DOI: 10.4149/BLL_2023_008

Bratisl Med J 2023; 124 (1)
53 – 58

CLINICAL STUDY

The effect of *AGTR1, AGT, LPL, ADRB2* gene polymorphisms on central obesity in adolescents of the Kazakh population

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ABSTRACT
BACKGROUND: Abdominal obesity, usually measured by waist circumference and waist-to-hip ratio, is more closely related to metabolic dysfunctions that are associated with cardiovascular diseases than general obesity, which is usually assessed by body mass index. The purpose of our study was to study the distribution of alleles and genotypes *AGTR1, AGT, LPL* and *ADRB2* among adolescents of the Kazakh population and to identify the relationship of these genes with predictors of obesity.
METHODS: The study involved 184 adolescents aged 15–18 years of the Kazakh population.
RESULTS: As a result of the study, it was revealed that the G allele of the rs328 polymorphism of the *LPL* gene reduces the risk of developing abdominal obesity compared to the C allele.The C/G genotype reduces the risk of developing abdominal obesity. We have identified among the studied adolescents of the Kazakh population an increase in the ratio of waist volume (WV) to hip volume (HV) among boys, which may in the future lead to obesity and cardiovascular diseases in general.
CONCLUSION: It was also found that the G allele of the rs328 polymorphism of the *LPL* gene reduces the risk of abdominal obesity. Therefore, in addition to determining BMI, we recommend determining the ratio WV to HP. It was found that an increase in the ratio of WV/HV by 1 cm increases the chance of developing hypoapolipoproteinemia A1 *(Tab. 4, Fig. 1, Ref. 23)*. Text in PDF *www.elis.sk*
KEY WORDS: obesity, body mass index, waist-to-hip ratio, *AGTR1, AGT,* LPL, *ADRB2.*

Introduction

Worldwide, the prevalence of obesity in childhood and adolescence is becoming dramatic. In the developed countries of the world, up to 25 % of adolescents are overweight, and 15 % are obese (1). There are more than 80 million overweight or obese children and adolescents registered in Europe. According to the National Center for Health Statistics (NCHS) in the United States, one in five children is overweight or obese. In Russia, 5.5 % of children living in rural areas and 8.5 % of children in urban areas are obese (2, 3).

In Kazakhstan, there is an increase in the prevalence of obesity and overweight in accordance with global trends and remains alarming: 5 % of children from 10 to 19 years old are obese and 20 % of children are overweight. It is well known that being overweight in childhood is associated with being overweight or obese in adulthood, and there is a higher probability that such people will remain overweight with risk factors for concomitant diseases. In addition, it is a direct risk factor for metabolic syndrome: in children, obesity – especially with a high level of visceral adipose tissue – affects the composition of the serum metabolome and is associated with an increase in intima-media thickness, higher levels of lipids and blood pressure (4) and an increased risk of coronary heart disease in older age (5). It is known that central obesity (high ratio WV/HV) contributes to a higher risk than general obesity. However, to date there are no established thresholds for clinical practice with children and adolescents. There are several methods for assessing body fat content: magnetic resonance imaging (MRI), which allows measuring both visceral and subcutaneous adipose tissue; dual-energy X-ray absorptiometry (Dual-Energy-X-RAY), which is still the gold standard in most studies; hydrodensitometry and ultrasound. However, these examination methods are expensive, time-consuming, or involve radiation exposure, which makes them unsuitable for use in pediatric examinations or even as a screening tool.

Various waist and hip parameters and their combination with the body mass index (BMI) are useful for assessing the distribution of body fat and, consequently, for assessing risk factors for

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Acknowledgements: This work was supported by the startup project "Molecular genetic foundations for predicting the development of metabolic syndrome in the Kazakh population" on the basis of the NCJSC "Semey Medical University".

cardiovascular diseases, especially during puberty. Measurements of waist volume (WV) and hip volume (HV) are good predictors of the presence of intra-abdominal fat and risk factors for cardiovascular diseases, they are also cheap and simple anthropometric methods. In addition, various pediatric studies have shown that BMI systematically underestimates the prevalence of obesity compared to waist volume (6, 7).

