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E. Xhardo, F. Agaçi
Department of Internal Medicine, University Hospital "Shefqet Ndroqi", Tirana, Albania

Very severe hypertriglyceridemia in a subject with poor glycemic control: a case report with general consideration

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Abstract. *Hypertriglyceridemia is defined as a value of fasting serum triglyceride over 150 mg/dl. The classification of hypertriglyceridemia according to the Endocrine Society includes mild and moderate hypertriglyceridemia, severe hypertriglyceridemia and very severe hypertriglyceridemia. Mild and moderate hypertriglyceridemia increases 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, and omega-3 fatty acid. Other triglyceride-lowering therapies are represented by plasmapheresis and lipoprotein lipase gene therapy. The present work refers to a 55-year-old man without a history of family diabetes mellitus (DM), dyslipidemia, premature coronary artery disease, diagnosed with type 2 DM in 2016, from 2018 on insulin treatment; he was hospitalized for endocrine evaluation. The patient had a history of high blood pressure for approximately 15 years, chronic kidney disease, very severe hypertriglyceridemia, and chronic obstructive pulmonary disease. The patient followed treatment with hypoglycemic, hypolipemic, low-salt diet, fibrates, statins, omega-3 fatty acid.*

Keywords: *very severe hypertriglyceridemia; diabetes mellitus; treatment*

Introduction

Hypertriglyceridemia is defined as a value of fasting serum triglyceride over 150 mg/dl. Clinical Practice Guideline published in 2012 about Evaluation and Treatment of Hypertriglyceridemia states that the diagnosis and classification of hypertriglyceridemia based on fasting levels include mild and moderate hypertriglyceridemia (triglycerides of 150–999 mg/dl), severe hypertriglyceridemia (1,000–1,999 mg/dl) and very severe hypertriglyceridemia (> 2,000 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 high triglyceridemia > 500 mg/dl [2]. The previously mentioned classification of hypertriglyceridemia according to the international medical societies is presented in Table 1.

General considerations

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

Mild and moderate hypertriglyceridemia increases the risk of cardiovascular events while severe and very severe hypertriglyceridemia increases the risk of acute pancreatitis.

For correspondence: Elona Xhardo, MD, Department of Internal Medicine, University Hospital "Shefqet Ndroqi", Tirana, Albania; e-mail: xhardo.elona@gmail.com
Full list of author information is available at the end of the article.

There are numerous studies on the potential role of elevated triglyceride levels in promoting coronary events. In an issue published in 1992 in British Heart Journal entitled "Plasma triglyceride and high-density lipoprotein cholesterol as predictors of ischaemic heart disease in British men", Bainton D. and coauthors report that plasma triglyceride levels predict major cardiovascular events, and triglyceride concentration is a more important predictor than total cholesterol levels [5]. Ten years later, Abdel-Maksoud M.F. and Hokanson J.E. after analyzing twenty-one studies involved 65,863 men and 11,089 women and evaluated the association between plasma triglycerides and cardiovascular disease indicated that triglyceride levels are an independent predictor for 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 triglyceride level is an important and independent predictor for 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 aged from 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 J.E. and Austin M.A. 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 of Kannel W.B. and Vasan R.S. "Triglycerides as vascular risk factors: New Epidemiologic Insights for Current Opinion in Cardiology", the authors mentioned 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 of the occurrence of acute pancreatitis. Acute pancreatitis is a condition with varying etiology: iatrogenic, genetic, gallstones, alcohol consumption, hypertriglyceridemia. The role of hypertriglyceridemia in the pathogenesis of acute pancreatitis is not fully elucidated. The mechanisms 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 the release of pancreatic lipase; pancreatic lipase hydrolyses triglyceride and generates 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 pro-inflammatory response. Inflammatory cytokines (interleukin-1β, interleukin-6) may be involved according to some studies at the early stage of acute pancreatitis induced by severe hypertriglyceridemia [13–15].

Case report

A 55-year-old man without a history of family DM, dyslipidemia, premature coronary artery disease, diagnosed with type 2 DM in 2016, receiving insulin treatment from 2018, was hospitalized in 2019 at the Department of Internal Medicine, University Hospital "Shefqet Ndroqi", Tirana, for endocrine and metabolic evaluation.

