http://rjdnmd.org
Rom J Diabetes Nutr Metab Dis. **25**(4):425-430
doi: 10.2478/rjdnmd-2018-0051

VERY SEVERE HYPERTRIGLYCERIDEMIA-CASE REPORT WITH GENERAL CONSIDERATIONS

Rucsandra Dănciulescu Miulescu [1,2,✉], ***Anna Maria Tinu*** [1], ***Denisa Margină*** [2], ***Daniela Grădinaru*** [2], ***Anca Ungurianu*** [2], ***Loreta Guja*** [2]

[1] "N.C.Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases Bucharest, Romania
[2] „Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

received: October 25, 2018 *accepted*: November 29, 2018
available online: December 25, 2018

Abstract

Hypertriglyceridemia is defined as a value of fasting serum triglyceride over 150 mg/dl. The classification of hypertriglyceridemia according to the Endocrinology Society include mild and moderate hypertriglyceridemia, severe hypertriglyceridemia and very severe hypertriglyceridemia. Mild and moderate hypertriglyceridemia increase the risk for cardiovascular events while severe and very severe hypertriglyceridemia is a risk factor for acute pancreatitis. Conventional pharmacological therapy of hypertriglyceridemia includes: fibrates, niacin, statins, ezetimibe, omega-3-fatty acid. Other triglyceride-lowering therapies are represented by plasmapheresis and lipoprotein lipase gene therapy. The present work refers to a 59-year old man without history of family diabetes, dyslipidemia, premature coronary artery disease, diagnosed with T2DM in 2012, from 2014 on insulin treatment; he was hospitalized for endocrine evaluation. History: high blood pressure for approximately 25 years, chronic kidney disease, very severe hypertriglyceridemia, thyroid papillary carcinoma. The patient followed treatment with hypoglycemic, hypolipemic, low salt content diet, fibrates, statins, omega-3-fatty acid. Due to the fact that the patient did not respond to conventional therapy plasmapheresis was considered.

key words: *very severe hypertriglyceridemia, diabetes, treatment*

Introduction

Hypertriglyceridemia is defined as a value of fasting serum triglyceride over 150 mg/dl. Clinical Practice Guideline published in 2012 by Berglund L *et al* in the Journal of Clinical Endocrinology & Metabolism about Evaluation and Treatment of Hypertriglyceridemia states that the diagnosis and classification of hypertriglyceridemia based on fasting levels includes mild and moderate hypertriglyceridemia (triglycerides of 150–999 mg/dl), severe hypertriglyceridemia (1000–1999 mg/dl) and very severe hypertriglyceridemia (>2000 mg/dl) [1]. Adult Treatment Panel III guidelines of the National Cholesterol Education Program (ATP III) published in 2001 proposed four categories: normal fasting triglyceridemia<150 mg/dl, borderline high triglyceridemia 150–199 mg/dl, high triglyceridemia 200–499 mg/dl and very

✉ 5-7 Ion Movila Street, Bucharest, District 2, Postal Code 11420, Tel: 0040748134500, Fax: 004021/2105575
corresponding author e-mail: rucsandra_m@yahoo.com

high triglyceridemia>500 mg/dl [2]. The previously mentioned classification of hypertriglyceridemia according to the international medical societies is presented in Table 1.

Table 1. The classification of hypertriglyceridemia.

The classification of hypertriglyceridemia	ATP III Serum triglyceride (mg/dl)	Endocrine Society Serum triglyceride (mg/dl)
Borderline hightriglyceridemia	150–199	
Mild and moderate hypertriglyceridemia		150–999
Severe hypertriglyceridemia	200–499	1000–1999
Very severe hypertriglyceridemia	>500	>2000

