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Clinical and genetic variants of hypertriglyceridemia in the practice of a lipidologist

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Abstract

Background. An important role in identifying the causes and determining the prognostic significance of dyslipidemia belongs to the level of triglycerides. High triglycerides are a risk factor for the development or early onset of cardiovascular disease.

Aim. To assess the frequency of detection and causes of hypertriglyceridemia among patients receiving outpatient appointments with a lipidologist.

Material and methods. An analysis of lipid metabolism disorders in patients of the Adult Lipidology Center was carried out: 1233 people aged 18–84 years, including 777 (63%) women and 456 (37%) men. Examination of patients with dyslipidemia included an examination by a cardiologist-lipidologist (with the calculation of the risk of cardiovascular complications), an assessment of the probability of familial hypercholesterolemia according to the British scale and the criteria of the Dutch lipid clinics, a biochemical blood test, an analysis of the thyroid status, the content of glycated hemoglobin, extracranial duplex scanning, according to indications — echocardiography. Biomaterial samples from 421 patients with the phenotype of inherited dyslipidemia were examined by next generation sequencing to identify the carriage of APOE gene isoforms, as well as genes associated with familial hypercholesterolemia (LDLR, LDLRAP1, APOB, PCSK9). For statistical processing of research data, descriptive statistics methods were used. In a non-parametric distribution, data were expressed as Me (Q_1; Q_3). When performing statistical processing of the obtained data, nonparametric tests (Mann–Whitney test, when comparing qualitative data — χ^2 and Fisher's exact test, odds ratio and relative risk) were used. The value of $p < 0.05$ was taken as a criterion of significance. The nature of the data distribution was assessed using the Kolmogorov–Smirnov test.

Results. Elevated triglyceride levels were detected in 341 (27.66%) patients: 220 (64.5%) women and 121 (35.5%) men. Mild degree of hypertriglyceridemia occured in 42.5% of cases, moderate — in 42.5%, severe — in 7.6%, extremely severe — in 7.4%. The genetic characteristics of patients with hypertriglyceridemia were determined, and 1 previously undescribed variant of the APOE mutation was found.

Conclusion. The most common forms of hypertriglyceridemia were mild and moderate, the most common variants of APOE mutations were p.Cys130Arg and p.Arg176Cys.

Keywords: lipid metabolism disorders, triglycerides, hypertriglyceridemia, dysbetalipoproteinemia.

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Background

Triglyceride (TG) levels are crucial in diagnosing and determining the prognostic significance of dyslipidemia [1]. Elevated levels of TG are associated with the early onset or development of cardiovascular diseases [1].

According to the American College of Cardiology guidelines [2], hypertriglyceridemia (HTG) can be classified into mild to moderate (fasting TG levels ≥150 mg/dL (≥1.7 mmol/L); after meals 175–500 mg/dL (1.97–5.65 mmol/L)), severe (TG level ≥500 mg/dL (≥5.65 mmol/L)), and extremely severe (TG level ≥1000 mg/dL (≥1.3 mmol/L)).

Meanwhile, the European Atherosclerosis Society defines TG levels >10 mmol/L as severe HTG [3].

HTG can be a result of either gene variants or secondary to diseases or drugs [4]. Secondary HTG is diagnosed in patients with obesity, type 2 diabetes mellitus, alcohol consumption, excessive consumption of simple carbohydrates, kidney disease, hypothyroidism, pregnancy, paraproteinemia, and autoimmune diseases such as systemic lupus

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erythematosus. It can also be caused by certain drugs such as glucocorticoids, estrogens, tamoxifen, and β-adrenoblockers [4].

The prevalence of the inherited form ranges from 1:100–200 (mixed dyslipidemia) to 1:1000 (familial dysbetalipoproteinemia) [5]. Evaluation of the nature of HTG is done by analysis of the genetic isoforms of AROE, in which the most common isoforms are AROE2, AROE3, and AROE4. The presence of these isoforms in a homozygous or heterozygous state is related to varying degrees of proatherogenic status in patients and early onset of coronary heart disease [6].

However, data published on the genetic characteristics of patients with HTG are often fragmentary or contradictory. Thus, determining the genetic features of patients with HTG would allow targeted prevention of cardiovascular diseases by influencing several modifiable factors.

