THE INFLUENCE OF SHBG AND LPL GENE POLYMORPHISMS ON LIPID METABOLISM PARAMETERS IN OVERWEIGHT MEN

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Abstract

Background: The relevance of this problem is determined by the high prevalence of obesity among older men. Studying the role of genetic variations of the Sex hormone–binding globulin and lipoprotein lipase transport proteins in the mechanisms of regulation of lipid metabolism is important for researchers investigating metabolic disorders. It also provides a basis for personalized strategies for the treatment and prevention of age-related hypogonadism.

Materials and methods: The association between polymorphisms (rs727428, rs10822184) and lipoprotein lipase (rs754493647) and lipid metabolism disorders in overweight Kazakh men has been examined for the first time in a cohort of 235 Kazakh men residing in Semey city, Abai region. The main group included overweighed men with a body mass index of 25-29.9 kg/m2 (n=70), and the control group indicated a normal BMI of up to 25 kg/m2 (n=145). Genotyping of single nucleotide polymorphisms rs727428[C/T], rs10822184 [C/T], and rs75449364 [C/T] was performed by the TagMan method.

Results: Polymorphism rs 10822184 demonstrated an increase in triglyceride and lipoprotein lipase levels in the TT genotype ($p \leq 0.04$) compared to the CC and TT genotypes. An association was found between rs 727428 and albumin ($p = 0.03$) and testosterone ($p = 0.001$).

Conclusions: In men of Kazakh ethnicity, triglyceride and lipoprotein lipase levels are associated with rs10822184, while rs727428 polymorphism is associated with total testosterone levels. In older men, a change in Sex hormone–binding globulin concentration is a predictor of lipid profile disorders.

Introduction

Excess weight and obesity represent pressing health issues among older men. These conditions display a wide range of adverse effects on overall health and contribute to the progression of age-related hypogonadism.

A decrease in testosterone levels and its biologically active fractions leads to alterations in male body composition, characterized by an increase in adipose tissue and a reduction in muscle mass.

This interplay creates a self-perpetuating cycle of obesity and hypogonadism.[1] Moreover, excess body weight and obesity are closely associated with disturbances in lipid metabolism.

In older men, fat deposition occurs mainly in the abdominal area, acting as a key contributor to hormonal and lipid dysregulation and thereby hastening the development of hypogonadism.[2]

The pathogenesis of lipid metabolism disorders is influenced by both external factors (such as diet and physical activity) and genetic predisposition. Sex hormone–binding globulin (SHBG) and lipoprotein lipase (LPL) are key regulators involved in the control of lipid metabolism.[3] SHBG, the primary transport protein for androgens, is synthesized in the liver and binds testosterone, thereby regulating its bioavailability to target cells.[4]

Individuals who are overweight or obese often exhibit altered SHBG levels, which can directly affect lipid metabolism. These alterations are associated

with the development of atherosclerosis, hyperlipidemia, and other metabolic disorders.[5]

In men, SHBG levels affect various aspects of metabolism, including lipid metabolism, insulin levels, and insulin sensitivity. They also affect the development of dyslipidaemia, a condition in which there are abnormalities in blood lipid levels.[6] Polymorphisms in the genes encoding GSPG can significantly alter its levels in the body. Some genetic variations can lead to elevated or reduced levels of this protein in the blood, which in turn can affect the concentration of free sex hormones and, as a result, lipid metabolism.[7] Studies have shown that in overweight people, changes in SHBG levels may be associated with an abnormal lipid profile, increased levels of 'bad' cholesterol (LDL) and triglycerides, and decreased levels of 'good' cholesterol (HDL). However, the exact mechanisms through which SHBG gene polymorphism affects lipid metabolism in overweight men remain unclear.

LPL plays a crucial role in the breakdown of triglycerides, primarily in the capillaries of muscle tissue. The functional activity of LPL is largely determined by genetic variants (polymorphisms) of the LPL gene. This affects the metabolic processes associated with adipose tissue metabolism.[8] The relevance of this problem is determined by the high prevalence of obesity among older men. It is also closely linked to various metabolic disorders. Understanding the role of SHBG and LPL gene polymorphisms in the regulation of lipid metabolism in older men may lead to more effective strategies for the treatment and prevention of diseases associated with metabolic disorders.

