Research Article / *Araştırma Makalesi*

Ege Journal of Medicine / *Ege Tıp Dergisi* 2022; 61 (4): 658-665

Prevalence of lipoprotein lipase mutation in patients with severe hypertriglyceridemia and the characteristic features of hypertriglyceridemic pancreatitis

Şiddetli hipertrigliseridemili hastalarda lipoprotein lipaz mutasyon prevalansı ve hipertrigliseridemik pankreatitin karakteristik özellikleri

Utku Erdem Soyaltın[1] Ayşe Bengu Kandemır Bozkurt[2] Asli Ece Solmaz[3]
Gulden Hakverdı[4] Ilgin Yıldırım Sımsır[1]

[1] Department of Internal Medicine, Division of Endocrinology and Metabolism Disorders, Faculty of Medicine, Ege University, Izmir, Türkiye

[2] Department of Internal Medicine, Faculty of Medicine, Ege University, Izmir, Türkiye

[3] Department of Medical Genetic, Faculty of Medicine, Ege University, Izmir, Türkiye

[4] Department of Biostatistics and Medical Informatics, Faculty of Medicine, Ege University, Izmir, Türkiye

ABSTRACT

Aim: We conducted a retrospective study with the aim of determining the prevalence of lipoprotein lipase (LPL) mutation in patients with severe hypertriglyceridemia (HTG) and to study differences in characteristic features of HTG induced acute pancreatitis (AP).

Materials and Methods: Seventy adults with a serum triglyceride (TG) level ≥500 mg/dL were included in the study. Baseline characteristics, LPL mutation and risk factors between those with and without HTG-AP were compared.

Results: The mean age was 43 ± 12 years, and males accounted for 55.7%. Of the patients 35 had TG level <2000 mg/dL, and 35 patients had TG ≥2000 mg/dL. LPL mutation was found in 19 (27.1%) of the cases. The prevalence of AP was 67.1% (47 patients). Younger age, TG level, hemoglobin A1c (HbA1c) were significantly independent risk factors for the development of HTG-AP**.** When patients were divided into groups based on TG levels (group 1 with TG <2000 mg/dL, group 2 TG ≥2000 mg/dL) the prevalence of AP was significantly higher in group 2 (51.4% vs. 82.9%). Age and HbA1c lost their significance for development of AP. When the relationship between the frequency of AP and TG value was evaluated, the specificity of TG threshold value for developing AP was found to be 2235 mg/dL. There was no difference in prevalence of AP and TG level between mutation detected and undetected groups.

Conclusion: There was no difference in prevalence of AP and TG level between variant detected and undetected groups. In contrast to the literature, higher levels of TG cut-off points to develop AP was determined.

Keywords: Hypertriglyceridemia, lipoprotein lipase, acute pancreatitis.

ÖZ

Amaç: *Şiddetli hipertrigliseridemili (HTG) hastalarda lipoprotein lipaz (LPL) mutasyon prevalansını belirlemek ve LPL varyantı olan ve olmayan HTG kaynaklı akut pankreatitin (AP) karakteristik özelliklerindeki farklılıkları araştırmak amacıyla retrospektif bir çalışma amaçladık.*

Corresponding author: Ilgin Yıldırım Sımsır
Department of Internal Medicine, Division of Endocrinology and Metabolism Disorders, Faculty of Medicine, Ege University, Izmir, Türkiye
E-mail: *ilginyildirim@hotmail.com*
Application date: 10.04.2022 Accepted: 27.09.2022

Gereç ve Yöntem: *Çalışmaya serum trigliserid (TG) düzeyi ≥500 mg/dL olan 70 yetişkin dahil edildi. HTG-AP'i olan ve olmayan olgular arasındaki temel özellikler, LPL mutasyonunu ve risk faktörleri karşılaştırıldı.*

