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

DOI 10.25789/YMJ.2019.67.07

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.

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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.

The study was carried out with the partial support of the Presidium of the Russian Academy of Sciences under the basic research Program «Exploratory Fundamental studies for the development of Arctic region of the Russian Federation» (FRC FTM) and the project budget № 0324-2019-0041 (FRC ICG SB RAS).

We used the equipment of Core Facility *"Modern Optical Systems", Federal Research Center of Fundamental and Translational Medicine (Novosibirsk, Russia).*

Conflict of interests. The authors declare that they have no conflict of interest.

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DOI 10.25789/YMJ.2019.67.08

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

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 liveborn 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-