The purpose of the study is to investigate the influence of polymorphisms in the SHBG and LPL genes on the parameters of lipid metabolism in overweight Kazakh men.

Materials and methods

The study involved 235 men of Kazakh ethnicity. All participants resided in the city of Semey, Abai region. The subjects were divided into two groups and stratified according to body mass index (BMI). The main group consisted of overweight individuals with a BMI of 25-29.9 kg/m² (n=70), while the control group included individuals with a normal BMI of up to 25 kg/m² (n=145).

Body Mass Index (BMI) was calculated using the formula: weight in kilograms divided by the square of height in meters (BMI =weight (kg) /height (m^2))

Body weight was measured with participants wearing only underwear and no shoes.

Inclusion criteria:

1. Male participants of Kazakh ethnicity, aged 35–79 years;
2. Availability of informed consent to participate in the study;
3. Presence of overweight (BMI 25–29.9 kg/m²).

Exclusion criteria:

1. Age below 35 or above 79 years;
2. Presence of diabetes mellitus;
3. Decompensated cardiovascular or renal failure.
4. Current cigarette smoking;
5. BMI below 25 kg/m² or above 30.0 kg/m².

Laboratory tests

Levels of high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and albumin were determined using commercial assay kits from *Roche Diagnostics GmbH* (*Germany*) on a Cobas 8000 analyzer (*Roche Diagnostics, Switzerland*) in the certified INVIVO laboratory.

The reference ranges were as follows HDL- 0.78- 2/2 mM/L, LDL- 2.33- 5.31 mM/L, triglycerides- 1.7- 2.25 mM/L and albumin- 35- 55 g/L.

Androgen status parameters — sex hormone-binding globulin (SHBG), luteinizing hormone (LH), and total testosterone — were analyzed using the *ARCHITECT i2000SR system* (*Abbott Laboratories, IL, USA*) with diagnostic kits in the certified INVIVO laboratory.Reference values for SHBG- 10- 57 nM /L, LH- 1.14- 8.75 mIU/mL, total testosterone- 5.41- 19.54 nM /L.

Fry testosterone was calculated using the online calculator http://www.issam.ch/freetesto.htm, developed by the Department of Endocrinology, Ghent University Hospital, Belgium. The online calculatorincorporated values of total testosterone, SHBG, and total albumin to estimate both free testosterone and biologically available testosterone levels.

Peripheral venous blood samples were collected for genetic testing. Genomic DNA was extracted using the *GeneJET Mini Kit* (*Thermo Scientific, Vilnius, Lithuania*) according to the manufacturer's protocol. DNA concentration was quantified using a Qubit 4 fluorometer (*Thermo Scientific, MA, USA*). The isolated DNA samples were stored at –20 °C until further analysis.

Genotyping was performed by real-time polymerase chain reaction (PCR) using a CFX96 *Touch Real-Time PCR System* (*Bio-Rad, CA, USA*) with predesigned TaqMan® probes and *TaqMan® Genotyping Master Mix* (*Life Technologies, Foster City, CA, USA*) for the *rs727428*, *rs5934505, and rs10822184* gene polymorphisms.

The total reaction volume for each well (96-well plate format) was 25 µL, comprising 12.5 µL of 2× TaqMan Master Mix, 1.25 µL of 20× probe mix, and 11.25 µL of genomic DNA (20 ng).

The PCR amplification protocol consisted of an initial denaturation at 95 °C for 10 minutes, followed by 15 cycles of denaturation at 92 °C and annealing at 60 °C for 90 seconds for all polymorphisms.

Ethical approval The study was approved by the Local Ethics Committee of Semey Medical University (Protocol No. 11, February 2, 2022) All participants provided written informed consent prior to enrollment. The study procedures complied with the ethical standards of the Declaration of Helsinki of the World Medical Association (WMA).

