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Management of severe hypertriglyceridaemia

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INTRODUCTION

Severe hypertriglyceridaemia (SHTG) may be a therapeutic challenge. This is related to poor understanding of its pathogenesis and management, particularly in the chylomicronaemia syndrome. Thus, we attempted to fill this knowledge gap from the perspective of lipid specialists with many years of experience in the treatment of SHTG.

DEFINITION

Various definitions of SHTG have been proposed [1]. Some experts define it as serum triglyceride (TG) level > 11.3 mmol/L (1000 mg/dL) due to a risk of acute pancreatitis related to the presence of chylomicrons in blood. Others diagnose SHTG already when serum TG level is > 5.6 mmol/L (500 mg/dL) as at some point it may increase acutely due to various factors (disease, nutrition, drugs) up to a level at which chylomicrons appear in blood.

METABOLISM OF TRIGLYCERIDE-RICH LIPOPROTEINS

To understand the pathophysiology of SHTG, some basic knowledge about the metabolism of TG-rich lipoproteins is required [2]. In plasma, TG are transported by 2 main lipoprotein classes, i.e. very low-density lipoproteins (VLDL) and chylomicrons.

Triglycerides present in VLDL are synthesised in the liver from carbohydrates and free fatty acids (FFA) released from the adipose tissue by lipolysis. VLDL particles are continuously synthesised in hepatocytes and released to circulation. Lipoprotein lipase (LPL) located on the surface of capillary endothelial cells hydrolyses VLDL triglycerides to fatty acids and glycerol. As a result of this process, these lipoproteins are transformed into particles containing less and less TG, known as VLDL remnants, some of them cleared by the liver, and some converted in the circulation to low-density lipoproteins (LDL). Physiologically, fasting plasma contains VLDL triglycerides and remnant TG, mostly reflecting VLDL-TG production.

Chylomicrons carrying TG are created in the intestinal epithelial cells (enterocytes) and contain dietary fat and cholesterol. Chylomicrons, which are the largest lipoproteins, are thus formed following a fat-containing meal. They enter circulation through the lymphatic vessels, bypassing the liver. Their half-life is short, less than 1 h. Physiologically, chylomicron TG are present in blood (after a fat-containing meal) in decreasing concentrations for up to several hours. LPL acts not only on VLDL triglycerides but also on chylomicron TG, resulting in their hydrolysis. Fatty acids are used in muscle as a source of energy or stored as fat in the adipose tissue. With this TG depletion, chylomicrons become progressively smaller chylomicron remnants which are ultimately cleared by the liver. It is thus clear that in the fasting state, plasma should not contain any chylomicrons.

PATHOGENESIS

Hypertriglyceridaemia may be an effect of increased VLDL production, decreased VLDL and/or chylomicron catabolism, or most likely both these mechanisms. As a result, hypertriglyceridaemia results from an increased or high serum TG level in the following types of lipoproteins: 1) VLDL (familial hypertriglyceridaemia, also known as Fredrickson type IV hyperlipoproteinaemia [HLP], or familial combined hyperlipoproteinaemia, or HLP type IIb, in which LDL cholesterol level is also increased; 2) VLDL and chylomicrons (HLP type V); 3) VLDL remnants and chylomicron remnants (dysbetalipoproteinaemia, also known as remnant disease or HLP type III); and 4) chylomicrons only (chylomicronaemia syndrome or HLP type I) [3].

Among these conditions, the most common is familial hypertriglyceridaemia (5–10% of the population) which is related to various genetic factors (polygenic aetiology) and secondary factors superimposed on genetic susceptibility, including environmental factors, leading to VLDL overproduction. Serum TG level is usually in the range of 200–500 mg/dL. Less frequent polygenic hypertriglyceridaemias (1–2% of the

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population) include familial combined hyperlipoproteinaemia which results from an increased hepatic synthesis of apolipoprotein B (apo B), leading to an increased in VLDL production. An even less frequent form is dysbetalipoproteinaemia (0.01% of the population). It results from an impaired catabolism of TG-carrying lipoprotein remnants due to a mutation in apolipoprotein E (apo E) which binds these remnants with their hepatocyte receptors.

SHTG results from an effect of either a strong genetic factor (very rarely), or weaker genetic factors combined with secondary factors, including environmental factors.