Bulgular: *Ortalama yaş 43 ± 12 idi ve erkekler çalışma popülasyonunun %55.7'sini oluşturuyordu. 35 hastada TG düzeyi <2000 mg/dL, 35 hastada TG ≥2000 mg/dL idi. 19 olguda (%27.1) LPL mutasyonu saptandı. AP prevalansı %67.1 (47 hasta) idi. Korelasyon analizinde genç yaş, TG düzeyi, hemoglobin A1c (HbA1c) HTG-AP gelişimi için anlamlı derecede bağımsız risk faktörleriydi. Hastalar TG düzeylerine göre iki gruba ayrıldığında (TG <2000 mg/dL olanlar grup 1, grup 2 TG ≥2000 mg/dL) AP prevalansı grup 2'de anlamlı olarak daha yüksekti (%51.4'e karşı %82.9), yaş ile HbA1c AP gelişimi için anlamsız saptandı. AP sıklığı ile TG değeri arasındaki ilişki değerlendirildiğinde, TG eşik değerinin pankreatit gelişimi için özgüllüğü 2235 mg/dL bulunmuştur. Mutasyon saptanan ve saptanamayan gruplar arasında AP ve TG prevalansı açısından fark saptanmamıştır.*

Sonuç: *Varyant saptanan ve saptanmayan gruplar arasında AP ve TG düzeyi açısından fark yoktu. Literatürden farklı olarak, AP geliştirmek için daha yüksek seviyelerde TG kesme noktası belirlendi.*

Anahtar Sözcükler: *Hipertrigliseridemi, lipoprotein lipaz, akut pankreatit.*

INTRODUCTION

Hypertriglyceridemia (HTG) is the third leading cause of acute pancreatitis (AP) and the estimated prevalence of hypertriglyceridemic AP (HTG-AP) is 1.3 to 10% (1). Accepted underlying pathophysiologic mechanisms for HTG-AP are; excess free fatty acids formed from excess triglyceride (TG) cause pancreatic acinar and capillary injury and hyperviscosity resulting from chylomicronemia leads to impaired pancreatic blood flow that resulted in further pancreatic injury (2-4).

Dietary fat carried in chylomicrons, and very-low-density lipoprotein (VLDL) synthesized from the liver are the two main sources of plasma TG. In capillaries within fat and muscle tissue, VLDL and chylomicrons are hydrolyzed into free fatty acids by lipoprotein lipase (LPL) which uses apolipoprotein (apo) C-II as a cofactor. As a consequence of increased dietary intake, increased production from the liver and intestine, or through decreased peripheral catabolism (mainly from reduced LPL activity), TG-rich lipoproteins and TG increase in plasma (5-7).

Severe HTG is defined as TG >500 mg/dL in the ATP III guideline and 1000-1999 mg/dL in the Endocrine Society clinical practice guideline (8, 9). Because of the chylomicrons usually presents when TG level ≥1000 mg/dL, this TG level is often cited as a cut-off value to develop pancreatitis. But some, advocate that the risk of pancreatitis increases when TG >500 mg/dL. Nevertheless, not all patients with severe HTG develops AP, but the general rule says that “the higher the levels of TG, the higher the probability to suffer from AP” (8). In the post genome era, molecular basis for primary HTG has been found in less than 5% of cases and LPL deficiency has autosomal recessive inheritance and its prevalence has been reported as 1-2/1.000.000 in the literature (5, 10, 11).

We conducted a retrospective study with the aim of determining the prevalence of LPL mutation in patients with severe HTG (TG ≥500 mg/dL) and to study difference in characteristic features of HTG induced pancreatitis with and without LPL mutation groups.

MATERIALS and METHODS

In this retrospective study, 70 adults with a serum TG level ≥500 mg/dL were included. Patients with severe HTG in endocrinology clinic record system were analyzed. Ethics approval was obtained from the Hospital Ethics Committee (19-5T/12). Inclusion criteria for this study were adult patients (≥18 years) who were found to have a fasting TG ≥500 mg/dL from 2013 to 2018. Exclusion criteria included age <18 years, TG <500 mg/dL, alcohol use and cholelithiasis. A diagnosis of HTG-AP was made when any two of the following three criteria were present: abdominal pain characteristic of pancreatitis, computed tomography (CT) evidence of pancreatitis or serum lipase levels three times the upper level of normal (12). In cases where multiple episodes of pancreatitis occurred in the same patient, the first episode of AP was included in the analysis.

