	5.3 (1.6-11.8)	11.5 (6.4-18.9)	15.7 (10.8-22.1)	11.1 (4.6-21.6)	5.9 (0-18.1)	10.0 (7.9-12.7)
HDL < 1.29 mmol/L							
n	17	31	30	42	24	18	162
% (95%ДИ)	18.7 (11.3-28.6)	27.2 (19.4-36.5)	24.6 (17.4-33.4)	23.6 (17.7-30.6)	33.3 (22.7-45.6)	35.3 (22.3-50.3)	25.8 (22.5-29.4)
Fasting blood glucose ≥ 5.6 mmol/L or Type 2 Diabetes							
n	6	3	17	31	12	3	72
% (95%ДИ)	6.6 (2.1-14.7)	2.6 (0-8.5)	13.9 (8.4-21.7)	17.4 (12.3-23.9)	16.7 (8.8-27.9)	5.9 (0-18)	11.5 (9.2-14.3)
SBP ≥ 130 mm Hg and/or DBP ≥ 85 mm Hg							
n	12	31	52	101	49	38	283
% (95%ДИ)	13.2 (6.9-22.4)	27.2 (19.4-36.5)	42.6 (33.8-51.9)	56.7 (49.2-64.0)	68.1 (55.8-78.5)	74.5 (59.7-85.9)	45.1 (41.2-49.0)
Waist circumference more than 80 cm							
n	34	61	89	150	64	46	444
% (95%ДИ)	37.4 (27.5-48.2)	53.5 (44.0-62.8)	73.0 (64.0-80.5)	84.3 (77.9-89.2)	88.9 (78.4-95.4)	90.2 (77.2-97.6)	70.7 (66.9-74.2)
Metabolic syndrome by IDF criteria							
n	3	13	30	54	27	15	142
% (95%ДИ)	3.3 (0-10.5)	11.4 (6.2-19.2)	24.6 (17.4-33.4)	30.3 (23.8-37.7)	37.5 (26.4-49.9)	29.4 (17.4-44.4)	22.6 (19.5-26.1)

with our data in the corresponding age group (33.5%) [2]. In a study conducted among small indigenous peoples of the North, the prevalence of MS according to the criteria of GNOK ranged from 25 to 61% [3].

Elevated blood pressure was one of the components of MS in 90.1% of cases of MS, hypercholesterolemia in 71.1%, Fasting Hyperglycemia/Diabetes Mellitus in 35.9%, and GGT in 34.5%. The most common variant of the clinical manifestations of MS was the combination of abdominal obesity with high blood pressure and dyslipidemia (Table 3). This combination of risk factors was observed in 89 of 142 women with MS. A combination of 4 risk factors (abdominal obesity, elevated blood pressure, dyslipidemia, fasting hyperglycemia (DM)) was detected in 21 cases of MS. In 18 women, MS was a combination of abdominal obesity, elevated blood pressure and fasting hyperglycemia (or DM). A rare variant of MS without elevated blood pressure was found in 10 women aged 30-69 years. Four cases of isolated lipid spectrum disorders in the form of a combination of hypertriglyceridemia and a reduced level of HDL cholesterol on the background of abdominal obesity were recorded in different age groups, and possibly reflect cases of primary dyslipidemia. In general, options with the inclusion of disorders of carbohydrate metabolism in the form of fasting hyperglycemia or diabetes were recorded from the age of 40-49 years. This suggests that in this population abdominal obesity is the main pathogenetic factor contributing to the development of a chain of metabolic disorders.

Conclusion. Thus, according to the results of a screening survey, the prevalence of metabolic syndrome accord-

Table 3

Variants of clinical manifestations of metabolic syndrome depending on the age of the examined, %

Age	AO+EBP+ DLP		AO+EBP+ FHG/ DM+DLP		AO+EBP+ FHG/DM		AO+FHG/ DM+DLP		DLP (GGT, CS HDL ↓)	
	n	%	n	%	n	%	n	%	n	%
20-29 years n=3	2	66.6	0	0	0	0	0	0	1	33.3
30-39 years n=13	12	92.3	0	0	0	0	1	7.7	0	0.0
40-49 years n=30	17	56.6	5	16.6	3	10.0	5	16.7	0	0.0
50-59 years n=54	29	53.7	9	16.7	11	20.4	3	5.6	2	3.7
60-69 years n=27	17	63.0	6	22.2	3	11.1	1	3.7	0	0.0
70-79 years n=15	12	80.0	1	6.7	1	6.7	0	0.0	1	6.7
Total n=142	89	62.7	21	14.8	18	12.7	10	7.0	4	2.8

Note. AO – abdominal obesity; EBP – elevated blood pressure; DLP – dyslipoproteinemia; FHG/DM – fasting hyperglycemia and/or proven case of DM.

ing to IDF criteria among the indigenous female population was 22.6% (95% CI: 19.5-26.1). With standardization on the age structure of the world's population, the prevalence of MS was 21.2% (95% CI: 17.7-24.7). The most common variant of the clinical manifestations of MS was a combination of abdominal obesity with high blood pressure and dyslipidemia (in 62.7% of cases). A combination of 4 risk factors (abdominal obesity, elevated blood pressure, dyslipidemia, fasting hyperglycemia/diabetes) was detected in 14.8% of cases of MS. Variants with the inclusion of disorders of carbohydrate metabolism in the form of FHG/DM were recorded from the age of 40-49 years. The dynamics of the frequency of metabolic disorders in different age groups suggests that abdominal obesity is the main pathogenetic factor contributing to the development of a chain of metabolic disorders in a given population. The statement of this fact contains the potential for correction by informing the public about the risks, creating conditions for an active lifestyle, improving the eating habits of the population, restricting advertising of unhealthy foods in the media, etc.

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THE HETEROGENEITY OF NON-MOTOR SYMPTOMS IN PATIENTS WITH PARKINSON'S DISEASE IN TOMSK REGION

This study was designed to survey the prevalence and distribution of non-motor symptoms (NMS) in Parkinson's disease (PD) patients in Siberian region, Russia, and to investigate the association between NMS and health-related quality of life.

Materials and methods. Two hundred six PD patients were evaluated using a battery of validated scales recommended by leading PD research Societies (Movement Disorders Society and the European Academy of Neurology). Clinical assessments were conducted using Uniform Parkinson's Disease Rating Scale (UPDRS), Hospital Anxiety and Depression Scale, Beck depression inventory II, Apathy Scale, Montreal Cognitive Assessment (MoCAtest), Epworth Sleepiness Scale, Sleep Assessment Questionnaire, Columbia-Suicide Severity Rating Scale, Parkinson's Disease Questionnaire-39 – PDQ-39. **Results.** Each PD patient had eight different individual NMS on average. The constipation (87%), depression (67%), insomnia (66%), anxiety (52%), apathy (35%), and impulsive behavior disorders (27%) were the most frequent complaints. NMS prevalence in PD patients in Tomsk region was consistent with that in the international study, although the composition proportions were different. There was a significant association of PDQ-39 score with anxiety (r = 0,474, p = 0,000), depression (r = 0,471, p = 0,000), apathy (r = 0,322, p = 0,000), UPDRS III score (r = 0,316, p = 0,000), Hoehn and Yahr stage (r = 0,267, p = 0,000), disease duration (r = 0,220, p = 0,005), and levodopa equivalent dosage (r = 0,213, p = 0,001).

Conclusion. This study confirmed that NMS are common in PD, occurring across all disease stages and have a great impact on quality of life. NMS progression contributes significantly to health-related quality of life decline, and should be well recognized and treated.

Keywords: Parkinson's disease, apathy, anxiety, depression, impulsive behavioral disorders, insomnia, constipation.

Introduction. Parkinson's Disease (PD) is one of the most common neurological disease reaching 1% among population with age more than 60. PD's morbidity is up to 40 cases per 100 000 of population per year. According to the results of different epidemiological researches conducted in the USA and some European countries the prevalence of this neurodegenerative disease ranges in wide limits from 18 to 328 cases per 100 000 of population, but on the average it is about 120 cases per 100 000 of population [9]. In the Russian Federation the prevalence of PD is at worldwide level and according to the epidemiological

researches conducted in different regions it is in the limit from 40 to 140 cases per 100 000 of population. The amount of patients with Parkinson's disease (PwPD) is suggested to increase in 1,5-2 times to 2030 year [4].

Non-motor symptoms of PD are common but might stay unrecognized in clinical practice due to the insufficient targeted detection by physicians and absence of active complaints from patients and their relatives [1]. While dominating in clinical case and being main factors that influence life quality and length of PwPD, such non-motor symptoms like emotional-affective, behavioral and psychotic symptoms accelerate progressing of invalidization and cause patients' accommodation in nursing home [13].

For the first time non-motor symptoms of PD were systematically described in 2006 by K. Ray Chaudhuri and all [9] and nowadays non-motor symptoms are paid great attention [7, 23]. Wide range of non-motor symptoms includes vegetative, neuropsychic, sensor disorders, fatigue, sleep and wakefulness disturbances. Some PD's non-motor symptoms are registered in almost all patients regardless of the age of onset and Hoehn and Yahr stage of disease and become more expressed with the course of the disease [2]. Some of non-motor symptoms (anxiety, fatigue and vegetative disorders) are registered at the early stage of disease before the beginning of treatment [12]; the others according to literature data and own clinical observations precede PD's motor symptoms for a few years (olfactory dysfunction, disturbed eye movement in the sleep phase with fast eye movement – REM sleep phase, constipation, pain and depression) [1]. At late stages of disease non-motor symptoms are observed in almost all patients with motor fluctuations [10]. A lot of researches have established that at the time of PD diagnose verification its prevalence is 21%, but in only 7 years after the disease onset it is 88% [12].

The **aim** of this study is to analyze heterogeneity of non-motor manifestation of PD in Tomsk region.

Materials and methods. This study was performed on the base of Department of Neurology and Neurosurgery, Siberian State Medical University. We examined 206 PwPD, 57 % (118 people) out of them were women. The examination of all patients was held according to our own designed individual registration card including information about social status, history of previous diseases, passport details, neurological status and results of neuropsychological testing with scales and questionnaries. Diagnose of PD was established according to UK Parkinson's Disease Society Brain Bank Diagnostic Criteria. While establishing the diagnosis clinical form, Hoehn and Yahr stage of disease (according to «Modified Hoehn and Yahr Scale», 1967), rate of progression, presence of postural unsteadiness, impaired walking, sidedness with a predominance of motor symptoms in the limbs, severity of different non-motor manifestations (depression, anxiety, apathy, cognitive and vegetative disorders) were considered.

Average age of examined patients was about 65,9±9,8 years (66 (60;74) years), varying from 40 to 85 years. People with secondary professional education (39,3%) and with higher education (46,6%) prevailed.

The study involved patients matching certain criteria: men and women from 50 to 86 years; presence of PD's diagnosis with I-IV stage by Hoehn and Yahr scale; patients who signed and dated voluntary informed agreement for taking part in the research.

Severity of motor manifestations of PD such as resting tremor, hypokinesia, rigidity and postural unsteadiness was determined according to III part of the Unified Parkinson's Disease Rating Scale (UPDRS) [11].

Validated neuropsychological tests provided in the study were focused on detection of such non-motor manifestations of PD as impulsive behavioral disorders, cognitive and emotional-affective disorders, psychotic manifestation and sleep disorders. Impulsive-compulsive disorders were evaluated by questionnaire for Questionnaire for Impulsive-Compulsive Disorders in PD Rating Scale (QUIP-RS). Anxiety-depressive disorders were evaluated according to Hospital Anxiety and Depression Scale (HADS), Beck's Depression Inventory – II (BDI-II), Apathy Scale and Columbia Suicide Severity Rating Scale (C-SSRS). Cognitive status was analyzed according to Montreal Cognitive Assessment (MoCA). Sleep disorders were studied according to Epworth Sleepiness Scale (ESS) and Sleep Attack Questionnaire (SAQ). Quality of life was studied by using specialized self-questionnaire for life quality assessment in PwPD, PDQ-39.

Statistical result processing was performed by using application package SPSS 11.5 for Windows.

Results and discussion. During results analysis it was revealed that among the examined 206 PwPD 27% (56 patients) had subclinical anxiety according to HADS and 25% (51 patients) had clinically manifested anxiety (table 1).

The average was 66 (61; 73) years in the group without anxiety, 64 (60; 74) years in the group with subclinical anxiety and 64 (57; 75) years in the group with clinically manifested anxiety (χ^2=0,162, p=0,922). During intergroup comparison it was revealed that younger patients (aged 50-59 years, 31,4%) prevailed in the group with clinically manifested anxiety as opposed to groups without anxiety and with subclinical anxiety which consisted of more older patients.

Table 1

Characteristics of patients with Parkinson's disease, depending on the presence and severity of anxiety according to the HADS scale

Indicator abs. %	Выраженность тревоги по шкале HADS, баллы		
	Norm 0—7	subclinical 8—10	Clinical ≥11
n=206 100 %	99 48.06	56 27.18	51 24.76

In the result of our research it was revealed that patients with clinically manifested anxiety had the longest duration of PD – about 8 (4; 10) years, patients with subclinical anxiety had the shortest – 4 (3; 9) years and without anxiety – 6 (3; 10) years. The received data correspond to the literary described as "parkinsonian personality" according to which anxiety preceding to first motor manifestations of PD is characteristic. On advanced stages of the disease PwPD with motor fluctuations have anxiety level depending on levodopa action phase. Thus, anxiety symptoms are increased by relative overdose of dopaminergic drugs [11, 16].

Analisys of motor disorders by III part of UPDRS depending on severity of anxiety revealed that patients with anxiety had more expressed motor manifestations of PD: in the group of patients without anxiety, with subclinical expressed and manifested anxiety average mean by UPDRS was 32 (25; 43), 33 (27; 46) и 35 (28; 44) points respectively. This fact can be explained on the one side by progressive

neurodegenerative process, from the other side by not always correct usage of antiparkinsonian drugs treatment in patients with emotional-affective disorders. While analyzing clinical form of PD debut we revealed that anxiety prevailed in patients with acinetic-rigidity form.

Statistically significant positive mean force correlation between anxiety and depression was revealed both by HADS (r=0,446; p<0,0001) and BDI-II (r=0,436; p<0,0001) questionnaires. Statistically significant difference in severity of apathy in patients with clinically manifested anxiety 14 (7; 19), with subclinical anxiety – 12 (7; 15) and without anxiety – 8 (5; 14), p=0,001 (table 2) was also detected. The obtained results indicate that anxiety in PD more often is not a separate neuropsychological disorder but a part of depression structure.

That means PwPD and more expressed anxiety usually have other emotional-affective disorders.

It was revealed that among our 206 researched patients with clinically significant diagnosis of PD there were only 4 patients with identified suicidal intent in history according to Columbia suicide severity rating scale C-SSRS and subsequent interviewed physicians. Herewith no active suicidal attempts were observed in anamnesis of these patients. Our results prove the literary data that "suicidal thoughts are rarity for PwPD" [7].

Analysis of drug-induced dyskinesia prevalence in PwPD with anxiety demonstrated statistically more significant prevalence (39,2%) in comparison with patients without anxiety (17,2%), z=2,77; p=0,006.

Significant influence of anxiety on quality of life in PwPD was revealed. Common health status index by self-questionnaire quality of life PDQ-39 in patients without anxiety was significantly lower in comparison with patients with subclinical and clinically manifested anxiety and means 28 (20; 44), 37 (26; 46) и 48 (39; 57) points, p<0,001 respectively. The more the total overall health status index is, the worse the quality of life of the subject is (table 2).

Among studied PwPD with anxiety there are statistically more occurring impulsive behavior disorders such as gambling (p=0,004), hobbysm (p=0,042) and compulsive obsessive taking of dopaminergic drugs within dofamin dysregulation syndrome (p=0,010) that correlates with literary data according to which anxiety disorders can be manifested both by common anxiety and panic attacks, social phobia and obsessive-compulsive disorders. Although impulsive compulsive disorders are different from obsessive-compulsive, there is phenomenological duplication indicating community of certain neurobiologocal mechanisms. Both disorders have common diagnostic criteria such as "excessive behavior" leading to "significant deterioration" in the main areas of life [13].

Analysis of impulsive behavior disorders rate indicates that it occurs in 27% of cases (in 56 patients) with the majority prevailing in men: gambling was registered in 6,7 %, among women – 2,7 %, p>0,05, hypersexuality – in 6,7 %, among women – 0,0 %, p>0,05, punding – in 20,0 %, among women – 8,1 %, p>0,05, hobbysm – in 20,0 %, among women – 5,4 %, p>0,05, dofamin dysregulation syndrome – in 20,0 %, among women – 13,5 %, p>0,05. Whereas among women such disorders as shopping mania prevailed in women and occurs in 8,1 %; among men such impulsive behavior disorder was not registered in men p>0,05 and compulsive overeating was registered in women – 10,8 % was not registered in men – 0,0 %, p>0,05. It should be noted that there are no statistically significant differences between the groups of both men and women in terms of the prevalence of any behavioral disturbance.

According to literary data prevalence of depression is 3-10% among population [10]. On the early stages of PD depression occurs in 27,6% patients [15], on later stages in 40-50% of patients [5, 8]. The last one is characteristic for all stages of PD. At the same time, it was established that in 30% of cases the diagnosis of depression preceded the first motor symptoms of PD. Emotional affective disorders can manifest themselves in some cases 20 years before the motor manifestation, but on average this period is 3–6 years [10]. According to the results of a study conducted at the Mayo Clinic, the risk of developing PD is 1.9 times higher in patients with depressive disorders, with anxious disorders - 2.2, and with both - 2.4 [9, 12].

Depression can be manifested by dysthymia (the frequency of which is about 13% in PwPD), major (17%) and minor (22%) depressive disorders. About 35% of PwPD have clinically expressed depressive symptoms [12, 16], however, according to various literary, the proportion of patients with severe depression is 3-8%, reaching a psychotic level, and it does not end with suicide attempts. In patients with motor fluctuations, transient depression ("off-period") occurs that is changes in depression and maniacal state, marked against the background of motor fluctuations [15].

One of the main problems that impede the diagnosis of depression in PD is similarity, common features inherent in depressive syndrome and PD: hypomimia, hypophony, decreased psychomotor activity, attention disorders, increased fatigue, decreased appetite, decreased libido and sleep disorder [3, 4, 13].

There is a point of view that depression in PwPD does not depend on the age, duration of PD and severity of disease [10]. However, some researchers claim that the most prevalence of this emotional and affective disorder occurs in patients with the initial stage of PD (first stage by Hoehn and Yahr scale). Such dependence can be explained by the importance of psychological factors in the development of depressive disorders in the early stages of PD associated with the onset of the disease and the establishment of a diagnosis. Then it decreases slightly to stage II (due to the patient's internal adaptation to a chronic

Table 2

Severe apathy and characteristic of quality of life in people with Parkinson's disease, depending on the severity of anxiety, in points; - Me (Q1; Q3)

	Norm n=99	Subclinical anxiety n=56	Clinical anxiety n=51	Kruskal-Wallis Criteria		Mann-Whitney Criteria
	Me (Q1; Q3)	Me (Q1; Q3)	Me (Q1; Q3)	χ^2	p	
Apathy, points	8 (5;14)	12 (7;15)	14 (7;19)	13.193	0.001*	p_{1-2}=0.093 p_{1-3}=0.002* p_{2-3}=0.170
PDQ-39, points	28 (20;44)	37 (26;46)	48 (39;57)	32.704	<0.001*	p_{1-2}=0.090 p_{1-3}<0.001* p_{2-3}<0.001*

Note. In the Tables 2, 3 * - statistically significant differences at p <0.005. Quantitative attributes are presented in the form of a median and interquartile interval - Me (Q1; Q3).

disease and the start of antiparkinsonian dopaminergic therapy, which has an antidepressant effect [2, 4]. Stages III — IV again are characterized by high prevalence of depression due to a continuously progressive neurodegenerative process. Among patients with stage V of PD the proportion of people with severe depression is reduced. Other researchers think that the frequency of depression is higher at the oneset of PD with akinetic-rigid form, at a younger age, in women, as well as at a faster rate of disease progression and burdened family anamneses of neurodegenerative pathology [9].

Among researched PwPD 10% had severe depression and 27% had depression with middle severity according to Beck's depression inventory scale (BDI-II).

The results of our researches prove that prevalence of depression in PD is more at the initial stage of the disease (up to 54%); it decreases at stage II of the disease to 45% and increases again up to 58% in patients with stages III and IV of PD.

Using a correlation analysis of the obtained data, a middle strength of the positive relationship between depression and poor quality of life was revealed in PwPD (r = 0.471; p<0.001 under the PDQ-39 questionnaire "cognitive functions" (r=0.451; p<0.001) and "emotional well-being"(r=0,450; p<0.001).

A special place in our work was devoted to analysis of motor disorders severity and drug-induced movement disorders in PwPD depending on the severity of emotional-affective disorders. In individuals without depression the lowest frequency of occurrence of drug-induced movement disorders was found (9.0%), while in patients with depression this index reached 31.7% (z=2.39; p=0.019).

Analyzing the frequency of occurrence of motor disorders in PwPD according to III part of the UPDRS scale depending on the severity of depression, it was found that in patients with severe depression they were more pronounced (p=0.007). It can be assumed that this fact is not always explained by the incorrect treatment of antiparkinsonian dopaminergic drugs by patients with emotional-affective disorders. So in patients without depression overall average score for UPDRS was 31 (24; 37), with slight depression - 32 (27; 43), with moderate - 35 (27; 47) and severe - 39 (33; 47), (table 3).

When assessing drowsiness it was found that the average score according to the Epworth sleepness scale (ESS) was statistically significantly higher in the group of patients with depression - (5; 11) points, compared with those without chronically lowered mood - 6 (3; 8), (χ2=8.424; p=0.038).

In recent years a new approach to defining apathy has been taken as a "loss of initiative" [12], that is, a lack of desire for any activity and indifference to what is happening around. Particular attention should be paid to the differential diagnosis of depression and apathy in PD, because they have such common symptoms as hypomimia, fatigue, social isolation, a decrease in pleasure from previously favorite activities and a decrease in interest in them. Often, these two emotional and affective states are combined in PD [16]. However, anxiety and melancholy affects are not characteristic of apathy as an independent syndrome [15].

Apathy is one of the most frequent affective disorders in PD, characterized by a loss of interest in the environment, a decrease in motivation, initiative and emotional dullness [4, 10, 19]. According to some researchers, the apathy rate in PD varies from 7 to 70% [4], while others researches suggest the much lower spread - from 30% to 40% [19]. It can occur both in the structure of depression, and independently of it (approximately in 14% of patients) [4].

According to our research 35% (71 PwPD) had apathy according to Apathy Scale.

It has been established that the onset of apathy is not affected by the age of PwPD and the age of neurodegenerative disease onset. Patients with apathy have a longer duration of the disease (U=3791.5; p=0.020), as a result, a more developed stage of PD according to Hoehn and Yahr scale (III and IV) and accordingly more severe motor disorders (U=3548.5; p=0.003).

In the group of patients with apathy, there are statistically significantly more patients with daytime sleepiness (z=0.93; p=0.352), anxiety (z=2.63; p=0.009), depression (z=2.13; p=0.034) and impulsive behavioral disorders (z=2.70; p=0.008), drug-induced dyskinesias (z=2.77; p=0.006), and cognitive impairment in the field of visual and constructive skills (χ2=3542,000; p=0,002).

Analyzing antiparkinsonian dopaminergic therapy, it was found that patients with apathy had a daily dose of various levodopa preparations in terms of equivalent dose of levodopa, LED (L-Dopa), higher - 300 (156; 375) mg, compared to patients without apathy - 150 (0; 350) mg, p<0.001.

After assessing the quality of life according to the specialized questionnaire for PwPD PDQ-39, it was found that the overall health index in patients without apathy was statistically significantly lower - 33.3 (21.8; 47.4) than in patients with apathy - 43.6 (32.7; 55.8) 43,6 (32,7; 55,8) (χ^2=3346,5; p<0,001).

Sleep disorders have significant impact on the quality of life registered in 66% of cases of PD (136 patients). Comparable results were obtained in a study conducted in Honolulu (The Honolulu-Asia Aging Study, HAAS), the risk of developing PD in patients with excessive daytime sleepiness was significantly higher compared with people not suffering from it (3.3 times). In contrast, the presence of other sleep-related disorders - insomnia, naps, morning shakiness (intoxication), and frequent nighttime awakenings - is not significant when considering the risk of developing PD. It should be noted that sleep disorders in the REM – phase precede the onset of other disease symptoms [9].

Constipation is perhaps the most common symptom in PD, due to the formation of α-synuclein in the dorsal motor nucleus of the vagus nerve (nucleus dorsalis nervi vagi), pre-vertebral ganglia and intestinal submucosal plexuses [6]. It has been

Table 3

Characteristics of the severity of motor disorders in patients with Parkinson's disease (according to the sum of the third part of the UPDRS) depending on the severity of depression, in points - Me (Q1; Q3)

	Norm n=67	Mild depression n=62	Moderate depression n=56	Severe depression n=21	Kruskal-Wallis criterion		Mann-Whitney criterion
	Me (Q1; Q3)	Me (Q1; Q3)	Me (Q1; Q3)	Me (Q1; Q3)	χ^2	p	
Movement impairments UPDRS	31 (24;37)	32 (27;43)	35 (27;47)	39 (33; 47)	12.0	0.007*	p_{1-2}=0.139 p_{1-3}=0.264 p_{1-4}=0.003* p_{2-3}=0.614 p_{2-4}=0.185 p_{3-4}=0.103

recently established that the pathology of α-synuclein can be detected by biopsy of the colon submucosa in patients with PD [9]. Studies have shown that constipation usually precedes the development of PD for more than 10–18 years [1, 2]. According to the results of our study, it was found that 87% of patients with PD had these gastroenterological disorders (constipation was regarded as reduction of the bowel movements frequency to once or less a week). This is one of problems of current interest for patients with PD and their physicians, as problems with the evacuation function of the intestine lead to a decrease in the bioavailability of dopaminergic antiparkinsonian therapy, and, as a result, to a deterioration in the physical activity of PwPD. In addition, interest to the studying of gastroenterological disorders in PwPD remains on high level due to the fact that constipation, along with depression and olfactory disorders, is the "Non-motor stage" of PD, which already is the beginning of a systemic degenerative process preceding the onset of motor disorders [1, 14]. Thus, according to the history of our patients, gastroenterological symptoms such as constipation, nausea, and flatulence were present 5–12 years before the clinical diagnosis of PD.

Conclusion. Questions about phenomenological independence of non-motor disorders in PwPD, their pathophysiological commonality with the motor manifestations of the disease due to the multifactorial nature of PD and insufficiently developed approaches to therapy are very relevant today. Well-timed and adequate identification of risk factors for the progression of non-motor manifestations of PD will allow correct therapy to be given to patients with high risk of their development. Thus in recent years the understanding of the essence of PD as a pathological, pathophysiological and developing clinical process has significantly changed, covering not only the motor sphere, but also causing a violation of the vegetative regulation, obvious changes in the psychoemotional state of patients and their behavior.

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AGE-RELATED DYNAMICS OF BONE MINERAL DENSITY IN THE ADULT POPULATION OF YAKUTSK

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ABSTRACT. There has been conducted a study of the age dynamics and characteristics of the of the bone mineral density (BMD) in the adult population of the Yakutsk city. There have been revealed the BMD maximum age rates in both women (aged between 40 and 49 years old) and men (aged between 60 and 69 years old). The first 10 years after menopause onset in women, BMD decreases by 18%. The correlation of body mass index and BMD depending on gender and ethnicity was revealed.

Keywords: bone mineral density, osteoporosis, body mass index, menopause.

Relevance. Yakutsk is acknowledged to be the largest city of central Yakutia. The climatic and geographical features of the location are known to be accompanied by a low level of insolation and a long winter period of 6-9 months per year [3, 4].

A low level of insolation is stated to lead to a deficiency in the synthesis of vitamin D, which in turn appears to be a trigger in the development of osteoporosis [7].

Osteoporosis is accepted to be one of the most common diseases which have been given a leading position in the structure of morbidity and mortality in the world [1, 6].

According to the International Osteoporosis Foundation, more than 200 million people worldwide have been suffering from osteoporosis. In Russia, the number of patients with osteoporosis is estimated to be about 14 million. The tendency to increase the life expectancy of the population is admitted to result in an increase in the incidence of osteoporosis in postmenopausal women, as well as in men, in the older age group [12, 17].

Women are known to have a higher risk of developing osteoporosis. This is supposed to be due to the peculiarities of the hormonal status; during the onset of menopause, the process of bone resorption is acknowledged to be accelerated, the volume of bone mass is stated to decrease, whereas the risk of fractures is accepted to increase [11].

The severity of osteoporosis is known to be caused by the presence of low-energy fractures one of which appears to be a fracture of the proximal femur including the femoral neck fracture. Some epidemiological studies which have been conducted in a number of Russian cities have revealed significant differences in the prevalence of proximal femur fractures in a population over 50 years of age. On average, the incidence of proximal femur fractures among residents in the Russian Federation has been accessed to be 174.7 for men and 267.5 for women for 100 thousand people [18].

According to the undertaken multi-site epidemiological study, the incidence of fractures of the proximal femur in Yakutsk has been estimated to be 216.64 per 100 thousand people [8].

Considering that Yakutia has its climatic and geographical features (which are low insolation, type of nutrition, long winter period, remoteness of settlements, their inaccessibility), the need to study the problem of osteoporosis and its complications is supposed to be viewed as relevant both for the Republic of Sakha (Yakutia) and for Russia in general.

Objective: to identify the age and gender features of the dynamics of bone mineral density in the adult population of the city of Yakutsk.