Table 1. The classification of hypertriglyceridemia

The classification of hypertriglyceridemia	Serum triglyceride, mg/dl	
	ATP III	Endocrine Society
Borderline high triglyceridemia	150–199	–
Mild hypertriglyceridemia	–	150–199
Moderate hypertriglyceridemia	–	200–999
Severe hypertriglyceridemia	200–499	1,000–1,999
Very severe hypertriglyceridemia	> 500	> 2,000

Table 2. The dynamics of metabolic and endocrine parameters

Parameter	July 2019	November 2019	February 2020
Total cholesterol, mg/dl (ref. range < 200)	259	278.5	211
HDL-cholesterol, mg/dl (ref. range > 40)	27.3	20.1	35.2
Triglycerides, mg/dl (ref. range < 150)	3,118	1,814.7	152
LDL-cholesterol, mg/dl (ref. range 80–130)	165	51.2	86
VLDL-cholesterol, mg/ml (ref. range < 30)	242.7	362.94	105
R1 (chol/HDL) (< 3.3)	9.49	13.86	5.99
R2 (LDL/HDL) (0.5–3 low risk)	6.04	2.55	2.44
Phospholipid, mg/dl (ref. range 125–248)	307	393.5	265
HbA1c, % (ref. range 4.5–6.3)	11.7	9.18	7.2
Fasting glucose, mg/dl	405	287	169
Random glucose, mg/dl	231	152	144
Amylase, U/L (ref. range 23–85)	83	55	17
Lipase, U/L (ref. range 0–160)	92	74	29

Note: HbA1c — glycated hemoglobin.

History: high blood pressure for approximately 15 years, chronic kidney disease, dyslipidemia, and chronic obstructive pulmonary disease stage B. The patient followed treatment with a hypoglycemic, hypolipemic, low-sodium diet, telmisartan 80 mg/day, bisoprolol hemifumarate 5 mg/day, fenofibrate 160 mg/day, atorvastatin 20 mg/day, omega-3 acid ethyl esters, insuman rapid 30 U/day and insulin glargine 26 U/day (with titration of doses based on glycemic values).

The patient says he does not consume excess alcohol and he gave up smoking recently. The clinical examination was as follows: height — 171 cm, weight — 92 kg, and body mass index — 31.5 kg/m^2. The clinical examination determined no other pathological elements. The dynamics of metabolic and endocrine parameters are shown in Table 2.

Lipoprotein electrophoresis (25.11.2019):

Alpha = 18.6 % (ref. range 18–36)

Pro-B = 40.3 % (2–25)

Beta = 32.7 % (41–66)

Chylomicrons = 8.4 % (0.0–2.0)

Lp(a)lipoprotein = 0.697 mg/dl (< 30)

On July 10–20, 2019 the patient was hospitalized, and under the treatment the level of triglycerides dropped from 3,118 mg/dl to 162 mg/dl. After he had left the hospital, the patient didn't take regularly the medication and he did not follow the therapeutic lifestyle changes as we recommended.

In November 2019, the patient was hospitalized because the level of triglycerides was again very high — 1,814.7 mg/dl. We restarted the regimen with fenofibrate 160 mg/day, atorvastatin 20 mg/day, omega-3 acids ethyl esters, insulin therapy and antihypertensive remedies. Under this treatment and a strict low-fat diet, the level of triglycerides dropped to 173 mg/dl. We recommend the patient to take fenofibrate 160 mg/day, insulin therapy, antihypertensive treatment, low-fat diet and physical activities 20–30 min every day.

In spite of such very severe hypertriglyceridemia, fortunately, he did not develop acute pancreatitis (lipase and pancreatic amylase were within the range).

The follow-up control was scheduled for February 2020, 3 months after he had discharged from the hospital.

The last lipid panel (February 2020) was borderline normal.

Treatment of hypertriglyceridemia

Optimizing lifestyle (fat-free diet, cessation of alcohol consumption, weight loss, exercise), control of DM are important measures in the treatment of very severe hypertriglyceridemia.

Conventional pharmacological therapy of hypertriglyceridemia includes fibrates, niacin, statins, ezetimibe, omega-3 fatty acid. Fibrate therapy can reduce plasma triglyceride 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 P.J. and Rye K.A. stated in the article published in 2006 in *Circulation* that fibrates significantly reduce plasma triglyceride levels and raise the HDL-cholesterol levels [17]. Nicotinic acid inhibits the lipolysis in adipose tissue and reduces plasma fatty acids. Daily administration of 3 g of nicotinic acid may lead to a reduction of plasma triglyceride levels by 45 % and increase plasma HDL-cholesterol [18]. Statins reduce levels of the cholesterol and may reduce triglyceride levels by inhibiting hydroxymethylglutaryl coenzyme A reductase [16]. Ezetimibe is a cholesterol absorption inhibitor that significantly reduces LDL-cholesterol, triglyceride levels and increases the HDL-cholesterol levels [16, 19]. Omega-3 fats may decrease triglyceride levels by 20 % when administered with other triglyceride-lowering therapies [16, 20]. The proposed mechanism by which omega-3 fatty acid decreases triglyceride levels are the decline in hepatic production of VLDL and the increase clearance of VLDL [21].

