CD19+, pro- and anti-inflammatory cytokines IL1b, IL4, an indicator of neuropeptide regulation (leptin) associated with polymorphism of alleles and genotypes of candidate genes of the adrenoreceptor gene ADRB2 rs1042713 (A allele and AA genotype) and the PPARA peroxisome receptor gene rs4253778 (CC genotype).

Reference

1. Andreevskaya M.V., Maryanovich A.T. Leptin v regulyacii potrebleniya pishchi [Leptin in the regulation of food consumption]. Rossijskie biomedicinskie issledovaniya [Russian biomedical research. 2019; 4 (4): 33-38 (In Russ.).]

2. Bunova S.S., Usacheva E.V., Zamakhina O.V. Vliyanie polimorfizma genov ADRB1, ADBR2 i CYP2D6 na effektivnost' i bezopasnost' B-blokatorov u pacientov s serdechno-sosudistymi zabolevaniyami [The effect of polymorphism of ADRB1, ADBR2 and CYP2D6 genes on the efficacy and safety of B-blockers in patients with cardiovascular diseases]. Sibirskij medicinskij zhurnal [Siberian Medical Journal. Irkutsk. 2014; 4: 5-10 (In Russ.).]

3. Vyzova L.S. [et al.] Gendernye i pubertatnye osobennosti urovnej dofamina i leptina v zavisimosti ot genotipa po polimorfnomu lokusu TaqIA gena dofaminovogo receptora 2-go tipa pri raznyh formah ozhireniya u detej [Gender and puberty features of dopamine and leptin levels depending on the genotype according to the TaqIA polymorphic locus of the type 2 dopamine receptor gene in various forms of obesity in children]. Medicinskie novosti [Medical News. 2018; 12:52-57 (In Russ.).]

4. Borodina S.V. [et al.] Geneticheskie prediktory razvitiya ozhireniya [Genetic predictors of the development of obesity]. Ozhirenie i metabolizm [Obesity and metabolism. 2016; 13(2): 7-13 (In Russ.).]

5. Grishkevich N.YU., Savchenko A.A., Manchuk V.T. Osobennosti informativnosti pokazatelej morfologicheskogo sostava limfocitov krovi u zdorovyh detej i s ozhireniem [Features of informative indicators of morphological composition of blood lymphocytes in healthy children and with obesity]. Sibirskij medicinskij zhurnal [Siberian Medical Journal. Irkutsk. 2002; 34 (5): 48-52 (In Russ.).]

6. Efremenko YU.R., Koroleva E.F., Gorshkova T.N. Pokazateli lipidnogo obmena i svobodnoradikal'nogo okisleniya pri metabolicheskom mindrome [Indicators of lipid metabolism and free radical oxidation in metabolic syndrome]. Vestnik Nizhegorodskogo universiteta im. N.I. Lobachevskogo [Bulletin of N.I. Lobachevsky Nizhny Novgorod University. 2011; 2 (2): 183-189 (In Russ.).]

7. Zhuravleva O.V., Romantsova E.B., Babtseva A.F. Metabolicheskij sindrom u detej i podrostkov: uchebnoe posobie dlya studentov lechebnogo i pediatricheskogo fakul'tetov, internov, ordinatorov [Metabolic syndrome in children and adolescents: a textbook for students of medical and pediatric faculties, interns, residents]. Blagoveshchensk: Bukvits, 2012; 29 (In Russ.).]

8. Belenkov Yu.N. [et al.] Metabolicheskij sindrom: istoriya razvitiya, osnovnye kriterii diagnostiki [Metabolic syndrome: the history of development, basic diagnostic criteria]. Racional'naya farmakoterapiya v kardiologii [Rational pharmacotherapy in cardiology]. 2018; 14 (5): 757-764 (In Russ.).]

9. Balykova L.A. [et al.] Metabolicheskij sindrom u detej i podrostkov [Metabolic syndrome in children and adolescents]. Pediatrics. 2010; 89 (3): 127-134 (In Russ.).]

10. Povarova O.V. [et al.] Metabolicheskie markery i okislitel'nyj stress v patogeneze ozhireniya u detej [Metabolic markers and oxidative stress in the pathogenesis of obesity in children]. Rossijskij vestnik perinatologii i pediatrii [Russian Bulletin of Perinatology and Pediatrics. 2020;65(1): 22-29 (In Russ.).]