Genomic DNA was extracted from peripheral blood leukocytes using a QIACube (Qiagen GmbH, Germany) according to the manufacturer’s recommendations. All exons and intron-exon junctions of the LPL (NM_000237)

gene were analyzed by direct sequencing. Detected variants were compared to Human Gene Mutation Database (HGMD), Ensembl and National Center for Biotechnology Information (NCBI) databases. Pathogenicity of novel variants were predicted using in silico tools, Mutation Taster, PolyPhen-2 and SIFT. The detected mutations were analyzed with databases. The newly detected variations were evaluated with in-silico modeling programs.

Statistical Analyses

Statistical Package for the Social Sciences (SPSS) version 25 software (IBM Corp) was used for all statistical analysis. Descriptive statistics were reported as percentages for binary and categorical variables as mean and standard deviation (SD) if normally distributed and as median (minimum-maximum) if nonnormally distributed for numerical variables.

The normal distribution of the numerical variables was tested by Shapiro-Wilk (n <50) and Kolmogorov-Smirnov (n >=50) tests. The significance of association between categorical variables were assessed by the χ^2 test. Numerical variables were compared between two groups by the independent-samples *t* test, or alternatively, by the nonparametric Mann-Whitney test.

Multivariate correlation analysis was used to test the association of age, TG levels, Diabetes Mellitus (DM) and LPL mutation with AP (Table-2). Linear regression analysis was used to determine most valuable risk factor for AP.

Receiver operating characteristic (ROC) curves were used to describe the best predictors for TG level for AP development. A 2-tailed p <0.05 was considered statistically significant.

RESULTS

Based on the inclusion criteria, a total of 70 patients with TG ≥500 mg/dL were included in the study; 35 patients had TG between 500 and 1999 mg/dL, and 35 patients had TG ≥2000 mg/dL. The clinical and laboratory characteristics are shown in Table-1. Mean age was 43 ± 12 years, and males accounted for 55.7% of the study population.

A previous diagnosis of DM was found in 62.9% of patients and DM prevalence was comparable among patients with and without AP. Interestingly, mean hemoglobin A1c (HbA1c) values were higher in patients without AP (9.4% vs 11.8%; p = 0.02).

The prevalence of AP in patients with severe HTG in this study was 67.1% (47 patients). Patients with AP were significantly younger than those without AP (41 years vs. 48 years; p = 0.04). There was no significant difference in prevalence of AP between male and female patients (51.1% vs. 48.9%).

In correlation analysis younger age, TG level and HbA1c were significantly independent risk factors for the development of HTG-AP (Table-2). Between these three components, TG level was the most prominent risk factor in the linear regression analysis (p = 0.009). The median TG level for patients with AP was higher than in those without AP (2437 mg/dL vs. 1270 mg/dL; p = 0.003). When patients were divided into two groups based on TG levels (group 1 with TG between 1000 and 1999 mg/dL; group 2 TG ≥2000 mg/dL) the prevalence of AP was significantly higher in group 2 (51.4% vs 82.9%), and age along with HbA1c lost their significance for to development of AP (Table-3). When the relationship between the frequency of pancreatitis and TG value was evaluated in the ROC curve, the specificity of TG threshold value to develop pancreatitis was found to be high at 2235 mg/dL (Figure-1). The areas under the ROC curve of TG 0.734 (with 95% CI 0.617-0.851).

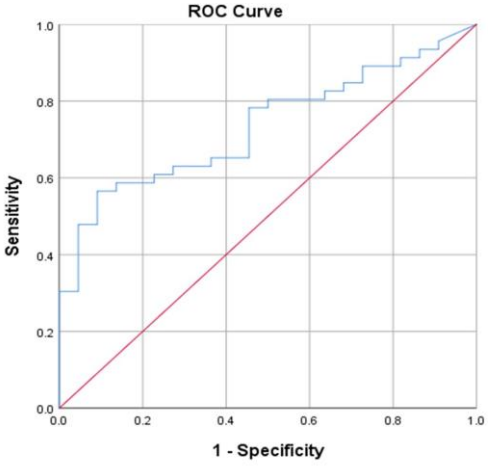

Figure-1. The relationship between hypertriglyceridemia and pancreatitis was evaluated by ROC curve. TG threshold value for the development of pancreatitis was found to be high at 2235 mg/dL.