Recent studies have been devoted to the study of polymorphic variants of genes in metabolic syndrome (MS) and arterial hypertension (AH) to determine their relationship with each other (8).

Using the biological candidate gene approach, more than 127 genes were associated with obesity and/or obesity-related phenotypes; while genome-wide associative studies (GWAS) identified more than 120 genes (the vast majority not previously identified as biological candidates) associated with obesity, mainly in European populations (9).

According to The Text-mined Hypertension, Obesity and Diabetes candidate gene database (T-HOD), candidate genes for hypertension, obesity, and type 2 diabetes mellitus (DM) were analyzed (10). Considering the pathogenesis of MS, we selected the following candidate genes: encoding angiotensin II type I receptor (AGTR1); angiotensinogen synthesis (AGT); β2 – adrenergic receptor (ADRB2) and lipoprotein lipase (LPL).

AGTR1, *AGT* belong to candidate genes of the renin – angiotensin – aldosterone system (RAAS) (8). Genetic variations of the genes encoding RAAS have a strong connection with the genetic basis of hypertension and metabolic syndrome (11). According to some authors, the renin-angiotensin system (RAS) is a possible link with obesity (12).

ADRB2 and *LPL* were selected to study lipid metabolism. Of these, the *ADRB2* gene encodes a β2 – adrenoreceptor, which is activated by adrenaline and causes increased glycogenolysis in muscles, increases the secretion of insulin, glucagon, increases heart contraction, thereby affecting lipid and carbohydrate metabolism. The *LPL* gene encodes the enzyme lipoprotein lipase, which releases fats from chylomicrons and VLDL, and is also responsible for the breakdown of triglycerides.

Therefore, the study of the role of polymorphic gene variants on the risk of obesity among adolescents of the Kazakh population is relevant.

The aim of this study was to study the distribution of alleles and genotypes *AGTR1, AGT, LPL* and *ADRB2* among adolescents of the Kazakh population and to identify the relationship of these genes with predictors of obesity.

Materials and methods

This study was conducted among adolescents of the Kazakh population aged 15 to 18 years in Semey, East Kazakhstan region. The subjects of the study were overweight/obese and non-overweight/non-obese adolescents. The exclusion criteria were adolescents with the presence of malignant neoplasms; patients with cardiac and/or renal insufficiency in the decompensated stage; patients with mental illnesses; pregnant women.

The study was conducted within the framework of a startup project on the topic "Molecular genetic foundations for predicting the development of metabolic syndrome in the Kazakh population" on the basis of the NCJSC "Semey Medical University". The approval of the Ethics Committee of the NCJSC "SMU" was received on 27.09.2017; protocol number No.11. This study meets the requirements of the Helsinki Declaration developed by the World Medical Association in 1964 with subsequent revisions in 2013. All participants of the study were informed about the objectives of the study and the upcoming procedures; all received informed written consent to participate in the study.

Height, weight, HV, WV were measured for all study participants and BMI was calculated using the formula BMI = weight (kg)/height (m^2) (according to WHO requirements) and the HV/WV ratio was determined. To clarify the BMI value, the type of fat distribution in the body was determined in all the examined individuals. To do this, HV and WV were measured. The ratio of HV to WV is a simple method of characterizing the distribution of fat in the human body. It increases with age in both, those with severe obesity and those predisposed to it. The calculation of the ratio HV to WV characterizes the localization of the predominant fat deposition and the type of obesity. The circumference HV and WV was measured using a tape measure. HV was measured as the smallest circumference between the thorax and the upper border of the iliac crest at the end of exhalation. WV was measured on large spits in the widest part of the thigh. The ratio of HV/WV was calculated as the ratio of HV (cm) to WV (cm), the indicators of which corresponded to the recommendations of the International Diabetes Federation (IDF) used for older adolescents and adults.