11. Chachhiani I. [et al.]. Posleoperacionnaya reakciya leptina i kortizola u bol'nyh bez oslozhnenij i s infekcionnymi oslozhneniyami [Postoperative reaction of leptin and cortisol in patients without complications and with infectious complications]. Klinicheskie issledovaniya [Clinical studies. 2004; 15 (3): 76-80 (In Russ.).]

12. Ruzhilo O.S. Rol' geneticheskih markerov v kliniko-gormonal'nyh i metabolicheskih harakteristikah sindroma polikistoznyh yaichnikov [The role of genetic markers in the clinical, hormonal and metabolic characteristics of polycystic ovary syndrome]. Medicinskie novosti [Medical news. 2015; 5: 67-70 (In Russ.).]

13. Bulavko Ya.E. [et al.] Formirovanie metabolicheskogo sindroma v detskom vozraste: teoreticheskie i prikladnye klinicheskie aspekty [Formation of metabolic syndrome in childhood: theoretical and applied clinical aspects]. Pediatr [Pediatrician]. 2019;10 (4): 67-68 (In Russ.).]

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THE FREQUENCY OF METABOLIC SYNDROME AND ITS COMPONENTS IN THE NON-INDIGENOUS POPULATION OF SOUTH YAKUTIA

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A one-stage study of the working non-indigenous population of South Yakutia was conducted. A high incidence of abdominal obesity, lipid-metabolic disorders has been shown. Dyslipidemia, arterial hypertension and metabolic syndrome, mainly represented by a three-component, were most often registered in men compared to women. The relationship of blood pressure with triglyceride and glucose levels was obtained.

Keywords: metabolic syndrome, dyslipidemia, arterial hypertension, non-indigenous population, South Yakutia.

Metabolic syndrome (MS) remains a global epidemic in the XI century, increasing its growth rates, causing terrible complications such as type 2 diabetes, stroke, myocardial infarction, etc. Often, the presence of MS exacerbates the course of cardiovascular pathology, increasing the risk factors for its development. Its prevalence in the world ranges from 10 to 30% according to foreign and domestic authors, depending on various criteria for its diagnosis [4;9;10]. According to some estimates, it reaches up to 1/3 of the world's population [7]. The total cost of treatment and economic losses associated with this syndrome are estimated in trillions. The study of MS in the working non-indigenous population of the North is relevant, research in this field is extremely scarce. The spread of MS and its patients becoming younger is the main reason for the relevance of the study. It is also due to the high risk of developing cardiovascular diseases and their mortality in the industrial cities of the Far North.

The aim of the study was to assess the frequency of occurrence of metabolic syndrome and its components in non-indigenous residents of South Yakutia.

Materials and methods of research. A one-time population study of the working population of non-indigenous nationality in the Aldan district of the Republic of Sakha (Yakutia) was conducted. According to the list of employees of industrial and social spheres, every 3rd employee was invited for examination. The response rate was 75%. 174 residents of the Aldan district of working age were analyzed, 66 of them were men, whose

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median age (Me) was 45.0 [34.5-53.0] years, and 108 were women, Me 43.0 [36.0-51.75] years.

All study participants were interviewed, complaints were collected, anamnesis was taken, an anthropometric study with the determination of height, body weight, measurement of waist circumference (WC) and hips, measurement of blood pressure (BP), blood was taken from the ulnar vein in the morning on an empty stomach with an 8-12-hour interval after the last meal, a clinical examination by a cardiologist was also conducted. Respondents signed a voluntary consent to the study according to the Protocol of the Ethics Committee of the YSC CMP.

To detect abdominal obesity, the circumference was measured from a standing position, patients were in underwear. The measurement point is the midpoint of the distance between the top of the iliac crest and the lower lateral edge of the ribs. It does not necessarily have to be at the navel level. When WC > 94 cm in men and > 80 cm in women, it can be assumed that the patient has abdominal type of obesity (criteria of the VNOK 2009).