Among 70 patients, 19 different cases (27.1%) had 13 different LPL gene mutations (Table-4). These mutations were heterozygous in 9 patients, homozygous in 9 patients and compound heterozygous in 1 patient. When the

patients were examined according to mutation types, 8 novel mutations were detected in 12 patients (7 missense and 1 splicing mutation). There was no difference in prevalence of AP and TG level between mutation detected and undetected group (Table-5). When these 19 cases were evaluated in terms of heterozygous and homozygous mutation state there was no difference in TG level and prevalence of AP (Table-6). The mean score of HbA1c of the heterozygous mutation group was 9.8 ± 2.5 vs 8.9 ± 4.3 in the homozygous mutation group. The mean score of body mass index (BMI) of the heterozygous mutation group was 30.2 ± 2.0 vs 25.1 ± 4.9 in the homozygous mutation group.

Table-1. Baseline characteristics for all patients with severe HTG (n: 70).

Variables	Findings
Male (n (%))	39 (55.7)
Age, years (mean ± SD)	43 ± 12
TG (mg/dL) (mean ± SD)	2253 ± 1450
Patients with LPL (n (%))	19 (27.1)
Pregnancy (n (%))	5 (7.1)
Pancreatitis (n (%))	47 (67.1)
Plasmapheresis (n (%))	33 (47.1)
Diabetes (n (%))	44 (62.9)
HbA1c (%) (mean ± SD)	10.2 ± 3.1
BMI (kg/m^2) (mean ± SD)	28.2 ± 4.9

Abbreviations: BMI: body mass index, HbA1c: hemoglobin A1c, HTG: hypertriglyceridemia, LPL: lipoprotein lipase, SD: standard deviation, TG: trigylceride

Table-2. Factors associated with acute pancreatitis in patients with severe HTG (n: 70).

	Patients with pancreatitis (n: 47)	Patients without pancreatitis (n: 23)	*p*
Male (n (%))	23 (48.9)	16 (69.6)	0.103
Pateints with LPL mutation (n (%))	15 (31.9)	4 (17.4)	0.259
Age in years, (mean ± SD)	41 ± 11	48 ± 14	0.04*
TG (mg/dL) med (min-max)	2437 (500-6678)	1270 (500-3167)	0.003*
Pateints with diabetes (n (%))	30 (63.8)	14 (60.9)	0.81
HbA1c (%) (mean ± SD)	9.4 ± 2.5	11.7 ± 3.6	0.02*
BMI (kg/m^2) (mean ± SD)	27.8 ± 5.0	29.0 ± 4.5	0.344

Abbreviations: BMI: body mass index, HbA1c: hemoglobin A1c, HTG: hypertriglyceridemia, LPL: lipoprotein lipase, med: median, max: maximum, min: minimum, SD: standard deviation, TG: trigylceride

Table-3. Characteristics for patients acording to TG level (n: 70).

	TG >2000 mg/dL (n: 35)	TG <2000 mg/dL (n: 35)	*p*
Male (n (%))	19 (45.3)	20 (57.1)	0.81
Pateints with LPL mutation (n (%))	11 (31.4)	8 (22.9)	0.42
Age in years (mean ± SD)	42 ± 11	45 ± 13	0.19
TG (mg/dL) med (min-max)	3023 (2008-6678)	1106 (500-1996)	<0.001*
Patients with pancreatitis (n (%))	29 (82.9)	18 (51.4)	0.005*
Pateints with diabetes (n (%))	23 (65.7)	21 (60.0)	0.621
HbA1c (%) (mean ± SD)	9.8 ± 2.5	10.5 ± 3.7	0.476
BMI (kg/m^2) (mean ± SD)	27.7 ± 5.5	28.8 ± 4.2	0.352

Abbreviations: BMI: body mass index, HbA1c: hemoglobin A1c, LPL: lipoprotein lipase, med: median, max: maximum, min: minimum, SD: standard deviation, TG: trigylceride

Table-4. Variant of the LPL gene.