Venous blood collected in vacuum tubes with K2/K3 EDTA was used for the study. Genomic DNA was isolated from blood using the Gene JET Thermo Scientific kit (Lithuania). The isolated DNA was frozen and stored at -20 °C. Quantitative and qualitative assessment of the isolated DNA was carried out using a nanospectrophotometer (Nanofhotometer P30) and electrophoretically in an agarose gel. Genotyping was performed by PCR in real-time mode on a CFX 96 device (BioRad, CA,USA) for 96 samples (25mcl) using ready-made mixtures of primers and TaqMan probes in the presence of the TaqMan Genotyping Mastermix reagent (Russia). The primer sets were as follows:

AGTR1 (rs5186) direct, 5'-CCAAATGAGCATTAGCTACTT-3' and reverse, 5'-GTTTACTCGTAATCGATGAA-3';

AGT (rs4762) direct, 5'-CCACCACCGTGGACAGCAG-3' and reverse, 5'-CGGGTGGTGGCACCTGTCGTC-3';

ADRB2 (rs1042714) direct, 5'-CGTCACGCAGGAAAGGGACGA-3' and reverse 5'-GCAGTGCGTCCTTTCCCTGCT-3';

LPL (rs328) direct,5'-AATAAGAAGTCAGGCTGGTGA-3' andreverse, 5'-TTATTCTTCAGTCCGACCACT-3'.

The amplification program for SNP *AGTR1* (rs5186), *AGT* (rs4762), *ADRB2* (rs328) included pre-denaturation at 95 °C for 3 minutes, followed by 40 cycles of 95°C for 15 seconds and 65°C for 40 seconds. The reagents were manufactured by Synthol, Moscow, Russia. For SNP *LPL* (rs328), the amplification program included a pre-denaturation stage of 93 °C for 1 min, then 35 cycles at 93

°C for 10 seconds, 64°C for 10 seconds and 72 °C for 20 seconds. The reagent was manufactured by Lytech, Moscow, Russia.

Statistical analysis

The data were analyzed using the IBM SPSS Statistics Version 21 statistical package (International Business Machines Corp, Armonk, NY, USA), the associative signal was characterized by the odds ratio (OR), its 95 % confidence interval and statistical significance (p value). The comparison between the groups was carried out using multidimensional logistic regression analysis. Gender and age data were taken into account in the associative genetic analysis. The frequencies of alleles and genotypes were determined by the observed genotype counts, and the Hardy–Weinberg equilibrium extensions were evaluated using the criterion χ^2. The differences were considered statistically significant at a value of $p < 0.05$.

Results

The study involved 184 adolescents of the Kazakh population. Of these, boys n = 62, girls n = 122. Among boys, the average age was 16 (95 %: 15.77–16.23) years, among girls, the average age was 16.07 (95 %: 15.90–16.23) years. The average BMI in boys was 23.61 (95 %: 22.75–24.46), and in the girls 22.01 (95 %: 21.39–22.63). We also analyzed the ratio of HV/WV, where the average for boys was 0.82 (95 %: 0.80–0.85) and for girls 0.81 (95 %: 0.80–0.82).

The frequency of prevalence of alleles and genotypes of polymorphisms of the genes *AGTR1/(A1166C), AGT/(Thr174Met), ADRB2/(Gln27Glu)* and *LPL/(Ser447Ter)* can be seen in Table 1. In the distribution of genotypes, a deviation from the Hardy–Weinberg equilibrium was detected only among the genotypes *AGTR1/A1166C* (rs5186) (p = 0.042). When studying the epidemiology of the *A1166C* polymorphism of the *AGTR1* gene among Kazakh adolescents, the A allele was more common than the C allele (Tab. 1). Analysis of the prevalence of the *Thr174Met* polymorphism of the *AGT* gene among adolescents of the Kazakh population showed that the G allele is more common by 9% than the A allele (Tab. 1). And when studying the occurrence of C and G alleles of *Gln27Glu* and *Ser447Ter* polymorphisms among adolescents of the Kazakh population, the G allele was less common than the C allele (Tab. 1). When analyzing the prevalence of genotypes of polymorphisms *Gln27Glu* and *Ser447Ter* of the *LPL* and *ADRB2* gene among Kazakh adolescents, we found that the CC genotype was more common than other genotypes of these genes. Also when considering polymorphs.