Aim

The objective of this study was to assess the frequency and causes of HTG among patients attending outpatient appointments with a lipidologist.

Materials and methods

The causes and characteristics of lipid metabolism disorders were examined in 1233 patients aged 18–84 years who were treated at the Adult Lipidology Center, of which 777 (63%) were women with a mean age of 58.5 ± 9.5 years and 456 (37%) were men with a mean age of 46.6 ± 11.5 years. Indications for referral to the Adult Lipidology Center included a family history of sudden cardiac death or early cardiovascular disease, individual early cardiovascular disease, severe lipid metabolism disorders (total cholesterol of >7.5 mmol/L, low-density lipoprotein cholesterol of >4.9 mmol/L), or lipid metabolism disorders that are refractory to treatment.

Examination of patients with dyslipidemia included an evaluation by a cardiologist-lipidologist. The SCORE scale was used to calculate the risk of cardiovascular complications, while the S. Broom scale and Dutch Lipid Clinic Network criteria were employed to assess the probability of familial hypercholesterolemia [7]. In addition, blood biochemical analysis, assessment of thyroid status, glycated hemoglobin content, extracranial duplex scanning, and echocardiography (if indicated) were performed. Dyslipidemia correction was performed according to current clinical recommendations [5, 7].

The study protocol was approved by the local ethical committee of Kazan State Medical University (No. 2, December 9, 2019).

Next-generation sequencing was used to investigate biomaterial samples from 421 patients with inherited dyslipidemia phenotype to detect the carriage of isoforms of the AROE gene and the genes associated with familial hypercholesterolemia (LDLR, LDLRAP1, APOB, and PCSK9) [8].

This study was conducted at the laboratory of the Institute of Fundamental Medicine and Biology at Kazan (Volga Region) Federal University. Bioinformatic data analysis was performed at the laboratory of Health in Code (Spain). Genetic variants were described according to The Human Genome Variation Society recommendations [9] (www.hgvs.org). Interpretation of results was performed using the data from the ClinVar database [10] (www.ncbi.nlm.nih.gov/clinvar/).

Data analysis was performed by descriptive statistical methods. For nonparametric distribution, the data were expressed as Me (Q_1; Q_3), where Me is the median, Q_1 is the 25th percentile, and Q_3 is the 75th percentile. Nonparametric criteria, namely, Mann–Whitney test for comparing two unrelated groups based on one quantitative characteristic, χ^2 and Fisher's exact test, odds ratio, and relative risk for comparing qualitative data, were used for statistical analysis. Statistical significance was $p < 0.05$. Data distribution was assessed using the Kolmogorov–Smirnov criterion.

Results and discussion

A total of 341 patients (28%) had elevated TG levels, of which 220 (65%) were women and 121 (35%) were men (Table 1). The severity of HTG was mild in 42.5% of cases, moderate in 42.5%, severe in 7.6%, and extremely severe in 7.4% of cases. Women outnumbered men 1.8 times in each group in the distribution of patients according to the severity of HTG ($p < 0.0001$).

The proportions of patients with atherosclerosis of the brachiocephalic or coronary arteries were almost comparable at different TG elevation levels. The same was observed in the groups of patients with normal and elevated TG levels (70.6% vs. 68.6%, $p = 0.138$).

The incidence of coronary heart disease with previously verified coronary artery atherosclerosis did not depend on the TG level, as it was diagnosed in 13.8% of cases with normal levels and in 13.5% with HTG (odds ratio 0.975, 95% confidence interval (CI) 0.677–1.403). Although the risk of acute cerebral circulatory failure was increased 1.7-fold in HTG (odds ratio 1.716, 95% CI 0.795–3.701), it did not reach statistical significance ($p = 0.392$).