An example of a strong genetic factor responsible for SHTG is LPL deficiency, or HLP type I, which manifests already in childhood. HLP type I may also be caused by a defect in apolipoprotein C II which is a LPL cofactor. This very rare disorder (1–2 cases per million population) is characterised by the presence of chylomicrons in plasma in the fasting condition. Plasma TG level is much above 1000 mg/dL, often in the range of several thousand mg/dL. It is not known why VLDL triglyceride level is not increased.

An acquired HLP type I may also occur in autoimmune diseases due to the presence of antibodies against LPL (e.g., systemic lupus erythematosus, Graves disease).

HLP type V may be hereditary but it is mostly an acquired lipid disorder. In patients with moderately severe hypertriglyceridaemia, TG level may increase significantly due to enhanced VLDL synthesis, e.g. resulting from the development of visceral obesity and/or diabetes or in relation to other factors discussed below. If TG level exceeds 5.6 mmol/L (500 mg/dL), and in particular 11.3 mmol/L (1000 mg/dL), LPL becomes saturated by VLDL triglyceride and chylomicrons appear in plasma in the fasting condition [4]. By this mechanism, fasting chylomicronaemia may develop in familial hypertriglyceridaemia, familial combined hyperlipidaemia, and dysbetalipoproteinaemia, resulting in HLP type V.

Numerous factors, both intrinsic (diseases, metabolic conditions) and environmental (diet, medication), may contribute to increased VLDL triglyceride synthesis, potentially leading to chylomicronaemia [1, 4–6]. Among disease conditions, common causes include obesity, diabetes, untreated hypothyroidism, and kidney disease. The most common disease accelerating hepatic TG overproduction is diabetes. In addition, insulin shortage in type 1 diabetes results in LPL deficiency leading to fasting chylomicronaemia, as insulin normally stimulates production of this enzyme.

Less frequent conditions associated with worsening of hypertriglyceridaemia up to the point when fasting chylomicronaemia develops include HIV infection, lipodystrophy, anorexia nervosa, Cushing syndrome, sarcoidosis, multiple myeloma, and systemic lupus erythematosus.

A physiologic metabolic condition resulting in an increased TG level is pregnancy, which is related to the demands of the developing foetus. In women with genetic hypetriglyceridaemia, fasting chylomicronaemia may develop and pose a risk of acute pancreatitis.

Among nutritional factors that may induce SHTG, the most important one is alcohol abuse. Synthesis of VLDL-TG is also increased by dietary carbohydrates, particularly simple sugars.

Numerous drugs may lead to SHTG, including chylomicronaemia syndrome. These include oral estrogens, glycocorticosteroids, protease inhibitors, some antihypertensive medications (hydrochlorothiazide, nonselective beta-blockers), retinoic acid (isotretinoin), tamoxifen, raloxifen, cyclosporin, sirolimus, bile acid-binding resins, and antipsychotic medications including clozapine and olanzapine.

To conclude this section, it should also be highlighted that the above discussed factors are widely believed not to cause hypertriglyceridaemia by themselves but only affect it severity in subjects with a genetic predisposition.

DIAGNOSTIC APPROACH

As stated above, SHTG is defined as serum TG level > 5.6 mmol/L, and particularly > 11.3 mmol/L. In the fasting conditions, serum is not clear but turbid or even frankly milky, depending on the TG content. If chylomicrons are not present but serum contains a lot of VLDL triglycerides, serum stored at 4°C for 10–12 h remains uniformly turbid or milky [7].

In contrast, if serum contains chylomicrons, by this time they will form a creamy top layer of varying thickness depending on the amount of chylomicrons.

If the serum below the chylomicron top layer is turbid, this indicates that fasting chylomicronaemia is accompanied by an increased VLDL-TG level, and HLP type V is diagnosed. Total cholesterol level is also increased, sometimes to a large extent. In these cases, however, this cholesterol excess is mostly contained in chylomicrons and VLDL, and not LDL.

If the serum below the chylomicron layer is clear, this indicates that VLDL-TG level is not increased and the rare form of HLP type I or chylomicronaemia syndrome may be diagnosed.

SHTG may be asymptomatic or associated with specific symptoms and signs including abdominal pain, acute pancreatitis, xanthomas, lipaemia retinalis, and hepatosplenomegaly [5].