Materials and methods: During the period of 2016-2017, in the Clinic of the Medical Institute of North-Eastern Federal University named after M.K. Ammosov Yakutsk, X-ray densitometry was performed in 868 patients. The analysis included data on 776 people aged 20 years and older, of which 22.7% were men and 79.3% were women. The distribution by nationality is as follows: in most cases, there were investigated Yakuts (76%) and Russians (20%), whereas there were also examined 4% of patients of other nationalities. The survey was conducted on an X-ray axial densitometer Lunar GE iDXA (USA) with the study of the BMD in the lumbar spine L1-L4 (g/cm^2) [13]. BMD was evaluated according to the WHO criteria (1970): in postmenopausal women and in men over 50 years old, the norm is T-test + 2.5-0.9 of standard deviations; osteopenia is -1.0 – -2.4 of standard deviations: osteoporosis is T-criterion -2.5 and below. In women before menopause and in men younger than 50 years, the Z-test was evaluated [14].

In addition, there was calculated the body mass index, BMI according to WHO, 2004 (18.50-24.99 is a normal weight, 25.00-29.99 is overweight, ≥30.00 is obesity, 30.00-34.99 is the 1st degree, 35.00-39.99 – the 2nd degree, ≥40.00 – the 3rd degree) [15].

Apart from that, there was indicated the hormonal status of women and the presence of menopause (absence of the menstrual cycle after 12 months), distinguishing between an early menopause up to 40–45 years old and a timely menopause at 46–54 years old [10].

In the course of collecting the history, there was revealed the presence of low-energy fractures (falling from the own height) as a risk factor for osteoporosis [11].

Checking the normality of the distribution of quantitative variables was implemented using Kolmogorov-Smirnov, Shapiro-Wilk with the amendment of Lilio-Fords. The descriptive statistics were presented in the form of Median (Me) and interval distribution (Q_1; Q_3). In the course of comparing independent groups, the Kruskal-Wallis test was used. To assess the strength of the direction of the relationship between the variables, the Spearman rank analysis was used. The level of the statistical significance of differences was compared to p = 0.05.

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Table 1

Distribution of the patients on gender and age, n (%)

Age, years	Total	Men	Women
20-29	17 (2.19)	4 (0.5)	13 (1.7)
30-39	25 (3.23)	9 (1.2)	11 (1.6)
40-49	77 (9.92)	22 (2.8)	55 (7.1)
50-59	222 (28.62)	56 (7.3)	166 (21.4)
60-69	319 (41.11)	64 (8.3)	255 (32.9)
70-79	100 (12.87)	18 (2.3)	82 (10.6)
80-87	16 (2.06)	4 (0.5)	14 (1.8)

Results and discussion of the research

We have investigated 776 people: 176 men (22.7%) and 601 women (79.3%) of the medium age of 59.0±1.0 (Table 1).

The maximum frequency of the examined patients has been witnessed in the age group of 50-79 years old, which comprises 82%. A decrease in bone mineral density is more often detected in women after menopause and in the age group over 70 years, regardless of gender [9, 10].

One of the risk factors for osteoporosis in women is considered to be early menopause [20]. Early menopause occurred in 10% of the surveyed women.

The formation of peak bone mass, as well as the general processes of bone tissue remodeling in men and women are acknowledged to differ [2].

The bone mineral density in women after menopause (40-49) during the first 10 years has been estimated to decrease by 18% (0.113 g/sm^2). BMD in men aged 60-69 years old has been witnessed to reach its maximum indexes and to decrease to 4% in the next decade (Fig. 1).

In accordance with the results of the undertaken research [5], the high body mass index is accepted to be associated with the mineral density of the bone tissue.

There have been revealed a direct tight correlation between BMI and BMD in men (p = 0.714) and a reverse correlation in women (p = -0.277) (Table 2).

Despite the great experience which has been gained, the results of the research by many authors are likely to be viewed as contradictory [16, 19].

The mineralization of the bone tissue in Russians has been assessed to be 13% higher than that in Yakuts. Low-energy fractures are seen to have occurred in Yakuts 4 times as often.

The ratio of fractures in men and women has not appeared to depend on the nationality and has been 1:3 respectively.

The frequency of fractures is proved to depend on the age, in the age group of 50 years and older (low-energy) fractures are likely to occur more common than in younger age groups (95% CI from 1.07 to 1.13). Most fractures – up to 83% –have been witnessed in women.

The history of low-energy fractures is known to be more common in the older age group [2].

Conclusion. Therefore, the mineralization of the bone tissue in women is admitted to reach its peak values in women aged 40-49 years old and in men aged 60-69 years old. The first 10 years after the onset of the menopause, the bone mineral density in women is accepted to reduce by 18%. BMI is proved to have a reverse correlation with the bone mineral density in women (p = -0.277) and a direct tight correlation in men (p = 0.714).

Table 2

The rates of the BMD g/sm^2 and the body mass index (BMI) kg/m^2 in men and women of various age groups

Age, years	BMD, g/sm^2	BMI, kg/m^2
Men		
20-29	1.1 (0.9; 1.2)	25.32
30-39	1.0 (0.9;1.6)	25.39
40-49	1.1 (1.0;1.2)	25.93
50-59	1.1 (1.1;1.2)	28.31
60-69	1.2 (1.1;1.3)	29.18
70-79	1.1 (1.0;1.3)	26.91
80-87	1.1 (0.9;1.2)	27.7
p	<0.001	<0.001
Women		
20-29	1.0 (0.9;1.2)	19.72
30-39	1.1 (1.0;1.2)	24.78
40-49	1.1 (1.1;1.2)	26.94
50-59	1.0 (0.9;1.1)	29.33
60-69	0.9 (0.9;1.0)	29.65
70-79	0.8 (0.8;0.9)	28.67
80-86	0.8 (0.7;1.1)	26.16
p	>0.001	>0.001

Note: the data is presented in the format of Me (Q_1; Q3)

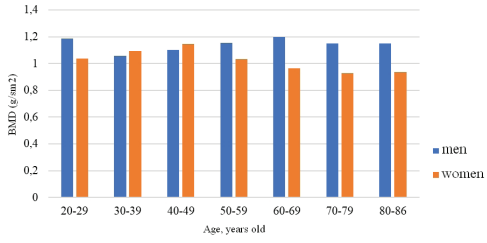

Fig.1. The mineral density of the bone tissue in men and women (g/sm^2) of various age groups

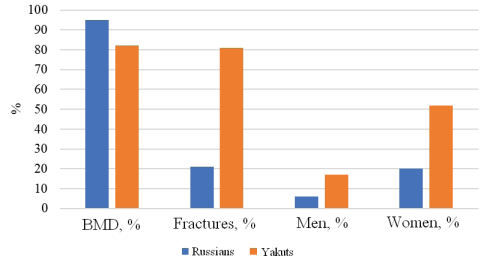

Fig.2. Comparison of BMI, BMD, and low-energy fractures based on the gender and nationality

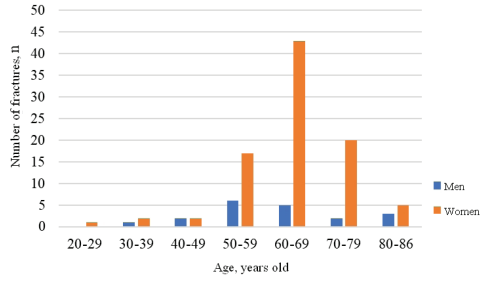

Fig.3. The rate of low-energy fractures based in the age ranks and gender (n, %)

The mineralization of the bone tissue in Yakuts has been estimated to be 13% lower than that in the Russians, and, hence, the number of low-energy fractures in them is assessed to be 4 times as high. The ratio of fractures in men and women has not been revealed to depend on the nationality.

The studies were conducted as part of the implementation of the topic of state assignment No. 19.9242.2017 / ITR.

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ANALYSIS OF GALLSTONE DISEASE RISK FACTORS USING SAMPLES FROM PATIENTS AFTER CHOLECYSTECTOMY AT REPUBLIC HOSPITAL №1- NCM SURGICAL WARD (YAKUTSK)

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The article analyzes the risk factors for the development of gallstone disease on the example of patients of the surgical ward the Republican hospital No.1 – NCM (Yakutsk, Russia) after cholecystectomy. It presents data on the analysis of the organic composition of gallstones using infrared spectrometry. It was revealed that gallstone disease is most common in hypersthenic women of the second adult stage, every third patient has a burdened familial history. Most of the examined stones were cholesterol ones. Analysis, synthesis, and accumulation of analytical material will bring to an understanding of the pathogenetic mechanisms of gallstones in the indigenous population, the role of endogenous and environmental factors, timely prevention and effective treatment of gallstone disease.

Keywords: gallstone disease, sludge, lithogenic bile, risk factors, chemical composition of gallstones, IR spectroscopy.

Introduction. In modern conditions, there is an increase in the incidence of gallstone disease in the Sakha (Yakutia) Republic, which can be attributed to the urbanization of the population and changes in the diet of the indigenous population of the Republic. Historically, the indigenous peoples of the North have developed a protein-lipid type of exchange according to the nature of their diet, due to the consumption of venison, fish products that are hypoallergenic and easily digestible products containing large amounts of polyunsaturated fatty acids. The separation of the inhabitants of the indigenous nationality from the natural habitat, traditional way of life and food ration cause their growth of the digestive system diseases [3, 9]. Currently, gallstone disease has become a social problem among the indigenous people of the Sakha (Yakutia) Republic. In the Russian Federation, the frequency of chronic calculous cholecystitis is about 12–20% [2]. As a rule, in the initial stages of gallstone disease, it is asymptomatic and is detected by chance with an ultrasound examination of the abdominal cavity organs. The generally accepted risk factors for gallstones are female gender, age over 50, obesity, multiple pregnancies, liver diseases (cirrhosis, hepatitis), and infections (giardiasis, amebiasis, opisthorchiasis, ascariasis, echinococcosis) [9, 10, 11, 14]. However, further research of the etiological and environmental factors of gallstone disease, chemical composition of gallstones, elucidation of the mechanisms of education, detection of gallstone disease at at an early stage, before the formation of stones, when it is possible to successfully use organ preservation, and conservative treatment methods remains relevant and needs to be clarified.

Research Objective: identify risk factors for gallstone disease and establish their priority importance, identify the features of the elemental composition of stones using IR spectrometry on the example of patients after cholecystectomy of the surgical ward of the FRH (NHC).

Study Materials: Using the surgical ward of FRH (NHC), we conducted a survey of 77 patients with gallstone disease in the period from February 4 to April 15, 2019. The majority of the studied were representatives of the indigenous nationality – 64 (83.1%). The respondents were asked to answer questions from a test questionnaire adapted to identify risk factors for gallstone disease. The calculation of body mass index (I) was determined using the formula $I = m/h^2$, where *m* is the body weight in kilograms and the height in meters. The study examined 11 samples of stones obtained after cholecystectomy of the patients surveyed. The organic status of the samples was determined by the method of IR spectroscopy using a Spotlight 200i IR microscope with an MCT-detector based on the FTIR SPECTRUM Two spectrometer in the Training Laboratory of Biophysics of NEFU'S Physics-Technical Institute.

Results and Discussion. The results of the data obtained revealed that females are more susceptible to gallstone disease than men. Thus, during the study period, 66 (85.7%) turned out to be in the female department; 11 (14.3%) were males. When analyzing the data obtained, the relationship between the frequency of occurrence of gallstones and female reproductive activity was revealed. So, out of 66 women surveyed, 40.9% had births up to 3 times, 48.5% from three or more times, whereas only 10.6% did not give birth. Perhaps this is due to both the increased lithogenicity of bile and dyskinesia of the biliary tract against the background of changing hormonal levels. The lithogenicity of bile increases during pregnancy by increasing the level of estrogen, which increases cholesterol transition through the sinusoidal membrane of hepatocytes, which leads to its saturation in bile, reducing the synthesis of fatty acids, changing the biochemical composition of bile and the formation of stones from cholesterol crystals [6, 8]. Hypokinesia of the gallbladder and biliary tract during pregnancy also contribute to the formation of biliary sludge, and subsequently the formation of gallstones [5].

According to our data gallstone dis-

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ease among the interviewed patients mainly occurs in the age period from 36 to 74 years. This is due to an increased level of bile acid formation, that is, an increase in the lithogenic bile mainly in the elderly. According to the literature, the metabolism slows down and disrupts over the years, the activity of enzyme systems is significantly reduced, in particular, the main enzyme for the synthesis of bile acids, which in turn keep cholesterol in bile in a dissolved state [1]. In addition, the incidence of gallstone disease with increasing age is due to the evolutionary processes of the gallbladder, reducing the body's need for cholesterol, as in building material, which increases its concentration in bile [2, 5].

According to the survey, we can talk about the hereditary factor. It turned out that 36 (46.8%) patients have close relatives with gallstones in history. From literary sources, it is known that there is a gene for the lithogenic bile. Disruption of cholesterol metabolism is associated with the polymorphism of apolipoprotein E (Apo-E), which is genetically determined and determines the nature of changes in cholesterol metabolism. It has been proven that differences in cholesterol metabolism in different Apo-E phenotypes affect bile cholesterol secretion and its stability in bile [4, 10].

According to our data, among the examined patients who indicated their height and weight, 77.3% turned out to be individuals with hypersthenic type, 18.7% with normosthenic type, 4% with asthenic type. Thus, gallstone disease occurs mainly in individuals with a BMI > 24.9. It is known that obesity is most often associated with increased synthesis and excretion of cholesterol. Its excess is transferred in phospholipid vesicles, which are unstable, easily aggregated. At the same time, large multi-layered bubbles are formed, from which cholesterol monohydrate crystals precipitate, creating the basis for the biliary sludge. While maintaining the conditions supporting the processes of lithogenesis, gallstones form over time [5].

Of the patients we surveyed, 63.6% lead an inactive lifestyle, 10.4% have high physical activity, and 26% have average physical activity. Thus, a sedentary lifestyle leads to the formation of gallstones. This explains the opinion that as a result of physical inactivity, the rate of bile evacuation from the gallbladder decreases and, as a result, the concentration of bile increases.

As a result of our study, it was found that the patients examined mainly consumed flour (59.7%) dairy (59.7%), strong tea (51.7%), meat (48.1%), fried foods (40.3 %). There was little plant food in their diet. It is known that the formation of gallstones is associated with a low content of fiber in food and a longer passage of food through the gastrointestinal tract, which contributes to increased absorption of secondary bile acids (deoxycholic) and makes bile more lithogenic. Fatty foods increase the level of lipids in the blood, respectively, increases the content of cholesterol in bile, which changes its normal ratio to cholates, increasing the lithogenicity of bile. Analysis of the multiplicity of nutrition of patients showed that more than half of patients eat 4-5 times a day. As is known, the number of evacuations of bile per day is multiple to meals, therefore, with rare consumption of food, bile becomes concentrated.

Analysis of bad habits showed that about half of patients have addictive addictions, such as drinking alcohol (26%), smoking (18%), and both of them (11%). Alcohol and smoking lead to a decrease in high-density lipoproteins, narrowing of blood vessels and, as a result, to their obliteration. When vascular inflammation occurs, lipoprotein receptors are activated for low-density lipoproteins (LDL), very low-density lipoproteins (VLDL). Next, cholesterol is separated from them, and settles in the inner lining of the vessels and contributes to the development of atherosclerosis. Due to this process, the level of LDL and VLDL in the bloodstream increases, which leads to hypercholesterolemia, which is one of the main factors for the formation of cholesterol stones [12, 13, 14].

Considering that the quantity and quality of water consumed can to some extent influence the formation of gallstones, we have analyzed the drinking regime of the interviewed patients. It was revealed that more than 51.9% of patients consume less than 1200 ml per day. At the same time, mainly the examined patients use river water (28.6%), bottled (36.4%), filtered (28.6%), lake water (28.6%), which contain a small number of mineral substances (including sulfate, sulfate-chloride compounds) (Fig.4). These compounds enhance bile formation and bile secretion, reduce the level of total cholesterol in the blood. Moreover, perhaps, the use of insufficient amounts of water leads to a thickening of bile and consequently the formation of stones.

Analysis of comorbidities showed that 20.7% of the interviewed patients suffer from hypertension. The results obtained are consistent with the opinion that the predisposing factor for the development of gallstones is the presence of hypertension, which develops, as a rule, in obesity and overweight, as a result of which an elevated level of cholesterol and a change in the lipid profile are observed in the blood. The overwhelming majority of respondents (64.9%) have impaired stool, manifested mainly by constipation (76%), which is a manifestation of decreased contractility of the gallbladder and lack of bile in the intestine. According to our data, cholecystitis (42.5%) and pancreatitis (38.9%) were the most common background diseases in patients with gallstones, due to the characteristics of the anatomy and topography of the gallbladder and pancreas ducts. This is followed by gastritis (32.5%), which is explained not only by the dysfunction of the sphincter of Oddi in gallstone disease but also by impaired duodenal motor activity, which leads to duodenogastric reflux. The above diseases are a consequence of gallstone disease [7].

IR absorption spectra of three stones of different chemical composition are presented in Figures 1-3. respectively. The peak of the cholesterol, bilirubin, mixed wavelengths corresponds to the values indicated in the literature [14]. Based on these data, we identified the type of stones. The results of IR spectrometry showed that 9 (81.8%) of 11 stones are cholesterol, 1 (9.1%) concrement was bilirubin and 1 (9.1%) was mixed [12].

Fig. 1 shows the IR spectrum of sample gall_1. The IR spectrum of the examined gallstone sample contains absorption bands in the 3401, 2933, and 2902, 2867, 2849 cm^{-1} oscillations, which correspond to asymmetric and symmetric C–H bonds in the CH_2 and CH_3 groups of cholesterol. Intensive absorption bands at 1466 cm^{-1} and the absorption band at 1377 cm^{-1} are related to ring deformation of cholesterol and deformation vibrations of C–H bonds in the CH_2 group of cholesterol, respectively. The intense absorption band at 1057 cm^{-1} is characteristic of the C–C vibrations of the ring bonds in the cholesterol molecule.

The intense absorption bands at 3302 and 2931 cm^{-1} observed in the IR spectrum of the gall-3 sample (Fig. 2) correspond to the stretching vibrations of the pyrrole NH group in bilirubin. Oscillations in the region of 1662 cm^{-1} and 1628 cm^{-1} are characteristic of vibrations of the O–C=O bonds in the bilirubin molecule and the absorption band at 1571 cm^{-1} corresponds to the stretching vibrations of the C=C bonds in the calcium bilirubinate molecule. The absorption band in the oscillation region of 1250...1235 cm^{-1} is characteristic of asymmetric stretching vibrations of the COOH group in the bil-

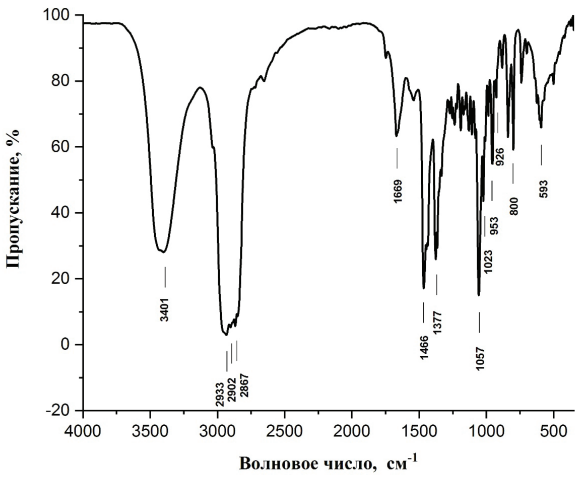

Fig. 1. IR spectrum of cholesterol stone (gall_1)

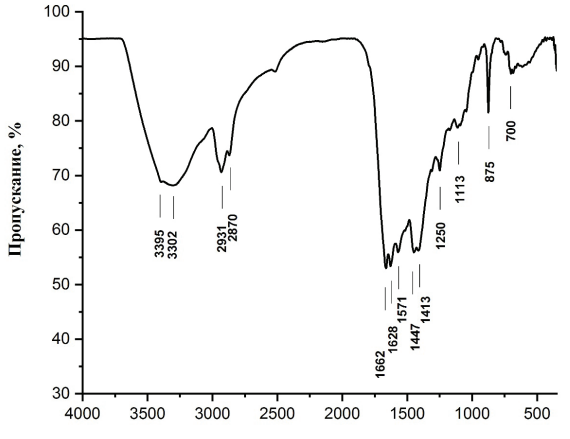

Fig. 2. IR spectrum of bilirubin stone (gall_3)

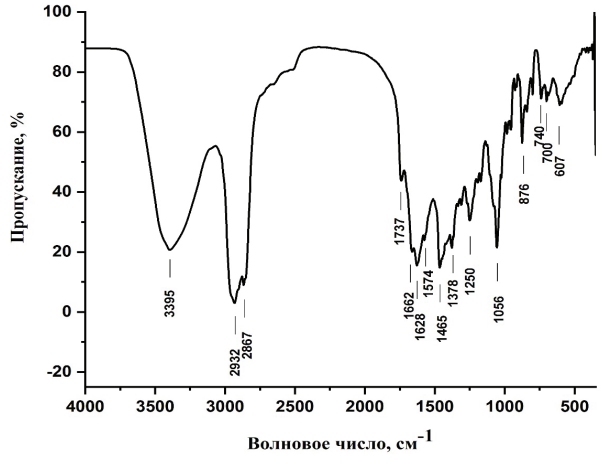

Fig. 3. IR spectrum of mixed stone (gall_8)

irubin molecule, as well as for vibrations of the ν(C–O), ν(C–H), δ(N–H) bonds in the molecule calcium bilirubinate.

The infrared spectrum of the gallstone of sample gall_8 (Fig. 3) shows the characteristic infrared absorption spectrum of mixed gallstones. The absorption bands at 3395 cm-1 and 2932 cm^{-1} are due to the asymmetric stretching of CH_2 and the asymmetric stretching of CH3. and the absorption band at 2867 cm-1 arises due to the symmetric stretching of CH_2. Calcium bilirubinate has characteristic bands at 1250 cm^{-1} (amide III), which is associated with stretching (C–O) or stretching C–N in combination with the deformation of N–H (C – N) [M. A. Subhan 1,2 *, P. Sarker, and T. Ahmed]. The absorption band at 1378 cm^{-1} is explained by the bending (CH_3) vibration of cholesterol in a mixed gallstone.

Conclusion. Our analysis showed that gallstone disease is a polietiologic disease. According to our data, the leading factors reflecting the risk of calculus are age, gender, lifestyle, and hereditary predisposition. So, gallstone disease is most common in hypersthenic women of the second mature age (50%) and identified the relationship of the frequency of occurrence of gallstones with the reproductive activity of women.

In addition, important risk factors for the occurrence of gallstones are lifestyle hypodynamia (in 63.6% of respondents), which undoubtedly affect the reduction of bile evacuation. Also, the consumption of foods rich in animal fats is observed in almost all the examined patients. This diet leads to a violation of fat metabolism, which is the main cause of increasing cholesterol levels in body fluids, including bile, whose lithogenicity increases. Low fluid intake (in 52% of the examined) leads to the loss of its body and, as a result, the condensation of all body fluids, including bile.

It was revealed that gallstone disease is closely associated with such pathologies of the digestive system, such as cholecystitis (41.5%), pancreatitis (38.9%), gastritis (32.5%), hepatitis (13%), constipation (76%), which may complicate the course of the disease being studied. In addition, many of the interviewed patients suffer from hypertension (20.7%), which may contribute to stone formation.

We have begun studies on the elemental composition of gallstones. The results of IR spectroscopy showed that most of the stones studied are cholesterol (81.8%).

Thus, identifying the features of lithogenesis will bring us closer to understanding the pathogenetic mechanisms of gallstone disease, the role of endogenous, environmental and technological factors in the formation of micro-elemental imbalances, as well as the correct choice of treatment tactics for patients with gallstone disease.

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THE GENDER FEATURES OF MANIFESTATIONS OF FRAILTY, EMOTIONAL CONDITION AND LIFE QUALITY OF LONG-LIVERS IN YAKUTSK

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The article analyzes the severity of frailty, anxiety and depression, parameters of quality of life depending on gender, and evaluates the effect of asthenia and anxiety-depressive states on the quality of life of long-livers in Yakutsk. The data of 70 long-livers are analyzed, whose average age was 92 ± 2.21 years. By gender distribution, the number of people was the same, with 35 respondents in each group. According to the ethnic composition of the sample was represented mainly by indigenous people. The study used the methods "Age is not a hindrance" (national validated questionnaire), the hospital scale of anxiety and depression (HADS) and the questionnaire for assessing the quality of life (SF-36). According to the results of the study, frailty was diagnosed in 64.3%, prevalence in 35.7% of the examined, no significant differences were found by gender. Indicators of frailty correlated with the level of anxiety, depression, and low rates across all scales of quality of life. Clinically significant anxiety was diagnosed in 5.8%, and depression in 2.9% of subjects. Subclinical anxiety and depression were noted in 42.8% and 35.7% of subjects, respectively. Anxiety and depression rates were significantly higher among females. The positive correlation of anxiety and depression was also noted. The results of assessing the quality of life of long-livers were within the age norm, except for indicators of role physical, role emotional and social functioning, which were higher among our respondents. Depending on the gender, values on the scales "bodily pain, "social functioning", "role emotional" and on the general indicator of physical health were obtained significantly lower among women. The assessment of the quality of life, depending on the degree of asthenia, showed significant differences in all scales of quality of life, except for role physical condition. And the presence of anxiety and depression was associated with pain and a decrease in general health.

Keywords: frailty, anxiety, depression, quality of life, long-livers, gender.

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Introduction. WHO experts noted the problem of population "aging". This problem includes not only the increase in elderly population but also the population of people living 90 years and more. This category of people is the most vulnerable and their share is growing faster than the share of people 60 years and older. Thus, over the past 25 years, the longevity index in Russia has increased by 1.7 times (from 9.0 to 15.4%) [8].

It is also well known that the incidence of senile asthenia syndrome (SAS) increases with age. Clinical manifestations of SAS include reduced strength, endurance, and physiological functioning, which increases the risk of dependence and death. According to some researchers, the prevalence of SAS among people aged 80 to 84 years old reaches 16% and at among the people elder than 85 years - 26% [4, 12].

Some authors note that the main factors determining the quality of life in later ages are somatic vulnerabilities, affective disorders and personal traits [17].

Therefore, it is obvious that issues related to the preservation of the life quality of long-livers in the future will be even more relevant.

Research objective: study gender differences in indicators of frailty, emotional state and life quality of long livers in Yakutsk.

Materials and Methods: In the period from February to March 2019 in the Republican Hospital No. 3 and with home visits, we conducted a socio-psychological and medical examination of 82 people at the age of 89 to 100 years. 70 people (92 ± 2.21) were able to undergo the psychodiagnostic examination. The criteria for exclusion from the study are severe dementia, complete deafness, and blindness. Gender distribution is equal: 35 women (92 ± 2.48) and men (92 ± 1.92). The ethnic composition of the sample was represented mainly by indigenous people - Yakuts (75.7%), small peoples of the North (2.8%) and Russians (21.5%).

A screening questionnaire "Age is not a hindrance," which includes 7 questions with two answers (yes or no) [2] had been used to identify the SAS. If there are 3 or more affirmative answers we diagnose SAS, at 1-2 points - preasthenia. The Hospital Anxiety and Depression Scale (HADS) and the Quality of Life Evaluation Questionnaire (SF-36) were also used.

Statistical processing of the research results was carried out using the IBM SPSS Statistics 23 software package with the calculation of the Spearman correlation coefficient and the significance of differences for independent samples — the Mann-Whitney test. The significance of the statistical significance of differences was taken at a value of $p < 0.05$.

Results and Discussion: According to the results of the "Age is not a hindrance" questionnaire, senile asthenia was diagnosed in 64.3%, preasthenia in 35.7% of the patients. The absence of asthenia had been not detected. The maximum number of affirmative answers was 6 and was noted in 4.3% of the subjects.

The average rate for the SAS index for the group was 2.96 ± 1.12 (M ± m), which corresponds to the index between the preasthenia and asthenia. The SAS index correlated with the level of anxiety ($p = 0.000$), depression ($p = 0.000$) and with a low index of life quality ($p \leq 0.01$).

In terms of gender distribution, the SAS index was slightly higher among women (3.09 ± 1.01) but has not reached the level of statistical significance (Fig. 1). In other studies, it is also noted that the prevalence of SAS among women is higher than among men, which is also seen in our study [16].

This is known that depending on the method of determining the prevalence of senile asthenia among persons over 65 ranges from 4.0% to 59.1% [7]. It reaches 32-45% among persons older than 90 [16]. The data we obtained are higher than the presented and close to the results of a study conducted by Soselia N.N. among seniors and long-livers with acute coronary syndrome: there is the prevalence of SAS equal to 66.1% [1]. It should be noted that the screening questionnaire "Age is not a hindrance" was also used in this study. Also, cardiovascular disease in a patient is accompanied by a threefold increase in the frequency of senile asthenia [10]. Thus, it is possible that the results we obtained may be related to the greater sensitivity of the questionnaire we used, or with the severity of chronic diseases and their comorbidity.

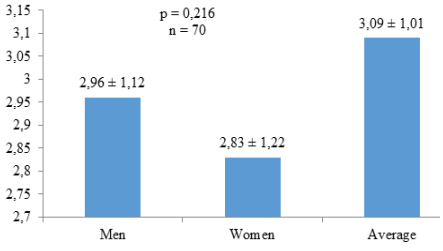

Fig.1. "Age is not a hindrance" questionnaire results.

Analysis of the items on the questionnaire showed that the overwhelming majority, regardless of gender, noted a decrease in hearing and vision (85.7% of men and 82.8% of women) (Table 1). Women more often complained of emotional depression, anxiety, falls and traumatization, and difficulties in moving around the house and on the street. Men more often answered affirmatively to the question of a decrease in memory and orientation in the locality. Both groups rarely complained about weight loss and urinary incontinence.