Mixed HTG was diagnosed in 265 (77.7%) patients, whereas isolated HTG was diagnosed in 76 (22.3%) patients. The frequency of HTG was

Table 1. Clinical and demographic characteristics of patients with different triglyceride levels

Characteristics	Triglyceridemia level, mmol/L (n)				
	<1.7 (892)	1.7–2.3 (145)	>2.3–5.7 (145)	>5.7–11.3 (26)	>11.3 (25)
Men, n (%)	335 (37,6)	48 (33,1)	59 (40,7)	10 (38,5)	4 (16)
Women, n (%)	557 (62,4)	97 (66,9)	86 (59,3)	16 (61,5)	21 (84)
Age, years (SD)	54,7 (12,8)	56,3 (11,7)	54,3 (12,0)	52,5 (12,8)	47,2 (12,2)
Atherosclerosis of brachiocephalic arteries, n (%)	630 (70,6)	99 (68,2)	103 (71)	18 (69,2)	14 (56)
IHD, n (%), including: PICS, n (%) CAS, n (%) CABG, n (%)	123 (13,8) 83 (9,3) 49 (5,5) 29 (3,3)	33 (22,8) 18 (12,4) 12 (8,3) 11 (7,6)	4 (2,8) 0 3 (2,1) 1 (0,7)	7 26,9) 1 (3,9) 5 19,2) 1 (3,9)	2(8) 0 0 1 (4)
ACCD, n (%)	17 (1,9)	9 (6,2)	1 (0,7)	1 (3,8)	0
DM, n (%)	42 (4,7)	17 (11,7)	19 (13,1)	9 (34,6)	7 (28)
Hypothyroidism, n (%)	53 (5,9)	10 (6,9)	11 (7,6)	0	1 (4)
Oncologic pathology, n (%)	7 (0,8)	3 (2,1)	4 (2,8)	0	0
HBS pathology, n (%)	9 (1)	2 (1,4)	2 (1,4)	2 (7,7)	0
BMI, kg/m^2 (SD)	25,9 (3,8)	27.1 (3,9)	27,7 (3,7)	27,76 (4,2)	28,15 (4,3)
<25, n (%)	319 (35,8)	47 (32,4)	30 (20,7)	6 (23,1)	5 (20)
25–29.9, n (%)	384 (43,1)	71 (49,0)	78 (53,8)	13 (50)	13 (52)
30–34.9, n (%)	80 (8,9)	21 (14,5)	30 (20,7)	5 (19,2)	5 (20)
35–39.9, n (%)	12 (1,4)	5 (3,4)	7 (4,8)	2 (7,7)	2 (8)
≥40, n (%)	3 (0,3)	1 (0,7)	0 (0,0)	0	0

Note: SD, standard deviation; IHD, ischemic heart disease; PICS, postinfarction cardiosclerosis; CAS, coronary artery stenting; CABG, coronary artery bypass grafting; ACCD, acute cerebral circulatory disorder; DM, type 2 diabetes mellitus; HBS, hepatobiliary system; BMI, body mass index.

comparable between the group of patients with preserved and reduced thyroid function: 5.9% vs. 6.5% (p = 0.262). In 15.3% of patients with HTG, suboptimal compensation of diabetes mellitus was identified as a possible cause (glycosylated hemoglobin content 8.58% ± 1.88%). The relative risk of HTG in patients with diabetes mellitus was 1.86 (95% CI 1.49–2.301, p < 0.0001).

No statistically significant differences in TG levels were observed among the subgroups of patients with cancer or hepatobiliary pathology (p = 0.531). HTG causes pancreatitis in approximately 10% of cases, and it can develop even in patients with a TG level of 5–10 mmol/L [8]. However, only three patients with moderately elevated TG levels and none with extremely high TG levels reported a history of pancreatitis. Elevated TG levels are only one of several possible risk factors for acute pancreatitis, as reported by a previous study [11].

In addition, it was found that among patients with normal TG levels, 64.2% were overweight or obese and 86.8% of patients with HTG levels were overweight or obese. The relative risk of increased body weight was 1.59 (95% CI 1.29–1.96). With increasing body mass index, HTG levels increased (Fig. 1). Furthermore, the relative risk of HTG increased with higher levels of obesity. Specifically, the relative risk was 1.45 (95% CI 1.16–1.8) for overweight patients, 1.98 (95% CI 1.52–2.59) for grade 1 obesity, and 2.57 (95% CI 1.75–3.78) for grade 2 obesity. However, the relative risk of grade 3 obesity was not statistically significant (1.16, 95% CI 0.21–6.38).