Evaluation whether hypertriglyceridaemia is related only to high VLDL-TG level or also to the presence of chylomicrons should be followed by search for factors aggravating hypertriglyceridaemia such as already mentioned disease conditions, alcohol abuse, or the use of drugs that increase TG level [8].

PANCREATITIS

The most severe complication of SHTG with fasting chylomicronaemia is acute pancreatitis. SHTG is the third common cause of acute pancreatitis after alcohol abuse and cholelithiasis [9], believed to be responsible for up to 10% of all episodes of acute pancreatitis [9]. On the other hand, the rates of SHTG among patients with acute pancreatitis in 3 prospective studies

were 12%, 21%, and 22% [10]. Although the threshold TG level for an increased risk of pancreatitis has not been defined, it is often arbitrarily set at > 11.3 mmol/L (> 1000 mg/dL).

The precise mechanism of pancreatitis due to SHTG is not known. It has been suggested that high local levels of FFA released by pancreatic lipase during hydrolysis of TG present in chylomicrons exceed the binding capacity of albumin and induce inflammation [11, 12]. According to another hypothesis, increased chylomicron levels lead to excessive plasma viscosity, resulting in hypoxia and local acidosis in pancreatic capillaries, which increases toxicity of FFA [13].

CARDIOVASCULAR DISEASE

The role of SHTG, chylomicrons and large VLDL particles in the development of atherosclerosis is still under debate. A major role in atherogenesis is played by cholesterol and not TG accumulation in the arterial walls. The question whether cholesterol may enter the vessel wall via noncatabolised large TG-laden lipoproteins (in particular chylomicrons) has not been definitely answered. Demonstration of the presence of apolipoprotein B48 (a component of chylomicrons only) in atherosclerotic plaques in humans and animals [14–18] does not prove that intact chylomicrons enter the subendothelial layers, as this protein may also be derived from chylomicron remnants which are much smaller particles than their parent lipoproteins. Chylomicron remnants penetrate the arterial wall and interact with macrophages, serving as cholesterol donors for the latter, as are VLDL remnants. They initiate vascular inflammation, including macrophage-mediated processes, induce endothelial expression of adhesion molecules, and promote thrombosis. However, LPL activity is required for conversion of large TG-laden lipoproteins into their remnants.

Recently, Goldberg [4] published a thorough analysis of the effect of TG-rich lipoproteins on the development of atherosclerosis, based on an extensive review of the literature. This paper was published under a revealing title "Triglycerides and heart disease. Still hypothesis?" The authors cited studies in humans with genetic defects of LPL activity which suggest that native TG-rich lipoproteins are relatively but not completely nonatherogenic. Although coronary artery disease (CAD) generally does not develop in chylomicronaemia syndrome, such cases have been reported. Familial hypertriglyceridaemia usually is also not associated with CAD [3]. Large VLDL particles contain little cholesterol and apo B level is not increased, unlike in familial combined hyperlipidaemia which also predisposes to coronary atherosclerosis. However, if familial hypertriglyceridaemia is associated with features of the metabolic syndrome, as is often the case, than the risk of CAD is increased [3, 19].

Animal model data support the hypothesis that large TG-rich lipoproteins are less atherogenic compared to smaller lipoprotein particles, i.e. smaller VLDLs, chylomicron remnants, and VLDL remnants. This does not mean, however, that they are completely harmless. In hypertriglyceridaemic mice with LPL deficiency [20] or glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein (GPIHBP) deficiency [21], aortic atherosclerosis develops but these lesions are not advanced and occur at a later stage of life. LPL is stored in the subendothelial layer, and GPIHBP facilitates transport of this enzyme from the subendothelial layer to the endothelial surface.

Thus, these observations suggest that large TG-transporting lipoproteins may be atherogenic and introduce cholesterol to the vessel wall but to a much smaller degree compared to smaller lipoprotein particles.

NONPHARMACOLOGIC THERAPY

Dietary treatment of HLP type V is a complex issue and patients require dietary advice of an experienced nutrition specialist. Resolution of chylomicronaemia is possible with immediate and significant reduction of fat intake to 10% of the total energy, i.e. not more than 25–30 g per day [8, 22]. This practically amounts to complying to a fat-free diet. Chylomicrons are formed from both animal and plant fat. Use of medium-chain triglycerides (MCT) as a source of energy may be considered. These are absorbed directly to the portal vein and undergo rapid oxydation in the liver, and chylomicrons are not formed from MCT.