The last two points with the lowest rates - weight loss and incontinence should be discussed. The prevalence of primary sarcopenia (a syndrome characterized by progressive and generalized loss of muscle mass and strength) among people over 80 years of age reaches 50% [4]. Our results are much lower than indicated. However, it should be noted that the body mass index among all the respondents in the normal range, but they did not have objective data about their weight and indicated that they do not monitor their weight. In earlier studies, it was stated that the incidence of symptoms of urinary incontinence in Russian women over 65 reaches 41.4%, and among men from 15 to 50% depending on living conditions [13], but in S.Maggi studies among people over 80 years, urinary incontinence was detected in 22.9% of men and 29.3% of women [15], which is consistent with our results. Also, literature data often indicates that symptoms associated with dysfunction of the urinary tract, and especially urinary incontinence, are not always easy to express patients' complaints due to patient embarrassment [14], which can also affect the accuracy.

According to the results of the Hospital anxiety and depression rating scale (HADS), the results of more than half of the subjects were within the normal range in terms of anxiety and depression (Fig. 2). Clinically significant anxiety was diagnosed in 5.8%, and depression in 2.9% of subjects. Subclinical anxiety and depression were noted in 42.8% and 35.7% of subjects, respectively.

Indicators of anxiety and depression depending on sex are presented in Table 2. It was noted that indicators of either anxiety and depression are significantly higher among females. A positive correlation between anxiety and depression was also noted ($p = 0.000$).

According to the literature, the symp-

Table 1

Distribution of the affirmative answers in the "Age is not a hindrance" questionnaire, (%)

Question	Men	Women
Have you lost 5 kg or more in the last 6 months?	5.7	8.6
Do you experience any restrictions in everyday life due to decreased vision or hearing?	85.7	82.8
During the past year, have you got a fall injury?	25.7	37.1
Do you feel depressed, sad, or anxious in recent weeks?	34.3	51.4
Do you have problems with memory, understanding, orientation, or the ability to planning?	62.8	54.3
Do you have urinary incontinence?	22.8	22.8
Do you have difficulties in moving around the house or outdoor?	48.6	68.6

Table 2

Anxiety and depression assessment results (HADS) (M±m)

	Total	Men	Women	p-value
Anxiety	6.91 ± 2.23	5.74 ± 1.75	8.09 ± 2.04	p=0.000
Depression	6.54 ± 2.47	5.83 ± 2.14	7.26 ± 2.60	p=0.020

toms of anxiety and depression are observed in 25-30% of people over 65 and with concomitant somatic diseases, this reaches 50% [5]. 10-14% of inpatients and residents of nursing homes have major depression, even more, have components of depressive disorders [3]. According to the results of our study, the rate of clinically expressed depression was lower which could be explained by the fact that almost all our subjects lived with their relatives, which is an alleviating factor to depression. It should also be noted the prevalence of depression was significantly lower among people over 90 years [9]. Regarding the gender distribution of depression, it was found that in old age (75–90 years), the difference in the frequency of depression in men and women decreases, and at an over-elderly age (after 90 years) it almost disappears. In our study, these data were not confirmed: we had obtained significant differences between men and women in terms of anxiety and depression.

We also analyzed the severity of anxiety and depression depending on the presence of preasthenia and SAS and obtained a significant difference in anxiety and depression between preasthenia and SAS (indicators prevail in the group with SAS) (p = 0.001 for these indicators)

According to the results of assessing life quality, the average values ranged from 33.50 to 80.47. The lowest values were noted for the general indicator of physical health and “physical functioning” (Table 3). The values of these scales correlate with age (p = 0.001), which indicates that the age of each age negatively affects physical well-being. The following scales are "intensity of pain" and "general health". The highest rates (role functioning based on physical and emotional condition) indicates that the daily activities of long-livers are not limited to a physical or emotional state. At the same time, the indicators of the mental component of health are reduced less than the physical component.

Depending on the sex, reliable low values were obtained on the scale “pain intensity” (p = 0.002), “social functioning” (p = 0.015), “role functioning based on the emotional state” (p = 0.037) and on overall indication of physical health (p = 0.015).

Deterioration of physical functioning is considered one of the key characteristics of the deterioration in the quality of life, and even minor negative changes in functional status are associated with an increase in mortality, an increase in the need for additional care and health-related expenses. Nevertheless, the low data we obtained are normal for this age group, as in the study conducted in Belarus, the average value of the physical functioning scale among the long-livers was 32.1, and the physical component of health was 33.1, which corresponds to our results. Focusing on the data of a multicenter MIRAGE study of the quality of life [11] among persons over 75 years old, it can be noted that the indicators on the scales are mostly within the average values of the population, except for role functioning based on physical and emotional state. In another study conducted in Yakutsk among the elder, high values on the scales of emotional and social functioning were found [6]. Regarding gender differences, many authors noted that the parameters of quality of life are higher among men of longevity than women [18]. In general, the obtained data are consistent with data from comparative studies of the quality of life in men and women.

The assessment of the life quality depending on the degree of asthenia, showed significant differences in all scales of quality of life, except for role functioning based on physical condition. It is logical to expect a decrease in daily activity due to SAS, which was not reflected in our study and requires further consideration. Considering the severity of cognitive deficit overestimated rates of activity may be noted, although this should have affected other indicators. In general, during the survey, there was satisfactory independence of respondents in daily life - the majority served themselves independently and showed sufficient physical activity. Many were engaged in everyday exercise, Nordic walking. For example, one respondent noted that she was doing a set of exercises every day, consisting of one hundred different options.

We also evaluated the effect of anxiety and depression on quality of life: subjects were divided into 2 groups, where the first group is individuals without detected anxiety and depression, the second is respondents with subclinical and clinically significant anxiety and depression. The results of statistical processing showed significant differences in the group of individuals with anxiety and depressive states for all scales of psychological health and some scales of physical health. The relationship of these indicators with the psychological components of health is clear, so we are focusing on physical indicators. Thus, the presence of anxiety was associated with pain syndrome (p = 0.038) and with a decrease in general health (p = 0.024). The presence of depression was also associated with a worse general health assessment (p = 0.002).

Conclusion:

1. Manifestations of senile asthenia syndrome were diagnosed in 64.3% of subjects. The SAS indicators correlated with the level of anxiety, depression, and low rates across all scales of quality of life.

2. Anxiety and depression rates were significantly higher among females. Values were positively correlated with each other and reflect comorbidity. High rates of anxiety and depression were associated with low rates of quality of life.

3. In general, indicators of the quality

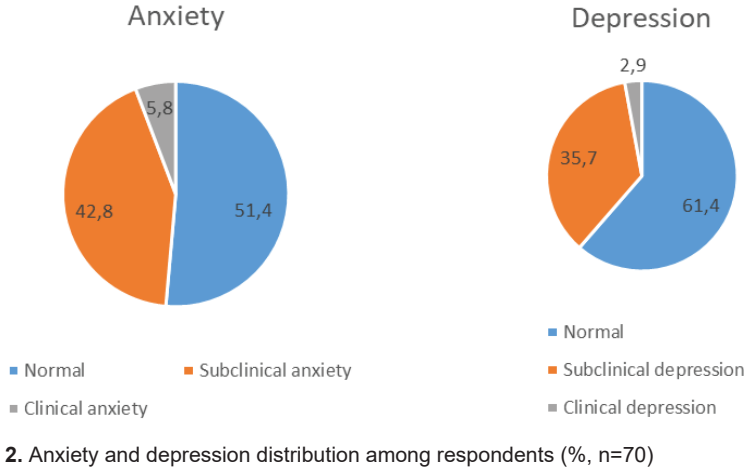

Fig. 2. Anxiety and depression distribution among respondents (%, n=70)

Table 3

Life quality assessment results (SF-36) (M±m)

	Total	Men	Women	p-value
Physical component of health	33.57 ± 6.87	35.57 ± 7.36	31.56 ± 5.77	p= 0.015
Physical functioning	33.50 ± 17.96	37 ± 17.49	30 ± 17.98	p= 0.163
PRole-Physical Functioning	78.57 ± 24.55	84.29 ± 21.07	72.86 ± 26.68	p= 0.064
Bodily pain	45.89 ± 17.14	52.14 ± 19.82	39.63 ± 11.07	p= 0.002
General Health	46.84 ± 12.79	49.17 ± 13.22	44.51 ± 12.09	p= 0.20
Psychological component of health	52.51 ± 6.91	53.47 ± 6.60	51.54 ± 7.16	p= 0.30
Vitality	50 ± 11.97	51.43 ± 12.40	48.57 ± 11.54	p= 0.28
Social Functioning	69.28 ± 21.14	76.07 ± 22.14	62.50 ± 17.93	p= 0.015
Role-Emotional	80.47 ± 23.74	85.71 ± 21.82	75.23 ± 24.72	p= 0.037
Mental Health	70.91 ± 12.10	71.43 ± 10.93	70.40 ± 13.30	p= 0.57

of life among long-livers corresponded to average values, except for the scales on "role functioning associated with the physical and emotional state" and "social functioning", which indicates sufficient independence in daily life and intact daily activity of long-livers.

4. Quality of life scales such as the physical component, pain intensity, social functioning, and role functioning due to the emotional state was significantly lower among women.

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ARCTIC MEDICINE

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ENVIRONMENTAL STATE AND HUMAN HEALTH IN THE ARCTIC ZONE: MEDICAL AND SOCIO-LEGAL ASPECT

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The authors investigate the environmental impact of the Arctic zone of the Russian Federation on human health. Noting the importance of the Arctic region for our country, the authors draw attention to the huge role of human capital in the processes of its further development. In their opinion, it is the “human factor” that is the main factor determining the possibility of implementing projects for the development of the Arctic zone. In turn, the quality of human capital in the extreme conditions of the North determined primarily by the state of health. This actualizes the need to study the adverse factors affecting the human body in the Arctic. The aim of the work was to analyze environmental problems in the Arctic zone of the Russian Federation and their impact on the health of the population living in this region. The analysis of these problems carried out by the authors not only from biomedical positions, but also from the positions of legal support of environmental protection as a condition for reducing risks to human health. The main research methods were the methods of statistical and logical analysis, the system-functional method, the comparative method, the generalization method. Results. In the course of the study, the authors identified the main factors of the negative impact of the environment of the Arctic zone on human health, having a natural and anthropogenic character. According to the authors, the main natural factorsare cold, increased electromagnetic activity and radiation, low absolute humidity of the air, frequent fluctuations in atmospheric pressure, unusual photoperiodism. The authors attributed the anthropogenic factors to pollution of surface and groundwater, as well as the soil cover with oil products; air pollution by emissions of mining, mining and metallurgical and metallurgical enterprises; radionuclides of technogenic origin. The paper describes the consequences of the impact of these environmental factors in the Arctic zone on human health. According to the results of the study, conclusions was drawn about the immanent nature of environmental risks, and, accordingly, risks to public health during intensive industrial development of the Arctic zone. The natural and climatic conditions of the Polar region objectively increase the harmful effects on human health of the effects of anthropogenic pressure on the environment. In order to prevent and minimize the risks of human health violations in the Arctic zone and environmental protection, it is necessary to amend a number of legislative acts of the Russian Federation, as well as to adopt a comprehensive Federal law "On the Arctic zone of the Russian Federation", which should be based on a unified concept of legal regulation, taking into account the climatic, environmental, medical and biological specifics of the Arctic.

Keywords: the Arctic, the Arctic zone of the Russian Federation, the Arctic region, natural factors of negative impact on health, negative environmental factors of anthropogenic origin, risks of impairment of health, environment, legislation, “Arctic synergy”, diseases, health protection.

In international law, the Arctic is usually understood as a part of the Earth's spheroid, whose center is the North Pole and the marginal boundary is the Arctic Circle (parallel 66 ° 33' north latitude)[13]. The Arctic region connects together two continents - Eurasia and North America, within its borders there are five states - Russia, Norway, Denmark, the USA and Canada, each of which has an exclusive economic zone and a continental shelf in the Arctic Ocean [3]. According to the Fundamentals of the State Policy of the Russian Federation in the Arctic for the period up to 2020 and beyond, the Arctic zone of the Russian Federation is understood as part of the Arctic which includes all or part of the territory of the Sakha Republic (Yakutia), Murmansk and Arkhangelsk Regions, Krasnoyarsk Territory, Nenets, Yamalo-Nenets and the Chukotka Autonomous Districts, as well as the lands and islands adjacent to these territories, internal sea waters, the territorial sea, the exclusive economic zone and the continental lf the Russian Federation, within which Russia has sovereign rights and jurisdiction in accordance with international law. This territory is the largest source and strategic reserve of mineral and energy resources of Russia. It produces 100% of domestic diamonds, 98% of platinum, 97.5% of gas, 75% of oil, 95% of nickel and cobalt [22, p.50-51]. The Arctic zone can rightly be called the source of raw materials for the development of the domestic economy. In addition, the Russian Arctic zone has a powerful logistical potential - in conditions of climatic warming, the Northern Sea Route we are reviving is able to reverse the existing global logistics schemes. Thus, the importance of the Arctic for our country cannot be overestimated.

Realization of the Arctic potential requires the involvement of human resources. This is also required by defense projects, since our competitors in the Arctic region are increasing their military presence and are seeking to question the sovereign rights of the Russian Federation to the natural resources belonging to it.

The circumstances noted above increase the importance of human capital. In turn, the quality of human capital is largely (and in the first place in the extreme conditions of the North) determined by the state of health. Hence, when planning and implementing plans for the development of the Arctic, it is extremely important to take into account a wide range of adverse factors affecting the human body. This actualizes the study of biomedical problems of the development of the Arctic zone in a wide range of scientific fields, including in the aspect of environmental protection and its legal support as directly related to human health.

The **purpose** of this work was to analyze environmental problems in the Arctic zone of the Russian Federation and their impact on the health of the population living in this region.

Based on the results of the analysis, the authors will propose legal measures to reduce risks to human health in the Arctic region (in the regions of the Far North).

Materials and methods of the research. The research process was based on the principles of scientific knowledge and objectivity of the knowledge gained. The material for the analysis undertaken was the results of previously conducted research in the field of human physiology and hygiene in the Far North, identifying the main risk factors for health problems

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in these areas, as well as materials from other biomedical research. In addition, data obtained from environmental monitoring in specific regions of the Arctic zone, as well as data from integrated geo-environmental studies were used. In addition, the content of the program strategic documents of the Russian state in the field of development and development of the Arctic zone, as well as the content of environmental legislation were analyzed. A specific methodology comprised a complex of general scientific and private scientific methods, among which the main ones were the method of statistical and logical analysis, the system-functional method, the comparative method, the generalization method.

Results and discussion.

1. The impact of environmental factors on the human body in the Arctic. The natural and climatic environment of the Arctic zone is characterized by an abundance of factors that have a negative impact on the health of the population living here. First of all, such factors should include cold, by which many researchers tend to understand the entire set of cooling meteorological conditions — low air temperatures, a long period of standing snow, strong winds, lack of solar insolation [18, p.5].

Cold affects the heat transfer and human performance. Labor load in cold conditions requires large physiological costs. Coefficient of performance (COP) of physical work in the open air in the conditions of the Extreme North is approximately 15–25% lower than in middle latitudes [12]. At the same time, there is an increased risk of chronic exposure to the cold factor in the Arctic zone for many workers.

The respiratory system, which is most vulnerable, as it cannot be completely protected from external conditions, is exposed to cold most often.The cold factor also contributes to the fact that the respiratory tract and respiratory membranes have the largest environmental contact surface among all tissues of the body, the area of which is approximately 50 times the surface of the body [20]. According to medical research, the local exposure to cold air on the mucous membrane of the upper respiratory tract, trachea and bronchial tree causes a significant loss of heat and moisture, which are used to warm and moisten the inhaled air. Negative temperature values of inhaled air require significant functional stress from the respiratory system and, in general, create an extremely aggressive environment for the respiratory system. In addition, the increase in pulmonary ventilation caused by cold exacerbates the harmful effects on the body of chemicals. It should be added that the super cooled organism more sensitive to industrial poisons.

In addition to the respiratory system, the primary objects of cold exposure in the Arctic zone are open areas of the face and head (most often the nose and ears), as well as the hands and feet. Blood supply in these parts of the body is peripheral and therefore and they are more prone to frostbite. In addition, the narrowing of peripheral blood vessels under the influence of cold strengthens the central circulation and provokes an increase in blood pressure.Even cooling the forehead and head can increase blood pressure and heart rate. Joints also suffer in this situation: under the influence of cold, they lose mobility due to an increase in the viscosity of synovial fluid [12]. It should be added that the effect of the cold factor in the Arctic is enhanced by the high speed of air movement (i.e. strong wind).

Another natural factor in the Arctic zone of the Russian Federation, which has a negative impact on human health, is increased electromagnetic activity and radiation. The first adverse phenomenon is due to the strong variability of the natural physical environment and is associated with the structural features of the Earth's magnetosphere in the Polar Regions. In these areas, the fluctuations of the variable geomagnetic field and the intensity of cosmic solar rays at the surface of the planet are most pronounced. This leads to the so-called geomagnetic storms, which affect the functional state of the human body [6, p. 44-52]. During this period, the number of hypertensive crises, strokes, myocardial infarction increases, the course of some mental diseases worsens, etc. Causing geomagnetic storms, solar activity also affects the radon content in the atmospheric air of the Arctic zone, thereby increasing the dose of ionizing radiation. For example, a study conducted in the Murmansk region (Apatity) showed that the average dose from natural sources of ionizing radiation due to atmospheric air is 12.5 times higher than the average in Russia [7, p. 93-111].

A characteristic natural factor of the Arctic that has a negative impact on human health is low humidity (especially on frosty days). This reduces the oxygen utilization factor in the lungs [8, p. 213-217]. In dry air the lungs hard to lose moisture. This leads to disruption of gas exchange in the alveoli and the formation of hypoxemia in the northerners (low oxygen content in the blood). In addition, the dry air of the Arctic region contributes to the loss of moisture in the skin and mucous membranes, which leads to a decrease in their protective functions. It should be noted that low air humidity is a constant environmental factor for residents of the Arctic and is typical not only for open areas of the territory, but also for residential and industrial premises, which in turn requires the moistening of air in these premises during the winter period and the development of individual means protection of the respiratory system to work in the cold 11 [8, p.213-217].

The Arctic zone is also characterized by frequent daily fluctuations in atmospheric pressure, and very significant ones. This fact also leads to serious risks of health disorders of the population.

A feature of the Arctic region is an unusual photoperiodism: polar night and polar day. Both natural phenomena affect the state of the human body, in particular, the development of aging, age-related pathology and neoplasm[9].

In general, it should be concluded that the human in the Arctic zone is a restructuring of all types of metabolism and hormonal regulation. The body of the inhabitants of the Arctic is functioning more intensively, in connection with which the physiological reserves are gradually depleted. In the Far North, morbidity and mortality rates of the population are increasedcompared with central Russia [17]. More often, there are diseases of the cardiovascular system and respiratory organs, musculoskeletal and nervous systems, digestive organs, damage to teeth and bone tissue. There is a reduction in the reproductive period and the acceleration of age-related changes in other physiological functions. In our opinion, this is due to negative natural-climatic and anthropogenic factors that give rise to the effect of "Arctic synergy"in their combined effect on the human body. This effect increases the harmful effects of each adverse environmental factor in the Arctic zone. All this leads to significant labor losses, early disability and reduced life expectancy [16, p. 33-40].

Unfortunately, it is impossible to eliminate the adverse effects of natural and climatic factors of the Arctic. At the same time, the interests of public health require the adoption of state measures aimed at reducing the harmful effects of such exposure. It seems to us that in this case it is necessary to focus on preventive measures and the development of new personal protective equipment. Note that this, among other things, is prompted by Russian legislation [2; 1], as well as documents adopted by the World Health Organization (WHO) [24] and the Arctic Council.

2. Human health and human impact on the environment. In addition to natural factors, technogenic pollution has a significant impact on human health in the Arctic zone of the Russian Federation (as well as in the entire Arctic).

The intensity and scale of the current anthropogenic impact on the environment is already incommensurable with the ability of the Arctic ecosystem to natural self-purification.The assimilation potential of the ecosystem has been exhausted at the present stage and the situation is close to critical. The Arctic ecosystem is under stress[4, p.85]. In this regard, the environmental problems of the Arctic attract the attention of both the Arctic states and the states located outside its territory [10, p.133].

Wherein the possibility of eliminating the consequences of emergency situations in Arctic is complicated by the conditions of the polar night, numerous storms with high waves, thick fog, multi-meter ice and the possibility of collision with icebergs [14, p.159].

Our country, as a state with a third part of its territory in the Far North, is aware of its responsibility for the preservation of the environment of the Arctic region and notes this in the fundamental strategic documents.The key document in this sense is the “Fundamentals of the state policy of the Russian Federation in the Arctic for the period up to 2020 and further perspective”. One of Russia's main national interestsin this document is saving unique ecological systems of the Arctic. The next most important document regarding the Arctic is the “Strategy for the Development of the Arctic Zone of the Russian Federation and Ensuring National Security until 2020”, which specified the planned results of environmental protection in stages: the first stage of the implementation of the Strategy should ensure the development of a unified national monitoring system the state and pollution of the environment of the Arctic zone, synchronized with similar international systems; at the second stage - the reduction and prevention of the negative impact on the environment of the Arctic zone.

Note that other Arctic states - the United States, Canada, Norway, Denmark also pay serious attention to environmental protection and environmental safety in the Arctic, but at the level of strategic planning, our country regulates these issues in more detail.

The above cannot be attributed to the current Russian legislation in the field of environmental protection. Neither the Federal Law “On Environmental Protection”, nor the Federal Law “On Specially Protected Natural Territories”, nor other federal laws and other regulatory legal acts in this area take into account the natural and climatic specifics of the Arctic zone. After all, it causes need of establishment of special (issued author) environmental protection requirements when carrying out economic and other activities in a given region. However, the Russian legislator in these matters is limited to existing legal approaches, i.e. legal tools used in the Arctic are almost the same as those used in mid-latitudes. For example, despite the fact that the Strategy for the Development of the Arctic Zone provides for the need to increase the responsibility of nature utilization enterprises operating in the Arctic, neither the Criminal Code of the Russian Federation nor the Russian Federation Code on Administrative Offenses still does not contain special rules governing liability for environmental pollution in the Arctic zone.

The special vulnerability of the Arctic ecosystem urgently requires the mandatory state environmental review when planning all types of economic activities without exception (issued by the author.). However, the current Federal Law "On Ecological Expertise" allows not to do this, allowing the possibility of carrying out certain types of economic activity without an expert examination. Of course, this lack of regulation creates the risk of irreversible environmental damage to the environment of the Arctic region, as well as harm to the health of the population living there.

In addition to the federal laws mentioned by us, adjustments require other regulations that play a huge role in the industrial development of the Arctic: the law of Russian Federation "On Subsoil", the Federal Law "On the Continental Shelf of the RF" and a number of others. A more radical and more acceptable option would be the adoption of a comprehensive Federal Law “On the Arctic zone of the Russian Federation”, which would be based on a single concept of legal regulation, taking into account the specific climatic, ethnic, cultural and medical biological features of the Arctic region and providing special approach to the use and protection of the environment as an environment that forms human health.

A powerful factor in the pollution of the Arctic is oil pollution in the basin of the Arctic Ocean. Most of the rivers of the Urals and Siberia flow into the Arctic seas, carrying oil emissions into them that have fallen into the rivers thousands of kilometers from the ocean coast. The scale of such pollution is several hundred thousand tons of petroleum products per year [19, p.118]. As a result, the concentration of pollutants in the Russian part of the Arctic Ocean is several times higher than normal. As a result - accumulation in the Arctic food chains - fish, terrestrial and especially marine mammals - persistent toxic substances (PTS). Many representatives of the Arctic fauna are traditional food sources for the indigenous peoples of the North, and this pathway for PTS in the human body remains one of the main risks to human health in the Arctic zone.

The main way of getting oil and oil products into the environment of the Arctic region of the Russian Federation is oil spills. However, relatively small accidents on oil pipelines occur with enviable regularity in Russia. At the same time, the cumulative amount of spilled oil is simply shocking - more than 5 million tons of oil annually (this figure was cited by an employee of the Department of American Studies at St. Petersburg State University - N. A. Chenskikh, after comparing the published data on the volumes of oil produced and mining and transportation in Russia). For comparison, this is more than the volume of oil spilled as a result of the disaster in the Gulf of Mexico in 2010, which led to environmental consequences of a global scale. According to experts, hundreds of drilling sites and pipelines cross the migration routes of wild animals and the routes of domestic deer migrations, having had a negative impact to date on more than 40% of the areas of reindeer pastures and hunting grounds [15, p.48]. In addition to damage to the environment, this circumstance creates real risks to human health, taking into account the food chain of indigenous peoples of the North that we noted earlier.

Oil pollution of water and soil cover are not the only negative environmental factors in the Arctic, which are of an anthropogenic character. In addition, the enormous risks of disruption to public health are created by the activities of mining enterprises, as well as enterprises of ferrous and non-ferrous metallurgy. In areas with developed industry concentrations of heavy metals, fluorides, sulfates, nitrogen compounds in surface and groundwater are often at the level of high and extremely high pollution. Serious anthropogenic impact on the atmosphere. If the total world industrial emissions of SO2 (sulfur dioxide, sulfur dioxide) is about 100 million tons per year, in Russia this figure is 9.2 million tons [23, pp.370-373]. At the same time, mining industry enterprises emit more than 3 million tons into the atmosphere annually [11, p.73-75]. The emissions of solid compounds, espe-

cially insoluble nickel, copper and cobalt compounds, carried out by enterprises in the north of the Krasnoyarsk Territory and the Kola Peninsula, are of great negative importance for human health in the Arctic zone. Emissions from ore-dressing enterprises largely determine the chemical composition of dust in the Arctic region. Thus, in the Western and Central Arctic, dust contains up to 25% Cu, 15% Ni, 11% S and 4% Co [5; 21, p. 369-374].

The impact of air pollution is most pronounced in the large industrial centers of the Arctic zone, especially in Norilsk, the coal-mining cities of the Komi Republic, and the industrial centers of the Kola Peninsula. This leads to pronounced changes in the immune, hormonal, cardiorespiratory, hematopoietic and other vital human systems (especially in children). In addition, the atmospheric air of a number of settlements, for example, the city of Monchegorsk (Murmansk region) and the city of Norilsk (Krasnoyarsk Territory), has an increased carcinogenic risk.

For the health of the Arctic population, a noticeable negative environmental factor of anthropogenic origin is exposure to radionuclides. It should be noted that for a long time, residents of the Arctic zone of the Russian Federation were subjected to chronic radiation by radionuclides formed in the atmosphere as a result of nuclear tests at arctic test sites. Falling out with precipitation, these radionuclides affected a huge area, causing significant harm to human health. The termination of nuclear tests reduced the value of radiation exposure as a risk of impairment of health in the Arctic region, but didn't completely eliminate it. Even now, residents of certain Arctic areas, especially the Murmansk region, are exposed to the potential danger of radiation contamination. This is facilitated by the presence of a large number of radiation sources of anthropogenic origin: nuclear reactors of operating and decommissioned submarines (NPS), radioactive waste storage facilities, infrastructure facilities of the icebreaking fleet of the Russian Federation.

Thus, negative environmental factors of anthropogenic origin continue to constitute a significant proportion of the risks to human health in the Arctic zone.

Conclusion. The study allowed the authors to draw the following conclusions:

- The Arctic zone of the Russian Federation is a unique natural resource, environmental and logistical resource not only of our country, but of the whole world. Industrial development of the Arctic zone acts as an objective need of the Russian Federation, as a condition for its successful economic development. At the same time, harsh climatic conditions create significant problems in the process of industrial and infrastructural development of the Arctic region, having a negative impact on human health. The consequences of anthropogenic pressure on the environment that have accumulated over many years have a huge negative impact on the health of the population of the Arctic;

- the main natural factors of negative impact on human health in the Arctic are the cold factor, increased electromagnetic activity, increased ionizing radiation, low absolute air humidity, frequent and abrupt changes in atmospheric pressure, and specific photoperiodism. These natural factors are immanent characteristics of the environment of the Arctic region and have a constant negative impact on human health;

- negative environmental factors of the Arctic zone, which are of anthropogenic origin, are pollution of surface and groundwater, as well as soil cover with oil products and waste from other industrial production; increased concentration of persistent toxic substances (PTS) in the atmospheric air of the industrial centers of the Arctic region, triggered by emissions of mining and ore-dressing complexes, as well as enterprises of ferrous and non-ferrous metallurgy; radionuclides accumulated in the environment of the Arctic zone as a result of past nuclear tests, as well as the potential danger from existing man-made sources of radiation. It should be noted that the negative impact of many of these factors on human health is increasing (the effect of "Arctic synergy") due to the influence of the natural climatic conditions of the North. In addition, environmental risks (due to the vulnerability of Arctic ecosystems) and, accordingly, risks to human health as a result of anthropogenic environmental impact, are also likely to be immanent;

- a significant contribution to reducing the harmful effects of anthropogenic pressures on the environment can be made by an effective mechanism of legal regulation of the relationship between man and nature, taking into account the specifics of the ecology of the Arctic region, in particular, its endemicity and vulnerability. According to the authors, it is necessary to adopt a comprehensive federal law "On the Arctic zone of the Russian Federation", providing a special legal regime for the use and protection of the environment of the Russian Arctic. In addition, it is necessary to include in the sectoral legislation the rules governing the legal status of natural and nature-resource objects in the Arctic.