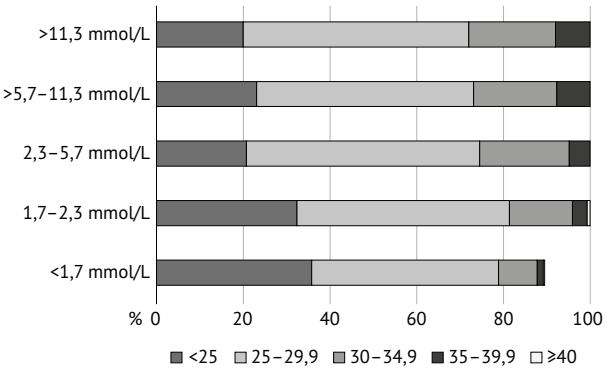

Fig. 1. Body mass index (kg/m^2) in patients with different HTG levels

Low-density lipoprotein cholesterol was calculated using the Friedwald formula:

Table 2. Frequency of detection of LDLR, APOB, APOE, and PCSK9 mutations in patients with hypertriglyceridemia

Characteristics	Triglyceridemia levels, mmol/L (n)				
	<1.7 (892)	1.7–2.3 (145)	>2.3–5.7 (145)	>5.7–11.3 (26)	>11.3 (25)
APOE, n (%)	90 (37.3)	17 (45.9)	14 (38.9)	4 (44.4)	1 (11.1)
LDLR, n (%)	50 (21.0)	11 (31.4)	5 (13.9)	1 (11.1)	1 (11.1)
APOB, n (%)	33 (13.7)	8 (21.6)	5 (13.9)	3 (33.3)	1 (11.1)
PCSK, n (%)	14 (5.9)	0 (0.0)	2 (5.3)	0	1 (10)

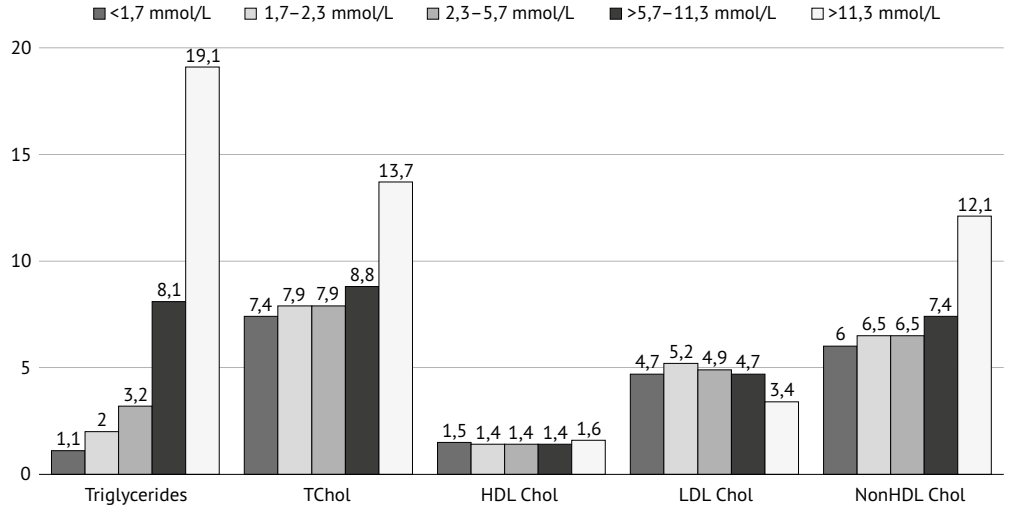

Fig. 2. Levels of major cholesterol fractions in patients with hypertriglyceridemia; Chol, cholesterol; TChol, total cholesterol; HDL, high-density lipoproteins; LDL, low-density lipoproteins; nonHDL, lipoproteins other than high-density lipoproteins

$$\text{LDL Chol} = \text{total Chol} (\text{HDL Chol} - \text{TG}/2.2),$$

where Chol refers to cholesterol, LDL refers to low-density lipoprotein, HDL refers to high-density lipoprotein, and TG refers to triglycerides.