We also conducted a comparative analysis of the frequency distribution of the above polymorphisms and revealed a significant relationship with the *LPL* gene and with the ratio HV to WV (p = 0.013), with other polymorphisms we found no relationship with the ratio HV to WV and the odds ratio for the CG genotype was 0.388 (CI: 0.181–0.830), and for the GG genotype 0.507 (CI: 0.120–2.146). We also found that CG+GG genotypes reduce the risk of developing central obesity (Tab. 2).

When performing a multidimensional logistic regression, it was revealed that the G allele of the rs328 polymorphism of the *LPL* gene reduces the risk of developing central obesity compared to the C allele. The C/G genotype reduces the risk of developing central obesity 0.39 times, compared with the C/C and G/G genotypes. And the dominant model of the rs328 polymorphism of the *LPL* gene showed that the C/G+G/G genotype reduces the risk of central obesity 0.40 times compared to the C/C genotype. It was also found that in the overdominant rs328 polymorphism model of the *LPL* gene, the C/G genotype reduces the risk of developing central obesity 0.43 times than the C/C+G/G genotypes. An additive model of the rs328 polymorphism of the *LPL* gene showed that the G/G +C/G genotype reduces the risk of developing central obesity 0.55 times (Tab. 3). When performing multidimensional logistic regression with polymorphisms rs5186, rs4762, rs1042714, no relationship with the ratio of WV to HV was found (Tabl.3).

We revealed a significant relationship of the *LPL* gene with the ratio WV to HV and found that the rs328 polymorphism of the *LPL* gene is associated with the risk of central obesity in adolescents of the Kazakh population and the G allele reduces the risk of developing central obesity 0.39 (95% CI: 0.18–0.83) times compared with the Sertic allele et al also The correlation of abdominal obesity with LPL genotypes was proved (13). In studies by Emdin et al genetic predisposition to a higher ratio of WV to HV and BMI

Tab. 1. Frequency of alleles and genotypes by polymorphisms of the genes *AGTR1, AGT, ADRB2* and *LPL* among adolescents of the Kazakh population.

Gene	SNP	Allele, n (%)	Genotype, n (%)	The Hardy-Weinberg equilibrium *p*
AGTR1	rs5186	A: 312 (85) C: 56 (15)	AA: 136 (74) AC: 40 (22) CC: 8 (04)	0.042
AGT	rs4762	G: 332 (9) A: 36 (1)	GG: 150 (82) GA: 32 (17) AA: 2 (0,01)	0.68
LPL	rs1042714	C: 255 (69) G: 113 (31)	CC: 83 (45) CG: 89 (48) GG: 12 (0,07)	0.083
ADRB2	rs328	C: 281 (76) G: 87 (24)	CC: 106 (58) CG: 69 (38) GG: 9 (0,05)	0.69

Tab. 2. Comparative analysis of the frequency distribution of the Ser447Ter polymorphism of the LPL gene in adolescents of the Kazakh population with a ratio ofWV/HV.

Genotypes	Frequency of genotypes		Significance level	OR	
	case	control	*p**	meaning	95%
CC	12	71		1.00	
CG	27	62	p=0.013	0.388	0.181–0.830
GG	3	9		0.507	0.120–2.146

*– criteria x^2

Tab. 3. rs328 relationship with the ratio WV to HV.

Model	Genotype	case	control	OR (95%)	R
Codominant	C/C	12 (28.6%)	71 (50%)	1.00	0.042
	C/G	27 (64.3%)	62 (43.7%)	**0.39 (0.18–0.83)**	
	G/G	3 (7.1%)	9 (6.3%)	0.51 (0.12–2.15)	
Dominant	C/C	12 (28.6%)	71 (50%)	1.00	0.013
	C/G-G/G	30 (71.4%)	71 (50%)	**0.40 (0.19–0.84)**	
Recessive	C/C-C/G	39 (92.9%)	133 (93.7%)	1.00	0.85
	G/G	3 (7.1%)	9 (6.3%)	0.88 (0.23–3.41)	
Overdominant	C/C-G/G	15 (35.7%)	80 (56.3%)	1.00	0.018
	C/G	27 (64.3%)	62 (43.7%)	**0.43 (0.21–0.88)**	
Log-additive	–	–	–	**0.55 (0.31–0.97)**	0.038

Tab. 4. Multiple logistic regression between WV/HV ratio and apolipoproteins A1.