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INFLUENCE OF ADDITIONAL VITAMINIZATION OF SCHOOLCHILDREN RATIONS IN THE ARCTIC ON VARIABILITY OF MORPHOFUNCTIONAL PARAMETERS OF THE IMMUNE SYSTEM

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The paper reports a representative study of the effect of vitaminization of children of the North on one of the most important indicators of health - immunity. **Objective** of the study: to identify the features of the variability of morphofunctional indicators of the immune system of schoolchildren after prolonged vitaminization in the Arctic.

Materials and methods. Practically healthy schoolchildren aged 10-11 years (60 people) living in the city of Norilsk was examined. Children from the same school, who regularly took a domestic multivitamin complex of 1 tablet once a day from September to March, made up the main group (n = 30). Children from another school who did not take multivitamins formed a comparison group (n = 30). The luminescent-histochemical method of H. Yokoo et al. (1982) modified by V.P. Novitskaya (2000), the content of catecholamines (CA) and serotonin (Ser.) in lymphocytes and the ratio of catecholamines: serotonin (CA / Ser.) were determined; hematological method was used to determine the blood composition indicators in percent: basophils, %, eosinophils, %, band neutrophils,%, neutrophils,%, lymphocytes,%, monocytes, %, and the Garkavi index : lymphocytes / neutrophils.

Results and discussion. It was established that after the inclusion of multivitamins in the diet of children, a decrease in the level of CA and an increase in the serotonin content in blood lymphocytes was observed. It was revealed that in boys of the main group the level of CA decreased by 2.6 times ($p < 0.001$), whereas in girls it was only 1.5 times ($p < 0.01$) relative to the children of the comparison group. Along with a change in the balance of neurotransmitters after taking multivitamins in girls and boys in the main group, an increase of 1.5-1.6 times ($p<0.05$) was observed in the percentage of band neutrophils relative to children in the comparison group.

Conclusion. The results of the study showed the multivariate functioning of the immune system of schoolchildren in the conditions of the Far North after the inclusion of multivitamins in the diets. A change in the balance of regulatory indicators in schoolchildren's lymphocytes, which can change the functional activity of these cells, has been established. Carried out vitaminization, among schoolchildren of the Polar region significantly changes the balance of the cellular elements of peripheral blood in children in this region.

Keywords: North, schoolchildren, vitaminization, variability of blood parameters.

Introduction. The demand for scientific studies detailing the results of additional vitaminization of schoolchildren is related to the fact that the actual nutrition of children aged 7-14 years in the Arctic is characterized by significant shortcomings in the form of a deficiency of micro and macro nutrients, which increases the risk of developing many diseases [1, 5, 7, 12]. Especially important is the optimal supply of vitamins of children of primary school age, when intensive growth and formation of the organism.

The national program for the optimization of the provision of vitamins and minerals of children in Russia emphasized that one of the methods of choice that favorably differ from others is the vitaminization of children's food rations using multivitamin preparations [5]. This has been justified earlier in Russia [1, 5, 7] and abroad [9, 11, 12].

For reliable evidence of the effect of the use of vitamin complexes for prophylactic purpose the object of study should include the characteristics of homeostatic systems of indicators of the adaptive capabilities of the organism. These requirements are met by blood cells as components of the immune system involved in adaptive responses to preserve the changed homeostasis [3, 10].

It is well known the participation of blood cells in the mechanisms of the adaptation syndrome, including the conditions of the Far North [2, 4]. Monoaminergic systems exert their influence on immune responses through the hypothalamus-pituitary-adrenal system. The realization of these processes occurs through the action of mediators and hormones on the corresponding receptor structures of the cells of the immune system [3, 10].

It is known that hormones and neurotransmitters can affect the functional activity of these cells, causing either stimulation of the immune response with an increase in the proliferative abilities of the cells, or activate suppressor activity, reducing the level of the immune response [2, 3, 10]. In the literature there is information that the complexes of vitamins and minerals exhibit immunomodulatory and antioxidant activity have an adaptogenic effect on the organism [1, 3, 7.

There are no studies on the variability of the immune system parameters in children of primary school age after prolonged vitaminization in the conditions of the Far North, which determines the relevance and scientific novelty of this work.

Aim of the study: to identify the features of the variability of morphofunctional indicators of the immune system of schoolchildren after prolonged vitaminization in the Arctic.

Material and methods of research. Schoolchildren - representatives of the alien population of the North aged 10–11 years living in the city of Norilsk (60 people) were under observation. The children of the same school, who regularly took a domestic multivitamin complex, 1 tablet once a day, during the school year from September to March, made up the main observation group (n = 30, 15 girls and 15 boys). Children from another school who did not take multivitamins constituted the comparison group (n = 30, 15 girls and 15 boys).

Both schools were located in areas with the same environmental situation.

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The criterion for inclusion in the study was that the children were somatically healthy, did not take other medications and vitamin complexes, did not undergo vaccination during this period. The examination of children was carried out in consultation with the school administration, when parents signed an informed consent to conduct this observation and study.

The exclusion criterion from the study was deviations in the condition of the children and the disagreement of the children and the parents.

As a means for prophylactic vitaminization, a multivitamin complex containing basic vitamins was used, whose composition is close to the physiological daily needs of school-age children [4]. The composition of one multivitamin bean contains the following components: vitamins – A – 3300 IU (200% of daily need); B_1 – 0.002 g (133%); B_2 – 0.002 g (153%); B_6 – 0.003 g (143%); B_{12} – 0.000002 g (6.7%); PP – 0.02 g (100%); P – 0.01g (6.7%); E – 0.01 g (56%); C – 0.075 g (107%); folic acid – 0.00007 g (17.5%) and calcium pantothenate 0.03 g (60%).

After vitaminization, the children took blood from a finger. On blood smears using the fluorescent-histochemical method of H. Yokoo et al. (1982) modified by V.P. Novitskaya (2000), the content of monoamines, catecholamines (CA) and serotonin (Ser.) [6] was determined in lymphocytes. The level of catecholamines and serotonin was expressed in conventional units (cu) and the ratio of catecholamines: serotonin (CA / Ser.) was calculated.

The hematological method determined the composition of blood leukocytes in percent (leukocyte formula): eosinophils,%, basophils,%, band neutrophils,%, neutrophils,%, lymphocytes,%, monocytes,%. As an integration test, the adaptation index Garkavi was used, calculated the ratio of lymphocytes:neutrophils. Statistical processing was performed using the software package “Statistica v. 6.1”. The data are presented as X ± x, where X – is the arithmetic average, x – is the average error. The Mann – Whitney U-test was used to estimate the difference between the average in pairwise unrelated samples, the difference of values was considered significant at p <0.05.

Results and discussion. Studies have shown that changes in the morphological and functional parameters of the cells of the immune system in the examined groups of children are characterized by significant differences (Table 1). First of all, it was revealed that the level of catecholamines in lymphocytes of children living in conditions of the North (comparison group) is significantly higher, and the level of serotonin is significantly lower than in children living in middle latitudes [6]. This ratio is probably related to the initially large voltage of adrenergic systems, in extreme polar conditions, when the child’s organism is to some extent protected from the effect of their excess, by accumulating catecholamines mainly in the blood cells.

The inclusion of a multivitamin complex in the diets of children of the Polar region, made it possible to identify the dependence of the variability of the morphofunctional parameters of the immune system on the sex of the child. After vitaminization in children of the main group of Norilsk, revealed a decrease in the content of CA and an increase in the level of serotonin in blood lymphocytes were found relative to the indicators of children in the comparison group (Table 1). So, when comparing the degree of decrease in the content in the lymphocytes of CA, it was found that in boys of the main group, the level of CA decreased by 2.6 times (p <0.001), whereas in girls only 1.5 times (p <0.01) relative to children comparison groups. Thus, after taking multivitamins in boys of the main group, the level of CA was lower by 41.7% (p <0.001) than in girls.

When comparing the degree of increase in the serotonin content in the lymphocytes of children, it was found that in girls of the main group the level of serotonin increased 2 times (p <0.01) whereas in boys only 1.5 times (p <0.05) compared to children of the comparison group. Accordingly, the ratio of CA / Ser. in boys of the main group, it was lower by 3.8 times (p <0.01), and in girls it was only 2.5 times lower (p <0.01) relative to the children of the comparison group. Thus, the ratio of CA / Ser. in boys 2 times lower (p<0.01) than in girls of the main group (Table 1).

By themselves, these facts indicate a possible decrease in the rate of capture of CA by lymphocytes or a decrease in their synthesis by cells. On the other hand, the level of monoamines characterizes sexual dimorphism of the reactivity of immune cells in schoolchildren of the Far North.

The decrease in this ratio in children of the North after vitaminization indicates a change in the balance of neurotransmitters, which play a huge role in the process of human adaptation to the conditions of the North. The study showed that the use of multivitamins selectively modulates the activity of peripheral monoaminergic structures,

Analysis of hematological parameters obtained by us (Table 2) in children of

Table 1

he content of monoamines in the blood lymphocytes of children of two schools in Norilsk after vitaminization (X ± x)

Indicator	Main group		Comparison group	
	Girls n=15	Boys n=15	Girls n=15	Boys n=15
Catecholamines (cu)	42.0± 3.57**	24.5± 1.9***	62.2± 3.99	63.93± 3.23
Serotonin (cu)	130.8± 21.34**	127.7± 12*	65.86± 6.14	85.2± 5.11
CA / Ser.	0.42± 0.09***	0.21± 0.02**	1.05± 0.11	0.8± 0.07

Note. In the Tables 1 and 2 statistically significant differences between the groups of children taking vitamins (main group) and the comparison group: * p<0,05; ** p<0,01; ***p<0,001.

Table 2

Leukocyte blood counts in children from two schools in the city of Norilsk after vitaminization (X ± x)

Показатель	Группа основная		Группа сравнения	
	девочки n=15	мальчики n=15	девочки n=15	мальчики n=15
Eosinophils, %	5.3± 1.31	4.47± 0.82	4.2± 0.93	5.53± 0.65
Basophils, %	0.3± 0.16*	0.31± 0.11	1.13± 0.28**	0.26± 0.12
Band neutrophils, %	4.7± 0.12*	4.15± 0.11*	3.13± 0.15	2.53± 0.12
Neutrophils, %	40.9± 1.74	39.73± 2.02	41.93± 1.79	43.4± 1.68
Lymphocytes, %	46.5± 1.69	50± 1.92	48.13± 1.49	47.06± 1.87
Monocytes, %	2.3± 0.38**	1.26± 0.2	1.46± 0.28	1.2± 0.2
Lymphocytes : Neutrophils	1.16± 0.08	1.34± 0.1	1.19± 0.01	1.12± 0.08

the alien population of the Polar region (comparison group) showed that the characteristic of the cellular composition of peripheral blood is mainly subject to patterns, studied in detail and well known in the literature. In these groups, high values of the Garkavi adaptation index are recorded, which correspond to the reaction of increased activation of the organism.

The shift in the level of neurotransmitters we noted after prophylactic vitaminization is also reflected in the composition of the leukocyte formula. (Table 2). The initial structure of the blood composition indicators (the comparison group) by gender did not significantly differ among schoolchildren in the Polar region. We can only note that in the comparison group girls, the level of basophils is 80% ($p<0.01$) higher than in boys. Such a structure of blood parameters, apparently, can be regarded as one of the variants of regional specificity.

We found that after vitaminization there are differences in the leukocyte formula between girls and boys. Thus, in the girls of the main group, a decrease in the basophil content by 3.76 times ($p<0.05$) relative to the girls of the comparison group was revealed. It is known that there is a close functional relationship between peripheral blood basophils and tissue basophils. It is noticed that with a decrease in cells of one type, the number of cells of another type increases [3]. Activation of tissue basophils is usually accompanied by the release of biologically active components, such as serotonin [3]. Confirmation of this, we see that after vitaminization in the lymphocytes of children in the main group of Norilsk, the level of serotonin was higher than in children of the comparison group.

Along with a change in the balance of neurotransmitters after taking multivitamins in children of the main group, a change in the percentage of band neutrophils was revealed. In both girls and boys of the main group, an increase of 1.5-1.6 times ($p<0,05$) was observed in the percentage of band neutrophils relative to the children in the comparison group. The increased level of band neutrophils in the blood indicates the activation of bone marrow cells to enhance proliferation and mitotic activity, probably due to multivitamins.

The results described clarify the idea that an increase in band neutrophils usually occurs during acute or moderate chronic stress. The development of neutrophilic leukocytosis is mainly associated with an increased intake of bone marrow or vascular neutrophils from the cellular reserve into the circulation, which are recruited by glucocorticoid and monoamines. According to modern concepts, central adrenergic, dopaminergic and serotonergic structures play a coordinating role in the implementation of the response of the blood system to the effects of extreme irritants of various etiologies [2].

In addition, in the main group of girls, an increase of 45.2% ($p<0.01$) in the percentage of monocytes relative to the main group of boys was established (Table 2)

After vitaminization in the main groups of schoolchildren, high values of the Garkavi adaptation index were also observed, which correspond to the reaction of increased activation of the organism.

Conclusion. The research results showed the complexity and multivariability of the functioning of the immune system of schoolchildren in the conditions of the Far North after the inclusion of multivitamins in the diets. A change in the balance of regulatory indicators in schoolchildren's lymphocytes, which can change the functional activity of these cells, has been established. The decrease in the level of CA and the increase in the serotonin content are associated not only with the effect of the vitamin complex on biochemical mechanisms, the synthesis and decomposition of monoamines, but also with the state of the metabolic and regulatory systems of the inhabitants of the North.

Vitaminization among schoolchildren of the Polar region significantly changes the balance of the cellular elements of peripheral blood in children in this region.

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DAYTIME SLEEPINESS AND SLEEP PARAMETERS IN CHILDREN LIVING IN THE EUROPEAN NORTH OF RUSSIA

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Parameters of sleep and excessive daytime sleepiness were studied in 601 children aged 7-12 years living in the Arctic zone of Russia. No gender differences in daytime sleepiness were found. Our work also found the delay in bedtime onset for most children 7-12 years old. Self-questionnaires revealed awakenings in the middle of the night in almost half of the children, and insomnia was mild or moderate in 43.3% of the examined children in the European North of Russia. We have shown that children's age affects the level of daytime sleepiness. Consequently, older children must sleep more than younger ones to achieve the same level of alertness and cognitive ability. Thus, children compensate for lack of sleep during the next day via daytime nap.

Keywords: daytime sleepiness, chronotype, children, Arctic, children, age, sex, sleep duration.

Introduction. Sleep parameters are determined by a number of biological, environmental and social factors [3]. In modern society people spend a significant part of their time in a closed space, so it is logical to assume that the signals of social time play a major role in synchronizing the rhythm of sleep-wakefulness. On the other hand, a recent study showed that the phase of the sleep-wake rhythm (chronotype) of a person is determined by the time of sunrise [18]. With the growth of industrialization of society, the difference between social and biological clocks is growing. Among the population of megacities, the frequency of detecting individuals with a late chronotype, which is characterized by desynchronization of the circadian system, called the "social jet lag" [2], is increased. For this reason, individuals with a late chronotype exhibit lower school performance [14] and are prone to consume stimulants 2]. At school age, most children retain a sleep duration of 10–11 hours, however, increased educational and physical activity can negatively affect a child's sleep. These disorders often come in conjunction with attention deficit hyperactivity disorder (emotional reactions and cognitive impairment) [1]. Studies of daytime sleepiness of schoolchildren in different countries revealed a rather high frequency of spread, especially during puberty, from 51% in Turkey [15] to 63% in Japan [12] and 68% in Canada [20]. In Russia, this problem has hardly been studied among schoolchildren of primary school age.

The aim of our work was to study the influence of various factors on excessive daytime sleepiness of children and adolescents living in the north of the European part of Russia.

Materials and methods. The study was conducted in 2018 among students of grades 1-6 of secondary schools located in 8 settlements of the European North of the Russian Federation: in the Republic of Karelia - Petrozavodsk, Kem, Kostomuksha, Vidlitsa, Rabocheostrovsk; in the Murmansk region - Apatity, Olenegorsk, Umba. The research program was approved by the Committee on Bioethics of the Institute of Biology of the Karelian Scientific Center of the Russian Academy of Sciences and by the Joint Ethics Committee on Medical Ethics under the Ministry of Health of the Republic of Karelia (Protocol No. 41 from 08.01.2018). All respondents or their legal representatives were informed with the purpose of the upcoming study and signed an informed consent to participate in it. Questionnaires were distributed to students by teachers or school psychologists. Incomplete questionnaires and questionnaires with several answers instead of one were excluded from the analysis.

At the preliminary stage, we conducted a study to assess the reliability and validity of the Russian version of the children's daily sleepiness scale (PDSS-RUS) [17]. Further, in the framework of the project, in a sample of schoolchildren it was proposed to evaluate the occurrence of various sleep disorders and to identify the relationship of sleep characteristics with various lifestyle factors. Assessed: demographic data, lifestyle, school performance and the self-adminstered scale of daytime sleepiness in children (Pediatric Daytime Sleepiness Scale). Each respondent was asked to answer questions regarding personal data, as well as fill out a questionnaire: Munich Chronotype Assessment Test (MCTQ). Questionnaires were processed according to the work of MCTQ [18]. The chronotype was expressed as the middle of the sleep phase on the day off in hours, adjusted for the "duty" of sleep accumulated over the school days. The higher the value of the indicator, the more a person belongs to a later chronotype. The average weekly sleep duration was calculated.

Statistical processing was performed in the PAST package (PALEONTOLOGICAL STATISTICS SOFTWARE PACK-

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AGE FOR EDUCATION AND DATA ANALYSIS, Norway).

Results and discussion. The average age of the children was 10.62 ± 2.87 years. Table 1 presents information on the sex and age composition of the respondents. In the questionnaires, the answers to the questions corresponded to the normal distribution, and the average total score was 11.95 ± 6.2. We did not find gender differences on the daytime sleepiness scale. The reliability and reliability of the PDSS-RUS questionnaire is validated and confirms its one-factor structure. The Russian version of PDSS can be used in our study to assess sleep hygiene among Russian children and adolescents [17].

Most of the surveyed children showed excess daytime sleepiness within normal limits (less than 16 points on the PDSS scale). Significant differences in the level of drowsiness were found in children of primary school age, both in northern Karelia and in the Murmansk region (PDSS (May) M ± m (11.95 ± 6.24) versus PDSS (February) M ± m (12.75 ± 6.06, p <0.05) .For the group of indigenous people of the same age category, there is a tendency to increase this indicator (PDSS (May) M ± m (12.01 ± 5.72) versus PDSS (October) M ± m (12.79 ± 5.79, p> 0.05), respectively) (Fig. 1B). In addition, there was an inverse correlation for the duration of sleep with estimates of the drowsiness scale (r = -0.122, p = 0.02). This suggests that children compensate for the lack of drinking during the next day due to daytime sleep. Our work also shows a delay in bedtime for most children 7-12 years old. According to self-questionnaires, awakenings were revealed in the middle of the night in almost half of the children, and in 43.3% of the examined children in the European North of Russia insomnia is expressed in mild or moderate degree (Table 2).

In all the settlements of the European North of the Russian Federation, where we conducted studies, it was found that daytime sleepiness increased with age (Fig. 1A). This fact is consistent with earlier studies for various ethnic groups [12, 4]. Thus, older children must sleep more than younger children in order to achieve the same level of alertness and cognitive ability [16, 20, 6]. Feinberg and Campbell suggested an alternative hypothesis - increased drowsiness in adolescents in the daytime is a consequence of the reorganization of their brain, which reduces the intensity of activity of the waking brain [11]. Surprisingly, these brain changes are not associated with puberty, but are reliably associated with age. Also, as a result of our research, it was found that gender is not associated with daytime sleepiness.

In most studies, PDSS was used as a tool for assessing drowsiness associated with sleep pathologies (respiratory, neurological and developmental disorders),

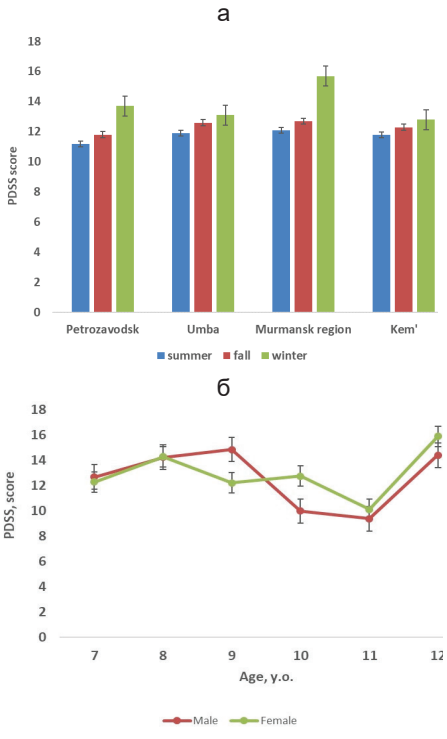

Fig. 1. Dynamics of infant drowsiness in children of the European North of the Russian Federation: a- age dependence, b – season dependence

as well as for monitoring the monitoring of side effects of sleepiness treatment [13, 7]. In several works, the authors used a questionnaire to assess healthy children and adolescents [21, 19, 22]. In a number of works, scores ranged from 6.7 to 25.7, showing a tendency to excessive drowsiness in the daytime. In addition, higher PDSS scores were associated with decreased overall sleep time, poor school performance, and frequent illnesses in different countries [18, 19]. The values obtained by us for the PDSS scale correspond to published data for healthy

Table 1

Sample parameters

Variable	Result
Sex, male/female, n (%)	321 / 280 (51.3 % / 48.7 %)
Age, n (%) 7 years 8 years 9 years 10 years 11years 12 years	 42 (6.9%) 135 (22.6%) 111 (18.5%) 118 (19.6%) 124 (20.6%) 71 (11.8%)
Physical activity 1-2 per week Every day Rarely	 421 (70 %) 90 (15%) 90 (15%)
Caffeine consumption, n (%) Daily Rarely Never	 120 (19.9 %) 331 (55 %) 150 (25.1 %)
Alcohol consumption, n (%) Often (every week) Never	 40(6.7%) 561(93.3%)
Smoking, n (%) Yes No	 110 (18.3%) 491(81.7%)

Table 2

Sleep disorders in children living in the European North of the Russian Federation, identified in the study (n = 601)

Low subjective sleep assessment, n (%)	341 (56.7)
Night awakenings, n (%)	360 (58.3)
Duration of falling asleep, n (%) 0-15 min 15-30 min 30-60 min >60 min	 180 (30) 350 (58.3) 51 (8.4) 20 (3.3)
Daytime sleepiness, n (%)	92 (15)
Insomnia severity scale, n (%) None Light Moderate	 341 (56.7) 220 (36.6) 40 (6.7)

children from the USA [9], Argentina [19], China [5] and Italy [9]. It should be noted that the average age in this sample was 10.62 years. This fact explains why in our study, scores on the PDSS scale are slightly lower than in studies on the drowsiness of Brazilian [10] or Argentinean children [4].

Conclusion. We have shown that the age of the child affects the level of daytime sleepiness, which, in turn, corresponds to the level of sexual development. Consequently, older children must sleep more than younger children in order to achieve the same level of alertness and cognitive ability. Thus, children compensate for lack of sleep during the next day due to daytime sleep.

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SCIENTIFIC REVIEWS AND LECTURES

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INDICES OF LIPID METABOLISM FOR THE EARLY DIAGNOSIS OF CARDIOVASCULAR DISEASE IN RESIDENTS OF THE NORTH

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Cardiovascular disease is one of the leading causes of morbidity and mortality among the adult population. In Russia, over a million people (around 700 people out of each 100 thousand population) die each year from cardiovascular diseases. The high prevalence of cardiovascular disease is observed in people living in the North, whose severe climatic conditions produce increased demands for a human body. Northern climatic factors lead to significant changes in human’s physiological functions based on modified functional condition of the endocrine system, metabolic processes, and lipid metabolism in particular. According to L.E. Panin’s concept (1978), in high-latitude regions we can observe “the changeover from carbohydrate-type metabolism to the lipid one”. This concept states transformation of the lipid profile in residents of the North caused by a number of external factors frequently leading to changes in metabolic pathways and abnormalities in lipid metabolism. Adequate assessment and correct interpretation of lipid metabolism variables are of major importance for early detection and timely prevention of cardiovascular pathology. The review considers key lipid metabolism indices. We also present our own data about the role of compound indices in lipid metabolism assessment in healthy inhabitants of the North.

Keywords: lipid metabolism, adaptation, North, cardiovascular disease, apolipoproteins.

The issues related to preservation of health in the North are of great medical and social significance. The process of human adaptation to adverse northern factors is aimed at maintenance of stable functioning of various systems separately and of a human body as a whole to ensure normal vital activities under inadequate environmental conditions. Transformation of energy metabolism through changeover of all types of metabolism (of lipids, proteins, carbohydrates, vitamins, macro and microelements) plays an important role in the complex sequence of adaptive changes [6, 28, 32]. According to the member of the Academy of Sciences L.E. Panin [27, 28], the northerners develop a peculiar type of metabolism – the so-called "polar metabolic type" characterized by decreased role of carbohydrates and increased role of the proteins and lipids in energy metabolism. The increased significance of lipids in the energy metabolism of a human body finds its reflection in the changed lipid profile of blood [2, 4, 6, 13, 28]. Within L.E. Panin's concept, we suggest the term "adaptive polar metabolic type" as a special type of metabolism typical for the adapted population of the North, including the indigenous residents of the Far North. Development of this "adaptive polar metabolic type" includes forming of a peculiar hormone profile and metabolism ensuring comfortable living in the Far North conditions in particular. For inhabitants of the North, if compared to residents of middle latitudes, such adaptive changes are related to the transformed metabolism, which is preconditioned by more active basal metabolic rate in particular seasons of year and more short-term reactions connected with some environmental factors of the North [6].

At present time, ideas of the regularities of adaptive processes in residents of the North are based both on the studies of transformation mechanisms of physiological functions and biochemical processes in migrants, and on detection of morphofunctional features in the indigenous populations for which the subextreme and extreme conditions of the northern regions can be considered adequate. The analysis of the literature on metabolism in non-native residents of the North demonstrated that data on their lipid metabolism transformation are quite various and often contradictory, which is probably related to the fact that most studies were carried out on migrants of the North found at different stages of the adaptation [1, 6, 21, 28, 31, 35]. According V.P. Kaznacheyev's classification [13], in the process of a person's adaptation to the Northern environment one can observe a phase of regulatory and homeostatic processes destabilization (from 6 months to over 1 year long), a phase of regulatory and homeostatic processes stabilization and synchronization (10–15 years long) and a phase of lowered resistance of one's body. It is considered that the stage of resistance in residents of the North is explained by efficient changeover from carbohydrate metabolism to the lipid one. Such lipid metabolism transformations occurring throughout the "polar metabolic type" development are to be accompanied by lipoprotein spectrum shifting towards an increase in the number of high density lipoproteins (HDL). However, multiple studies showed that migrants of the North do not develop an optimal metabolic background as a rule. Contrariwise, they develop "northern dyslipidemia" which is reflected as increased atherogenic lipid fractions in blood [8, 12, 30].

Metabolism with predominantly protein-lipid metabolism ("arctic adaptive type") is observed in the indigenous populations of the North. Descendants of several generations of migrants who had been adapting to the northern environment for centuries possess similar ability to switch to the northern type of metabolism. For the indigenous populations of the North, the change of energy metabolism from the carbohydrate type to the lipid one comes on account of exogenous fats, i.e. food lipids [26]. In general, the basal metabolic rate in the northern aborigines is higher than the one in the residents of the middle latitudes [32]. The protein-fatty diet in the northerners implies primarily the use of lipids as the most energy intensive utilizable material and is accompanied by the increased activity of lipolytic enzymes and activated lipid mobilizing processes [26, 35].

The indigenous inhabitants of the North following the traditional lifestyle and diet with their "polar" metabolic type demonstrate more favourable lipid metabolism profiles with regard to the risk of development of a cardiovascular disease than the non-native populations of the North. The indigenous residents of the North (Evenki Autonomous Area, Yakutia, Amur River Region, Khanty-Mansi Autonomous Area, Yamal-Nenets Autonomous Area) have lower total cholesterol (TC) levels and its atherogenic fractions and higher levels of HDL cholesterol (HDL-C) in blood serum than migrants of the North [10, 11, 21-23, 25, 31].

However, social and economic changes of the recent decades, the inflow of migrants and urbanization have affected the traditional lifestyle and diet in the indigenous inhabitants, which has resulted in disturbed adaptive processes followed by increased morbidity. In addition, the indigenous populations of the North suffer adverse metabolic changes with intensified carbohydrate metabolism and increased atherogenic lipid levels in blood more frequently now [3, 9, 18-20, 33].

Atherogenic disorders of lipid metabolism play a major role in the pathogenic mechanism of atherosclerosis [17, 47]. At present time, atherosclerosis is one of the most relevant and important health problems. Atherosclerosis mostly affects aorta, arteries of heart, brain, lower limbs and kidneys. Therefore, coronary disease, myocardial infarction, aortic aneurism rupture, ishemic and haemorrhagic stroke are among top causes of death. In this connection, diagnostics and prevention of lipid metabolism disorders are some of the most significant tasks of today's medicine.

Currently, much attention is paid to studying the role of apolipoproteins in a human's lipid metabolism. It is believed that the analysis of the level of apolipoproteins in health and lipid metabolism disorders doubtlessly bring certain benefits, as it allows to identify accurately features and defects of lipoprotein metabolism. Apolipoproteins were discovered more than 40 years ago. Over 10 apoproteins have been identified and described so far. Apolipoproteins are classified into major and minor proteins. The former ones include apoA, apoB, apoC, apoD, apoE. Minor apolipoproteins include apoF, apoJ, prolin-rich protein, etc. [34, 39]. Depending on the key role performed, apolipoproteins are conditionally divided into two classes. One is apoproteins forming the micellar structure of lipoprotein complexes and serving as lipoprotein "nucleus". This group of apolipoproteins includes apoB (apoB-100 and apoB-48) and apoA (A-I and A-II) which are responsible for afferent and efferent transport of lipids. The other class contains apolipoproteins focusing on lipoprotein and lipid metabolism regulation in the bloodstream and their internalization by cells. These apolipoproteins are present in lipoproteins in low concentrations and transfer between lipoprotein classes as protein-lipid complexes in the process of lipoprotein particles' interconversion in the bloodstream. Key representatives of metabolically active apolipoproteins are apoE with three isoforms (E2, E3, E4) and apoC (C-I, C-II, C-III) [34, 63]. Meanwhile, the functional role of apolipoproteins in lipid metabolism in residents of the North has not been studied thoroughly.

