ABSTRACT

Objectives: Obesity raises the risk for many chronic illnesses. Clinically, obesity is determined using the body mass index (BMI). The lipoprotein lipase (LPL) gene was linked to the metabolism and obesity of lipoproteins. This study aimed to study investigate the Ser447Ter (C-G) polymorphisms of the LPL gene and rs9939609 of the FTO gene and obesity in children and young Rostov people from Russia.

Methods: The research investigated the relationship between the Ser447Ter in the LPL gene with obesity in 870 participants of both sexes aged (3–17) years: the major group consisted of 540 obese, and the control group - had 330 participants without obesity. Genotyping of the gene LPL Ser447Ter polymorphisms rs328 was performed using polymerase chain reaction (PCR)-allele-specific primers. Polymorphisms (rs328) of the LPL gene in donor DNA samples were typed by the electrophoretic method using commercial test systems from the Litekh research and production company (Russia).

Results: The relationship between the LPL Ser447Ter gene obesity (p > 0.05) was not significant established between the main and control groups in the frequency of occurrence of the genotype SerSer (p = 0.381) and allele Ser447 (p = 0.404; OR 1.17; 95% CI 0.82–1.67) of the rs328 polymorphism of the LPL gene. Even though recessive and dominant models are constructed, for LPL gene was statistically not significant TerTer vs SerTer + SerSer (p = 1.000 OR 1.84; 95% CI 0.07–45.05).

Conclusions: An observed absence of an association between the gene Ser447Ter of the LPL gene with the obesity. However, more studies are needed to confirm these findings.

Keywords: Children and adolescents, Lipoprotein Lipase, Obesity, Ser447Ter polymorphism.

INTRODUCTION

Obesity prevalence has increased all over the world as a pandemic.1 Obesity is a complex disease that is based on the interaction of environmental factors and genetic predisposition. To date, more than 30% of the world’s population is obese (WHO, 2014). Along with an increase in the number of adults who are overweight and obese, there is an increase in the number of children and adolescents with established diagnoses of obesity.2,3 The question of the role of heredity in the formation of obesity is still controversial.4 Obesity can be defined as the biological case resulting from the accumulation of excess fat or these fats which have little use as a source of bio-energy due to the weakness of human activity or individual tendency to avoid movement, work, or environmental interaction.5

Lipoprotein lipase (LPL) is a key enzyme involved in the process of removing triglycerides from plasma. LPL catalyzes the hydrolysis of triglycerides in very low-density lipoprotein (VLDL) particles and chylomicrons. The maximum amount of LPL is determined in skeletal muscle and adipose tissue. Apolipoprotein CII is involved in LPL activation.6 LPL plays a significant role in lipid metabolism and lipid transport. Therefore, chylomicrons and VLDLs produce chylomicron and lipoprotein intermediate density residues (IDLs); accordingly,
it is considered the enzyme responsible for the hydrolysis of core triglycerides.\(^7\)

The \textit{LPL} is located on chromosome 8p22, consists of 10 exons, and encodes a 474 amino acid precursor for the enzyme. Two mutations of the \textit{LPL} gene are known. This is a point mutation 1595C> G (Ser447Stop), which leads to the formation of a stop codon at the site of serine-447, and thus an abridged copy of the enzyme is synthesized. The polymorphic marker Ser447Ter is located in exon 9. The presence of the 447Ter allele, which leads to the loss of two C-terminal amino acids, is associated with an increase in the catalytic activity of lipoprotein lipase and, as a result, an 8% decrease in the average level of triglycerides in blood plasma.\(^8\)

On the other hand, Ser447X polymorphism is associated with increased HDL-C and decreased triglyceride levels in certain populations and, thus, may be associated with protective effects in atherogenesis via its favorable lipoprotein profile.\(^8\) A study done among Italian patients showed that carriers of the Ser447X polymorphism presented with higher HDL-C concentration as well as significantly reduced risk of high triglyceride/low HDL-C dyslipidemia.\(^9\) A study of a homogenous Caucasian population likewise showed significantly lower levels of triglyceride levels among those with Ser447X polymorphism.\(^10\) In this study, we investigated and correlated the Ser447Ter polymorphism within obesity. Estimate the \textit{LPL} gene in association with obesity and obesity-associated phenotypes.

\section*{METHODS}

\subsection*{Subjects}

In 870 children and adolescents of both 3 and 17-year-olds, an example study investigated the relation between \textit{LPL} gene polymorphisms of the Ser447Ter (S447X) and obesity. The obese group consisted of 540 participants. Group control: 330 healthy individuals, children, and adolescents. The major selection criterion for the study was the BMI. The obese population included children and adolescents people with BMI>30 kg/ m\(^2\), while participants of children and adolescents without obesity (BMI range 18.5 to 24.9 kg per m\(^2\)). Genotypes study have been undertaken in the Genetics Institute of the South Federal University. Patients were recruited to the Center of Science Medicine (Rostov region, Russia).