In general, the calculation method is not applicable if the TG concentration is greater than 4.5 mmol/L [7]. Direct determination of low-density lipoprotein cholesterol also has several limitations, including the possibility of systematic error and inaccuracy when used in patients with dyslipidemia, particularly with high TG levels [7]. In this case, the level of nonhigh-density lipoprotein cholesterol can be estimated by calculating the difference between total cholesterol and high-density lipoprotein cholesterol. In patients with varying degrees of overweight, nonhigh-density lipoprotein cholesterol levels are comparable to total cholesterol and triglyceride levels (Fig. 2). When triglyceride levels are elevated, there may be an erroneous underestimation of high-density lipoprotein cholesterol and low-density lipoprotein cholesterol, which can lead to an underestimation of the risk of cardiovascular disease.

The genetic characterization of patients with HTG allowed estimating the frequency of LDLR, APOE, APOB, and PCSK9 gene carriage for the first time. Table 2 summarizes the results.

As observed in Table 2, there was no statistically significant difference in the detection frequency of various mutations of the LDLR, APOB, APOE, and PCSK9 genes between the groups of patients with normal and elevated TG levels ($p = 0.283$). Worth noting is the frequency of detection of the APOE isoforms. A total of 36 (10.6%) patients with HTG had different APOE mutations: 25% of cases increased the risk of cardiovascular diseases, whereas 10% decreased it. In addition, a previously undescribed variant of the APOE mutation was found.

The AROE isoforms E2, E3, and E4 are the most common. Among patients with HTG, the p. Cys130Arg mutation, which defines the APOE4 allele, is the most frequent AROE isoform associated with cardiovascular disease risk. It was reported that individuals with this allele exhibit a statistically significant increase in total cholesterol, low-density lipoprotein cholesterol, and TG levels compared with noncarriers. However, this increase does not reach the threshold for familial hypercholesterolemia. Thus, the risk of atherosclerotic diseases may be slightly elevated [12]. A correlation between the presence of AROE and an increased risk of stroke was observed [13], as well as an influence on the severity of coronary heart disease [14].

The most common variant of the AROE2 haplotype was p.Arg176Cys, which is associated with the slow conversion of intermediate-density lipoproteins to low-density lipoproteins, resulting in a decrease in plasma cholesterol and an increase in TG levels.

Approximately 10%–18% of individuals with the E2/E2 genotype develop dysbetalipoproteinemia, also known as type 3 hyperlipoproteinemia, which is a condition characterized by elevated total cholesterol and increased postprandial triglyceride content. Dysbetalipoproteinemia increases the risk of premature development of atherosclerosis, including coronary heart disease and peripheral arterial disease. Some patients may also experience cutaneous manifestations of dyslipidemia, such as tuberous or eruptive xanthomas, particularly on the elbows and knees, as well as palmar xanthomas in the skin folds of the hands and wrists.

Importantly, development of dysbetalipoproteinemia in patients with E2/E2 is associated with secondary risk factors such as obesity, diabetes mellitus, hypothyroidism, renal failure, and alcohol abuse. Therefore, implementing preventive programs aimed at eliminating these risk factors in patients with this genotype can help prevent the development of TG. This opens up a wide range of opportunities for the implementation of preventive cardiology measures.

Patients with persistent HTG and compensated "secondary" causes should be referred for genetic testing, the results of which may help determine the right treatment and management plan, such as primary or secondary prophylaxis.

Two patients were found to have both isoforms, E3 and E4. Six patients with HTG were confirmed to have familial hypercholesterolemia, and in two cases, the patients were carriers of a combination of ARB and AROE genes.

Conclusions

1. In patients with significant lipid metabolism disorders, elevated TG levels were found in 27.66% of cases, with a higher prevalence in women.

2. The most common forms of HTG are mild and moderate.

3. Severe or extremely severe HTG is not always associated with pancreatitis.

4. Elevated TG levels are more frequently associated with overweight, grade 1 and 2 obesity, and poorly compensated diabetes mellitus.

5. Elevated triglyceride levels may be due to a mutation in the AROE gene, which was found in 10.6% of patients with HTG.

6. The most common AROE mutation variant was p.Cys130Arg and p.Arg176Cys.

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