Parameters	B	OR (95%CI)	p
Ratio WV/HV			
ApoA1	–1.11	1.32 (1.10–3.44)	0.005

was associated with an increased level of quantitative risk factors (lipids, insulin, glucose and systolic blood pressure), as well as a higher risk of type 2 diabetes (14). These data confirm the genetic support of previous observations of abdominal obesity and cardiometabolic disease (15, 16).

In this study, we found high ratios of WV to HV among boys, which is consistent with other studies conducted among young people in Europe (17). As some studies have shown , the determination of the ratio WV/HV is a more accurate tool for diagnosing obesity and a better prediction of associated health risks than BMI (18, 19).

We also found that the dominant rs328 polymorphism model of the *LPL* gene is associated with the risk of developing central obesity. The C/G genotype reduces the risk of developing central

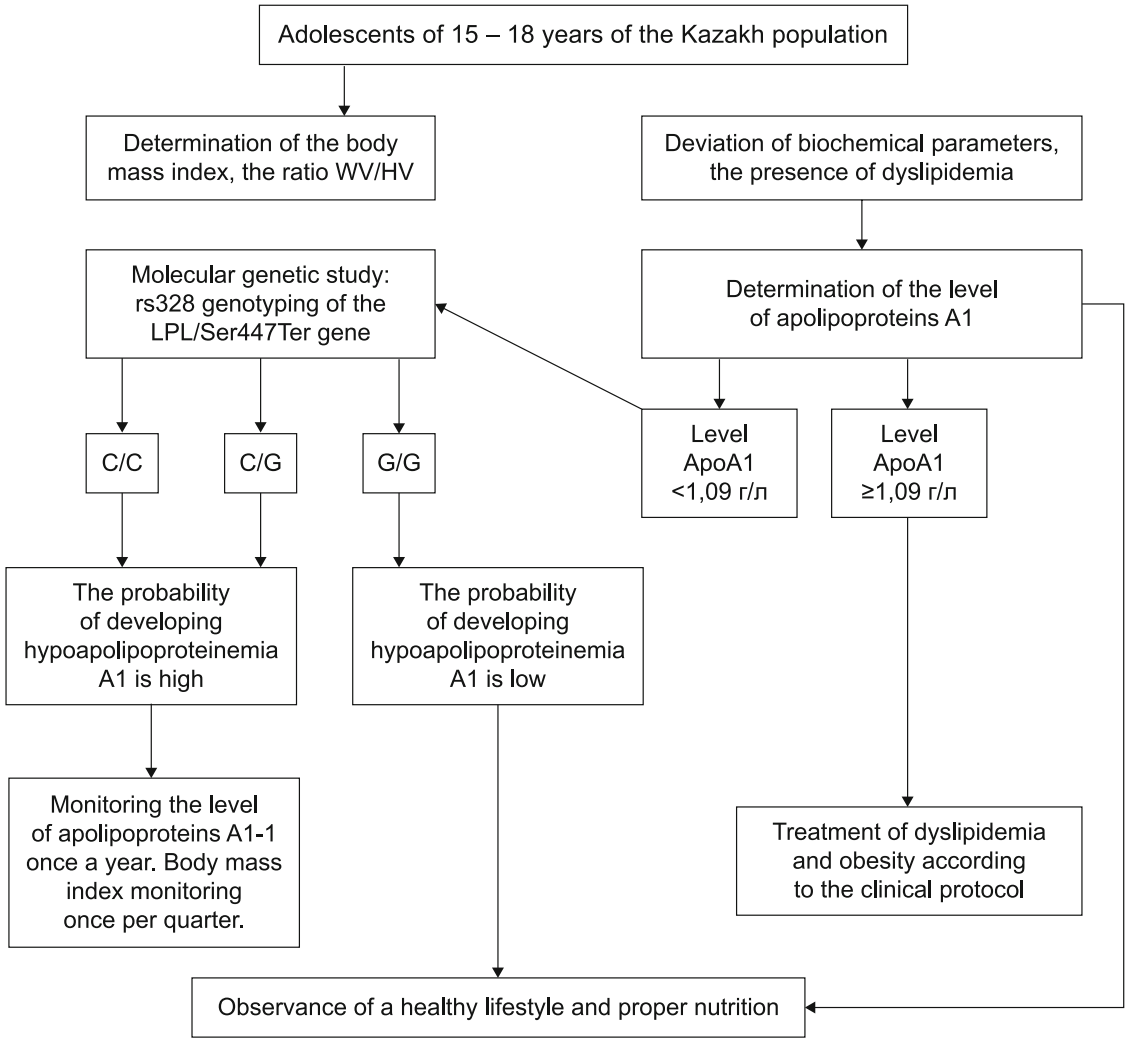

Fig. 1. Obesity prediction algorithm based on molecular genetic analysis.

obesity 0.39 times compared to the C/C and G/G genotypes, and the C/G+G/G genotypes of the dominant model reduce the risk of developing central obesity 0.40 times compared to the C/C genotype. Karen E. Smith and co-authors also conducted a study among Latinos and identified the interaction between *LPL* and *APOA5* with antpropometric indicators such as height, weight, WV and HV in obesity (20).

During the multidimensional logistic regression of polymorphisms rs5186, rs4762, rs1042714 with the ratio WV to HV, no connection was found. In studies by Li S. et al. *LPL Ser447Stop* polymorphism was not associated with BMI in childhood and adulthood, nor with the annual change in BMI from childhood to adulthood, both in black and white subjects (21). In some studies, it has been proved that the *Arg16Gly ADRB2* polymorphism is largely associated with obesity in Taiwanese adolescent girls (22).