Mutation		Mutation type	Additional information
Protein	**cDNA**		
p.L99P	c.296T>C	Missense	Novel
p.A125T	c.373G>A	Missense	Novel
p.G186E	c.557G>A	Missense	Novel
p.G215E	c.644G>A	Missense	
p.I221T	c.662T>C	Missense	
p.V227A	c.680T>C	Missense	Novel
p.R270C	c.808C>T	Missense	
p.H273R	c.818A>G	Missense	
p.N318S	c.953A>G	Missense	
p.R333C	c.997C>T	Missense	Novel
p.L392P	c.1175T>C (p.Leu392Pro)	Missense	Novel
p.C465Y	c.1394G>A	Missense	Novel
IVS1-1G>A	c.89-1G>A	Splicing	Novel

Table-5. Characteristics for patients acording to LPL state (n: 70).

	With LPL variant (n: 19)	Without LPL variant (n: 51)	*p*
Male (n (%))	8 (42.1)	31 (60.8)	0.162
Age, years (mean ± SD)	45 ± 15	43 ± 11	0.418
TG (mg/dL) med (min-max)	2045 (500-6678)	1977 (577-5412)	0.890
Patients with pancreatitis (n (%))	15 (78.9)	32 (62.7)	0.259
Patients with diabetes (n (%))	9 (47.4)	35 (68.6)	0.102
HbA1c (%) (mean ± SD)	9.6 ± 2.7	10.3 ± 3.2	0.559
BMI (kg/m^2) (mean ± SD)	26.4 ± 4.2	28.9 ± 4.9	0.049

Abbreviations: BMI: body mass index, HbA1c: hemoglobin A1c, HTG: hypertriglyceridemia, LPL: lipoprotein lipase, med: median, max: maximum, min: minimum, SD: standard deviation, TG: trigylceride

Table-6. Characteristics for patients acording to variant state (n:19).

	Homozygous LPL variants (n: 10)	Heterozygous LPL variants (n: 9)	*p*
Male (n (%))	4 (40.0)	4 (44.4)	1.000
Age, years (mean ± SD)	43 ± 16	48 ± 13	0.542
TG (mg/dL) (mean ± SD)	2005 ± 1063	2797 ± 2247	0.331
Patients with pancreatitis (n (%))	9 (90.0)	6 (66.7)	0.303
Patients with diabetes (n (%))	2 (20.0)	7 (77.8)	0.023

Abbreviations: LPL: lipoprotein lipase, SD: standard deviation, TG: trigylceride

DISCUSSION

In our study, LPL mutation was found in 19 (27.1%) of 70 cases. Because of the small sample size of the study, this prevalence does not reflect the community prevalence but the LPL mutation was seen in approximately one third of the study group and this should not be ignored. There was no difference observed in the prevalence of pancreatitis and TG values between the LPL mutation and non-mutation groups and also between LPL mutation heterozygous and homozygous groups.

Thirteen different mutations were detected in 19 patients. The N318S mutation was the most common mutation, homozygous in one patient and heterozygous in four patients. The N318S mutation is one of the most common mutations in Europe, with a frequency of carriers of ~5% and studies have shown that N318S mutation is related to reducing the catalytic activity of LPL by 40% (13, 14).

Another common mutation was the G215E mutation. Two cases were homozygous, one was heterozygous and one was compound heterozygous associated with L392P mutation. The origin of this change is not clear and has been identified in different ethnic groups around the World and the G125E mutation has been reported to cause complete loss of catalytic activity of LPL. It has been associated with familial LPL deficiency in homozygous or compound heterozygous state and hyperlipoproteinemia in heterozygous state (15-17).

Each of the remaining 11 mutations were detected in only one patient. 8 of these were not defined in the databases and were reported for the first time in this study. Functional analysis and larger studies are needed to confirm the clinical effect of these new mutations.

Familial hyperchylomicronemia is a rare disorder, which is attributed to single gene mutation in LPL and apo C-II and it usually seen in childhood period. Polygenic chylomicronemia usually seen in adulthood period and is related to simultaneous different point mutation in LPL, apo C-II, apo C-III, apo A-V, GPIHBP1, and LMF1 genes locus. In our study population, there were no patients with defined HTG in childhood, therefore all LPL mutations detected were probably associated with polygenic chylomicronemia or were single point mutations but had residual LPL activity, they suffered triggering factors in adulthood period and became clinically apparent (18, 19).