In addition, all study participants of children and adolescents were informed, and consent was given in accordance with the Helsinki Declaration of the World Medical Association “Ethical Principles for Medical Science and Human Participation” (as amended from 2000) and the “Rules of Clinical Practice in the Russian Federation” (approved by order of the Ministry of Health Russia dated June 19, 2003 No. 266).

\subsection*{Genotyping Methods}

Genomic DNA using blood expression reagent was extracted from whole blood leukocytes (NPF Litech, Russia). In addition, Spectrophotometer NanoDrop 2000c has checked the purity of DNA samples (Thermo Scientific, USA). Therefore, DNA samples have used commercial NPF-Litech test equipment with electrophoretic detection for the type of the \textit{LPL} gene Ser447Ter (C>G) polymorphism.

The SNP-Express reagent kit was used to study the allelic variant \textit{LPL} Ser447Ter gene (Lytech, Russia). The study is based in two pairs of allele allele-specific primers on amplification reactions. Horizontal electrophoresis in 3% agarose gel separated amplification products.

\subsection*{Statistical Analysis}

The parametric data for normality is analyzed, though significant variations in the genotyping and alleles frequencies were computed using the online Hardy-Weinberg.\(^11\)

Compatibility with the theoretically expected distribution in the equilibrium of Hardy-Weinberg of alleles and genotypes variant of the \textit{LPL} Ser447Ter gene was analyzed with the \(\chi^2\) test. Continuity and odds Ratio (OR) and confidence intervals were adjusted (95% CI). The association between obesity and genotypes was estimated using the odd-ratio (OR) and 95% (CI) confidence interval in assessing obesity risk associated with investigated alleles, where was using version 11.65 of WinPepi computer software.\(^12\)

\section*{RESULTS}

The study associating the analyzed gene \textit{LPL} Ser447Ter with obesity has been performed in obese and control groups of children and adolescents. Table 1 shows the comparison between genotypes and frequencies of the distributions for Ser447Ter polymorphisms in the patients and controls. The SerSer genotype was observed in 463 patients (85.7%) in the obesity community for the Ser447Ter genotype, while 76 patients (14.1%) carried the SerTer genotype. The SerSer and Ser447Ter genotypes were found in the control group in 275 (83.3%) and 55 (16.7%). We have detected no TerTer genotypes for this gene in the control group, while in other group detected TerTer genotypes 1 (0.2%) only. In the obesity group, a higher frequency of the SerSer genotype and a lower frequency of the Ser447Ter genotype, and the absence of the TerTer genotype were observed compared with the control group.

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
Gene/Genotypes & Obesity & Controls \\
& \(n = 540(\%)\) & \(n = 330(\%)\) \\
\hline
\textit{LPL} Ser447Ter & & \\
SerSer & 463 (85.7) & 275 (83.3) \\
SerTer & 76 (14.1) & 55 (16.7) \\
TerTer & 1 (0.2) & 0 (0.0) \\
\hline
\end{tabular}
\caption{\textit{LPL} Ser447Ter Polymorphisms frequency and percentage in the studied groups.}
\end{table}

\(\chi^2\): Pearson chi-square, \(P\): Fisher’s probability (two-tailed).
We were analyzing the distribution of Ser447Ters polymorphism genotype locus, which showed that the SerSer genotype of 83% of obese participants was typical. But it was observed that the polymorphism locus Ser447Ter of the LPL gene has not been confirmed for obesity (p > 0.05). The alleles results shown comparing the LPL gene alleles distribution, the frequency of the ser44 allele was found to be greater in both groups (92.8 and 91.7%) respectively compared to the 447Ter allele frequency (7.2 and 8.3%). Simultaneously, our findings showed that no substantial variation had been detected in the frequency of the ser44 allele was greater in both groups (92.8 and 91.7%).

Table 3 shows the genotypes of the frequencies observed. The distribution of the genotypes yielded from the Hardy-Weinberg equilibrium was calculated for Ser447Ter polymorphism in the patients’ group compared to the control group.

<table>
<thead>
<tr>
<th>Genotypes LPL Ser447Ter</th>
<th>Controls n = 330</th>
<th>( \chi^2 )</th>
<th>P</th>
<th>OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SerSer</td>
<td>275</td>
<td>0.922</td>
<td>0.381</td>
<td>1.20 (0.83–1.75)</td>
</tr>
<tr>
<td>SerTer</td>
<td>55</td>
<td>1.076</td>
<td>0.329</td>
<td>0.82 (0.56–1.19)</td>
</tr>
<tr>
<td>TerTer</td>
<td>0</td>
<td>0.612</td>
<td>1.000</td>
<td>1.84 (0.07–45.05)</td>
</tr>
<tr>
<td>Allele frequency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ser</td>
<td>605 (91.7)</td>
<td>0.716</td>
<td>0.404</td>
<td>1.17 (0.82–1.67)</td>
</tr>
<tr>
<td>Ter</td>
<td>55 (8.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P: Fisher’s exact probability (two-tailed), \( \chi^2 \): Pearson chi-square, OR: odds ratio, 95% CI: 95% confidence interval.