For the first time ever we have ana-

lyzed plasma apoE levels in residents of the European North of Russia. It has been established that apoE levels in residents of the North shifted towards lower values [7, 16, 62]. This observation is consistent with the results of a large international research comparing apoE levels in people residing in six European countries. According to results of this study, there is a north-south increasing gradient of apoE concentrations. The lowest apoE levels were observed in residents of Finland [38, 75]. Low apoE levels in the northerners can be considered as adaptive changes providing metabolic transformation, on the other hand, it can serve as a cause for adverse changes in the lipid profile. One of the key mechanisms for the "northern" dyslipidemia was determined during the research. It has been shown that a low apoE level is risk factor for the development of hypertriglyceridemia [7]. ApoE distribution among the major lipoprotein classes was also studied. It has been found that the preservation of constant concentration of apoE in HDL fraction due to its redistribution among lipoprotein classes is priority at decrease of the total plasma apoE level [15].

The levels of TC, HDL-C, low density lipoprotein cholesterol (LDL-C) and triglycerides (TG) are used as classic indicators of lipid metabolism. However, it has been recently established that these conventional lipid parameters do not always reflect correctly the pro-atherogenic potential of blood [48, 51, 73]. Cases of atherosclerosis occurrence among subjects with normal TC levels have been described [60, 61, 65]. According to the literature, determination of TC and TG levels contributes to detection of 50% of all lipid metabolism disorders only [29]. Several computed indices have been defined in an attempt to raise the clinical benefit of lipid metabolism indicators [56, 80].

There are several types of lipid indices. Some indices reflect the balance between atherogenic and anti-atherogenic lipids, these include atherogenicity coefficient, Castelli 1 (TC/HDL-C) and Castelli 2 (LDL-C/HDL-C) indices, apoB/apoA-I ratio, and atherogenic index (ATH index). Their predictive capacity has been proved by many clinical examinations [36, 37, 47-49, 50, 55, 56]. Meanwhile, of these, the apoB/apoA-I ratio is the best marker of cardiovascular risk. The common method for assessing lipoprotein levels in blood by measuring cholesterol content in them does not always reflect the exact number of lipoproteins adequately. It is related to the fact that the amount of cholesterol within lipoproteins may vary widely due to active exchange of lipid components between lipoprotein particles [71]. Unlike lipoprotein cholesterol, the lipid-transporting apoproteins – apoB and apoA-I do not leave the lipoprotein molecules they build [69]. Therefore, apoB and apoA-I are assumed to be superior markers for lipid abnormalities. ApoB (we mean apoB-100) is an essential structural component of very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL) and low-density lipoproteins (LDL). Because each particle of these lipoproteins contains one molecule of apoB, the total atherogenic particles number can be accurately estimated by measuring the plasma level of this apoprotein. By contrast, apoA-I is the structural component of antiatherogenic HDL. So, the apoB/apoA-I ratio displays the balance between atherogenic and antiatherogenic lipoproteins in blood and serves as an early potential marker for the cardiovascular risk [64, 70, 76, 78, 79].

Other indices (LDL-C/apoB, TC/TG and atherogenic index of plasma (AIP)) are surrogate markers of LDL particle size [44, 54, 59, 77, 78]. These indices are thought to indicate the presence of small dense LDL particles which are known to be the most atherogenic lipoproteins. These particles are characterized by prolonged plasma half-life, lower resistance to oxidative stress, affinity to proteoglycans, and higher penetration into the arterial wall [66, 68]. Of note, since the determination of LDL-C levels in subjects with a predominance of small dense LDL leads to significant underestimation of the total amount of these lipoproteins [69-71], it explains the need to take the qualitative composition of this lipoprotein fraction into account as well. There are different views on the rationale for using the LDL-C/apoB ratio as a marker of LDL particle size. Some authors found high correlation between LDL-C/apoB values and the measured LDL particles' size [43, 54, 57, 77], while the others do not recommend using this ratio as marker of small dense LDL particles [40, 53].

Clinical studies globally widely use lipid metabolism indices to characterize lipid profile changes in case of various pathologies or to monitor the results of hypolipidemic or hormone replacement therapy, as well as in prospective epidemiology research aimed at detection of predictive factors of atherosclerosis and related cardiovascular diseases [41, 42, 45-47, 54, 67, 72, 80]. At the same time, usefulness of composite indices in the overall evaluation of lipid metabolism in healthy subjects has hardly been studied. The variation range for lipid metabolism indices and functional relations between them have not been found out yet.

The results of our studies made it possible to enlarge today's view about the lipid metabolism in residents of the North and to define main indices for early detection and monitoring of dyslipidemia risk. The comprehensive study of the lipid profile in apparently healthy residents of the North (157 men aged 20-59) with normolipidemia (TC<5.2 mmol/l, TG<1.7 mmol/l, HDL cholesterol>1.0 mmol/l) showed nonmanifest disturbances of lipid metabolism. Increased atherogenicity of the lipid profile in subjects with normolipidemia occurred as a distorted balance between atherogenic and antiatherogenic lipoproteins and changed qualitative composition of lipoproteins. The analysis of individual data revealed that values above the reference limits for the atherogenicity coefficient, Castelli 2 index, atherogenic index of plasma (AIP) and atherogenic index (ATH index) were observed in 7.0-10.2% of the men with normolipidemia. The study subjects most frequently demonstrated lower values of LDL-C/apoB (26.0%) and higher apoB/apoA-I ratio (19.1%). Deviation of these indices from the reference range was observed on the background of low levels of apoE which is a regulatory protein of lipid transport system [14, 24, 52, 74]. It is known that insufficient amount of apoE leads to slower receptor-mediated elimination and accumulation of TG-rich lipoproteins in blood [5, 39, 58]. In our case, higher levels of TG in the subjects with the unfavorable LDL-C/apoB and apoB/apoA-I ratios indicated the delayed clearance of TG-rich lipoproteins. Thus, the atherogenic changes of lipid profile observed in the healthy subjects with normolipidemia may be due to disturbances in catabolism and metabolic turnover of lipoproteins. Decrease of regulatory effect of apoE on lipoprotein metabolism in healthy subjects at early stages is latent and it does not appear as hyperlipidemia. The LDL-C/apoB and apoB/apoA-I ratios are more sensitive indices compared to conventional indicators and are capable to detect atherogenic changes of the lipid profile even in case of normolipidemia.

In general, it should be noted that the results of our own studies indicate the necessity to conduct determination of the apolipoprotein levels and calculation of compound lipid indices in addition to the conventional indicators of lipid metabolism, which makes it possible to detect metabolic disorders at early stages. Deviation of lipid metabolism indices from the reference range in case of normolipidemia can be considered as early predictor of metabolic transformations

occurring on the background of changes in performance of regulatory systems, but not having shown any clinical implications yet.

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OBESITY IN VARIOUS ETHNIC POPULATIONS

This article presents a review of the literature. The authors conducted a scientific search on the epidemiology of obesity and overweight in different ethnic groups, using the relevant keywords, on the search engines PubMed and Google Scholar, on the Scopus, Web of Science, MedLine, The Global Health databases, CyberLeninka, eLIBRARY.RU and others. Obesity is widespread among children, adolescents and adults. Most of the epidemiological studies conducted to identify obesity and overweight used the most accessible method - the determination of body mass index (BMI). Data on ethnic origin can provide additional information for a personalized prognosis; to date, there is no single classification for obesity and overweight for Asians.

Keywords: obesity, overweight, body mass index, ethnos, population, prevalence, complications.

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Obesity is an increase in body fat, leading to the appearance of overweight, is a common chronic metabolic disease in Russia and the world that occurs at any age. Currently, there is an increase in overall morbidity and mortality from complications (metabolic syndrome, type 2 diabetes, liver steatosis, arterial hypertension, IHD, etc.) in this condition.

It is well known that the causes of obesity are: hereditary predisposition (increased activity of lipogenesis enzymes and reduced activity of lipolysis enzymes), failure to follow the mode and nature of nutrition (frequent, excessive food), endocrine disorders, stressful situations (psychogenic overeating), hormonal drugs, a sedentary image life (motor mode must be combined with proper nutrition and the rejection of bad habits).

Overweight is not only a socio-economic and cosmetic problem, but primarily a medical one. It is proved that the greater the body weight, the lower the life expectancy due to the development of serious diseases. In this regard, significant efforts of modern endocrinology are aimed at studying the causes and mechanisms of the development of overweight and obesity [3; 12; 13] and their correction.

The epidemiology of obesity depends

on the characteristics of ethnic groups, many complications directly correlate with ethnicity.

In this regard, the study of the prevalence of obesity in various ethnic populations is one of the urgent problems of modern medicine. Russia, being a multinational state, is characterized by a large ethnocultural diversity. The structure of the Russian Federation includes 85 subjects: 46 - regions, 22 - republics 9 - edges, 3 - cities of federal value, 4 - autonomous regions, 1 - autonomous region. There are about 157 thousand settlements in the country.

In Russia, more than 2 million people are obese, and patients with overweight are even more, each year the problem only increases.

This review analyzes scientific studies on the epidemiology of obesity in various ethnic populations and, depending on the place of residence, urban or rural population.

The prevalence of obesity in the world according to WHO (2016) is 11% in men and 15% in women older than 18 years and 39% of men and 40% of women were determined to be overweight.

According to the results of studies conducted in the Republic of Buryatia in adolescents of ethnic groups in rural areas, it was revealed that, regardless of their ethnicity, the risk factors for obesity and overweight are the presence of overweight in the mother and the irregular nutrition of adolescents. Risk factors for adolescents of indigenous Asian ethnic groups (Buryats and Soyots) and Slavic ethnic groups can be social factors, such as children living in single-parent families, and in families where mothers do not work [16].

The prevalence of obesity and diabetes in various ethno-social populations of the urban and rural populations of the European Far North and the territories equated to the Far North from 1996 to 2006 was reported in studies [1]. It has been established that among the rural inhabitants of the European North, obesity is more pronounced among the local Russians of the Far North compared to the Komi who live in the territories of the Far North. The Komi people living in the Far North and leading a traditional lifestyle have a lower incidence of obesity compared with other populations of northerners [1].

Metabolic syndrome and type I diabetes are common in the Asian part of Russia, and in the indigenous people of the North and the Far East both types of diabetes are less common than among Caucasians who live in the same regions [10].

Currently, the complex effect of genetic, geographical, socio-economic factors behind ethnic groups has been proven. Over the past few years, there has been a deterioration in the quality of life of small peoples living in conditions of the North and Siberia. Compared to the Russians, the Buryat population is characterized by a favorable course of diabetes, cardiovascular diseases, arterial hypertension [5].

When examining the population of Kyrgyz nationality, it was established that in this ethnic group the ATP III (2005) classification is the optimal classification for diagnosing MS. [20].

For comparison, in the population of Novosibirsk 45-69 years old, the prevalence of abdominal obesity according to the NCEP ATP III criteria (2001) is only 43%, according to the criteria of VNOK (2009) 65% and according to the criteria of IDF (2005), IDF and AHA / NHLBI (2009) 67% [17, 8].

The prevalence of metabolic syndrome increases significantly with age and has gender, ethnic and regional differences, with a significant role played by age and ethnicity. The IDF criteria (2005) emphasize the relevance of research in various ethnic groups in order to further refine the criteria [9].

Ethnic differences are revealed not only in MS, but also in normal body weight [22].

To this day, there is no classification of obesity and overweight for Asians. For example, for residents of Thailand they apply their own criteria, for the Korean subpopulation - their own. Representatives of various Asian ethnic groups (Buryats, Yakuts, etc.) live on the territory of our country, so there are difficulties with the use of the classification [2].

The Asian population is characterized by a large amount of fat with a low BMI and waist circumference [23, 27].

It has been established that in women of the Far North, the prevalence of obesity is 34.7%, the metabolic syndrome is 14.6% and is more often recorded in non-indigenous women. The abdominal type of distribution of adipose tissue with low lipid metabolism was observed in the population of indigenous women. In non-indigenous women, the abdominal distribution of adipose tissue was formed mainly during obesity. The author determined the high diagnostic value of MC markers, which are recommended by IDF (2005), for non-indigenous women of the Far North. In the population of indigenous women, the low diagnostic value of HDL cholesterol indicator was found, the ethnic marker of MS was identified [11; 21].

Abdominal obesity and body mass index of the elderly (Yakuts) of elderly and senile age were recorded less than those of non-indigenous (Caucasians), and patients who were not overweight, abdominal obesity and metabolic syndrome were observed equally in indigenous and non-indigenous [nineteen].

Obesity in the Chuvash Republic is (5.5-39.1%) depending on the area of residence. The prevalence of obesity in the Chuvash Republic is lower than in the Russian Federation, the author explains this by an ethnic factor: for the most part, the incidence among Chuvash ethnic groups, who live in this region is about 70% of the population, for the Russian population is comparable to the prevalence of obesity in other regions of Russia. Factors affecting the formation of obesity: Russian ethnic group, female gender, city residence, age over 50 years [7].

According to the results of several studies, it was established that all patients with arterial hypertension of the Russian and Mordovian nationalities, regardless of gender, had a predisposition to overweight according to the definition of BMI. This indicator was increased in 29.1% of Russian women and 33.0% in the Mokshan ethnic group, 22.9% Erzyan, which made it possible to identify overweight. Obesity was observed in 64.1% of Russian women, 57.8% of moksha and 66.7% of Erzi. In men with hypertension, BMI was increased in 25.6% of Russians, 38.9% of mokshan and 35.5% of Erzyans, and with obesity, respectively, in 56.4%, 41.7% and 45.2% [4]. Thus, in the population of the Kyrgyz Republic, abdominal obesity is 52.3%, for women, abdominal obesity and arterial hypertension are typical, for men, hypertriglyceridemia is observed [15].

In European countries, the prevalence of metabolic syndrome in the general population is 3-4 ‰ at the age of 18 to 40 years, in Russia this figure rises to 5.5 with a tendency to increase after 40 years [24-26].

The indigenous population of the Baikal region has a high degree of adaptation to the region in which they live relative to the alien population. The representatives of the Buryat ethnogroup have a higher incidence of arterial hypertension, cardiovascular diseases, and diabetes mellitus type I than among Russians. Consequently, information on ethnic origin may provide additional information for a personalized forecast [6].

It should be noted that in the adult population of Cheboksary, in a random sample, a high incidence of traditional risk factors was recorded, such as eating

disorders - 76.1%, hypercholesterolemia - 62%, a sedentary lifestyle - 52.6%, arterial hypertension - 39.2%, reduced cholesterol and HDL cholesterol - 25%, smoking in men, alcohol consumption 43% and 27.4%, and metabolic risk factors: hypertriglyceridemia -27%, abdominal obesity - 22.1% and elevated levels stress. Most of them have a linear dependence on age and gender differences [14].

Thus, obesity is widespread among children, adolescents and adults. Most of the epidemiological studies conducted to identify obesity and overweight used the most accessible method - the determination of body mass index (BMI). Data on ethnic origin may provide additional information for a personalized prognosis, but to date there is no single classification for obesity and overweight for Asians.

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ENDOCRINE MECHANISMS OF BRONCHIAL CONTROL IN PATIENTS WITH BRONCHIAL ASTHMA

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The analysis of works published according to the results of studies by foreign and domestic authors on the role of the pulmonary neuroendocrine system in the functioning of the bronchi is carried out. Modern ideas about the endocrine mechanisms of bronchial control in patients with bronchial asthma are presented. A brief description of pro-inflammatory and anti-inflammatory peptide substances produced in the bronchopulmonary system is given. The possibilities of using some peptide substances as drugs in the treatment of patients with bronchial asthma are indicated.

Keywords: pro-inflammatory peptides, anti-inflammatory peptides, bronchopulmonary system, bronchial asthma.

Introduction. According to GINA (2018), bronchial asthma (BA) is a heterogeneous disease characterized by chronic inflammation of the airways and the presence of respiratory symptoms (wheezing, shortness of breath, congestion in the chest, cough), which vary in time and intensity and occur along with variable airway obstruction [16]. At the same time, the neurogenic and immune mechanisms of the development of BA are described in detail in the literature; at the same time, the role of the endocrine system in the development of this disease has not been studied enough.

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The active study of the role of the endocrine system in the development of lung diseases, including bronchial obstruction, began at the end of the 20th century. The impetus for their active study in pulmonology was the confirmation by a number of scientists of the influence of gastrointestinal peptides previously detected in the gastrointestinal tract (GIT) on the bronchopulmonary system (BPS) [1]. Later, endocrine cells secreting similar peptides were also detected in the BLS. One of the first to be identified was the Klara and Kulchitsky cells. By the beginning of the twenty-first century, a large number of endocrine-active cells were synthesized in the BPS, synthesizing peptides similar to gastrointestinal peptides: the tachykinin family, bradykinin, a peptide related to the calcitonin gene (PRCG), bombesin, a vasoactive intestinal peptide (VIP), peptide-histidine-methionine (PHM), adrenomedullin, neuropeptide "Y" and others. It was found that the effect of peptide substances on the functioning of the lungs is carried out by means of receptors located throughout the BPS [12, 22, 23]. Their functional activity was manifested in the blockade of the parasympathetic and sympathetic nervous systems, in connection with which non-adrenergic and non-cholinergic, i.e. peptidergic system of functioning of the lungs.

Later it was proved that certain immune competent cells (mast cells, macrophages, neutrophils, eosinophils and lymphocytes), as well as neurons, also have the ability to secrete peptides [22]. The presence of receptors for neuropeptides on the surface of the cell membranes of immune-competent cells, as well as neurons, was found [12]. It has been found that neuropeptides, acting through different types of receptors, can lead to different pharmacological effects, i.e. possess multidirectional pharmacological activity. The latter was the theoretical justification for a more in-depth study of the pro- and anti-inflammatory effects of various peptide substances on BPS in animal experiments and in patients with BA. It was found that the pro-inflammatory effect on the bronchi has: a family of tachykinins (substance P, neurokinins, chemokinin-1), bradykinin, PRCG, endothelin-1, bombesin, granin. The anti-inflammatory peptides included: VIP, neuropeptide "Y", neuropeptide pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38), PHM, adrenomedullin, atrial natriuretic peptide (ANP).

Pro-inflammatory peptides and their role in the development of inflammatory diseases of the lower respiratory tract

Tachykinins play an active part in the development of inflammatory processes in many organs, including the gastrointestinal tract and BPS [23, 29, 30]. They

are produced in the central nervous system and peripheral tissues, including in the BPS. They are synthesized in the BPS by epithelial cells of the mucous membrane of the bronchi, endothelial cells, endocrine and endocrine-active immune-competent cells of the lamina of the bronchial mucous membrane (mast cells, eosinophils, neutrophils, lymphocytes, monocytes, macrophages), bronchial smooth muscle cells, neurons. It has been established that the BPS of BA patients is more sensitive to tachykinins than the BPS of healthy individuals [22].

Tachykinins act through neurokinin receptors: NK1 (substance P), NK2 (neurokinin-A, neurokinin B) and NK3. Tachykinins are important in the regulation of the peptidergic mechanisms of asthma and are by far the most studied neuropeptides in pulmonology.

Allergic sensitization of the respiratory tract of guinea pigs leads to the induction of tachykinins (substance P, neurokinin A) and a peptide related to the calcitonin gene (PRCG) by sensory neurons, which is one of the pathogenetic mechanisms of inflammation in the bronchi and bronchoconstruction [30]. Through NK1 receptors, tachykinins lead to the development of powerful inflammation in the mucous membrane of the bronchi causing vasodilation, an increase in vascular permeability, hypersecretion, stimulation of mast cells, lymphocytes, and chemotaxis of neutrophils and eosinophils, and through NK2 receptors they cause bronchospasms. Bronchial hyperreactivity (BGR) develops as a result of the isolation of tachykinins from capsaicin-sensitive centripetal nerves via the NK1/NK2 receptors [30].

The substance P, which was discovered in 1931, is the most studied of the tachykinin family. Substance P is encoded by the preprotachikinin-A gene and is expressed predominantly in sensory neurons sensitive to capsaicin. Receptors, through which substance P functions, were found in the lamina propria of the bronchial mucosa, the smooth muscles of the bronchi, near blood vessels, ganglia and nerve bundles of the submucosa. They are absent in the submucous glands and alveolar septa [12].

The substance P is actively synthesized in various immune inflammatory processes in the bronchi. It has been established that the content of substance P increases in serum, sputum, bronchoalveolar lavage, endocrine and endocrine-active BPS cells and sensory neurons of patients with BA [5, 22, 27]. The latter implies the direct participation of substance P in the development of the inflammatory process in the bronchial wall. Substance P affecting the vessels causes their dilatation, affecting the goblet cells of the respiratory tract and submucosal cells causes hypersecretion and stimulation of mucociliary clearance, affecting the smooth muscles of the bronchi causing bronchospasm. Substance P activates inflammation of the bronchi through the activation of immune-competent cells (mast cells, eosinophils, neutrophils, lymphocytes, monocytes, macrophages), chemotaxis of lymphocytes, neutrophils and eosinophils, as well as degranulation of target cells of allergies, predominantly mast cells [5, 22, 23].

Neurokinin-A, which has been actively studied in recent years, is a product of the preprotakhinin-A gene. As well as substance P, it is synthesized by immune, inflammatory, endothelial and epithelial cells, as well as by the smooth muscle cells of the bronchi in various immune inflammatory processes in the bronchi. It participates in the activation of immune cells, prolonging the inflammatory process in the bronchi [22]. There is an increase in its content in sensory neurons, as well as in endocrine and endocrine-active BPS cells of patients with BA. It causes contraction of smooth muscles, mainly in the BPS and gastrointestinal tract [13, 23, 31].

In patients with physical asthma, exercise-induced sputum was collected at the beginning and 30 minutes after exercise. In the induced sputum, secreted mucin 5AC, eicosanoids, cysteinyl leukotrienes, 15S-hydroxyethylisatetraenoic acid and tachykinins (neurokinin-A, substance P) were determined. At the same time, there was a twofold increase in the induced sputum of asthma patients in the physical effort of mucin 5AC, as well as tachykinins: neurokinin A and substance P. The authors assumed that the release of mucin 5AC after exercise may occur through activation of sensory nerves of the respiratory tract associated with cysteinyl leukotrienes tachykinins and the development of bronchial obstruction. Exercise-induced pathogenesis of bronchial obstruction involves the release of mediators (including tachykinins) in response to physical exertion. However, the mechanism that prevents airflow obstruction during exercise is not fully understood [28].

The bronchoconstrictive effect of neurokinin-B has also been proven. This peptide is derived from the preprotachikin-B gene and is acted upon by the NK3 receptors. Neurokinin-B and NK3 receptors are predominantly found in the central nervous system, as well as on the periphery, mainly in the respiratory tract and gastrointestinal tract [19, 23].

Among proinflammatory neuropeptides, the peptide of the tachykinin families, chemokinin-1, has been actively studied in recent years, which, like substance P, interacts through NK1 receptors. It is synthesized predominantly by leukocytes, as well as by immunocompetent cells of the bronchial mucosa, including macrophages and causes a reduction in the bronchi in humans. In experimental mice, it has been established that it is generated by activated mast cell allergens and contributes to experimental chronic allergic inflammation of the airways [34]. Chemokine-1-induced bronchial contraction can be mainly associated with NK2 receptors in humans and with NK1 receptors in the guinea pig [15]. Chemokinin-1 800 times more powerful effect on the bronchi of people than neurokinin-A [22]. It has been established that chemokine-1 increases in patients with asthma and causes mast cell degranulation, an immune inflammatory process in the bronchial mucosa and bronchospasm [34].

As can be seen from the literature data presented, tachykinins are considered as possible mediators of asthma, and tachykinin receptor antagonists can be considered as a new class of drugs in the treatment of patients with asthma [13, 23]. For example, it was established that bronchospasm induced by inhalation of neurokinin-A in patients with BA is blocked by the double antagonist of NK1/NK2 receptors of the tachykinin DNK333 [13] and the antagonist of NK2 receptors of the tachykinin MEN11420 (nepadutant) [32]. It has been proven that dual NK1/NK2 receptor antagonists (DNK-333, AVE-5883 and MEN11420) have the property of weakening bronchial hypersensitivity (BHS) [13, 14, 32].

The NK2 receptor antagonist SR 48968 (saredutant) also prevents bronchoconstriction caused by neurokinin-A in patients with BA [5]. The NK2 receptor antagonist SR 144190 selectively inhibits the binding of neurokinin A to NK2 receptors in humans and various animal species. It prevented BHS in guinea pigs caused by citric acid to acetylcholine [6].

The NK3 receptor antagonist osanetant (SR142801) reduces the level of TNF-α and interleukin-6, as well as the activity of matrix metalloproteinase-9 in the inflammation of the respiratory tract caused by mouse endotoxin. A high anti-inflammatory activity in airway inflammation was observed in the combination of the NK1 receptor antagonist SR140333 and NK2 SR48968 [19].

The bronchoconstrictive effect of chemokine-1 is blocked by the NK2 receptor antagonist SR 48968, while the receptor antagonist SR 140333 only slightly reduced the effects of chemokinin-1 [22].

The triple antagonist of the NK1/NK2/NK3 receptor CS-003 reduced BGR and bronchoconstriction caused by neurokinin-A in BA patients [31].

The presented data are convincing evidence of inhibition of bronchoconstriction by selective antagonists of tachykinin receptors in patients with BA, and open up broad prospects for their use.

The role of nonapeptide bradykinin in the development of inflammation has also been studied. It is established that he is one of the mediators of inflammation in asthma. Its content increases in the bronchoalveolar lavage of patients with BA. Bradykinin affects vascular tone and permeability, causes hypersecretion and reduces the smooth muscles of the bronchi through cholinergic mechanisms. By activating fibroblasts, it is directly involved in the remodeling of the bronchi. It has been proven that NK2 (SR48968) and NK3 receptor antagonists (SR142801 or SB223412) suppress cough caused by bradykinin in guinea pigs [25].

PRCG also belong to pro-inflammatory peptides. The main sources of PRCG in the respiratory tract are believed to be unmyelinated and fine myelin sensory nerve fibers and neuroendocrine cells. PRCG receptors, as well as substance P, are found in the lamina propria of the bronchial mucosa, near blood vessels, as well as in the ganglia and nerve bundles of the submucosa [12]. In its own plastic of the bronchial mucosa, PRCG is localized predominantly on CD3 + / CD4 + and CD68 + cells [4]. In the smooth muscles of the bronchi, in contrast to substance P, very few PRCG receptors are detected, and in the glands and alveolar septa they are absent [12].

It has been established that the content of PRCG increases in bronchoalveolar lavage, sputum, peptidergic nerves and sensory neurons of the lower respiratory tract of patients with asthma [27]. PRCG may contribute to the late phases of asthmatic reactions after provocation by respiratory allergens [5]. This peptide enhances the effect of substance P, causes potent vasodilation, hypersecretion, bronchial edema and bronchial smooth muscle spasm, more pronounced than in substance R. In addition, it contributes to the release of inflammatory mediators, including histamine from mast cells, which increases inflammatory reaction of the bronchi and bronchospasm. It has been established that in this case the bronchospasm is not blocked by histamine, acetylcholine and leukotriene antagonists [4].

Endothelin-1, refers to peptides with pro-inflammatory, profibrotic, broncho-and vasoconstrictive effects. It plays an important role in the development of airway inflammation and remodeling in asthma [17].

Bombesins are synthesized by the nervous system, as well as various types of neuroendocrine cells, including lung cells. In the lungs, bombesins contribute to the differentiation of epithelial cells and play an important role in modulating the physiology of the respiratory tract. They cause hypersecretion of mucus and marked bronchial obstruction and are one of the main mediators of inflammation in patients with asthma. Bronchospasm develops due to the direct effect of Bombesin on the receptors of the smooth muscles of the bronchi. At the same time, bronchial obstruction caused by Bombesin is not affected by atropine, hexametonium, propranolol, triprolidine, methysergide, Ro 19-3704 [10].

In recent years, interest in facets has revived, mainly chromium granules A and B. The study of serum granules today is used to diagnose lung tumors. Some researchers have reported that chromogranin A is increased in patients with broncho-obstructive diseases, including those with asthma. The relationship between the amount of serum chromogranin A, smoking, respiratory symptoms and spirometry indicators has been studied. Studies were conducted on smokers with normal lung function and bronchial obstruction. At the same time, high figures of serum chromogranin A were detected in smokers with bronchial obstruction confirmed spirometrically, in contrast to smokers with a normal spirogram. At the same time, the increase in chromogranin A correlated with the degree of bronchial obstruction. The latter, according to the authors, suggests neuroendocrine activation in inflammatory and remodeling processes in the lungs [18].