Statistical analyses The statistical analysis was performed using IBM SPSS Statistics Version 21 (*International Business Machines Corp., Armonk, NY, USA*). To analyze the descriptive statistics of quantitative variables when comparing independent samples, the non-parametric Mann–Whitney and Kruskal–Wallis tests were used. The differences between samples were considered statistically significant at $p < 0.05$. The distribution of alleles and genotypes was compared using the x2 criterion, where differences between samples were considered statistically significant at a value of $p \leqslant 0.004$ (taking into account the correction for multiple comparisons).

Results

When analyzing the age parameter, the difference between men in the main (46 ± 7.9) and control (51.43 ± 7.6) groups was 5 years. However, this indicator was not statistically significant (p=0.7). When comparing the parameters of the lipid profile, there was a noticeable increase in the level of triglycerides in the main group (2.76 ± 1.6), the reference value (1.7- 2.25 mM/l). The analysis of hormonal status in men of the main group showed a decrease in total testosterone (10.62 ± 2.4) and SHBG (25.96 ± 10.7) compared with the control group (total testosterone (11.98 ± 3.4), SHBG (33.43 ± 13.6), without achieving statistical significance. There was also an increase in free testosterone (2.52 ± 0.6) and luteinizing hormone (4.30 ± 2.3) in the main group compared with the indicators in the control group (2.14 ± 0.6) (4.08 ± 1.8) accordingly (Table 1).

Table 1.
Demographic indicators

Indicators	Main group, (n=70)	Control group, (n=130)	P value
Age (years)	46 ± 7.9	51.43 ± 7.6	0.759
BMI (kg/m²)	35.44 ± 3.4	24.73 ± 2.4	0.004*
Total testosterone (nM /L)	10.62 ± 2.4	11.98 ± 3.4	0.086
Free Testosterone (nmol / L)	2.52 ± 0.6	2.14 ± 0.6	0.325
Sex hormone binding globulin (nM /L)	25.96 ± 10.7	33.43 ± 13.6	0.226
Luteinising hormone (mIU/mL)	4.30 ± 2.3	4.08 ± 1.8	0.705

Triglycerides (mM/L)	2.76 ± 1.6	1.95 ± 1.4	0.164
High-densitylipoproteins (mM/L)	1.39 ± 1.4	1.36 ± 1.1	0.446
Low-density lipoproteins (mM/L)	3.89 ± 0.7	3.29 ± 0.7	0.963
Albumin (g/l)	44.36 ± 5.1	42.56 ± 4.9	0.857

To conduct genetic analysis TagMan technology was applied in real time.

The frequency of rare alleles was similar in patient groups and in the control group, amounting to approximately 0.1 for *rs727428* and 0.04 for *rs10822184*. No Hardy-Weinberg deviation was detected in any of the groups ($p > 0.05$). This indicates the absence of technical errors in the genotyping results.

When studying the *rs754493647* [A/G] polymorphism of the LPL gene, all Kazakh men with excess weight and normal weight had the GG genotype (100%), which was comparable to the data from the 1000Genomes project (1000 Genomes, http://www.1000genomes.org/).

Table 2.
Association analysis of gene polymorphisms between the main and control groups

Genotypes	Main group, n (%) (n=70)	Control group, n (%) (n=130)	P value	x^2
rs727428				
CC	20 (27)	52 (40)		
CT	34 (48)	54 (42)	0.199	3.238
TT	18 (26)	24 (18)		
rs10822184				
CC	14 (20)	28 (22)		
CT	32 (46)	76 (58)	0.047*	6.129
TT	24 (34)	26 (20)		

*P value < 0.05 statistically significant
CC, CT and TT are genotypes reflecting the homozygous (CC, TT) or heterozygous (CT) state for the allele of a given SNP.

Data on the association of polymorphisms *rs727428* and *rs10822184* with lipid profile and sex hormone levels in the study population are presented in Table 3.