Table 4: The LPL Ser447Ter gene frequency genotypes of recessive and dominant in both groups.

<table>
<thead>
<tr>
<th>Genes</th>
<th>Genotypes</th>
<th>Obesity n = 540</th>
<th>Controls n = 330</th>
<th>( \chi^2 )</th>
<th>P</th>
<th>OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPL Ser447Ter</td>
<td>aTerTer + SerTer vs SerSer</td>
<td>77</td>
<td>55</td>
<td>0.922</td>
<td>0.381</td>
<td>0.83 (0.57–1.21)</td>
</tr>
<tr>
<td></td>
<td>bTerTer vs SerTer + SerSer</td>
<td>463</td>
<td>275</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P: Fisher’s probability (two-tailed), \( \chi^2 \): Pearson chi-square, OR: odds ratio, 95% CI: confidence interval, (a) dominant model, (b) recessive model.

DISCUSSION

This research represents the first report in the Rostov-on-Don population on the frequency of lipoprotein lipase polymorphisms Ser447Ter genotypes of participations that have obesity. Some studies have suggested that LPL activity in obesity is high in adipose tissue. \(^{13,14}\) LPL has dual main functions: hydrolase triglyceride and lipoprotein adsorption by the receptor. \(^{15}\) The S447X of the LPL gene variation is linked to differences in plasma lipids in different populations. \(^{16}\) In addition, a gene LPL imbalance may change the TG plasma partition between the adipose tissue and the muscle and so affect resistance to insulin and obesity. \(^{13,14}\)

The study investigated the frequencies of genotype and allelea associated with overweight of the gene Ser447Ter Lipoprotein lipase and association with overweight in the Rostov on Don of children and adolescents from Russia. As also, and as far as of our knowledge, this is the first related study for the Rostov region. And therefore, found that LPL Ser447Ter SNP was not significantly associated with obesity. The observed results were consistent with similar earlier investigations that were conducted in other populations. \(^{17,18}\) In addition, in the present study, the Ser447Ter polymorphism frequencies (CC, 85.50; CG, 13.50 and GG, 0.0) were similar to those observed in different ethnic groups, And the Ser447Ter polymorphism (C) and (G) allele frequencies in this sample.
were similar to those observed in other populations of Zhichun Z. et al.\textsuperscript{17}

In addition, there are several meta-analysis studies on stroke risk and hypertension, and blood pressure with the \textit{LPL} gene is considered to be a protective factor.\textsuperscript{19–21} There are also several original studies on coronary heart disease, stroke, hyperinsulinemia and insulin resistance with a gene \textit{LPL} considered to have an effect on plasma lipid levels,\textsuperscript{22} while an original study showed that the lipoprotein lipase gene has no association with coronary heart disease.\textsuperscript{23,24} There is also an original study on hyperinsulinemia and insulin resistance with a gene \textit{LPL} that is not considered to be associated with hyperinsulinemia and insulin resistance in the Kazakh population.\textsuperscript{25} Therefore, there are few studies on the association of the gene \textit{LPL} Ser447Ter polymorphism with obesity to be discussed with our current study, which showed in our study that there is no association with obesity.

In this study, however, there was no association between \textit{LPL} rs328 and obesity in children and adolescents, and also this corresponds to Arezoo A. K. \textit{et al.}\textsuperscript{26} Therefore, It could be explained by the ethnic differences, eating habits, and limitations that may affect the study. In this case, it is advisable to study the prevalence and associations of the above gene polymorphisms in different ethnic groups. Giving regard to the ethnic characteristics of the population within examination, The mutation’s interaction with the phenotype in order to establish subsequent causal relationships in disease development. In addition, to study the pathogenesis of obesity, a comprehensive study of the polymorphisms of different genes is needed to develop the disease.

**CONCLUSIONS**

In conclusion, the investigation in this study observed the absence of an association of the \textit{LPL} gene in the Ser447Ter polymorphisms with obesity. Therefore, a study of domestic and foreign literature suggests that further research is needed to investigate the genetic aspects of obesity pathogenesis.

**ACKNOWLEDGMENTS**

The authors appreciate all the participants in the study, and we gratefully acknowledge them. This work was supported through the postgraduate programs of the Department of genetics, Southern Federal University, Rostov-on-Don, Russia.

The study was performed under State Science Agreement No. 0852-2020-0028, with financial support from the Russian Federation Ministry of Science and Higher Education of the Russian Federation.

**REFERENCES**


14. SADUR UN, YOST TJ, ECKEL RH. Insulin responsiveness of adipose tissue lipoprotein lipase is delayed but preserved in obesity. The Journal of Clinical Endocrinology & Metabolism. 1984;59: 1176–1182. doi.org/10.1210/jcem-59-6-1176


Investigation of LPL-Ser447Ter Polymorphism with Obesity