Blood pressure was measured twice with an automatic tonometer "OMRON M2 Basic" (Japan) in a sitting position with the calculation of average blood pressure with a limit of permissible measurement error of ± 3 mm Hg (ESH/ESC, 2013). Arterial hypertension (AH) was assumed at a blood pressure level≥140/90 mmHg or if the patient was taking antihypertensive drugs during the examination period (ACC/AHA Guideline, 2017).

Laboratory analyses were carried out by the enzymatic method on an automatic biochemical analyzer "Labio" using "Analyticon" reagents (Germany). Laboratory research methods included: determination of the lipid spectrum (total cholesterol (TC), low-density lipoprotein cholesterol (LDL cholesterol), high-density lipoprotein cholesterol (HDL cholesterol), triglycerides (TG)) and glucose.

For diagnosing lipid disorders, the Russian recommendations of the VII revision of the Russian Society of Cardiology 2020, compiled taking into account the European Recommendations of 2019, were applied. Hypercholesterolemia (HCH) was established at the level of TC ≥ 5.0 mmol/l (190 mg/dl), taking into account the cardiovascular risk on the SCORE scale, elevated LDL cholesterol - LDL cholesterol 3.0 mmol/l (115 mg/dl) low, 2.6 mmol/l, moderate, 1.8 mmol/ll, high, 1.4 mmol/l, very high risk on the SCORE scale. Hypo-α-cholesterolemia (Hypo-α-CS) is the level of HDL cholesterol < 1.0 mmol/l (40 mg/dl) in men and 1.2 mmol/l (46 mg/dl) in women. Hypertriglyceridemia (HTG) was attributed to a TG level of 1.7 mmol/l (150 mg/dl). Hyperglycemia (HG) on an empty stomach was established at a glucose level of 6 mmol/l. Also included are patients with these disorders receiving specialized medical treatment for these conditions.

The criteria of metabolic syndrome (MS) were applied according to the recommendations for the management of patients with MS [6]:

The presence of the main component of the disease – abdominal obesity (AO) and 2 additional criteria: an increase in blood pressure > 140/90 mmHg, an increase in TG>1.7 mmol / l, a decrease in HDL cholesterol (in men <1.0, in women < 1.2 mmol / l), an increase in LDL cholesterol>3.0 mmol / l, hyperglycemia (glucose > 6 mmol/ L) or impaired glucose tolerance (glucose 2 hours after the glucose tolerance test >7.8 and < 11.1 mmol/ L).

Statistical analysis was carried out using the SPSS STATISTICS software package (version 26.0). Qualitative variables are described by absolute and relative frequencies (%), quantitative variables are described using the mean and standard error of the mean, median (Me) and interquartile range (Q1—Q3). The share comparison of the groups was carried out using the nonparametric Spearman criterion χ2. The odds ratio (OR) and 95% confidence interval (95% CI) were calculated. The correlation analysis was carried out using the Spearman coefficient. The statistical significance of the differences (p) was assumed to be equal to 5%.

The work was carried out under the research project of the YSC CMP "Regional peculiarities of biochemical, immunological and morphological indicators in the indigenous and non-indigenous population of the Republic of Sakha (Yakutia) in normal conditions and pathology" (FGWU-2022-0014) and the research of the Academy of Sciences of the Republic of Sakha (Yakutia) "Assessment of radiation exposure of the population of the Aldansky district due to natural sources of radiation and recommendations for carrying out protective measures to reduce it."

Results and discussion. A comparative analysis of clinical, laboratory and anthropometric indicators in the non-indigenous population of South Yakutia was carried out.

Comparing the average concentrations of biochemical and immunological parameters depending on gender, we obtained significant differences in the average values of TC, HDL, LDL and uric acid (Table 1). Thus, in men, compared to women, the average concentrations of TC, LDL and uric acid significantly prevailed.