We also compared the average values of biochemical indicators by sex and the difference in average indicators was found only in ApoA1 indicators ($p = 0.002$), and for other indicators, such as TCH, HDLP, LDLP, TRG, glucose, insulin, IR, ApoB, there was no difference between the sexes, and when considering the average values of biochemical parameters, a difference in the mean values between the ApoA1 groups was revealed in the levels of HDLP, insulin, insulin resistance index and ApoB. According to other biochemical parameters, no difference in average values between the ApoA1 groups was detected (23)

We performed multiple logistic regression between the ratio of WV/HV with apolipoproteins A1 and obtained a significant model (Tab. 4).

The observed dependence is described by the equation $r = 1/(1+e\text{-}z)*100\%$

$z = –0.282+(–2.62)*X_{AnoA1}$

where r – is the probability of having central obesity (%), $X^{a\text{-}}_{poA1}$ – is the presence of hypoapolipoproteinemia A1.

The resulting regression model is statistically significant ($p = 0.005$). Based on the value of the Nigelkirk coefficient, the model takes into account 3.7 % of the factor determining the probability of the development of hypoapolipoproteinemia A1. Based on the values of regression coefficients, the BMI factor has a significant relationship with the probability of developing hypoapolypoproteinemia A1. An increase in BMI by 1 kg/m^2 increased the chances of hypoapolypoproteinemia A1 ($p = 0.005$) 1.32 times (1.10–3.44).

When constructing a logistic regression between the ratio of WV/HV and apolipoproteins A1, it was found that an increase in WV/HV increases the risk of developing hypo-apolipoproteinemia A1 1.32 times.

Based on the results obtained, we have developed an algorithm for predicting the risk of obesity among adolescents based on molecular genetic analysis (Fig. 1).