The role of anti-inflammatory peptides in the functioning of the bronchopulmonary system

Among the anti-inflammatory peptides, the most studied is the VIP, which causes vasodilation, has a pronounced bronchodilatory effect, has a positive effect on bronchial secretion and mucociliary clearance. The bronchodilation activity of the latter is 100 times higher than that of isoproterenol. It has been proven that VIP has a powerful anti-inflammatory effect and inhibits the migration of eosinophils [5, 11]. It is detected in the intestine, in the central and peripheral nervous system, cardiovascular, respiratory, urogenital and immune systems, as well as in the thyroid gland. VIP receptors are found in the smooth muscles of the pulmonary vessels, large bronchi, on the surface of epithelial and glandular cells, and are practically absent in the bronchi of small caliber. The latter is due to the lack of its influence on their tone. Their receptors are also present in the nerve fibers of normal lungs [8, 11]

In order to determine the VIP in the lungs in patients with BA, the lung tissue obtained during autopsy and lobectomy in 5 patients with BA and 9 without BA was examined. Conducted immunohistochemical staining of lung tissue for the detection of VIP and histological examination of at least 80 sections of lung tissue of each patient. VIP was detected in more than 92% of the sites from the lungs of patients without BA. It was not found in any of the 468 sections of lung tissue of patients with BA. It was noted a significant decrease in the number of VIP in the nerves in the tissue from the lungs in all patients with asthma. According to the authors, patients with asthma have a loss of VIP from the pulmonary nerve fibers. At the same time, it is unclear whether this loss is a cause or a result of BA [2].

A number of authors have established that IL-5, which is a key cytokine for BA, acts directly on the nociceptors of the respiratory tract and causes the release of VIP. VIP, in turn, stimulates CD4+ lymphocytes, resulting in a Th2 response and allergic inflammation of the bronchi. Nociceptors are believed to enhance pathological adaptive immune responses [29].

It has been established that immune-competent cells involved in the development of inflammation in the mucous membrane of the bronchi (eosinophils, mast cells, macrophages, neutrophils) have the ability to release peptide substances that block the secretion of VIP [11]. Some authors suggest that in patients with BA, active peptidases, released in a BPS, result in the destruction of some peptides, including VIP. It has also been proven that persistent respiratory syncytial infection causes significant changes in the peptidergic innervation of the respiratory tract, namely, in this category of patients, VIP-reactive nerve fibers decreased [27].

VIP may be considered as a new anti-asthma drug due to its bronchodilating activity, vasodilation and immunomodulating and anti-inflammatory effects [9, 11]. When systemic injection of VIP has its drawbacks, such as hypotension, heart rate reduction. There have been attempts to use VIP as a drug in patients

with asthma, however, its only and serious drawback, restraining its use in these patients, is a very short half-life after intravenous administration [9]. These peptide effects are minimized by inhalation administration. The development of highly active analogues of VIP and systems for their delivery to the respiratory tract is a promising direction for the pharmacotherapy of broncho-obstructive diseases, including BA. Confirmation of the latter is the successful use of inhalation administration of the powder derivative VIP - [Arg 15, 20, 21, Leu17] - VIP-GRR (IK312532). The drug showed its high anti-inflammatory efficacy on the bronchi in the experiment [8].

PACAP-38 as well as VIP has anti-inflammatory and bronchodilating effects. Its effects are mediated by three receptors associated with G-protein: PAC1R, VPAC1 and VPAC2, which have similarities with VIP. PACAP-38 and its receptors are present in the central nervous system and peripheral organs, including the endocrine system (adrenal glands, pancreas, ovaries, testicles), gastrointestinal tract, BPS, cardiovascular system, urinary system, and immune competent cells [21]. In the BPS, it is localized in the nerve fibers innervating the lungs. PACAP-38 released from peripheral nerve endings with neurogenic inflammation. Plays an important role in the functioning of the lungs. It is a powerful bronchodilator and causes marked dilatation of the pulmonary vessels. It plays the role of the regulator of respiration with the catecholaminergic system in the medulla oblongata [21]. It has been established that PACAP-38 reduces the release of inflammatory neuropeptides from nerve endings. Agonists PACAP-38 can also be considered as possible drugs for the treatment of asthma.

The effect of PHM on BPS was studied. It resembles the action of VIP. However, its bronchodilating activity is several times higher than that of the VIP, the vasodilating activity is somewhat weaker. Secretory function is more pronounced as well. This peptide can also be considered as a drug for the treatment of BA.

The neuropeptide "Y" was first isolated from the pig hypothalamus in 1982. Its abnormal regulation is associated with the development of a wide range of diseases, including obesity, hypertension, atherosclerosis, epilepsy, metabolic disorders, and many cancers [26]. At the end of the twentieth century, began to be widely studied in pulmonology. It is synthesized both in the peripheral and central nervous systems. The content of neuropeptide “Y” increases in the peptidergic nerves of the lower respiratory tract and sensory neurons. In the smooth muscles of the bronchi, their number decreases. The effect of the neuropeptide "Y" is closely related to the sympathetic nervous system. In patients with asthma, an increase in serum adrenaline, norepinephrine and neuropeptide "Y" was detected. Apparently, this peptide having a neuronal origin leads to the release of vasopressors, which is accompanied by vasoconstriction and bronchodilation. It plays an important role in the regulation of airway blood flow, smooth muscle contraction and modulation of the immune response. Its content increases in the airways of patients with asthma. According to the authors, the neuropeptide "Y" can participate in the regulation of cytokines and the cellular activity of immune cells in asthma. At the same time, it remains unclear whether such an increase in it is a protective or compensatory mechanism [24]. Although some authors suggest a protective role of the peptide in patients with asthma. A decrease in its quantity contributes to the hypersecretion of mucus in patients with asthma. The content of neuropeptide "Y" is increased in the bronchoalveolar lavage. There was an increase in the content of neuropeptide “Y” in the serum of experimentally allergenic mice. An inflammatory reaction of the respiratory tract was detected in these mice, which was confirmed by an increase in the content of neutrophils and eosinophils in bronchoalveolar lavage. A direct strong correlation was noted between the content of neuropeptide “Y” in the serum and an increase in the bronchoalveolar lavage of experimental mice of neutrophils and eosinophils. An increase in the level of neuropeptide “Y” in peripheral blood was attributed by the authors to increased inflammation of the airways in allergenized mice [20].

In recent years, the role of ANP has been studied. Its receptors are found in the lung tissue, expressed by type II pneumocytes. Its concentration in the blood plasma increases with severe exacerbations of asthma. Intravenous administration of it to experimental animals significantly reduced bronchospasm provoked by inhalation administration of histamine. It has been proven that ANP has a powerful bronchodilator effect. The disadvantage of this peptide is the short half-life, in connection with which the possibilities of inhalation administration of ANP for the purpose of bronchodilation and bronchoprotection are considered [7, 33].

Adrenomedullin was isolated in 1993 from human pheochromocytoma cells. It belongs to the family of PRCG and is an effective vasoactive peptide. It is detected in the blood, heart, blood vessels, lungs, kidneys, endocrine glands, cerebrospinal fluid. Its main properties are: vasodilation, diuretic and natriuretic effects, positive inotropic effect, inhibition of endothelial cell apoptosis, induction of angiogenesis, inhibition of cardiomyocyte apoptosis, suppression of aldosterone formation, anti-inflammatory effect and antioxidant activity. The physiological effects of adrenomedullin are mediated by the participation of type 1 receptors - PRCG. The amount of peptide increases during an attack of asthma. The peptide also acts as a bronchodilator. The effect of adrenomedullin on bronchoconstriction induced by histamine and / or acetylcholine in anesthetized guinea pigs in vivo was studied. At the same time, the peptide inhibited bronchoconstriction caused by acetylcholine and induced a prolonged bronchodilation response [3].

Conclusion. As the literature data show, the connection between the nervous, endocrine and immune systems is carried out by means of neuropeptides [22]. The classical definition of neuropeptides has been changed in recent years, since they are not produced exclusively by neurons, but are also synthesized by endocrine and immunocompetent cells. They are considered as neuroendocrine immune modulators and play an important role in the functioning of the general neuroimmune-endocrine system [23]. Thus, the discoveries of recent years make it possible to isolate the neuroimmune-endocrine mechanisms of the development of BA, i.e. combine neurogenic, immune and endocrine mechanisms into one.

Many peptide substances in animal experiments have proven their anti-inflammatory and bronchodilation effects. This allows us to consider them as possible drugs for the treatment of BA. A number of proinflammatory peptides, lead to the activation of the inflammatory process in the bronchi and bronchial obstruction through exposure through various receptors. The search for antagonists acting on these receptors is a new direction of anti-inflammatory and bronchodilatory therapy of asthma.

It is known that many anti-inflammatory neuropeptides reduce the inflammatory response by reducing inflammatory and regulating anti-inflammatory mediators. Anti-inflammatory neuropeptide receptors can also be promising targets in the treatment of BA [23].

Sometimes contradictory, but encouraging data on the possibility of using peptides as drugs in pulmonology open

up broad horizons in the treatment of patients with broncho-obstructive pulmonary diseases, including asthma.

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POINT OF VIEW

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EFFECTIVENESS OF 3D-MODELLING LABORATORY IMPLEMENTATION INTO THERAPEUTIC AND DIAGNOSTIC MEDICAL INSTITUTIONS

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The article presents the analysis of 3D modeling laboratory efficiency after its introduction in the departments of radio diagnostics. Prospects and risks of the work of this unit is presented in the study. The calculation of economic indicators shows that the payback is around 2 years, the breakeven point is 60 – 70 clients per month. Results obtained economically and technologically justify active deployment labs 3D simulation in medical institutions.

Keywords: healthcare, economy, 3D modeling.

Using of 3D-modeling in medical institutions has not yet become a routine procedure, but it is in this direction that a qualitative breakthrough in the field of personalized medicine is the most likely [11, 16] since a technological basis has already been formed for this and in the process of its practical testing it should additionally take shape relevant organizational, economic and ethical standards. In this regard, a systematic analysis of the effectiveness of the implementation of these decisions in medical practice is necessary [7, 8].

The department of radiation diagnostics, which is standard for Russian medical institutions [2], could be the most suitable unit for the implementation of 3D modeling and printing. Firstly, a 3D modeling group is better positioned as an independent technological unit bearing in mind its transformation into a separate laboratory in the event of a significant increase in the volume of work [8, 13, 14]. It should be noted that the trend of increasing volumes of medical activity using medical imaging, and data processing technologies with an ever-growing consumer market has been observed everywhere in the last decade [18]. For example, steady increase in mortality from malignant neoplasms of the brain and spinal cord recorded in Russia requires significant optimization of their diagnosis and treatment [1]. Due to the rapidly improving Big Data technologies, increasing the productivity of electronic computing power, it is possible to overcome the lack of radiation diagnostic data and accelerate digital processing [15]. High quality hardware / software complex, management and good work organization aimed at achieving continuous improvement of preanalytical, analytical, and postanalytic phases in diagnosis are an integral guarantee of making a correct diagnosis (Table 1).

Today, it has already become possible to qualitatively supplement and improve the differentiation of diseases of various genesis with the help of slicer programs that convert 2D data of radiation diagnostics into full-fledged three-dimensional models, so the doctor has a chance to carry out preliminary surgical preparation and choose the most effective and optimal tactics for performing surgical operations with minimal risk for the patient and a decrease in the trauma of healthy tissues. Successful high-quality recognition of diseases of various origins in the radiation laboratory complex also reduces the need for repetition of studies and time saving, leading to an increase in the efficiency of staff and the medical institution as a whole [3, 10, 12, 17].

The main threats to the work of the 3D modeling laboratory are hacking and theft of information by hackers (Table 1). This problem can be solved by using more advanced cryptography algorithms, using specialized security software, Blockchain technologies and integrated security systems for user authentication [4, 5, 9].

The introduction of the laboratory with the addition of information processing of data can improve the organization of labor, save time and more carefully control of the research process [6, 19]. At the first stage, this new technology requires additional investments, the financial viability

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Table 1

Analysis of prospects for the implementation of 3D modeling laboratory

	Opportunities	Threats
Strengths	Increased productivity and lower costs resulting from using of machine learning, categorization, artificial intelligence algorithms	Certified software and integrated security systems
Weaks	Dependence on electronic computing power and access to specialized databases	Imperfection of authentication and personification systems when working with databases

of which can be characterized by comparing the expected costs and revenues [13]. The time variation of these economic values in relation to the economic conditions of the Primorsky Krai is presented in Fig.: for the 3D modeling laboratory, the payback period is about 2 years, the break-even point is 60-70 clients per month; the net present value with a rate of 10% and an investment of 500,000 rubles is 187,734 rubles (Table 2).

The creation of a 3D modeling laboratory in medical institutions as an additional module to the department of radiation diagnostics or autonomous education allows us to significantly expand existing methods of non-invasive examination and use them in the areas of preoperative planning and prosthetics. The results obtained during the work economically substantiate the creation of this laboratory in hospitals and clinics to improve the quality of medical services to the population.

Table 2

Economic indicators (rubles) for the 3D modeling laboratory

Indicator	Months											
	2	4	6	8	10	12	14	16	18	20	22	24
Profit from 1 client	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500
Number of customers per month	63	56	70	43	73	73	53	63	73	43	73	73
Total revenues	157500	140000	175000	107500	182500	182500	132500	157500	182500	107500	182500	182500
Payment of utility services	50000	50000	50000	50000	50000	50000	50000	50000	50000	50000	50000	50000
Salary	75200	75200	75200	75200	75200	75200	75200	75200	75200	75200	75200	75200
Payment for communication services	1500	1500	1500	1500	1500	1500	1500	1500	1500	1500	1500	1500
Taxes	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000
Cost of raw materials	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000	10000
Capital expenses	565000	0	0	0	0	0	0	0	0	0	0	0
Equipment depreciation costs	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000
The total cost of production	711700	146700	146700	146700	146700	146700	146700	146700	146700	146700	146700	146700
Hospital net profit	-554200	-6700	28300	-39200	35800	35800	-14200	10800	35800	-39200	35800	35800
Discounted flow	-511530	-6180	26120	-36180	33040	33040	-13110	9970	33040	-36180	33040	33040
Amount of initial investment	250000	0	0	0	0	0	0	0	0	0	0	0
Profit / loss for an individual entrepreneur	-1473230	-1333230	-1158230	-1050730	-868230	-685730	-553230	-395730	-213230	-105730	76770	259270
The total cost of production	656700	91700	91700	91700	91700	91700	91700	91700	91700	91700	91700	91700
Hospital net profit	-499200	48300	83300	15800	90800	90800	40800	65800	90800	15800	90800	90800
Discounted flow	-460760	44580	76890	14580	83810	83810	37660	60730	83810	14580	8381	83810
The amount of secondary investment	250000	0	0	0	0	0	0	0	0	0	0	0
Profit / loss for the hospital	-1367460	-1227460	-1052460	-944960	-762460	-579960	-447460	-289960	-107460	40	182540	365040

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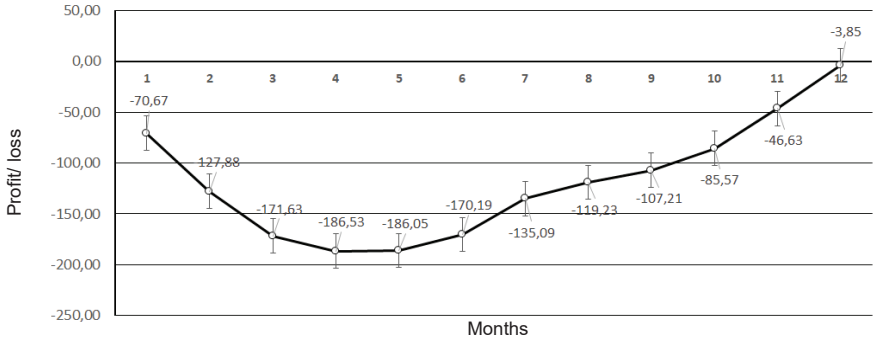

Profit / loss dynamics in the process of introducing a 3D modeling laboratory in state medical institutions

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ETHNIC AND AGE-RELATED CHARACTERISTICS OF NEUROLOGICAL SYMPTOMS AND FUNCTIONAL STATE OF THE KIDNEYS IN ELDERLY AND SENILE AGE PEOPLE OF YAKUTIA

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The study was conducted in patients of elderly and senile age, representatives of the indigenous and non-indigenous ethnic group. It has been established that the development and progression of chronic cerebral ischemia occurs in parallel with the progression of chronic kidney disease. At the same time, representatives of the non-indigenous population showed more severe neurological symptoms due to structural changes in the cerebral vascular bed due to hypertension and atherosclerosis, as well as severe renal dysfunction. Evens had milder clinical symptoms of chronic cerebral ischemia and lower renal abnormalities.

Keywords: ethnos, elderly and senile age, chronic brain ischemia, chronic kidney disease.

The problem of cerebro-renal interactions in elderly and senile age patients suffering from chronic cerebral ischemia (CCI) in modern medicine is relevant primarily due to the large medical and social significance. This is due to the fact that impaired renal function plays a significant role in accelerating the development and progression of CCI associated with atherosclerosis and arterial hypertension [1]. The high prevalence of CCI is explained not only by demographic changes in modern society with an increase in the proportion of elderly and senile age people, but also by an increase in the prevalence of risk factors, which include arterial hypertension, atherosclerosis, diabetes and obesity [3]. It is known that each ethnic group of the population determines its own characteristics in the epidemiology of a disease. CCI in combination with chronic kidney disease (CKD) is no exception.

The aim of the study was to research the ethnic and age-related characteristics of neurological symptoms and functional state of the kidneys in elderly and senile age people of Yakutia.

Materials and research methods.

This study was performed in the confines of the neurological department of the Geriatric Center of the Republican Hospital of Sakha (Yakutia) "Republican Hospital №3". 522 patients from 60 to 89 years, of comparable age and sex, were examined. CCI was diagnosed according to the Classification of Vascular Brain Lesions of the Institute of Neurology, Russian Academy of Medical Sciences (1985), the diagnosis was worded in accordance with ICD-10. The criterion for the diagnosis was instrumentally con-

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firmed lesion of cerebral vessels with the corresponding clinical picture of the stages of CCI in accordance with the classification of E.V. Schmidt (1985) - patients with chronic cerebral ischemia stage I (CCI I) and patients with chronic cerebral ischemia stage II (CCI II).

The following diseases were excluded:

- identified malignant neoplasms or operations for such pathology in the patient's medical history;
- diseases of the blood system, including anemia;
- angina pectoris of the 4th FC, as well as acute myocardial infarction (up to 40 days), the presence of congestive heart failure of the 3rd and more functional class (NYHA, New York, 1964);
- Alzheimer's disease and vascular dementia;
- chronic renal failure >3rd stage according to M.A. Ratner;
- acute inflammatory pathology of the articular apparatus;
- chronic obstructive diseases of the bronchopulmonary apparatus with respiratory failure (RF) stage II-III and manifestations of chronic pulmonary heart disease;
- obliterating arteriopathy of the lower limbs stages III-IV according to Fontaine.

Strict elimination criteria are justified by the fact that the clinical manifestations of the diseases listed above come to the forefront, changing the clinical picture and the course of chronic cerebral ischemia.

All patients were divided into three ethnic groups:

1st group - 174 patients of the Even nationality (representatives of small indigenous peoples of the North), living in the Arctic zone. 87 people were in the subgroup of CCI I, CCI II - 87.

2nd group - 177 patients of the Yakut nationality (CCI I - 90, CCI II - 87),

3rd group - 171 patients of the Russian nationality (CCI I - 86, CCI II - 85).

The age of the examined patients ranged from 60 to 89 years; the average age of the examined was 72.7 ± 7.2 years, for men - 72.9 ± 7.2, for women - 72.6 ± 7.2 years. The age groups were formed based on the WHO classification: early elderly people - 60-74 years, late elderly people - 75-89 years.

In order to study the functional state of the kidneys and assess the severity of chronic kidney disease (stage) in patients with different stages of CCI, depending on ethnicity, the level of glomerular filtration rate was calculated, the parameter most correctly (in the form of one specific numerical value) reflecting global kidney function. The speed of the glomerular filtration rate was determined by two computational methods with the subsequent determination of the stages of chronic kidney disease:

Cockcroft&Gault

GFR (ml/min) = (140-age) × body weight (kg) × E blood creatinine (μmol/l),

where E-1,23 for men and 1,04 for women

MDRD:

GFR (ml/min/1.73 м2) = 186 x (serum creatinine (mg/dL)-1.154 x (age)-0.203 x (0.742 for women).

The stages of chronic kidney disease were determined in accordance with the classification of the National Kidney Foundation of the USA [4].

Statistical processing of the research results was performed using the SPSS 19.0 software package. To describe the quantitative data, an average value with a standard deviation was calculated. Qualitative attributes are presented in the form of frequency tables containing absolute values and the relative share of the attribute (percentage). Verification of the laws of distribution of quantitative traits for compliance with the normal law was performed using the Kolmogorov-Smirnov test. The test results showed that the distribution of the studied parameters differs from the normal distribution. The Mann-Whitney paired test was used to compare the average values of the studied parameters. In all statistical criteria used, the value of p <0.05 was taken as the threshold level of significance.

Results and discussion. The main **objective** of our work was to study the functional state of the kidneys, which was determined by the decrease in the glomerular filtration rate, a parameter that most correctly (as one specific numerical value) reflects global kidney function, and an assessment of the severity of chronic kidney disease (stage) by the glomerular filtration rate [2]. The value was determined by two computational methods with subsequent determination of the stages of chronic kidney disease.

Table 1

Distribution of patients with chronic cerebral ischemia by ethnicity and age groups

Age group	Evens n=174		Yakuts n=177		Russians n=171	
	n	%	n	%	n	%
CCI I						
60-74 years	42	48.3	61	67.8	54	62.8
75-89 years	45	51.7	29	32.2	32	37.2
CCI II						
60-74 years	46	52.9	58	66.7	40	47.1
75-89 years	41	47.1	29	33.3	45	52.9

As shown in table 2, manifestations of renal dysfunction with glomerular filtration rate from 58.78 to 77.87 are observed in all patients with CCI, a more pronounced decrease in renal function is observed in the representatives of the 3rd group in both computational formulas. In patients of the 1st group, the glomerular filtration rate is higher than in patients of the 2nd and 3rd

Table 2

The average value of glomerular filtration rate by calculation formulas (unit)

Formula	Subgroup	Evens		Yakuts		Russians		P_{e-ya}	P_{e-r}	P_{ya-r}
		M	m	M	m	M	m			
Cockroft&Gault	CCI I	74.21	2.34	72.19	2.26	72.64	2.57	0.536	0.652	0.895
MDRD		77.97	2.48	72.54	2.23	73.93	2.63	0.669	0.991	0.687
Cockroft&Gault	CCI II	70.06	2.31	65.05	2.22	58.78	2.25	0.121	0.001	0.005
MDRD		77.87	7.17	66.52	2.29	67.87	10.00	0.194	0.416	0.895

Note: M - average value, m - standard error of the mean

Table 3

The average values of glomerular filtration rate, depending on age and ethnicity

	Calculation formula	Evens		Yakuts		Russians		P_{e-ya}	P_{e-r}	P_{ya-r}
		M	m	M	m	M	m			
CCI I	60-74 years									
	Cockroft&Gault	91.81	2	81.72	2.29	86.54	2.08	0.002	0.078	0.127
	MDRD	90.25	2.96	81.89	2.25	85.87	2.29	0.025	0.521	0.66
	75-89 years									
	Cockroft&Gault	57.79	2.15	53.13	2.40	49.18	2.81	0.092	0.016	0.434
	MDRD	58.78	2.19	52.88	2.41	50.40	2.71	0.083	0.018	0.501
CCI II	60-74 years									
	Cockroft&Gault	78.10	2.86	70.67	2.57	70.79	2.96	0.057	0.81	0.976
	MDRD	78.27	2.89	74.44	2.68	69.9	20.65	0.145	0.552	0.319
	75-89 years									
	Cockroft&Gault	61.04	3.21	53.80	3.44	48.10	2.43	0.136	0.002	0.169
	MDRD	77.42	14.97	54.88	3.43	48.29	2.42	0.213	0.048	0.123

groups. Statistically significant differences were observed in patients with CCI II in Evens and Yakuts compared with Russians.

Old age and CCI increasing severity decreases GFR in all ethnic groups (table 3). In Yakuts and Russians with CCI I and CCI II of all age groups GFR is lower compared with the Evens. Significant differences were noted in patients with CCI I of the Yakut nationality compared with Evens in the elderly (60-74 y/o) age group and in Russians compared with the Evens in the senile (75-89 y/o) age group according to the two computational formulas. In patients with CCI II, statistically significant differences were noted only in Russians aged 75-89 years compared with the Evens in the same group. Decrease in GFR, depending on the stage of CCI, is less pronounced in Evens, more in Russians, Yakuts occupy an intermediate position.

Evaluation of the functional state of the kidneys in patients using the computational formulas revealed a high incidence of the formation of chronic kidney disease in patients with CCI. In our opinion, the cause of such relationships may be the parallelism of atherogenesis processes.

Thus, in patients with CCI, both in stage I and stage II, in the elderly and the senile, the best indicators of kidney function are observed in Evens rather than in Yakuts and Russians. Moreover, with age, the severity of chronic kidney disease increases in parallel with the stage of chronic cerebral ischemia in each ethnic group.

We also carried out a comparative analysis of the dependence of the neurological symptoms of chronic cerebral ischemia on the mean value of the glomerular filtration rate in the elderly and senile, taking into account national identity and age group (Table 4). We have

Table 4

Neurological symptoms in the studied patients by age depending on the magnitude of the glomerular filtration rate

Neurological symptoms	Evens		Yakuts		Russians		P_{e-ya}	P_{e-r}	P_{ya-r}
	M	m	M	m	M	m			
60-74 years									
Vestibulopathy	74.81	4.26	70.83	3.63	71.83	3.54	0.083	0.595	0.844
CCF	82.28	2.29	76.04	1.91	78.53	2.05	0.039	0.225	0.377
Extrapyramidal syndrome	85.95	9.47	65.86	9.45	51.56	11.34	0.19	0.083	0.381
MCI	76.11	4.55	71.10	3.39	71.50	4.17	0.384	0.462	0.941
POR	41.04	2.96	39.09	4.83	54.45	17.87	0.753	0.589	0.544
Ataxia	77.62	4.03	73.30	3.67	72.52	4.18	0.432	0.385	0.889
Pyramidal syndrome	77.32	4.19	71.79	3.23	71.95	3.52	0.303	0.334	0.973
Pathological reflexes	50.00	9.12	36.77	2.20	43.32	3.65	0.282	0.552	0.209
Vegetative symptoms	84.07	3.92	78.20	5.04	82.87	2.48	0.368	0.798	0.418
Sensory disorders	85.04	5.14	76.45	4.99	80.01	3.86	0.238	0.441	0.575
Reflex asymmetry	89.35	5.51	85.24	3.70	85.48	3.78	0.544	0.570	0.965
Vestibular-ataxic disorders	95.55	4.31	85.57	3.21	92.50	3.74	0.078	0.60	0.172
Changes in muscle tone	102.09	5.50	86.95	7.56	84.66	5.04	0.141	0.044	0.807
75-89 years									
Vestibulopathy	59.87	4.36	54.78	7.64	47.78	2.71	0.576	0.026	0.417
CCF	59.20	2.39	53.13	2.26	49.71	1.95	0.069	0.003	0.256
Extrapyramidal syndrome	79.85	6.69	37.28	1.05	52.29	5.27	0.125	0.235	0.035
MCI	60.47	6.31	55.02	4.14	48.75	3.41	0.408	0.124	0.250
POR	41.41	2.29	38.79	6.04	54.83	6.77	0.742	0.101	0.152
Ataxia	56.33	4.74	52.92	4.08	48.10	3.23	0.590	0.161	0.361
Pyramidal syndrome	62.93	4.52	54.34	5.50	44.89	2.41	0.239	0.001	0.134
Pathological reflexes	39.29	1.25	38.23	1.43	40.97	2.29	0.588	0.537	0.335
Vegetative symptoms	54.54	4.23	50.07	4.12	41.93	3.02	0.457	0.022	0.429
Sensory disorders	61.68	5.93	51.54	4.61	49.69	3.50	0.192	0.098	0.751
Reflex asymmetry	56.81	6.23	52.44	3.15	51.38	5.95	0.547	0.540	0.879
Vestibular-ataxic disorders	54.05	5.20	53.47	3.33	55.20	4.36	0.926	0.818	0.756
Changes in muscle tone	49.55	4.21	50.24	1.87	45.66	8.78	0.809	0.846	0.657

identified changes in the clinical picture, neurological status. Persons of Russian nationality had more pronounced changes in the clinical picture of neurological symptoms.

At the same time, according to the symptoms, high numbers of GFR are observed in elderly Evens, except for primitive oral reflexes (POR). Yakuts have low GFR, except for extrapyramidal syndrome, ataxia and changes in muscle tone. Russians have a high GFR with POR, a low with extrapyramidal syndrome, ataxia.

Among the senile, the Evens have a more favorable clinical picture, with the exception of POR, pathological reflex, vestibular-ataxic disorders (VAD), changes in muscle tone. Renal dysfunction is expressed in Russians, apart from extrapyramidal syndrome, POR, pathological reflexes, VAD. Late elderly Yakuts occupy an intermediate position, except for the extrapyramidal syndrome, POR, pathological reflexes, VAD, where there are lower rates of GFR.

An interesting fact is that in the elderly the low rate of GFR is observed in representatives of all nationalities with POR and pathological reflexes, which explains the parallelism of the stages of CKD and CCI.

In the senile Evens, GFR is reduced with all objective symptoms of CCI, except for the extrapyramidal syndrome, it is mild cognitive impairment (MCI), pyramidal syndrome, and sensory disorders. A more pronounced decrease in GFR is also observed in representatives of all nations with POR, pathological reflexes, in addition, in Evens, with the changes of the muscle tone, in Yakuts with extrapyramidal syndrome, ataxia, in Russians with vestibulopathy, CCF (craniocerebral failure), MCI, ataxia, pyramidal syndrome, and sensitive disorders, change in muscle tone.

Thus, the presence of chronic kidney disease was associated with the most pronounced cognitive and neurological disorders, and a worsening of symptoms with the severity of CCI was noted.