General considerations

The elevated values in plasma triglyceride may be the result of increased production from the liver and intestine or decreased peripheral catabolism by a reduced lipoprotein lipase activity. Two forms are described: primary and secondary hypertriglyceridemia [3]. Primary hypertriglyceridemia is relatively rare and in its etiology a gene mutation of lipoprotein lipase, the enzyme involved in the catabolism of lipids rich in triglycerides, is involved [4]. Secondary hypertriglyceridemia has many causes: fat diet, excessive alcohol intake, medical conditions (obesity, *metabolic syndrome*, hypothyroidism, diabetes mellitus, renal disease, autoimmune disease), medication (corticosteroids, estrogens, antiretroviral therapy, tamoxifen. antihypertensives, antipsychotic medications) [3]. The association between type 2 diabetes mellitus (T2DM) and dyslipidemia is a relatively common condition. The lipoprotein abnormalities commonly present in T2DM consist of hypertriglyceridemia, increased level of low-density lipoprotein (LDL) and decreased plasma in high density lipoproteins (HDL). Alterations in lipid profile in hypothyroidism are similar to those in T2DM, respectively serum total cholesterol, LDL-cholesterol and triglycerides are significantly increased, and HDL-cholesterol levels are reduced.

Mild and moderate hypertriglyceridemia increase the risk for cardiovascular events while severe and very severe hypertriglyceridemia increase the risk for acute pancreatitis.

There are numerous studies on the potential role of elevated triglyceride levels in promoting coronary events. In an issue published in 1992 of *British Heart Journal* entitled: "Plasma triglyceride and high density lipoprotein cholesterol as predictors of ischemic heart disease in British men", Braiton D and coauthors report that plasma triglyceride levels predicts major cardiovascular and triglyceride concentration is a more important predictor than total cholesterol levels [5]. Ten years later Abdel-Maksoud MF and Hokanson JE after analyzing twenty-one studies including 65.863 men and 11.089 women evaluating the association between plasma triglycerides and cardiovascular disease, indicate that triglycerides levels are an independent predictor of cardiovascular disease [6]. The role of serum triglyceride levels as a risk factor for cardiovascular diseases was evaluated in a meta-analysis which included 26 studies conducted in the Asia-Pacific region. Data analysis highlights that serum triglycerides is an important and independent predictor of cardiovascular disease and stroke risk in the previously mentioned region [7]. Another study that evaluated the role of hypertriglyceridemia in the development of cardiovascular disease, included 13.953 men-age

26 to 45 years, also stated that a decrease in initially elevated triglyceride levels is associated with a decrease in cardiovascular risk [8]. A meta-analysis based on prospective studies, published by Hokanson JE and Austin MA in the *Journal of Cardiovascular Risk* concludes that: *"Based on combined data from prospective studies, triglyceride is a risk factor for cardiovascular disease for both men and women in the general population, independent of HDL cholesterol"* [9]. In a review published by Kannel WB and Vasan RS entitled "Triglycerides as vascular risk factors: New Epidemiologic Insights for Current Opinion in Cardiology" the authors mention the role of fasting and non-fasting triglycerides as vascular risk factors even in subjects with low LDL-cholesterol [10].

Severe and very severe hypertriglyceridemia is a risk factor in the occurrence of the acute pancreatitis. Acute pancreatitis is a condition with various etiologies: iatrogenic, genetic, gallstones, alcohol consumption, hypertriglyceridemia. The role of hypertriglyceridemia in the pathogenesis of acute pancreatitis are not fully elucidated. The mechanism proposed for the occurrence of acute pancreatitis in patients with severe hypertriglyceridemia include: occlusion of the pancreatic capillaries by chylomicron-triglyceride-rich lipoprotein particles, which is followed by release of pancreatic lipase; pancreatic lipase hydrolyses triglyceride and generated enhanced concentration of free fatty acids, which can generate cell injury: elevated amylase levels, edema and hemorrhage [11,12]. The degradation of lipoprotein to free fatty acids may generate a proinflammatory response. Inflammatory cytokines (interleukin-1β, interleukin-6) may be involved according to some studies in the early stage of acute pancreatitis induced by severe hypertriglyceridemia [13-15].