This algorithm includes the determination of the body mass index, the ratio of WV /HV, by measuring weight and height, waist and hip volume in adolescents from 15 to 18 years of the Kazakh population. Biochemical analyses (glucose, cholesterol, triglycerides, lipoproteins) will be determined in overweight and/or obese persons with an increased WV/HV ratio. Adolescents with abnormalities in biochemical analysis (hyperglycemia, hypercholeserinemia, hypertriglyceridemia, dyslipidemia) will be sent to have the level of apolipoprotein A1 determined. Persons with hypo-apolipoproteninemia A1 are sent for molecular genetic analysis, where the polymorphism of the *LPL/Ser447Ter* (rs328) gene is determined using polymerase chain reaction (PCR) in Real-time mode. Adolescents with a high risk of developing hypoapolipoproteinemia A1 (presence of the CC and SG genotype) will be monitored in the polyclinic and once a year the level of apolipoprotein A1 is monitored. Adolescents with low risk of development (presence of genotype G/G) hypoapolipoproteins

Based on this algorithm, it is possible to predict the risk of developing obesity in adolescents of the Kazakh population, which will allow timely prevention of lipid metabolism disorders, which will help prevent the development of overweight and /or obesity, diabetes mellitus, metabolic syndrome and cardiovascular diseases.

Discussion

We revealed a significant relationship of the *LPL* gene with the ratio WV to HV and found that the rs328 polymorphism of the *LPL* gene is associated with the risk of central obesity in adolescents of the Kazakh population and the G allele reduces the risk of developing central obesity 0.39 (95 % CI: 0.18–0.83) times compared with the C. J. allele. Serticet.al also proved correlation of abdominal obesity with *LPL* genotypes (13). In studies by Emdin et al genetic predisposition to a higher ratio of OT to OB and BMI was associated with an increased level of quantitative risk factors (lipids, insulin, glucose and systolic blood pressure), as well as a higher risk of type 2 diabetes (14). These data confirm the genetic support of previous observations of abdominal obesity and cardiometabolic disease (15, 16).

In this study, we found high ratios of WV to HV among boys, which is consistent with other studies conducted among young people in Europe (17). As some studies have shown, the determination of the ratio WV/HV is a more accurate tool for diagnosing obesity and a better prognostic marker of associated health risks than BMI (18, 19).

We also found that the dominant rs328 polymorphism model of the *LPL* gene is associated with the risk of developing central obesity. The C/G genotype reduces the risk of developing central obesity 0.39 times compared to the C/C and G/G genotypes, and the C/G+G/G genotypes of the dominant model reduce the risk of developing central obesity 0.40 times compared to the C/C genotype. Karen E. Smith and co-authors also conducted a study among Latinos and identified the interaction between *LPL* and *APOA5* with anthropometric indicators such as height, weight, WV and HV in obesity (20).

During the multidimensional logistic regression of polymorphisms rs5186, rs4762, rs1042714 with the ratio WV to HV, no connection was found. In studies by Li et al *LPL Ser447Stop* polymorphism was not associated with BMI in childhood and adulthood, nor with the annual change in BMI from childhood to adulthood, both in black and white subjects (21). In some studies, it has been proved that the *Arg16Gly ADRB2* polymorphism is largely associated with obesity in Taiwanese adolescent girls (22).

Conclusions

As a result of the study among the studied adolescents of the Kazakh population, an increase in the ratio of WV to HV among boys was revealed.

It was also found that the G allele of the rs328 polymorphism of the *LPL* gene reduces the risk of developing central obesity. Therefore, in addition to determining BMI, we recommend determining the ratio WV to HV. It was found that the G allele of the rs328 polymorphism of the *LPL* gene reduces the risk of developing hypo-apolipoproteinemia A1 in adolescents of the Kazakh population. Further work is needed to study the relationship between the ratio of WV to HV with obesity and morbidity in adolescents. With an increase in the WV to HV ratio by 1 cm, the chance of developing hypoapolipoproteinemia A1 increases.

In addition, an algorithm for predicting the development of obesity based on molecular genetic analysis is proposed.

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Received July 26, 2022.
Accepted August 24, 2022.