Conclusion. Based on our study, it can be stated that in the studied elderly and senile age patients, the development and progression of chronic cerebral ischemia occurs in parallel with the progression of chronic kidney disease. At the same time, more severe neurological symptoms were discovered in the representatives of the non-indigenous population due to structural changes in the cerebral vascular bed due to arterial hypertension and atherosclerosis, as well as severe renal dysfunction. The Evens, the indigenous inhabitants of the northern regions of Yakutia, who retained a calmer, more traditional lifestyle and nutrition of the peoples of Yakutia, had lighter clinical symptoms of chronic cerebral ischemia and lower renal abnormalities.

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DISTRIBUTION OF CARRIERS OF "INDO-EUROPEAN" HAPLOTYPES OF HLA SYSTEM ON THE TERRITORY OF EURASIA

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The age of the "Indo-European" haplotypes HLA-A1/B17 and HLA-A1/B8 is calculated for different populations of Eurasia. The obtained data are compared with historical events. The results show that the most ancient carriers of the HLA-A1/B17 haplotype are Latvians, and the HLA-A1/B8 haplotype are the Turks. The distribution of the HLA-A1/B17 haplotype in populations is consistent with the migration patterns of Indo-European tribes. This is not observed for HLA-A1/B8; therefore, it has been suggested that the majority of Indo-European tribes did not have this haplotype.

A definition of allele frequencies is proposed by directly counting the number of haplotypes by alleles without using the Bernstein formula.

Keywords: Inlo-Europeans, HLA system, haplotype, population, founder effect.

Since the 70-s of the last century, antigens of the HLA system have been widely used for genetic characterization of populations along with other polymorphic systems. On the basis of allele frequencies, similarities or differences between individual populations were identified, and phylogenetic trees were constructed. At the end of the 20th century, a new approach to the study of population genetics appeared, called genetic archeology. The new approach pays great attention to the study of haplotypes, since it can provide more specific information about some population events.

For the new approach, the HLA system with highly polymorphic and closely linked loci is a very convenient tool for studying the genetic history of populations. From the literature data on the frequencies of alleles and haplotypes of the HLA system from different populations, one can determine the critical moments in their history, the age of expansion of those or other haplotypes, and associate them with a specific historical event.

According to V.V. Fefelova [23] L. Degos and J. Dausset believed that the *HLA-A1* and *HLA-B8* genes, also HLA-A1/B8 haplotype are Indo-European, since they appeared in Europe together with Indo-European tribes. At the time, Indo-Europeans in Siberia distributed the haplotype HLA-A1/B17. Therefore, this paper discusses the distribution of haplotypes HLA-A1/B17 and HLA-A1/B8 over the territory Eurasia.

To calculate the age of the haplotype in population, the formula according to [3] is used:

$S_{1/2} = 1 - p^{1/n}$,

where S is the genetic distance between the loci under study, p is the level stability (the proportion of chromosomes

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that preserve the founder chromosome), n is the number of generations between the founder chromosome and modern chromosomes.

The genetic distance (S) between the HLA-A and HLA-B loci is 0,8 cM. To determine the level stability (p) of the haplotype under consideration, one should first find out its initial (maximum) equal to the square root of its theoretically alive frequency, that is $h_1 = (h_A h_B)^{1/2}$, where h_A is the allele frequency, component of the haplotype from locus A, h_B is the frequency of allele, component of the haplotype from locus B. The value of h_1 can also be calculated using the linkage disequilibrium value of the haplotype *D* as follows: $h_1 = (h_2 - D)^{1/2}$, where h_2 is modern, that is, the observed frequency of the haplotype, D is the delta value or magnitude of the linkage disequilibrium. The level of stability (p) will be equal to the fraction of the modern, that is, the observed frequency of the haplotype h_2 from its initial frequency h_1. The ages of the studied haplotypes calculated in this way in a number of populations are shown in Table 1.

As can be seen Table 1, of the population examined here, the first haplotype HLA-A1/B17 began to split from the ancestors of Latvians about 9200 years ago and from them fell to the ancestors of Russians and Ukrainians and further spread to other peoples. The haplotype HLA-A1/B8 first appeared among the ancestors of the Turks 7846 years ago and spread exclusively throughout Europeans. The Mongoloids and Pakistanis do not have this haplotype, and Latvians began to multiply only 40 generation ago. Buryats and Sherpas have no HLA-B8 allele.

According to current calculation, the haplotype HLA-A1/B8 in Latvians began to multiple about 1000 years ago. In the history it is just noted that at the end of the first millennium AD as a result of the wars between the stronger western and eastern neighbors of the Latvians, very little remained, and their number began to increase after partial assimilation by the Belarusians and the Russians.

At the end of the I millennium AD major changes took place in the life of the ancient Latvian tribes: feudalism, a new socio-economic formation, began to take shape, while the territory of Latvia became the crossroads of trade routes. Russian merchants walked along the Daugava up to its lower reaches and by land from Pskov and Novgorod. Consequently, it is quite legitimate to assume that the impetus for an increase in numbers after a strong decline was their acquisition of the HLA-A1 / B8 haplotype from Russian merchants as a result of the development of trade.

HLA antigens in Turks were studied by two group of authors. Albert et al. [22] investigated 162 Turkish workers and students working in Germany, and as a control group – 442 Germans. The group of Turks was from different regions of Turkey, most of them were from rural areas. The persons included in study of A. Svejgaard were also from different places in Turkey, but from urban areas. In total there were 119 samples, of which 117 were not relatives.

At first glance, the results of the two groups of authors seemed to differ, but due to the small samples analyzed, these differences turned out to be unreliable. According Albert et al. HLA-A1/B17 haplotype is estimated to be 4020±870 years old, and according to A.Svejgaard et al. 3600±900; HLA-A1/B8 age – like 7800±1900 and 5870±1400 years ago, respectively.

The splitting of the HLA-A1/B17 haplotype in the ancestors of Belorusians, Komi, Germans, Pakistanis and Turks coincides with the movements of the first nomads of Europe – Indo-European tribes in III millennium BC. Iranian tribes went to Iran, Afghanistan, Indo-Arians went to India, the Hittites invaded Asia Minor, and the Celts moved to Western Europe [4].

The arrival of theHLA-A1/B8 haplotype in ancestors of Germans in the VII century AD due to the seizure of land by the Slavs east of Elbe with the partial assimilation of German population. This was facilitated by the great migration of peoples. This is the name of the combination of ethnic movements in Europe in the IV – VII centuries, caused mainly by the general cooling of the climate. People from areas with continental climate rushed to areas with a milder climate. Wars, frequent floods, crop failures, famine epidemics greatly reduced the population of Western Europe in VI, VII centuries.

The studied I.G. Udina and G.S. Rautian three Komi groups here are combined into one population. As a result, the Komi haplotype ages turned out to be very close with the corresponding haplotype age in Belorusians. This suggest that the Komi and Belorusians have common ancestors 3-4 thousand years ago.

According to historical data, the first Indo-European tribes invaded the territory of modern Pakistan in the late II and early I Millennium BC, therefore the studied population is Caucasian. Therefore B.G. Solheim et al. [20] were surprised by the absence of haplotype HLA-A1/B8 in Caucasian population and highest frequency of non-Caucasian haplotype HLA-A10/B8 with a very high D-value.

Table 1

Age of haplotypes HLA-A1/B17 и HLA-A1/B8 in different populations of Eurasia

Population	A1/B17		A1/B8		A source
	n	years ago	n	years ago	
Latvians	368	9196	40	995	[14]
Russians (Moscow)	341	8525	78	1950	[15]
Russians (Nizhny Novgorod)	247	6187	78	1950	[10]
Ukrains (southeast)	283	7064	206	5140	[9]
Germans (Munich)	185	4625	54	1350	[22]
Belorusians (Minsk)	174	4350	117	2933	[5]
Komi	173	4325	114	2854	[16]
Turks a)	161	4020	314	7820	[22]
b)	144	3600	235	5870	[18]
Buryats	156	3900	no B8 allele		[23]. [11]
Spanish	147	3675	-	-	[23]
Tofs	129	3225	-	-	[23]
Turkмen	128	3200	-	-	[23]
French People	126	3150	89	2215	[13]
Pakistanis	108	2696	no A1/B8		[20]
Ashkenazi Jews	106	2650	-	-	[23]. [19]
Sherpa	104	2606	no B8 allele		[21]
Indiaan Hindu	82	2050	-	-	[23]
Yakuts а)	63	1572	no A1/B8		[12]
б)	59	1489	no A1/B8		[23]
Basque	40	1000	-	-	[23]
Khanty	34	850	no A1/B8		[7]

Calculation from the data of B.G. Solheim et al. [20] showed that with the invasion of the Indo-Europeans in Pakistan, the haplotypes HLA-A1/B5 (since 980 BC) and HLA-A1B17 (since 724 BC) spread, and haplotype began to multiply later, since 312 BC. At the time, Pakistan was ruled by Persian Sassanid dynasty, which ruled from Asia Minor to Central Asia. At the end of III, beginning of the IV century a number of regions in East dis appeared from the Empire. These territories were conquered during the reign of Shapur II in 309-372 BC. Therefore, due to coincidence of time, Shapur II is supposed to be founder in Pakistan of the chromosome with the haplotype HLA-A10/B8.

From the data of Table 1 it is seen that the first Indo – European influence of the Siberian peoples were the Buryats - at the beginning of the II Millennium BC. Probably the ancestors of the Buryats gained haplotype HLA-A1/B17 with penetrated into Western Mongolia Indo-Europeans who inhabited this region in D. E. Eremeev [4] at the turn of III-II Millennium BC, the ancestors of Turkmens Tofs and this haplotype came seven centuries after drilled.

The emergence of the haplotype HLA-A1 / B17 in Western Europe – 3675 years ago in Spain and 3150 years ago in France, in all probability, due to the Celts. They caused a great genetic change in Spain – with their conquest, the men before them in the Iberian Peninsula completely disappeared from the gene pool, as can be seen from the Y-chromosome ["New Scientist"].

The Celts were called Gauls by the Romans. Apparently, they gave the French the haplotype HLA-A1/B8 – 236 BC during the first Millennium BC the Greeks, Romans and Carthaginians had established colonies on the Mediterranean coast and coastal Islands. The Roman Empire captured the southern part of Gaul and turned it into a province called Norbonne Gaul.at the end of the II century BC.

The population of Ashkenazi Jews passed through the "bottleneck" of a small number 106 generations ago, after which the haplotype HLA-A1/B17 began to multiply. At this time, the Kingdom of Israel was greatly weakened by the division into two kingdoms – Jewish and Israeli, and by rivalry between them. This was not slow to take advantage of the neighbors.

First, the Egyptian Pharaoh Sheshonk II raided Judea, took Jerusalim and robbed many other cities of the country. In 722 BC, the capital of the Northern Kingdom of Israel – Samaria-was defeated by the warriors of Assyria, and its population was resettled by the Assyrians in media and there was lost among the surrounding peoples. In 586 BC the Babylonians conquered the Kingdom of Judah, destroyed the temple of Jerusalem, and took the color of its population to Babylon (the Babylonian captivity). 70 years later, due to the generous Cyrus of Persia, who broke the power of Babylon, the Jews were able to return to their land and build a new Temple in Jerusalem, which helped to restore the number of Jews.

In 1972, the Sherpas had a population of approximately 13,000 living in solu Khumbu in the Eastern Nepal region. Sherpas come from a small group of families who, according to historical documents, came from the city of Salmo Ganges in the Eastern Tibetan province of Han and who migrated West to settle in the high valleys near Everest. This migration occurred around 1530 A.D. the Sherpas ' Single families established so-called tribal villages where only members of the clan's family, not foreigners, are allowed to live. Clans of Sherpas was established in strictly patrilineal fashion, which in the genealogies record the names of only through the male line. Sherpas marry only members of other Sherpas clans, but do not mix with other populations. The rule of exogamy is very strictly enforced. Therefore, inbreeding does not occur in the Sherpa population [21]. As can be seen from table1, Caucasian haplotype HLA-A1/B17 introduced Sherpa 104 generations ago in 624 BC, that is, in the Eastern Tibetan.

The expansion of the haplotype HLA-A1 / B17 in Hindus (2050 years ago) historically coincides with the formation of the Indo-Saka state, which began with king Maues. According to numismatic data, beginning his rule applies no later than the middle of the I century BC. After Maues there were five kings in this dynasty [2].

Previously it was published that the Yakuts have mainly Mongoloid antigen frequencies of the HLA system, and the Indo-European haplotype HLA-A1/B17 began to split them 70 generations ago. This result was obtained from the work of V. V. Fefelova [23] by calculating the frequency of genes from the frequency of antigens according to the formula $h = 1 - \sqrt{1 - f}$. But in the Table 3 in Fefelova there is no blank graph and the sum of haplotype frequencies by alleles. Because of this, it is impossible to understand whether the number of chromosomes corresponds to the number of people in alleles. The article shows that the antigen A1 was found in 97 people and B17-in 96, and the sum of chromosomes with such alleles turned out only 92. It is clear that 5 people have haplotype A1/Bx and 4 people – Ax / B17. In the same way, it can be understood that 12 people are carriers of the haplotype Ax/B27 (Table 2)

Layout by haplotypes shows that the actual frequency of alleles in the work of V. V. Fefelova other than that specified in article, for example, the frequency of A1 is 01414, not 0,1531, frequency B17 – 0,1399, not 0,1514. With the correction of data, the age of the haplotype HLA-A1/B17 in Yakuts changes from 70 generations to 59. From this we can conclude that in such works a more accurate result will come out when the frequencies of alleles and haplotypes will be derived by direct counting after the layout of haplotypes in the lattice, without the use of Bernstein's formula $h = 1 - \sqrt{1 - f}$.

In the paper "About the Yakuts origin…" (Genetics, 2004), we hypothesized that the haplotype HLA-A1/B17 fell to the Yakuts, as well as to the Indians, from the Saks. You can still add the hypothesis that the introduction of this haplotype with the Huns. When comparing the English language belonging to the German group of languages and the Yakut language belonging to the Turkic group, the matches of the words of the compared languages in sound and meaning were revealed. Therefore, linguists express the ancient historical connection of the Huns (Turkic-speaking tribes) with the Germanic tribes. It is known that the Huns in the 70s of the IV century, subordinated a number of Germanic tribes. Among turkologists there is an opinion that the direct descendants of the Hun substrate of those times are modern Yakuts, as part of the Huns migrated to the East, to Central Asia and further [17].

Basques – a people that lives in the mountains and the Atlantic ocean between Spain and France and speaks in cryptic language eskuara. The strange thing is that the Indo-European haplotype HLA-A1/B17 was introduced to the Spaniards 3675 years ago, the French 3150 years ago, and the Basques only 1000 years ago. Indeed, in history it is noted that the Basques did not submit to any invader and kept their language and traditions, although they were pushed to the mountains and clamped to the ocean. According to the calculations of haplotype HLA-A1/B17 got to the Basque population in the period of the Reconquista. So called the process of winning the Iberian Peninsula from the yoke of Mauritania, which lasted from 718 to 1492.

In 905-925 Basque king Sancho Garc-

Table 2

Distribution of haplotypes in Yakuts (n = 343)

HLA		A1	A2	A3	A9	A10	A11	Aw19	A28	Ax	Total
	N	97	183	35	186	24	19	7	1		
B5	*37*	0	16	3	7	2	1	1	0	7	37
B7	*16*	1	10	3	4	0	0	0	0	0	18
B8	*6*	0	2	1	2	4	0	1	0	0	10
B12	*31*	4	11	11	6	0	0	0	0	0	32
B13	*21*	6	5	0	15	0	2	0	0	0	28
B15	*126*	2	59	9	37	3	9	5	1	1	126
B16	*2*	1	0	0	2	0	0	0	0	0	3
B17	*96*	60	17	1	10	2	0	1	1	4	96
Bw22	*2*	0	0	0	1	0	1	0	0	0	2
B27	*59*	3	7	2	30	1	4	0	0	12	59
B35	*53*	7	23	4	25	3	0	0	0	0	62
B40	*139*	8	59	2	67	11	5	2	0	0	154
Bx		5	0	0	0	0	0	0	0	54	59
Total		97	209	36	206	26	22	10	2	78	686

Note: the number of samples is written in italics, otherwise the number of haplotypes.

es strengthens the Kingdom of Pamplona and proclaims the Kingdom of Navarra. It was one of the outposts of the Reconquista. Under Sancho III the Great (970-1035) the Kingdom expanded the borders of their possessions in the South and distributed the authority over all of Christian Spain. At this point, the Basque haplotype HLA-A1/B17 appeared. Therefore, Sancho III the Great can be considered to have spread in the Basque studied haplotype from Spanish Christians.

V.P. Alekseev points out that the resettlement of Indo-Europeans began in the south-east of Europe rushing west, they occupied all of Europe as far as the Atlantic. Part of the Indo-European tribes that spread to the north and east did not go further than the Ural Mountains. In this regard, the age of the HLT-A1 / B17 in Khanty is only 850 years old, showing the acquisition of the haplotype in the XII century.

Since the turn of the X-XI centuries, the role of fur hunting, acquiring commercial value, has been growing. In the X-XIII centuries, Komi-Zyryan and Russian Novgorod merchants, "industrial people" (fur hunters) penetrated to the north of the Urals and Western Siberia. In this regard, it is assumed the appearance of the European haplotype HLA-A1 / B17 among the Khanty from Russian or Komi-Zyrian traders.

Perhaps, the ancestors of the Russians were Indo-Europeans or faced Indo-Europeans in the 7th millennium BC in the steppes of the Black Sea or Caspian region. They could come on horseback from the Urals, as there at that time the horse was domesticated.

The most ancient remains of a domestic horse found in the southern Urals in the Parking lots of Mullino and Davlekanovo. They are dated by C-14 by the turn of VII-VI millennia BC [6]. This is also consistent with the opinion of most scientists who consider the black sea and Caspian steppes to be the probable ancestral home of Indo-Europeans. Then, at the beginning of the VI Millennium BC Indo-Europeans could conquer Eastern Anatolia.

Haplotype HLA-A1/B17 spread to all populations conquered by Indo-European tribes, and the time of its appearance coincides with historical events, but the appearance of haplotype HLA – A1/B8 - not quite often. The fact that the representatives of the Indo – Aryan people-Pakistanis this haplotype is absent, and migrated to Western Europe Celts spread there only haplotype HLA-A1/B17, indicates that neither the Arians nor the Celts haplotype HLA-A1/B8 was not.

Probably it arose by mutation only arrived in Asia Minor and the Hittites, and from them came the ancestors of the Ukrainians. The rest of the Europeans this haplotype spread much later. Probably, the frequency of HLA-B8 haplotype and the HLA-A1/B8 Europeans increased, as suggested by V. Bodmer, after the pandemics of plague, smallpox and cholera. It was later found that carriers of haplotype HLA-A1/B8/DR3 were highly resistant to infections regardless of the nature of their pathogens [8]. If this is the case, it is not the founder's effect, but the natural selection that changed the immunogenetic profile of Europeans in antiquity, the Middle Ages and the Renaissance as a result of epidemics.

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CLINICAL CASE

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CLINICAL CASE OF SUCCESSFUL APPLICATION OF REOSTEOSYNTHESIS STERNUM IN CHRONIC POSTOPERATIVE STERNOMEDIASTINITIS

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The authors described the clinical observation of postoperative sternomediastinitis. The feasibility of a two-stage surgical treatment of this pathology was noted: the first stage is the removal of ligatures and necrectomy of the sternum, the second is the resection of the sternum with plastic replacement of the wound defect. At the integrity of the sternum, the authors propose to perform surgical intervention, including the preservation of bone tissue, sternal rheosteosynthesis.

Keywords: osteomyelitis of the sternum, sternomediastinitis.

Postoperative sternal wound infections is a severe threatening complication of open cardiac surgery and it is associated with high mortality [2, 4]. Clinical experience of postoperative sternal wound infections treatment [1, 3, 5, 6] indicates the need for two-stage treatment of this pathology, due to the severe general condition of patients in the onset of the disease, the severity of concomitant chronic pathology and the inability to perform wound plastic operation in purulent necrotic infection conditions.

According to the accepted technique of treatment in the Regional Clinical Hospital №1 in Khabarovsk [5], the first stage is the wound surgical treatment, including the removal of foreign bodies, necrectomy of infected bone fragments of the sternum. Due to the inflammatory nature of the wound, it is not sutured and open treatment is carried out by bandaging. As the wound is cleaned, which is controlled macroscopically and microbiologically, the second stage is the extensive resection of the sternum with plastic replacement of the chest wall wound defect. However, it should be noted that it does not always achieve a positive result in the form of primary healing. In this regard, in our view, this clinical case of the reosteosynthesis execution in the process of two-stage treatment of the patient with postoperative sternal wound infections with a positive outcome would be interesting to experts.

18.04.18 Patient K. aged 70, first entered the Thoracic Department of the Regional Clinical Hospital №1 in Khabarovsk. At the time of admission, he complained of pain in the lower third of the sternum, the presence of fistulas in the middle third of the scar with purulent discharge. During examination: the chest in the region of the median line had the sternotomy immature scar in the lower third of which there was a fistula sized 0.2

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x 0.5 cm with purulent discharge. There was redness of the skin and swelling of the edges of the tissues around the fistula. At palpation moderate soreness in the lower third of the sternum was determined. SCT showed the features of the sternum subtotal osteomyelitis.

From the history of the disease: 2.04.2018 in the Federal Center of Cardiovascular Surgery in Khabarovsk, the sternotomic access surgery mammarocoronary bypass of the anterior descending artery, autovenous bypass of the artery of the blunt edge, posterior interventricular artery were performed. In the postoperative period, after discharging, 12.04.2018 there was redness of the skin on the sternal scar, the occurrence of pain, and 17.04.2018 in the lower third of the scar fistula with purulent discharge opened. He was examined by a thoracic surgeon and then sent to the Thoracic Department in Regional Clinical Hospital №1 for treatment. Anamnesis of life: Coronary heart disease: Stable angina of FC III. Postinfarction cardiosclerosis (2008). Atherosclerosis of the coronary arteries: the defeat of several vessels. Hypertension, stage III, degree 2, risk 4. CH2 A, II FC by NYHA. Prostate cancer T2NxM0, II CL. gr.. ICD (DT 2016). CKD 2 st. (GFR 68 ml/min). Chronic cholecystitis, adipose hepatosis, chronic obstructive pulmonary disease, remission phase.

The patient was hospitalized in the Thoracic Surgery Department with the acute postoperative sternal wound infections diagnosis (fistula formation). At the first stage of the treatment (18.04.18 - 25.05.18) a surgical revision of the wound was performed (24.04.18), the sternal ligatures were removed, the sanation of the mediastinum was performed. In the process of surgical intervention the consolidation of the sternum was not stated, the severe acute sternal wound infection was observed. In the postoperative period, open wound care was performed. The patient got a course of antibacterial (cefepime, ciprofloxacin, vancomycin), anti-inflammatory and cardiotropic therapy, bandages with antiseptics, including vacuum bandages, were used. As a result of the therapeutic measures, the patient's condition was stabilized, the discharge from the wound decreased, became meager and mucous. The microbiological spectrum of the wound allowed to continue further surgical treatment.

The patient returned to the hospital for the second stage (02.07.18 – 03.08.18) of the surgical treatment (Fig. 1). Taking

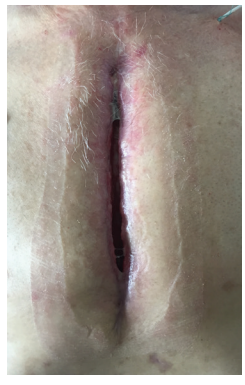
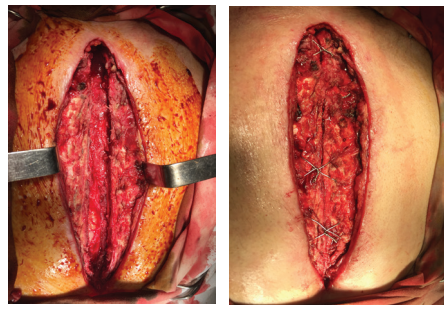


Fig. 1. Patient K., 70 years old: the appearance of a wound in the sternum area before the second stage of surgical treatment

the integrity of the sternum (there was an isolated fracture of the left half of the sternum) and absence of purulent changes in the bone tissue we decided to perform sternal rheosteosynthesis.

20.07.2018 there was the operation - mediastinotomy excision, the sternal rheosteosynthesis. In the process of surgery, the edges of the mediastinotomy were cut; the skin wound was expanded in the cranial direction to the edge of the sternal hilt. Fragments of the sternum were mobilized from the anterior mediastinum, while the right pleural cavity in the lower third of the sternotomy was opened. The drainage of the right pleural space was performed in the 5th intercostal space along the middle clavicle line of the PVC drainage valve along the Bulau. The revision revealed a transverse fracture of the upper third of the left half of the sternum. The thorough curettage of the surface of the sternal fragments with partial edge resection of the protruding edges, the scraping of the granulation tissue were conducted. The mediastinum was sanitized. The sternum fragments were fixed with three 8-shaped and one U-shaped sutures. The wound was sutured tightly. The postoperative period passed without complications, the patient got vancomycin, metrogil, kvamatel and cardiac medications. The pleural drainage was removed on the fifth day. The wound was healed by the primary intention. On the 14th the patient was discharged with detailed recommendations for further outpatient treatment.

Conclusion. In the treatment of sternomediastinitis, in our opinion, it is advisable to use a two-stage method of the surgical treatment: on the first stage it is necessary to perform a resternotomy,



a b

Fig. 2. a) Mobilized half of the sternum
b) Fixation of the sternum

remove foreign bodies and sequesters of the sternum; the second stage is the implementation of resection of the sternum with plastic replacement of the wound defect of the chest wall. In the case of the sternum integrity, the absence of pus and adequate microbiological purity of the wound the implementation of sternal rheosteosynthesis is justified as the second stage.

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EXPERIENCE EXCHANGE

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DETERMINATION OF THE THERMAL CHARACTERISTICS OF THE MATERIAL OF THE INSULATING SHEATH FOR THE TREATMENT OF COLD INJURIES

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In the treatment of cold injuries for maximum tissue recovery is very important temperature. The frostbitten area must be warmed up due to the natural heat exchange by the blood circulation, for this the condition of maximum thermal insulation of the affected area must be observed. The article describes the method and provides data on the laboratory determination of thermal conductivity and heat transfer resistance of the material from which the heat-insulating sheaths are made for treatment frostbitten limbs. The results were obtained by the method of stationary thermal conditions at the facility assembled in the department of heat and mass transfer processes of the IPTPN SB RAS. In this paper, a climate chamber, a precision "Tercon" signal converter and non-standard heat flux transducers of the PTP-1B type with integrated temperature sensors are used.

Keywords: climatic chamber, frostbite, low temperatures, heat insulation, thermal conductivity.

The Republic Sakha (Yakutia) is famous for its extremely low temperatures, it is here that the so-called "Pole of Cold" is located - Oymyakon village, where the air temperature in winter falls to -71.2°C. In severe climatic conditions, the problems associated with frostbite and hypothermia of people is of indisputable relevance. During the winter, about 200 people come to hospitals in the Republic of Sakha (Yakutia) with frostbite of the extremities and in a state of profound hypothermia. Proper, timely provision of medical care in the regions of the Far North is largely ensured by qualitative preliminary clinical and technical research [2].

The vast majority of cold injuries cause frostbite of the extremities. In case of severe frostbite of the extremities, for the maximum possible tissue repair, it is necessary to observe the condition of slow and gradual warming of frostbitten tissues due to natural heat exchange by the blood circulation. To this end, the injured limb is thermally insulated as much as possible and various means are used to accelerate blood circulation [1]. One of the original solutions is "Hotutent" developed and produced by the Yakut developer's multilayer insulating material.

The **purpose** of the work is to determine the thermal conductivity of a heat-insulating material "Hotutent", which is used as thermal insulation for extremities of people, who received frostbite under conditions of low climatic temperatures.

A rectangular sample of material "Hotutent" with dimensions of 29.5 cm by 26 cm was examined. The material is stitched through the seams and has a layered structure.

The structure of the material consists of 8 layers:

1. Outer layer: oxford fabric.
2. Bamboo heating insulation filler.
3. Insulation №1. Fuzz
4. Insulation number 2: Deer wool.
6. Bamboo heating insulation filler.
7. Oxford fabric.
8. Inner layer: heat reflective material (foil).

Thermal conductivity was determined by the stationary method at the facility assembled in the department of heat and mass transfer processes of the IPTPN SB RAS. To create a constant temperature difference across the sample thickness, the BINDER MK-53 climate chamber was used. The working temperature range of this chamber is from -40 to +180 °C. Thermostat accuracy in a chamber is ± 1 °C. One side of the plate is maintained at a negative temperature in the chamber of -30 °C, and the other side is at room temperature + 22 °C.

The temperature and heat flux were recorded using a multichannel, precision Tercon signal converter. Converter is coupled with IBM PC through a serial interface type RS -232 C , and allows you to record measurement data of heat fluxes and temperatures in the form of a table or graph.

PTP-1B converters, developed by the Institute of engineering thermophysics of the National academy of sciences of Ukraine (Kiev), were used to measure the heat flux. The PTP-1B sensor is a round thin plate made of a PCB with a diameter of 100 mm and a thickness of 2 mm with six leads. The PTP-1B sensor also contains a resistance thermometer, where the Pt 100 platinum thermometer with a nominal static characteristic W_{100} = 1.385 is used as sensitive element. The nominal value of the resistance thermometer at 0 °C is 100 Ω. The limit of permissible basic relative error of heat flux measurement is ± 4%, and the limit of permissible absolute error of temperature measurement is ± 0.5 K [3].