Table 3.
Association between genotypes, lipid profile and androgen status in the study population

Biochemical indicators	Genotypes			P value
	CC	CT	TT	
	rs727428 Me (Q1-Q3)			
Triglycerides	1,9 (1,1-2,7)	1.7 (1.0-2.8)	2.1 (1.2-2.6)	0.8
HDL	1.1 (0.9-1.2)	1.2 (0.9-1.5)	1.1 (0.8-1.2)	0.06
LDL	3.3 (3.0-3.8)	3.4 (3.1-4.0)	3.3 (2.9-3.8)	0.8
Albumin	43.6 (41.6-45.6)	44.7 (42.5-47.1)	43.5 (36.7-45.4)	0.03*
Total testosterone Free testosterone SHBG Luteinising hormone	11.7 (10.2-14.4) 2.5 (1.6-2.8) 33.1 (19.5-41.1) 4.1 (2.9-5.4)	10.5 (9.6-12.3) 2.3 (1.8-2.7) 27.6 (17.9-39.1 3.5 (2.5-4.4)	10.3 (9.0-11.3) 2.3 (1.7-2.6) 36.9 (22.6-40.7) 3.9 (3.0-5.2)	0.001* 0.6 0.07 0.1
rs10822184 (Q1-Q3)				
Triglycerides	1.8 (1.0-2.4)	1.7 (1.0-2.5)	2.2 (1.6-3.1)	0.04*
HDL	1.2 (0.9-1.3)	1.1 (1.0-1.3)	1.0 (0.9-1.3)	0.5
LDL	3.4 (3.1-3.8)	3.2 (2.8-3.8)	3.7 (3.1-4.0)	0.01*
Albumin	44.0 (41.6-46.3)	44.4 (42.6-45.8)	43.5 (38.4-45.0)	0.1

Total testosterone Free testosterone SHBG Luteinising hormone	11.3 (9.5-12.8) 2.5 (1.6-2.8) 28.6 (19.5-41.2) 3.6 (2.7-4.3)	10.2 (9.1-12.0) 2.0 (1.6-2.6) 33.4 (18.2-40.9) 4.0 (2.5-5.2)	11.2 (10.1-12.1) 2.5 (2.1-2.8) 31.2 (22.7-37.2) 4.1 (3.2-5.2)	0.9 0.5 0.3 0.1
CC, CT and TT are genotypes reflecting the homozygous (CC, TT) or heterozygous (CT) state for the allele of a given SNP.				

Polymorphism 727428 showed that the albumin level in the CT genotype is higher than in the CC and TT genotypes (p= 0.03). In this polymorphism, the CC genotype shows an increase in the level of total testosterone (p= 0.001). Polymorphism 10822184 showed an increase in triglycerides and LDL levels in the TT genotype (p < 0.04) compared with the CC and TT genotypes.

Discussion

This study is the first to examine the associations between single nucleotide polymorphisms *rs727428, rs10822184,* and *rs754493647* and their relationship with lipid metabolism in overweight men. Excess body weight, especially abdominal obesity, is stated as the key pathogenetic factors exacerbating age-related hypogonadism in men.[2,9] Carriers of mutant forms of LPL often have an increased risk of dyslipidaemia and cardiometabolic diseases. In men who are overweight and insulin resistant, the effect of unfavourable LPL polymorphisms may be more pronounced, which highlights their importance as genetic risk factors for lipid metabolism disorders.[10] Thus, genetic variability of LPL contributes significantly to individual characteristics of lipid metabolism and can be considered an important biomarker for assessing predisposition to metabolic syndrome and cardiovascular disease.

In our study, in Kazakh men of both analyzed groups, the *rs754493647* [A/G] polymorphism of the LPL gene is represented exclusively by the GG genotype (100%), which indicates the absence of an association of this polymorphism with lipid metabolism disorders in this sample.

The SHBG gene polymorphism appears to influence not only circulating levels of sex hormone-binding globulin but also the regulation of lipid metabolism. It is well established that, with advancing age, most men tend to accumulate visceral fat due to reduced physical activity and increased caloric intake. Numerous studies have reported the negative impact of excess adipose tissue on both total testosterone and SHBG levels.[11,12]

This study identified the direct relationship between the decrease of total testosterone and BMI. In our view, the visceral fat accumulation is influenced not only aging itself, but by alterations in androgen status. Lipid metabolism parametersexceeded reference values in the main study group.