Case report

A 59-year old man without history of family diabetes, dyslipidemia, premature coronary artery disease, diagnosed with T2DM in 2012, receiving insulin treatment from 2014, was hospitalized in 2018 at the Oncological Institute and National Institute of Diabetes Bucharest for endocrine and metabolic evaluation.

History: high blood pressure for approximately 25 years, chronic kidney disease, mixed dyslipidemia, thyroid papillary carcinoma operated in 2014 and treated with radioactive iodine in 4 steps. The patient followed treatment with hypoglycemic, hypolipemic, low salt content diet, Irbesartanum 300 mg/day, Betaxolol hydrochloride 30 mg/day, *Atorvastatinum 40 mg/day*-the maximum tolerated dose, Fenofibratum 145 mg/day, Omega-3-Esters Ethyl Acid, Levotiroxinum 200 µg/day, Levotiroxinum+Liothyronine 100 µg+20 µg/day, Lispro 60 U/day and Insulin Glargine 64 U/day (with titration of doses based on glycemic values). The patient says he does not consume excess alcohol and is non-smoking. The clinical examination highlights height - 185 cm, weight - 134 kg and body mass index - 39 kg/m^2 and thyroidectomy scars. No other pathological elements have been highlighted at the clinical examination. The dynamics of metabolic and endocrine parameters are shown in Table 2.

Treatment of hypertriglyceridemia

Optimizing lifestyle (fat free diet, cessation of alcohol consumption, weight loss, exercise), control of diabetes and hypothyroidism are important measures in the tratment of very severe hypertriglyceridemia.

Conventional pharmacological therapy of hypertriglyceridemia includes: fibrates, niacin, statins, ezetimibe, omega-3-fatty acid. Fibrate therapy can reduce plasma triglycerides levels by modulation of the activity of peroxisome

proliferator–activated receptor-α in the liver, with a decrease of hepatic secretion of very-low-density lipoprotein (VLDL) and increased lipolysis of plasma triglycerides [16]. Barter PJ and Rye KA state in an article published in 2006 in *Circulation* that fibrates significantly reduce plasma triglycerides levels and raise the HDL-cholesterol levels [17]. Nicotinic acid inhibits the lipolysis in adipose tissue and reduced plasma fatty acids. Daily administration of 3 gr of nicotinic acid may lead to reduction of plasma triglyceride levels by 45% and increase plasma HDL-cholesterol [18]. Statins reduce levels of the cholesterol and may reduce triglycerides levels by inhibiting hydroxymethylglutaryl coenzyme A reductase [16]. Ezetimibe is a cholesterol absorption inhibitor that significantly reduce LDL-cholesterol, triglycerides levels and increase the HDL-cholesterol levels [16,19]. Omega-3 fats may decrease triglycerides levels by 20% when administered with other triglyceride-lowering therapies [16,20]. The proposed mechanism by which omega-3-fatty acid decrease triglycerides levels are decline in hepatic production of VLDL and the increase clearance of VLDL [21].

Table 2. The dynamics of metabolic and endocrine parameters.
Abbreviation: HbA1c-glycated hemoglobin, TSH- thyroid stimulating hormone.

	2014	2015	2016	2017	February 2018	July 2018	July 2018
Total cholesterol (mg/dl)	235	280		244	174	1007	519.19
HDL cholesterol (mg/dl)			59		26.67	9.19	9.19
Triglycerides (mg/dl)	640	1960		2989	975.58	9184	3981.37
HbA1c (%)	8.60	9.40	8.19	8.5	9.30		12.17
Glucose (mg/dl)	270	140		257		376	247
Serum calcium (mg/dl)		9.06		9.3		10.3	
TSH (μIU/ml)		4.69		6.36	6.83	1.93	

Other triglyceride-lowering therapies include plasmapheresis and lipoprotein lipase gene therapy [16].