The prevalence of HTG-AP in our cohort was 67.1%, which is very higher than (8 to 31%) reported by a recent systematic review of observational studies (20). Because of being a tertiary center, this very high prevalence may be related to referral of patients with a history of pancreatitis or high risk of pancreatitis to our clinic.

It was remarkable that there was a 2-fold difference between the TG values of the patients with and without pancreatitis (p = 0.003). When the relationship between the frequency of pancreatitis and TG value was evaluated in the ROC curve, the specificity of TG threshold value to develop pancreatitis was found to be high at 2235 mg/dL (Figure-1). In contrast to the literature, in the previous studies and in our study, higher levels of TG cut-off points to develop AP was found (21, 22). Despite appropriate medical treatment, patients with TG levels greater than 1000 mg/dL are recommended to consider lipid-apheresis (23, 24). With new clinical findings, we think that new TG level cut-off point must be determined for lipid-apheresis treatment.

In type 2 diabetes worse metabolic control is related with high TG level. The mean HbA1c (%) of the patients with pancreatitis (9.4 ± 2.5) was significantly lower than that of the patients without pancreatitis (11.7 ± 3.6) (p = 0.02). This was an unpredictable finding for us and we did not record patients medication history throughout the study, so maybe we can speculate that if worse metabolic control patients may be using insulin and insulin may protect them against pancreatitis by stimulating LPL.

Patients who developed AP were younger, and younger age showed to be an independent risk factor associated with AP in previous studies (21, 25). There was no clear explanation in the literature why older patients with similar risk factors less suffer AP.

The major limitations of our study were the small number of the study group and the lack of registered medical therapies due to retrospective evaluation.

CONCLUSION

In our study, LPL mutation was found in 19 (27.1%) of 70 cases. Because of the small sample size of the study this prevalence does not reflect the community prevalence, but the LPL mutation was seen in approximately one third of the study group and this should not be ignored. There was no difference in prevalence of AP and TG level between mutation detected and undetected group. In contrast to the literature, higher levels of TG cut-off points to develop AP was found. With new clinical findings, we suggest that determination of new triglyceride cut-off levels may be necessary with wide range trials for lipid apheresis treatment.

Conflict of interest: Authors have no conflict of interest to declare.