Table 1

Average concentrations of laboratory parameters of residents of the Aldan district (M±m)

Parameter	all	men (66)	women (n=108)	p_{m-w}
TC (mmol/L)	5.40±0.10	5.74±0.23	5.20±0.08	0.012
HDL cholesterol (mmol/L)	1.97±0.04	1.70±0.06	2.14±0.05	0.000
LDL cholesterol (mmol/L)	2.57±0.09	3.12±0.19	2.24±0.09	0.000
TG (mmol/L)	1.88±0.10	2.02±0.20	1.80±0.11	0.324
glucose (mmol/L)	5.43±0.12	5.57±0.26	5.34±0.11	0.350
uric acid (mkmol/L)	324.06±5.97	358.64±9.72	302.94±6.85	0.000

Table 2

Comparative characteristics of lipid and carbohydrate metabolism disorders depending on gender

Parameter	all		men		women		χ^2	p_{m-w}
	n	%	n	%	n	%		
HCH	90	51.7	43	65.2	47	43.5	7.67	0.005
HCL LDL	57	32.8	32	48.5	25	23.1	11.93	0.000
Hypo-α-CS	5	2.9	2	3.0	3	2.8	0.009	>0.05
HTG	73	41.9	31	46.9	42	38.9	1.09	>0.05
GG	25	14.4	8	12.1	17	15.7	0.436	>0.05
Hyperuricemia	43	24.7	16	24.2	27	25.0	0.013	>0.05

A correlation analysis of SBP with biochemical parameters of blood was carried out. The relationship of SBP with TG (r=0.306, p=0.000) and glucose (r=0.192, p=0.011) was obtained. In a gender comparison, a significant correlation of SBP in men was obtained only with the level of TG (r=0.254, p=0.040), in women - with the levels of TG (r=0.336, p=0.000), glucose (r=0.209, p=0.030) and uric acid (r=0.224, p=0.020). For the rest of the parameters, no reliable relationship was obtained.

Lipid spectrum disorders were more often recorded in men (Table 2). HCH was found in more than half of the men examined, its atherogenic fraction - in almost half. These values had statistically significant differences in men compared to women.

Atherogenic HCH and HTG were also common, and were registered in almost half of the men. There was no significant difference in the HTG indicator. There are some concerns about the high incidence of HTG in the examined individuals, especially in men. The data revealed by us significantly exceeds the data of a large-scale epidemiological study of PROMETEUS, where HTG is present in 29.2% of the Russian population, where its level is also 1.25 times higher in men compared to women [8].

Metabolic disorders', such as HG, frequency was 14.4%, and were slightly more common in women. In the study in the open urban population of Western Siberia, men accounted for 7.7% and women - 11.9%.

Thus, in men of non-indigenous nationality of South Yakutia, unlike women, dyslipidemia, represented by HCH, including its atherogenic fraction, and HTG, was most often detected.

When analyzing anthropometric indicators, namely the WC criterion, a high incidence of abdominal obesity (AO) was shown in both men (n=42 or 63.6%) and women (n=75 or 69.4%), there were no significant differences between them (χ2=0.694, p=0.405). The results obtained showed higher AO figures compared to the data of studies by Russian scientists in Tyumen, where, according to the criteria of the 2009 VNOK, the frequency of AO in men was 38.8% and 49.8% in women [1;3]

The mean SBP did not differ, in men it was 129.09±2.40 mmHg and 129.91±2.20 mmHg in women. More than half of the respondents had hypertension (56.3% of the total number of surveyed). In gender comparison, it was most often registered in men (n=41 or 62.1%), compared with women (n=57 or 52.8%), no significant differences were obtained (p=0.228). According to the degrees of AH, the same distribution was obtained: AH of the 1st degree 32 people, or 18.4%, 2nd – 34 or 19.5%, 3rd – 32 or 18.4%, respectively. The gender attribute did not have any differences. In the open urban population of Tyumen, the frequency of hypertension was 61.3% in men and 36.8% in women [1;3]. The data obtained in men of non-indigenous nationality are consistent with the research, in women of our pilot study, the frequency of hypertension exceeds the results almost twice as much. We conducted an analysis of the correlation relationship between AO and SBP, during which a direct correlation was obtained between these parameters (r=0.448, p=0.000), confirming the close relationship between hypertension and obesity, which was confirmed by earlier studies of ESSE-RF [5].

Metabolic syndrome (MS) is a combination of the most important risk factors for the development of cardiovascular diseases. The analysis of the prevalence of MS according to the recommendations for the management of patients with MS [6]. As a result, MS was detected in 51 respondents, which amounted to 29.3% of the total number of study participants. The data obtained by us are coordinated with Russian researchers on the study of MS in the framework of ESSE-RF-2 [4]. The gender analysis did not show significant differences, in men the frequency of MS was 33.3% (n=22), in women 27.8% (n=30) (χ^2=0.603, p=0.437). Our data are consistent with previously conducted studies of the working non-indigenous population in the western territory of Yakutia in the industrial city of Mirny, where it is shown that 30.5% of men and 25.9% of women also had MS according to the 2009 VNOK criteria [2].