Indications of plasmapheresis are:

- patient with triglyceride levels above 1000 mg/dl that do not respond to conventional therapy,
- values of serum lipase that exceed three times reference values,
- severe hypocalcemia,
- lactic acidosis [22].

The beneficial effect of plasmapheresis is generated by a rapid decrease in triglyceride levels. A multicenter study in which 17 patients with very severe hypertriglyceridemia were included, revealed that plasmapheresis significantly reduces mean plasma triglycerides (from 1929 mg/dl to 510 mg/dl) and total cholesterol levels (from 762 mg/dl to 227 mg/dl) [23]. Plasmapheresis performed in 18 patients that did not respond to conventional therapy reduced levels of triglycerides from 1.977.1 mg/dl to 692.6 mg/dl and levels of cholesterol from 436.7 mg/dl to 222 mg/dl [24].

Lipoprotein lipase deficiency is an autosomal recessive condition characterized by reduced chylomicron triglyceride lipolysis and persistently elevated triglyceride levels. It was developed an adeno-associated virus vector (AAV)1-lipoprotein lipase Ser447X gene therapy, variant of the human lipoprotein lipase gene that administered intramuscularly to patients with lipoprotein lipase deficiency can reduced significant the levels of plasma triglycerides [25-27].

Our patient has been prescribed a combination of fenofibrate, statins and omega-3 fatty acids. Due to the fact that the patient did

not respond to conventional therapy, plasmapheresis was considered. Plasmapheresis seems to be, according to the experts, a safe therapeutic option in patients with very severe hypertriglyceridemia but its effect is transient. The diseases treated with plasmapheresis are uncommon, most reports evidences are case reports or small case studies. There are currently no controlled trials to highlight benefits of plasmapheresis in treatment of very severe hypertriglyceridemia. The American Society of Apheresis guidelines recommend plasmapheresis for treatment of hypertriglyceridemia in the context of pancreatitis [28]. Plasmapheresis is an expensive treatment option in such medical emergencies and is available in specialized centers.

Conclusion

Patients with very severe hypertriglyceridemia that do not respond to conventional therapy can have benefits from plasmapheresis.

REFERENCES

1. **Berglund L, Brunzell JD, Goldberg AC et al.** Evaluation and Treatment of Hypertriglyceridemia: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 97(9): 2969–2989, 2012.

2. **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* 285(19): 2486–2497, 2001.

3. **Yuan G, Al-Shali K., Hegele RA.** Hypertriglyceridemia. Its etiology, effects and treatment. *Can Med Assoc J* 176(8): 1113–1120, 2007.

4. **Bouabdellah M, Iraqi H, Benlian P et al.** Familial hypertriglyceridemia: biochemical, clinical and molecular study in a Moroccan family. *Ann Biol Clin* 73(4): 474–484, 2015.

5. **Bainton D, Miller NE, Bolton CH, et al.** Plasma triglyceride and high density lipoprotein cholesterol as predictors of ischaemic heart disease in British men: The Caerphilly and Speedwell Collaborative Heart Disease Studies. *Br Heart J* 68(1): 60–66, 1992.

6. **Abdel-Maksoud MF, Hokanson JE.** The complex role of triglycerides in cardiovascular disease. *Semin Vasc Med* 2(3): 325-333, 2002.

7. **Patel A, Barzi F, Jamrozik K et al.** Serum Triglycerides *at al*. Risk Factor for Cardiovascular Diseases in the Asia-Pacific Region. *Circulation* 110(17): 2678–2686, 2004.

8. **Tirosh A, Rudich A, Shochat T et al.** Changes in Triglyceride Levels and Risk for Coronary Heart Disease in Young Men. *Ann Intern Med* 147(6): 377–385, 2007.

9. **Hokanson JE, Austin MA.** Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk* 3(2): 213–219, 1996.