References

1. DeFrances CJ, Podgornik MN. 2004 National Hospital Discharge Survey. Adv Data 2006;(371):1-19. PMID: 16703980.
2. Saharia P, Margolis S, Zuidema GD, Cameron JL. Acute pancreatitis with hyperlipemia: studies with an isolated perfused canine pancreas. Surgery 1977;82(1):60-7. PMID: 877857.
3. Valdivielso P, Ramírez-Bueno A, Ewald N. Current knowledge of hypertriglyceridemic pancreatitis. Eur J Intern Med 2014;25(8):689-94. doi: 10.1016/j.ejim.2014.08.008.
4. Havel RJ. Pathogenesis, differentiation and management of hyper-triglyceridemia. Adv Intern Med 1969;15:117-54. PMID: 4908616.
5. Burnett JR, Hooper AJ, Hegele RA. Familial Lipoprotein Lipase Deficiency. 1999 Oct 12 [updated 2017 Jun 22]. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Ledbetter N, Mefford HC, Smith RJH, Stephens K, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017.
6. Davidson MH, Toth PP, Maki KC. Familial lipoprotein lipase deficiency. Therapeutic Lipidology. Humana Press. Totowa, NJ. 2007:465-6.
7. Demacker PNM, Stalenhoef AFH. Familial lipoprotein lipase deficiency. In: NORD Guide to Rare Disorders. Lippincott Williams & Wilkins. Philadelphia, PA. 2003:465-6.
8. Berglund L, Brunzell JD, Goldberg AC, et al. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012;97(9):2969-89. doi: 10.1210/jc.2011-3213.
9. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285(19):2486-97. doi: 10.1001/jama.285.19.2486.
10. Hegele RA. Monogenic dyslipidemias: window on determinants of plasma lipoprotein metabolism. Am J Hum Genet 2001;69(6):1161-77. doi: 10.1086/324647.
11. Gaudet D, Methot J, Kastelein J. Gene therapy for lipoprotein lipase deficiency. Curr Opin Lipidol 2012;23(4):310-20. doi: 10.1097/MOL.0b013e3283555a7e.
12. Tenner S, Baillie J, DeWitt J, Vege SS, American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol 2013;108(9):1400-15; 1416. doi: 10.1038/ajg.2013.218.
13. Wittrup HH, Tybjaerg-Hansen A, Nordestgaard BG. Lipoprotein lipase mutations, plasma lipids and lipoproteins, and risk of ischemic heart disease. A meta-analysis. Circulation 1999;99(22):2901-7. doi: 10.1161/01.cir.99.22.2901.
14. Wright WT, Young IS, Nicholls DP, Graham CA. Genetic screening of the LPL gene in hypertriglyceridaemic patients. Atherosclerosis 2008;199(1):187-92. doi: 10.1016/j.atherosclerosis.2007.10.029.
15. Monsalve MV, Henderson H, Roederer G, et al. A missense mutation at codon 188 of the human lipoprotein lipase geneis a frequent cause of lipoprotein lipase deficiency in persons ofdifferent ancestries. J Clin Invest 1990;86(3):728-34. doi: 10.1172/JCI114769.
16. Hata A, Ridinger DN, Sutherland SD, et al. Missense mutations in exon 5 of the human lipoprotein lipase gene: inactivation correlates with loss of dimerization. J Biol Chem 1992;267(8):20132-9. PMID: 1400331. doi: 10.1016/S0021-9258(19)88676-3.
17. Ooi EMM, Russell BS, Olson E, et al. Apolipoprotein B-100-containing lipoprotein metabolism in subjects with lipoprotein lipase gene mutations. Arterioscler Thromb Vasc Biol 2012;32(2):459-66. doi:10.1161/ATVBAHA.111.238493.
18. Dron JS, Wang J, Cao H, et al. Severe hypertriglyceridemia is primarily polygenic. J Clin Lipidol 2019;13(1):80-8. doi: 10.1016/j.jacl.2018.10.006.
19. Dron JS, Hegele RA. Polygenic influences on dyslipidemias. Curr Opin Lipidol 2018;29(2):133-43. doi: 10.1097/MOL.0000000000000482.

20. Carr RA, Rejowski BJ, Cote GA, Pitt HA, Zyromski NJ. Systematic review of hypertriglyceridemia-induced acute pancreatitis: a more virulent etiology? Pancreatology 2016;16(4):469-76. doi: 10.1016/j.pan.2016.02.011.
21. Amblee A, Mohananey D, Morkos M, et al. Acute Pancreatitis in Patients with Severe Hypertriglyceridemia in a Multi-Ethnic Minority Population. Endocr Pract 2018;24(5):429-36. doi: 10.4158/EP-2017-0178.
22. Sandhu S, Al-Sarraf A, Taraboanta C, Frohlich J, Francis GA. Incidence of pancreatitis, secondary causes, and treatment of patients referred to a specialty lipid clinic with severe hypertriglyceridemia: a retrospective cohort study. Lipids Health Dis 2011;10:157. doi: 10.1186/1476-511X-10-157.
23. Schaap-Fogler M, Schurr D, Schaap T, Leitersdorf E, Rund D. Long-term plasma exchange for severe refractory hypertriglyceridemia: a decade of experience demonstrates safety and efficacy. J Clin Apher 2009;24(6):254-8. doi: 10.1002/jca.20224.
24. Padmanabhan A, Connelly-Smith L, Aqui N, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice - Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue. J Clin Apher 2019;34(3):171-354. doi: 10.1002/jca.21705.
25. Zhang XL, Li F, Zhen YM, Li A, Fang Y. Clinical Study of 224 Patients with Hypertriglyceridemia Pancreatitis. Chin Med J (Engl) 2015;128(15):2045-9. doi: 10.4103/0366-6999.161361.