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

Our patient has been prescribed a combination of fenofibrate, statins and omega-3 fatty acids. Due to the fact that the patient responded to conventional therapy, plasmapheresis wasn't considered.

Conclusions

Patients with very severe hypertriglyceridemia respond to conventional therapy.

Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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Information about authors
Elona Xhardo, MD, Department of Internal Medicine, University Hospital "Shefqet Ndroqi", Tirana, Albania
Feçor Agaçi, Professor, Department of Internal Medicine, University Hospital "Shefqet Ndroqi", Tirana, Albania

Xhardo E., Agaçi F.
Department of Internal Medicine, University Hospital «Shefqet Ndroqi», Tirana, Albania

Різко виражена гіпертригліцеридемія в пацієнта з незадовільним глікемічним контролем: клінічний випадок і загальні положення

Резюме. Гіпертригліцеридемія визначається як рівень тригліцеридів сироватки крові натще понад 150 мг/дл. Сучасна класифікація включає легку та помірну, тяжку та дуже тяжку гіпертригліцеридемію. Легка й помірна гіпертригліцеридемія підвищує ризик серцево-судинних подій, тоді як тяжка й різко виражена є фактором ризику гострого панкреатиту. Звичайна фармакотерапія гіпертригліцеридемії включає фібрати, ніацин, статини, езетиміб, омега-3 жирну кислоту. Інші способи, які дозволяють знизити рівень тригліцеридів, представлені плазмаферезом та терапією ліпопротеїновою ліпазою. Описаний клінічний випадок 55-річного чоловіка без анамнезу родинного цукрового діабету (ЦД), дисліпідемії, ранньої ішемічної хвороби серця. ЦД 2-го типу діагностований у 2016 році; із 2018 року пацієнт отримує інсулінотерапію. В анамнезі: артеріальна гіпертензія протягом приблизно 15 років, хронічна хвороба нирок, різко виражена гіпертригліцеридемія, хронічна обструктивна хвороба легень. Пацієнт дотримувався лікування гіпоглікемічною, гіполіпідемічною дієтою з низьким умістом солі, препаратами фібратів, статинів, омега-3 жирної кислоти.

Ключові слова: різко виражена гіпертригліцеридемія; цукровий діабет; лікування

Xhardo E., Aga i F.
Department of Internal Medicine, University Hospital «Shefqet Ndroqi», Tirana, Albania

Резко выраженная гипертриглицеридемия у пациента с неудовлетворительным гликемическим контролем: клинический случай и общие положения

Резюме. Гипертриглицеридемия определяется как уровень триглицеридов сыворотки крови натощак более 150 мг/дл. Современная классификация включает легкую и умеренную, тяжелую и очень тяжелую гипертриглицеридемию. Легкая и умеренная гипертриглицеридемия повышает риск сердечно-сосудистых событий, тогда как тяжелая и резко выраженная является фактором риска острого панкреатита. Обычная фармакотерапия гипертриглицеридемии включает фибраты, ниацин, статины, эзетимиб, омега-3 жирные кислоты. Другие способы, которые позволяют снизить уровень триглицеридов, представлены плазмаферезом и терапией липопротеиновой липазой. Описан клинический случай 55-летнего мужчины без анамнеза семейного сахарного диабета (СД), дислипидемии, ранней ишемической болезни сердца. СД 2-го типа диагностирован в 2016 году; с 2018 года пациент получает инсулинотерапию. В анамнезе артериальная гипертензия в течение примерно 15 лет, хроническая болезнь почек, резко выраженная гипертриглицеридемия, хроническая обструктивная болезнь легких. Пациент придерживался лечения гипогликемической, гиполипидемической диетой с низким содержанием соли, препаратами фибратов, статинов, омега-3 жирной кислоты.

Ключевые слова: резко выраженная гипертриглицеридемия; сахарный диабет; лечение