10. **Kannel WB, Vasan RS**. Triglycerides as vascular risk factors: New Epidemiologic Insights For Current Opinion in Cardiology. Curr Opin Cardiol, 24(4): 345-350, 2009.

11. **Gan SI, Edwards AL, Symonds CJ, Beck PL.** Hypertriglyceridemia-induced pancreatitis: A case-based review. *World J Gastroenterol* 12(44): 7197–7202, 2006.

12. **Yang F, Wang Y, Sternfeld L et al.** The role of free fatty acids, pancreatic lipase and Ca^{2+} signalling in injury of isolated acinar cells and pancreatitis model in lipoprotein lipase-deficient mice. *Acta Physiol (Oxf)* 195(1): 13-28, 2009.

13. **Sztefko K, Panek J.** Serum free fatty acid concentration in patients with acute pancreatitis. *Pancreatology* 1(3): 230–236. 2001.

14. **De Beaux AC, Ross JA, Maingay JP et al.** Proinflammatory cytokine release by peripheral blood mononuclear cells from patients with acute pancreatitis. *Br J Surg* 83: 1071–1075, 1996.

15. **Kusnierz-Cabala B, Gurda-Duda A, Dumnicka P et al.** Analysis of selected inflammatory markers for

early prediction of severe clinical course of acute pancreatitis. *Przegl Lek* 70: 392–396, 2013.

16. Kota SK, Kota AK, Jammula S et al. Hypertriglyceridemia-induced recurrent acute pancreatitis: A case-based review. *Indian J Endocrinol Metab* 16(1): 141–143, 2012.

17. Barter PJ, Rye KA. Cardioprotective properties of fibrates: Which fibrate, which patients, what mechanism? *Circulation* 113: 1553–1555, 2006.

18. Carlson LA. Nicotinic acid: the broad-spectrum lipid drug. A 50th anniversary review. J Intern Med 258: 94-114, 2005.

19. Bays H. Ezetimibe. *Expert Opin Investig Drugs* 11(11): 1587-604, 2002.

20. Hooper L, Thompson RL, Harrison RA et al. Risks and benefits of omega 3 fats for mortality, cardiovascular disease and cancer: Systematic review. *BMJ* 332: 752–760, 2006.

21. Shearer GC, Savinova OV, Harris WS. Fish oil–how does it reduce plasma triglycerides? *Biochim Biophys Acta* 1821(5): 843-851, 2012.

22. Nasa P, Alexander G, Kulkarni A et al. Early plasmapheresis in patients with severe hypertriglyceridemia induced acute pancreatitis. *Indian J Crit Care Med* 19(8): 487–489, 2015.

23. Stefanutti C, Di Giacomo S, Vivenzio A et al. Therapeutic plasma exchange in patients with severe hypertriglyceridemia: a multicenter study. *Artif Organs* 33(12): 1096–1102, 2009.

24. Yeh JH, Chen JH, Chiu HC. Plasmapheresis for hyperlipidemic pancreatitis. *J Clin Apher* 18(4): 181–185, 2003.

25. Burnett JR, Hooper AJ. Alipogene tiparvovec, an adeno-associated virus encoding the Ser(447)X variant of the human lipoprotein lipase gene for the treatment of patients with lipoprotein lipase deficiency.*Curr Opin Mol Ther* 11: 681-691, 2009.

26. Gaudet D, De Wal J, Tremblay K. Review of the clinical development of alipogene tiparvovec gene therapy for lipoprotein lipase deficiency. *Atheroscler Suppl* 11(1): 55-60, 2010.

27. Stroes ES, Nierman MC, Meulenberg JJ et al. Intramuscular administration of AAV1-lipoprotein lipase S447X lowers triglycerides in lipoprotein lipase-deficient patients. *Arterioscler Thromb Vasc Biol* 28: 2303–2304, 2008.

28. Schwartz J, Winters JL, Padmanabhan A 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 sixth special issue. *Journal of Clinical Apheresis* 28(3): 145–284, 2013.