The SNP *rs727428* showed association with total testosterone levels, consistent with findings reported in studies involving European populations.[13]

Specifically, the CC genotype of *rs727428* was linked to the higher total testosterone concentrations (p = 0.001), whereas the CT genotype was associated with elevated albumin levels (p = 0.03). SHBG plays a pivotal role in regulating the bioavailability of testosterone and oestrogen, both of which arecrucial mediators in lipid metabolism control.

In our study, the *rs754493647* [A/G] polymorphism of the LPL gene in Kazakh men exhibited the GG genotype in both study groups (100%). This finding suggests that this polymorphism is not associated with lipid metabolism disorders in the Kazakh male population.

The literature review we conducted demonstrated that the single nucleotide polymorphism *rs10822184*shows a stronger association with LDL levels and testosterone.[14] The results of our study confirmed the association of *rs 10822184*with lipid profile parameters. There was an increase in LDL and triglyceride concentrations observed inindividuals withTT genotype (rs10822184), which may contribute to the atherosclerotic changes.[15]

Research data have revealed that in overweight men, certain polymorphisms of GSPG genes can lead to changes in the level of this protein in the blood, which affects the concentration of lipids

such as cholesterol and triglycerides. In addition, GSPG polymorphism can interact with other genetic and environmental factors, such as lifestyle, diet, and physical activity. In overweight men, changes in GSPG levels may be more pronounced against a background of insufficient physical activity and poor nutrition, which exacerbates lipid metabolism problems.

The present study underscores the importance of adopting a comprehensive approach to the treatment and prevention of metabolic disorders in overweight men, which should include both genetic testing and lifestyle changes.

The finding of are consistent with previous research emphasizing the role ofSHBG in regulating lipid metabolism in overweight men.[16] Studies involving larger sizes have demonstrated that SHBG levels may be associated not only with lipid profile, but also with the risk of developing cardiovascular disease. This association is particularly relevant for overweight men, who are at a significantly increased risk for such diseases.[9]

It should be noted that the relationship between SHBG polymorphism and lipid metabolism in overweight men is not entirely clear and requires further study. There may be additional factors, such as age or comorbidities that could influence this process and alter the strength of the relationship. It is also important to consider possible epigenetic mechanisms that may influence the expression of GSPG genes and its blood levels.

Thus, the results of this study open new horizons for understanding the mechanism of interaction between SHBG gene polymorphism and lipid metabolism in overweight men. These data may serve as a basis for further research aimed at developing personalised approaches in ethnic groups to the prevention and treatment of metabolic diseases associated with lipid metabolism disorders and excess weight.

Limitations The study sample was relatively small (235 men), which may affect the statistical power of the analysis and limit the ability to detect weak associations between SHBG and LPL gene polymorphisms and lipid metabolism parameters. In addition, potential modifying factors such as lifestyle, physical activity level, and comorbidities, which could influence lipid metabolism and hormonal status, were not taken into account in this study.

What's known? In men with age-related androgen deficiency, obesity, insulin resistance, and atherogenic alterations of the lipid profile are more frequently observed, all of which increase the risk of cardiovascular disease. Polymorphic variants of the SHBG gene may alter the concentration and binding capacity of the protein, thereby affecting the levels of free and bioavailable testosterone. Several studies have demonstrated an association between specific LPL alleles and an increased risk of atherosclerosis and metabolic syndrome.

What's new? Analysis of SHBG gene polymorphism makes it possible to identify associations with specific features of lipid metabolism in overweight men. SHBG gene polymorphism determines the level of bioavailable testosterone and indirectly influences the lipid profile through hormonal and metabolic mechanisms. In the present study, LPL gene polymorphism in Kazakh men was not found to be associated with lipid metabolism disorders.

Conclusions

In men of Kazakh ethnicity, triglyceride and LDL levels are associated with *rs10822184* of the SHBG gene, while *rs727428* polymorphism is associated with total testosterone levels. A decrease in SHBG levels in older men serve as a predictor of lipid profile disorders and a marker of risk for developing cardiovascular disease in the context of excess weight.

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