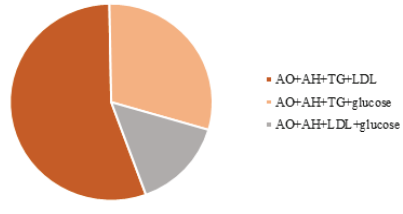
The analysis of the combinations of the main and two additional criteria of MS showed that the most frequent combination were: AO+AH+TG (n=43; 24.7%), AO+AH+LDL (n=25; 14.4%); AO+LDL+TG (n=17; 9.8%). The greatest contribution to the development of MS, in addition to AO, was made by such parameters as hypertension, elevated concentrations of TG and LDL.

Gender comparison shows that men have 4.57 times more chances of developing metabolic syndrome than women with a combination of 3 components - AO+LDL+TG (p<0.003) and 1.97 times more with a combination of AO+AH+LDL (p>0.05), proving atherogenic HCH and HTG, which are significantly often observed among them (Table 3). It should be noted that women most often have elevated glucose levels in MS combinations compared to men, increasing the odds ratio by 2.52 times with a combination of AO + LDL + glucose (p>0.05).

Table 3

Distribution of combinations of metabolic syndrome parameters depending on gender

Combination of components MS	men		women		OR [CI 95%]	p
	n	%	n	%		
AO+AH+TG	16	24.2	27	25.0	0.96 [0.47-1.95]	0.910
AO+AH+LDL	13	19.7	12	11.1	1.97 [0.83-4.60]	0.117
AO+LDL+TG	12	18.2	5	4.6	4.57 [1.53-13.67]	**0.003**
AO+AH+glucose	4	6.1	10	9.3	0.63 [0.19-2.10]	0.451
AO+TG+glucose	3	4.5	7	6.5	0.68 [0.17-2.75]	0.594
AO+ LDL+glucose	3	4.5	2	1.9	2.52 [0.41-15.51]	0.302
AO+TG+HDL	1	1.5	1	0.9	1.64 [0.10-26.77]	0.723
AO+AH+HDL	1	1.5	0	0	-	
AO+HDL+glucose	0	0	1	0.9	-	
AO+HDL+LDL	0	0	0	0	-	



Distribution of 4-component combinations of metabolic syndrome

The analysis of the occurrence of 4-component MS in the general population depending on gender was also carried out. Fig. 1 shows the share distribution of the most common combinations of 4 MS components. The most common variant of MS was a combination of AO+AH+TG+LDL, which accounted for 6.3% of the total number of respondents. It was registered more often in men (10.6%) compared with women (3.7%), no significant differences were obtained (OR 3.08, 95%CI [0.86-10.97], p=0.069). In second place is the combination of AO+AH + TG + glucose (3.4%), in third place – AO +AH +LDL + glucose (1.7%). There were no significant differences by gender. Five-component version of MS (AO +AH+LDL+TG+glucose) was registered only in one man. There were no such variants of 5 combinations of MS in women.

Thus, among the working non-indigenous population of the Aldan district, MS is mainly represented by 3 components, where AH, TG and LDL occupy leading positions among additional criteria. 4-component MS was registered less frequently, it was mainly registered in men with no significant difference.

Conclusion. A comprehensive medical examination of the health status of the working population of South Yakutia of non-indigenous nationality showed a high incidence of abdominal obesity, lipid-metabolic disorders. Dyslipidemia, arterial hypertension and metabolic syndrome were most often registered in men compared to women. The relationship of blood pressure with triglyceride and glucose levels was obtained. Considering that the examined contingent belonged to a non-indigenous or "alien" population, the syndrome of chronic adaptive overstrain can be assumed. Perhaps the reason for this is the low level of medical care, low coverage of medical examinations or the lack of highly qualified specialists. Primary health care, including general practitioners, as well as health schools for patients with hypertension and type 2 diabetes mellitus, play an important role in the early detection of metabolic syndrome and prevention of risk factors for major chronic non-communicable diseases, and timely effective medical care. Among the steps to improve the health of the population are improving urban planning, encouraging an active lifestyle, sports, promoting the principles of healthy eating, subsidizing whole-grain products, limiting the advertising of unhealthy food in the media, etc.