Such combined sensors are very convenient for use in the experimental determination of resistance to heat transfer and thermal conductivity of materials, since when placing them on both sides of the sample under study, we obtain a complete set of initial data for the calculation.

To place the sample in the boundary plane between the chamber and the room, an extruded polystyrene foam screen with a size of 550 × 550 × 100 mm was made with an opening in the center for the dimensions of the sample plate.

After reaching the specified negative temperature in the climate chamber, the value of which was chosen as - 30 °C,

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and the establishment of a stationary mode, data recording continues for another 5 minutes for calculations, we took the values of fluxes and temperatures averaged over this stationary period.

The value of thermal resistance to heat transfer is determined by the formula 1 [4]:

$$R_k = \frac{t_2 - t_1}{\bar{q}}, \qquad (1)$$

Where t_2, t_1, are temperatures on the warm and cold surfaces of the plate, °C; $\bar{q}$ - the average density of the heat flux W / m2, determined by the formula 2:

$$\bar{q} = \frac{u_2 K_2 + u_1 K_1}{2}, \qquad (2)$$

Where u_2, u_1 , – voltage signals from two heat meters, mV; K_2, K_1, – the corresponding values of the conversion coefficients, W / (m² · mV).

The value of thermal conductivity λ plate, W / (m·°C) is determined by the formula 3:

$$\lambda = \frac{h}{R_k}, \qquad (3)$$

Where - *h* is the plate thickness, m; R_K – calculated by the formula (1) thermal resistance to heat transfer, (m² ·°C) / W. The thickness h was taken as the average profile of about 3 centimeters.

In fig. 3 and fig. 4 shows the graphs of the development of the density of the heat flux and temperatures on the surfaces of the sample.

Thermal resistance to heat transfer of the heat-insulating material for isolation of frostbitten extremities is equal to 1.050 (m ² · K) / W. Thermal conductivity of the material corresponding to the given thickness is 0.028 W / (m · K).

These results confirm declared thermal insulation properties of the material. The obtained value of thermal conductivity is below the tabulated values of thermal conductivity of materials such as mineral wool and low density polystyrene insulation (0.045 W/(m*K)) [5].

Fig.1. Installation for measuring thermal conductivity

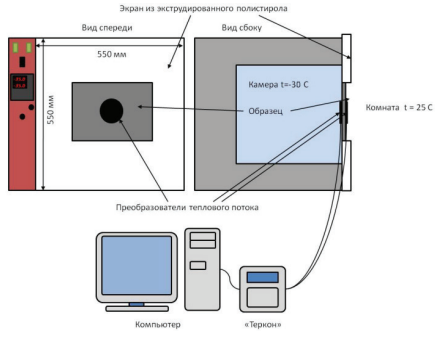

Fig.2. Diagram of the measurement setup

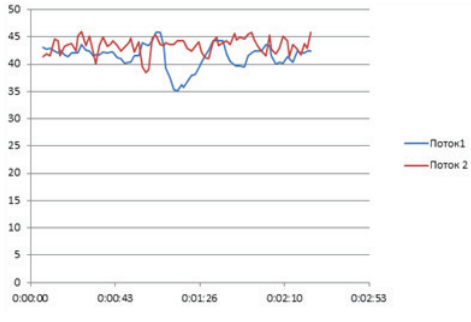

Fig. 3. Graphs of change in the density of the heat flux on the warm and cold sides of the sample on time

Fig. 4. The graphs change the temperature of the warm and cold sides of the sample over time

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COMPARATIVE ANALYSIS OF MAXILLOFACIAL AREA DISEASES, WHICH LED TO TEMPORARY DISABILITY IN DENTAL MEDICAL ORGANIZATIONS

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In this article the authors studied the temporary disability cases in patients with the maxillofacial area diseases that received treatment and rehabilitation in the dental medical organizations in the period of 2007-2016.

Methods.The groups of the maxillofacial area diseases that lead to restriction and/or loss of capacity for work of the adult population in the Republic of Tatarstan: inflammatory (of odontogenic and neodontogenic genesis), traumatic, benign and malignant lesions, secondary jaw edentulism (full or partial), as well as tooth eruption diseases.

Results. The odontogenic inflammatory processes made the largest share in the causes of temporary disability in patients of dental medical organizations (66.1% of cases), the injuries took a second place (13.9%), the secondary jaw edentulism observed in 7.4% of cases took the third place.

Conclusions. The authors found that during the period under study, the statistically significant changes in the duration of temporary disability cases with odontogenic inflammatory processes, tooth eruption diseases, secondary jaw edentulism, injuries and neoplasms were noted. The analysis showed statistically significant differences in the structure of temporary disability cases by nosological groups, depending on sex, age and year of observation.

Keywords: stomatology, dental medical organization, treatment and rehabilitation of patients, examination of temporary disability, maxillofacial area diseases.

Introduction. The examination of temporary disability (ETD) is a type of medical activity aimed at assessing the patient's health status, the quality and effectiveness of the treatment, the possibility of professional activities, determining the timing of temporary disability [3]. The examination of temporary disability in the Russian Federation is regulated by the following orders: On approval of Procedure for Issuing Sheets of Disability No. 624н dated June 29, 2011; On Introduction of Changes in Procedure for Issuing Sheets of Disability No. 31н dated January 24, 2012; On Approval of Procedure for Examination of Temporary Disability No. 625н dated August 23, 2016; On Introduction of Form for Registration of Clinical and Expert Work in Treatment and Prevention Institutions No. 154 dated May 21, 2002. Among the nosologies with temporary disability, the digestive system diseases occupy the sixth place after the respiratory and circulatory organ diseases, injuries and poisonings, and musculoskeletal system diseases [1,2]. When appealing to a dental medical organization, the patient is given a temporary sheet of disability based on the patient's testimony, the duration of which is determined by the time of treatment and the patient rehabilitation for a full return to the work process. Many authors in their studies assert that the case of temporary or total disability with the disease of any organs and systems of the body leads to the patient's somatic and mental imbalance [4,5,6]. The person of working age: women - up to 55 years, men - up to 60 years makes the main category of patients seeking medical dental care. Most patients almost always present a temporary sheet of disability to the social insurance fund for the payment of corresponding allowance.

Duration of disability by a patient may depend on various factors, such as the type and course of the maxillofacial area disease, seasonality, individual characteristics of the organism. The estimated periods of temporary disability for digestive diseases (class XI according to ICD-10) are established relative to the group of the maxillofacial area diseases in the Russian Federation. However, we have not revealed any data on the effect of various factors on the duration of temporary disability in the patient with maxillofacial area disease during treatment in dental medical organizations.

The purpose of the study is to analyze temporary disability cases in the maxillofacial area diseases in dental practice over a period of 10 years.

Material and methods. The temporary disability cases, established by the dental medical organizations of the Republic of Tatarstan served as a source of the information was (analysis of accounting and reporting forms 16-BH, 036/y, 035/y, 043/y for the period 2007-2016). The material of the study was subjected to statistical processing using the methods of parametric and nonparametric analysis in accordance with the results of testing the compared populations for the normal distribution. The accumulation, updating, systematization of the initial information and visualization of the obtained results were carried out in Microsoft Office Excel 2016. The statistical analysis was carried out using the IBM SPSS Statistics 23.

Results and discussion. The maxillofacial area is an important element of the anatomical and functional unity of the human body. Taking into account the peculiarities of the structure of soft tissues, maxillofacial bones, their blood supply and innervation, we have defined the groups of the maxillofacial area diseases that lead to the limitation and/or loss of the working capacity of the adult population: inflammatory (of odontogenic and non-dontogenous genesis), traumatic, benign and malignant lesions, secondary jaw edentulism (full or partial), as well as tooth eruption diseases. When appealing to a dental medical organization, as a rule, in most cases, the sheet of disability is issued by a dentist-surgeon, somewhat less often by a dentist-therapist.

The total number of temporary disability cases studied by us in dental medical organizations of the Republic of Tatarstan for 2007-2016 totaled 12,891 units, which we accepted as the general population. The statistical analysis was carried out by

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the method of a sample, in which, based on mathematical calculations, the number was 5,204 cases. The distribution of temporary disability cases in the Republic of Tatarstan by years is shown in Figure 1.

According to the presented figure, the greatest number of temporary disability cases due to dental diseases was registered in 2013 (904 cases), the smallest - in 2009 (253 cases). At this stage of our study, we estimated the time dependence of the incidence of temporary disability from various factors, including the nosological group of the disease, sex, age, and doctor's experience.

The results of the comparison of the duration of temporary disability cases, depending on the nosological group to which the underlying disease was related, are presented in Table 1.

According to the study, the duration of temporary disability cases in maxillofacial area diseases had statistically significant differences, depending on the nosological group to which the underlying disease belonged ($p<0.001$). The mean duration of the case was greatest in patients with abnormalities of maxillofacial area development and with injuries, amounting to 12.18±1.26 and 11.79±0.36 days, respectively. The lowest values were taken in the case of odontogenic inflammatory processes in the maxillofacial area and tooth eruption diseases (5.61±0.08 and 6.13±0.35 days, respectively).

Comparison of the duration of temporary disability cases corresponding to certain nosological groups was also performed in dynamics. The following diagram was obtained for the group of odontogenic inflammatory processes (Fig. 2).

In accordance with the results of a single-factor analysis of variance, the statistically significant differences in the duration of cases of odontogenic inflammatory processes in dynamics over 10 years were established ($p<0.001$). During the study period, there was a significant increase in the average from 2008 to 2013 from 4.88 to 6.47 days. In 2015, the average duration of cases fell sharply to 5.29 days, and in 2016 it fell to 5.05 days.

When comparing the duration of cases of temporary disability caused by tooth eruption diseases, the data presented in Figure 3 were obtained in the dynamics.

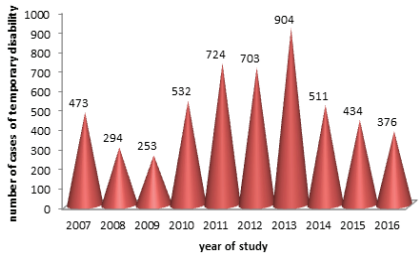
Based on the data obtained, the statistically significant differences in the duration of cases of tooth eruption diseases, depending on the year of observation, were noted ($p=0.006$). At the same time, the average duration of cases took the maximum values in 2009 and 2012 (8.0 and 9.36 days, respectively), in the remaining years the fluctuations of the indicator were insignificant, ranging from 4.68 days in 2010 to 6.54 days in 2008.

The results of the comparison of the duration of cases of temporary disability due to secondary jaw edentulism in the dynamics from 2009 to 2016 (in 2007-2008 there was a small number of cases of this pathology) are shown in Figure 4.

The analysis made it possible to reveal statistically significant differences in the duration of cases of temporary disability at secondary jaw edentulism in dynamics ($p<0.001$). When comparing the values of the indicator, the significantly different average duration of the case in 2015 came under our notice, which was 17.29 days, which was almost twice as high as the next largest indicator of 2013, equal to 9.36 days. We associate the growth of this indicator with an insignificant number of cases of temporary disability at jaw edentulism in the structure of the maxillofacial area diseases leading to the occurrence of the case of temporary loss of capacity for work by the patient, hence, in this case, the median fluctuation was minimal.

The average levels of the duration of cases of temporary disability caused by maxillofacial area injuries were compared in dynamics in Figure 5.

As in the case of other studied diseases, the changes in the duration of cases of temporary disability due to maxillofacial area injuries in 2007-2016 were statistically significant ($p<0.001$). For this indicator, a gradual decrease from 14.89 to 7.88 days, observed from 2008 to 2015, was characteristic. However, in 2016 the average duration of the case increased significantly, reaching 15.92 days. The growth of this indicator we associate with the increase of cases of joint treatment and rehabilitation of patients with the maxillofacial area injuries in the dental medical organization in 2016 and the conditions of the maxillofacial department of the profile hospital.



Distribution of temporary disability cases in a sample during the period under study

The next nosological group, for which the dynamics of the average duration of cases of temporary disability was studied, were the maxillofacial area neoplasms. In this section of our study, we consider the maxillofacial area neoplasms of only benign genesis, treatment and rehabilitation of these patients was performed in the dental medical organizations or the maxillofacial department of the profile hospital according to indications. The resulting graph is shown in Figure 6.

In accordance with the data obtained, the average duration of the case was characterized by statistically significant positive dynamics, increasing during the study period from 4 to 17 days ($p<0.001$).

According to the results of the analysis, the differences in the duration of cases of temporary disability with non-dental inflammatory diseases and maxillofacial anomalies, depending on the year of observation, were statistically insignificant ($p=0.125$ and 0.257, respectively).

In the study, we also revealed the effect of the patient's sex on the duration of temporary disability in various nosologies of maxillofacial area diseases. The results are shown in Table 2.

According to the presented Table, the statistically significant differences in the duration of cases of temporary disability, depending on sex were noted in most nosological groups. The index took significantly higher values among men in

Table 1

Comparison of duration of temporary disability cases, depending on affiliation of disease to particular nosological group

Nosological groups	Duration of cases, days
	M±m
Odontogenic inflammatory processes of maxillofacial area	5.61±0.08
Tooth eruption diseases	6.13±0.35
Secondary jaw edentulism	8.57±0.36
Maxillofacial area injuries	11.79±0.36
Neodontogenic inflammatory processes of maxillofacial area	7.61±0.46
Maxillofacial area neoplasms	7.83±0.63
Anomalies in maxillofacial area development	12.18±1.26
Polypathia	8.15±0.8

Table 2

The duration of cases of temporary disability, depending on patients' sex of in nosological groups of maxillofacial area diseases

Nosological group	Duration of cases of temporary disability (M±m)		p
	Men	Women	
Odontogenic inflammatory processes of maxillofacial area	5.88±0.15	5.52±0.09	0.039*
Tooth eruption diseases	7.04±1.05	5.88±0.32	0.296
Secondary jaw edentulism	10.77±0.79	7.38±0.3	<0.001*
Maxillofacial area injuries	13.37±0.54	9.07±0.43	<0.001*
Neodontogenic inflammatory processes of maxillofacial area	8.17±0.79	6.36±0.46	0.051
Maxillofacial area neoplasms	8.89±0.97	5.89±0.44	0.007*
Anomalies in maxillofacial area development	15.07±2.01	9.82±1.58	0.043*
Polypathia	10.81±2.04	6.92±0.76	0.083

* - differences in indicators are statistically significant (p<0.05)

case of odontogenic inflammatory processes in the maxillofacial are (p=0.039), secondary jaw edentulism (p<0.001), injuries (p<0.001), neoplasms (p=0.007), developmental abnormalities (p=0.007). The average duration of temporary incapacity in patients with non-pediatric inflammatory processes and associated diseases was also increased in men, the significance level was very close to the critical level (p=0.051 and p=0.083, respectively).

Another factor, whose influence on the nosological structure of cases of temporary disability was studied, was the patients' age. As the analysis showed, the patients' age had statistically significant differences depending on the nosological group (p<0.001). The lowest values of the median age were observed in tooth eruption diseases (29 years of age), injuries and developmental anomalies (32 and 33 years of age, respectively). Later, other causes were secondary jaw edentulism (38 years of age) and odontogenic inflammatory processes of maxillofacial area (37 years of age).

Conclusion. Taking into account the peculiarities of the structure of soft tissues, maxillofacial bones, their blood supply and innervation, we have identified groups of maxillofacial area diseases that lead to the limitation and/or loss of capacity for work of the adult population in the Republic of Tatarstan: inflammatory (of odontogenic and neodontogenic genesis), traumatic, benign and malignant lesions, secondary jaw edentulism (full or partial), as well as tooth eruption diseases. We established that during the study period, the statistically significant changes in the duration of cases of temporary disability due to odontogenic inflammatory processes in the maxillofacial area, tooth eruption diseases, secondary jaw edentulism, injuries and neoplasms were noted. The statistically significant differences in the structure of cases of temporary disability on nosological groups of maxillofacial area diseases were established depending on sex, age, and year of observation.

There is no conflict of interest.

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RISK FACTORS INFLUENCING THE PERSISTENCE OF PATENT DUCTUS ARTERIOSUS IN NEONATES WITH CHD IN THE REPUBLIC SAKHA (YAKUTIA)

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The authors present their research of factors, possibly influencing the duration of persistent patent ductus arteriosus (PDA) in the neonates with congenital heart defects (CHDs) in the Republic Sakha (Yakutia). Such factors as multiple pregnancy, operative delivery, gestational arterial hypertension, preeclampsia, fetoplacental insufficiency, anemia in pregnancy, threatened miscarriage, congenital heart defects in future mother, and ethnicity of a mother or a father are examined.

A retrospective clinical research work was based on the data of the Perinatal Centre of the Republican hospital No1, National Centre of medicine. A research work is based on clinical results of medical tests, taken from 162 medical records of the patients with a diagnosed “Congenital heart disease” (CHD).

According to the results of statistical analysis there were revealed most significant risk factors for long-term persistent arterial ducts among the neonate population of the Republic Sakha (Yakutia). They may be associated with: complicated course of pregnancy, i.e. gestational arterial hypertension with or without proteinuria, pregnancy edema associated with presence or absence of proteinuria, fetoplacental insufficiency, anemia of the current pregnancy and presence of CHD in the mother’s past history.

Keywords: congenital heart defect, arterial duct, hemodinamically insignificant patent ductus arteriosus.

Introduction. The prevalence of the patent ductus arteriosus (PDA) in the newborns remains unknown as there are no distinct criteria from what period of gestation PDA is considered pathologic. Nominally it is supposed to close within the first two weeks after birth. Under such criteria the prevalence of the isolated pathology is 0.14-0.3 per 1,000 live-born children, 7% among all the CHDs and 3% among all the critical defects [7]. Persistence of the arterial duct considerably depends on the term of gestation besides that the data that some factors of the mother, such as intrauterine hypoxia, non-steroid anti-inflammatory medication intake etc., are known. A number of several factors which can be associated with high risk of long-term persistence of PDA in neonates are not well studied in the territory of the Republic of Sakha (Yakutia).

Objectives: The factors that are possibly associated with the long-term persistence of PDA in neonates with CHDs are studied.

Methods and materials: A retrospective clinical research work was based on the data of the Perinatal Centre of the Republican hospital No1, National Centre of medicine. A research work is based on clinical results of medical tests, taken from 162 medical records of the patients with a diagnosed “Congenital heart disease” (CHD). The time distance of the medical records is registered two times, thus from 2001 to 2003 and from 2013 to 2015. The CHD is recorded according to Q20-Q28 (ICD-10, chapter XVII: Congenital malformations, deformations and chromosomal abnormalities). The delivery case reports (#010u) and patient’s discharge statistic card (#066/u-02) were the initial documentations for analysis.

All the neonates had experienced ultrasound examination (Doppler echocardiography) of the heart to evaluate the anatomical structure and cardiovascular function. The selection is based on the cases with bypass through interatrial septum according to the results of ultrasound investigation. The functioning activity of the arterial duct was evaluated by colour Doppler test to define additional flow in the vessel projection, i.e. pulmonary trunk. According to the results of the ultrasound investigation, all the selection of CHDs was divided into groups: the 1st group consists of the patients with non-revealed shunting according to the Doppler monitoring of the vessel with pulmonary artery projection, non-functioning arterial flow; the 2nd group consists of the patients with revealed systolic and diastolic disorders or systolic shunting, according to the Doppler monitoring of the vessel with pulmonary artery projection, functioning arterial flow; the 3rd group consists of all cases of CHD. The research was performed from 2001 to 2003 on the base of ATL-HDI-3000 Philips, from 2013 to 2015 on the base of EPIQ-7 Philips.

The age of the neonates included in the selective group was from 17 to 40 for mothers and from 17 to 48 for fathers. The period of gestation at the moment of birth of a child with CHD was from 25 to 41 weeks. The body weight at moment of the birth was from 564 gr to 4,500 gr. The height at the moment of the birth was from 30 cm to 58cm.

The family history of the both parents was retrospectively evaluated. Thus, the following factors were included: 1) the factors complicating pregnancy (gestational hypertension with or without proteinuria, edema with or without proteinuria for the current pregnancy, preeclampsia, fetoplacental insufficiency, anemia during the current pregnancy, multiple pregnancy, threatened miscarriage, operative delivery of the current pregnancy); 2) CHD in the mother’s past history; 3) ethnicity of the parents (was registered by self-determination of the survey).

On data processing χ^2 criteria were used (comparing binary / nominal vari-

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ables) and the Mann-Whitney U test (comparing continuous variables). When $p<0.05$ the intergroup accuracy was considered significant. The initial data were accumulated in the database by means of Microsoft® Excel software, all the statistic operations were conducted by means of SPSS® Statistics software (IBM® USA).

Results and discussion. The statistical analysis of the repeated ultrasound investigations of one and the same child with CHD confirming the presence or absence of PDA was carried out. 162 cases were selected. A possible association of multiple pregnancy with the risk of long-term persistence of the ductus arteriosus during the medical reexaminations was analyzed (Table 1).

The following factors aggravating pregnancy were investigated, i.e. gestational arterial hypertension and edema with or without proteinuria, preeclampsia, fetoplacental insufficiency, anemia of the current pregnancy and threatened miscarriage, as well as operative delivery.

According to the research statistically unconfirmed results were obtained, i.e. the results were higher for multiple pregnancies among hemodinamically insignificant patent ductus arteriosus (HIS-PDA) (n=86) – 5.8% than in groups with the hemodinamically significant patent ductus arteriosus (HS-PDA) (n=76) – 1.3%. Multiple pregnancy as a predictor of long-term persistence of the patent ductus arteriosus among all the selections became statistically unsatisfactory.

The association of the gestational arterial hypertension with or without proteinuria of the current pregnancy with a risk of persistence of PDA (p=0.948) was revealed, but the results are not statistically verified. In 34% of all cases of re-examination of the arterial duct (n=162) the following factors were registered. The prevalence of the gestational arterial hypertension with or without proteinuria, and edema of the pregnancy with or without proteinuria in the structure of the arterial duct was equal in both groups: HIS-PDA– 33.7% (n=86) and HS-PDA – 34.2% (n=76).

According to the results, preeclampsia of the current pregnancy was registered in 72.8% of all cases of CHDs and was more significantly associated with the risk of long-term persistence of the ductus arteriosus. A part of preeclampsia in the groups of HIS-PDA (n=86) was higher – 73.1%, (in a case of the patent ductus arteriosus (n=76) – 65.8%). These results were statistically unverified (p=0.058).

The results show an equal association of fetoplacental insufficiency with the risk of persistence arterial duct and closure of the arterial duct (p=0.157), the revealed data are not statistically confirmed. The fetoplacental insufficiency of the current pregnancy was registered in 36.4% of all cases born with CHDs (n=162). A higher association of the fetoplacental insufficiency with a risk of persistence of PDA (p=0.157) in comparison with closure of PDA are noticed, but not confirmed statistically.

Anemia in pregnancy was most common for the group of HIS-PDA (n=86), in the group of the patent ductus arteriosus (n=76), it composed 56.6% and 50.0% respectively. The revealed data were not statistically confirmed (p=0.402), but they showed possible association of anemia with a risk of persistence of PDA, nevertheless a part of anemic turned considerably higher in both groups and were of the same degree (Table 1).

Threatened miscarriage of the current pregnancy in the past history of the neonates as a possible predictor of a long-term persistence of the arterial duct was also studied. According to the common data, threatened miscarriage was revealed in 38.3% of all the selected groups of the arterial duct. The results of this research show that threatened miscarriage most commonly occurred in groups of HIS-PDA (n=86)-45.3% than in groups of PDA (n=76) – 30.3%. The results are not statistically verified (p=0.049) and show the association of the threatened miscarriage with a risk of persistence of PDA as well as closure of PDA.

Table 1

The proportion of factors aggravating the course of pregnancy in groups of newborns with HIS-PDA and PDA

Group	No factor	multiple pregnancy	p
1 n=86	94.2	5.8	0.130
2 n=76	98.7	1.3	0.130
Total n=162	96.3	3.7	0.130
	No factor	Gestational arterial hypertension with or without proteinuria	
1 n=86	66.3	33.7	0.948
2 n=76	65.8	34.2	0.948
Total n=162	66.0	34.0	0.948
	No factor	Preeclampsia	
1 n=86	20.9	73.1	0.058
2 n=76	34.2	65.8	0.058
Total n=162	27.2	72.8	0.058
	No factor	Fetoplacental insufficiency	
1 n=86	68.6	31.4	0.157
2 n=76	57.9	42.1	0.157
Total n=162	63.6	36.4	0.157
	No factor	Anemia	
1 n=86	50.0	50.0	0.402
2 n=76	43.4	56.6	0.402
Total n=162	46.9	53.1	0.402
	No factor	Threatened miscarriage	
1 n=86	54.7	45.3	0.049
2 n=76	63.7	30.3	0.049
Total n=162	61.7	38.3	0.049
	No factor	Mothers with CHD	
1 n=86	93.0	7.0	0.075
2 n=76	84.2	15.8	0.075
Total n=162	88.9	11.1	0.075
	No factor	Operative delivery	
1 n=86	53.5	46.5	0.821
2 n=76	55.3	44.7	0.821
Total n=162	54.3	45.7	0.821

Note. In the Tables 1-2 1st group - there were no signs of the functioning of the ductus arteriosus during re-examination (HIS-PDA); 2nd group - signs of the functioning of the arterial duct (PDA) were revealed.

Also the cases of CHD in the mother's past history of a CHD neonate as a possible predictor of long-term persistence of PDA are also studied. The research data show that mother's CHD was registered in 11.1% of all selected groups. Statistically unconfirmed data showed association of mother's CHD in PDA groups (p=0.075). In PDA groups (n=76) this factor far doubled than in groups of HIS-PDA (n=76), it was 15.8% and 7.0% respectively.

The operative delivery of the current pregnancy as a factor of possible long-term persistence of the ductus arteriosus turned to be statistically unsatisfactory, it was common for HIS-PDA group of neonates – 46.5% (Table 1).

The ethnicity of the mothers and fathers in children with PDA and HIS-PDA was investigated (Table 2).

Among all the cases of reexamination of the arterial ducts (n=162), it was most common for the Yakut and Russian mothers 71.6% and 16.0% respectively, Evenks - 8.6%, peoples of the Caucasus – 3.1%. Statistically unconfirmed data (p=0.601) of the distribution according to mothers' ethnicity were received when comparing the groups of arterial ducts. According to the results of the research there were Yakut mothers in both groups almost equally – 72.2% and 71.1% respectively. Evens were only in PDA group (n=76), 1.2%. It was most common for Russian 17.1% and Evenks 9.2% in PDA group rather than in HIS-PDA group (16.1% and 8% respectively). In a group of HIS-PDA 4.7% corresponded to the peoples of Caucasus (1.3% in PDA group).

Among the fathers of the CHD neonates it was most common for Yakuts and Russian 73.51% and 17.3% respectively. There were 14.9% for Evenks, 2.5% for peoples of Caucasus and other nations (Ukrainians, Polishes, Germans, Tatars, Buryats, Kumyks and Khakasses) – 0.6% for each group. Statistically unconfirmed results show that the ethnicity of the father is associated with groups of arterial ducts (p=0.565). The research revealed that PDA group was most common for Yakuts (75%). Russian and Evenks commonly occurred in the groups of HIS-PDA (n=86) – 18.6% and 5.8%, and in a group PDA (n=76) – 15.8% and 3.9%. Other nations (Evens, peoples of the Caucasus, Ukranians, Polishes, Germans, Tatars, Buryats, Kumyks and Khakasses) were present only in a group of PDA.

Table 2

Ethnicity of Parents of Newborns with HIS-PDA and PDA

Groups of arterial duct	Mother ethnicity, %								P=
	1	2	3	4	5	6	7	8	
1 n=86	72.1	15.1	0.0	8.1	0.0	4.7	0.0	0.0	0.601
2 n=76	71.1	17.1	1.2	9.2	0.0	1.3	0.0	0.0	0.601
Total n=162	71.6	16.0	0.6	8.6	0.0	3.1	0.0	0.0	0.601
	Father ethnicity. %								P=
	1	2	3	4	5	6	7	8	
1 n=86	72.1	18.6	0.0	5.8	1.3	0.0	0.0	0.0	0.585
2 n=76	75.0	15.8	1.3	3.9	1.3	1.3	0.0	1.3	0.585
Total n=162	73.5	17.3	0.6	4.9	0.6	2.5	0.0	0.6	0.585

Note. 1 – Yakuts, 2 – Russians, 3 – Evens, 4 – Evenks, 5 – other indigenous small-numbered peoples of the North, Siberia and the Far East: Dolgans, Yukaghirs, Chukchis, 6 – peoples of the Caucasus, 7 – peoples of the Central Asia, 8 – others: Ukranians, Polishes, Germans, Tatars, Buryats, Kumyks and Khakasses.

Conclusions:

1. Multiple pregnancy as a predictor of long-term persistence of arterial ducts on reexamination, according to current research, occurred statistically unreliable. Preeclampsia and operative delivery of the current pregnancy as factors of possible association with long-term persistence of PDA turned statistically unreliable, and most commonly occurred in groups of HIS-PDA.

2. The association of a risk of persistent PDA and PDA closure with such factors as gestational hypertension with or without proteinuria, pregnancy edema associated with presence or absence of proteinuria, anemia in pregnancy and threatened miscarriage was statistically unconfirmed.

3. The association of fetoplacental insufficiency with risk of persistent PDA was unconfirmed statistically.

4. The association of mother's CHD in a group of PDA was also unconfirmed statistically.

According to the results of statistical analysis there were revealed most significant risk factors for long-term persistent arterial ducts among the neonate population of the Republic Sakha (Yakutia). They may be associated with complicated course of pregnancy, i.e. gestational arterial hypertension with or without proteinuria, pregnancy edema associated with presence or absence of proteinuria, fetoplacental insufficiency, anemia of the current pregnancy and presence of CHD in the mother's past history.

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