Reference

1. Akimova E.V., Akimov M.YU., Petelina T.I. Rasprostranennost' komponentov metabolicheskogo sindroma u muzhchin otkrytoj gorodskoj popu-lyacii po raznym kriteriyam ocenki [Prevalence of components of metabolic syndrome in men of the open urban population according to different evaluation criteria] // Profilakticheskaya medicina [The Russian Journal of Preventive Medicine]. 2021; 2(24): 37-43. [(In Russ.)] https://doi.org/10.17116/profmed20212402137

2. Ginsar E.A. Komponenty metabolicheskogo sindroma i gormonal'nye mekhanizmy ego formirovaniya u nekorennyh zhitelej Yakutii [Components of metabolic syndrome and hormonal mechanisms of its formation in non-indigenous residents of Yakutia]: avtoref. dis. … kand. med. Nauk [abstract of the dis. ... candidate of medical sciences]: 14.00.16 / Ginsar Elena Aleksandrovna; Novosibirsk, 2009; 24 [(In Russ.)]

3. Komponenty metabolicheskogo sindroma po raznym kriteriyam ocenki sredi zhenshchin sredneurbanizirovannogo goroda Zapadnoj Sibiri [Components of the metabolic syndrome according to different evaluation criteria among women of the average urbanized city of Western Siberia] / Kayumova M.M. [et al.] // Sibirskij nauchnyj medicinskij zhurnal [Siberian Scientific Medical Journal]. 2021; 41 (5): 121–128. (In Russ.)] doi: 10.18699/SSMJ20210515

4. Metabolicheskij sindrom i ego associacii s social'no-demograficheskimi i povedencheskimi faktorami riska v rossijskoj populyacii 25-64 let [Metabolic syndrome and its associations with socio-demographic and behavioral risk factors in the Russian population aged 25-64 years.] / Y.A. Balanova [et al.] // Kardiovaskulyarnaya terapiya i profilaktika [Cardiovascular therapy and prevention]. 2020. №4 (19). pp. 45-57. (In Russ.)]. Doi:10.15829/1728-8800-2020-2600

5. Ozhirenie v rossijskoj populyacii - rasprostranennost' i associacii s faktorami riska hronicheskih neinfekcionnyh zabolevanij [Obesity in the Russian population - prevalence and associations with risk factors of chronic non-communicable diseases] / Y.A. Balanova [et al.] // Rossijskij kardiologicheskij zhurnal [Russian Journal of Cardiology]. 2018; 6:123-30. [(In Russ.)] DOI:10.15829/1560-4071-2018-6-123-130

6. Rekomendacii po vedeniyu bol'nyh s metabolicheskim sindromom. Klinicheskie rekomendacii [Recommendations for the management of patients with metabolic syndrome. Clinical recommendations] (In Russ.)]. 2013. https://mzdrav.rk.gov.ru/file/mzdrav_18042014_Klinicheskie_rekomendacii_Metabolicheskij_sindrom.pdf

7. Engin A. The definition and prevalence of obesity and metabolic syndrome. in Advances in Experimental Medicine and Biology. Obesity and Lipotoxicity. Adv Experim Med Biol. 2017; 960: 1-17. doi:10.1007/978-3-319-48382-5_1.

8. Karpov Yu, Khomitskaya Yu. PROMETHEUS: an observational, cross-sectional, retrospective study of hypertriglyceridemia in Russia. Cardiovascular Diabetology. 2015, 14: 115.

9. Pucci G, Alcidi R, Tap L, et al. Sex- and gender-related prevalence, cardiovascular risk and therapeutic approach in metabolic syndrome: A review of the literature. Pharmacol. Res. 2017; 120: 34–42. https://doi.org/10.1016/j.phrs.2017.03.008

10. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. *Curr Hypertens Rep.* 2018 Feb 26;20(2):12. doi: 10.1007/s11906-018-0812-z.