Alcohol intake is contraindicated. Dietary treatment is difficult as reduction of VLDL-TG level also requires limiting intake of simple carbohydrates which are a good and easily accessible substrate for hepatic TG production. Carbohydrates should be provided in the form of fibre-rich products characterised by a low glycaemic index. Although fructose is also characterised by a low glycaemic index, it induces a large increase in TG level and thus its intake should be limited [22]. Fructose is present in sucrose, honey, and fruits. In obese patients, body weight reduction is an important measure to reduce insulin resistance, hyperinsulinaemia, and resulting increased VLDL-TG synthesis. Triglyceride level is also decreased by physical activity, as muscles use fatty acids as a source of energy.

Reduction of body weight is the most important measure in SHTG related to VLDL-TG overproduction, without fasting chylomicronaemia (HLP type IV), which is often associated with obesity and diabetes. This improves tissue insulin sensitivity and results in a decrease in TG level. Total carbohydrate, and particularly simple carbohydrate intake should be limited, and alcohol intake needs to be eliminated. In addition, similarly to general cardiovascular disease prevention, saturated fat should be replaced with unsaturated fat. As discussed below, n-3 polyunsaturated fatty acid supplements are recommended but these should be used in pharmacologic doses.

DRUG THERAPY

Drug therapy of SHTG is summarised in Table 1 [8, 23, 24]. First-line drugs are fibrates which are indicated in patients with

Table 1. Drug treatment of severe hypertriglyceridaemia (modified from references [8, 23, 24])

Drug	Mechanism of action	Dosage	TG level reduction [%]	Comments
Fenofibrate	Increased LPL activity and reduced hepatic TG synthesis by induction of FFA oxidation	1 × 200 M 1 × 267 M 1 × NT 145 mg 1 × supra 160 mg 1 × supra 215 mg	~ 50%	• First-choice drugs • Slow onset of action
Gemfibrozil		2 × 600 mg	~ 50%	
n-3 fatty acids	Reduced hepatic TG synthesis by induction of FFA oxidation and increased LPL activity	2 × 2 g (ethyl esters)	~ 25–50%	• Rapid onset of action
Extended--release nicotinic acid	Reduction of VLDL secretion by decreasing FFA supply to the liver (inhibition of lipolysis in the adipose tissue)	1–2 g/day, starting from the lowest dose	~ 15–35%	• Slow onset of action • Unpleasant side effects (flushing, hot flushes)
MCT ("formula diet")	No chylomicron formation	Source of energy, replacing other fat during meal preparation		• Immediate TG level reduction • No data regarding long-term safety
Statins	• Reduced cholesterol availability leads to decreased synthesis and secretion of apo B-containing VLDL particles • Increased remnant catabolism via LDL receptors		~ 10–20% The more potent statin and the larger dose, the greater TG level reduction	• Not as monotherapy • Combined treatment with fibrates and n-3 fatty acids

FFA — free fatty acids; LDL — low-density lipoproteins; LPL — lipoprotein lipase; MCT — medium-chain triglycerides; TG — triglycerides; VLDL — very low-density lipoproteins

serum TG level equal to or above 5.6 mmol/L (500 mg/dL). The major mechanism of fibrate action on the TG level is inhibition of VLDL-TG synthesis. In case of VLDL-TG overproduction accompanied by plasma chylomicron retention due to LPL saturation, a decrease in VLDL triglyceride level reduces the amount of TG-rich lipoproteins competing for LPL activity and chylomicronaemia resolves. In addition, fibrates increase LPL activity.

The effect of fibrate may by enhanced by addition of a large dose of n-3 polyunsaturated fatty acids (fish oil preparation) which inhibit hepatic TG synthesis and act rapidly, in contrast to fibrates. Of note, they are the only pharmacologic agents recommended for reduction of TG level in patients with severe chronic kidney disease.

Another therapeutic option in SHTG is extended-release nicotinic acid which is not available in Poland. Similarly to fibrates, it is characterised by slow onset of action. Its use is limited by unpleasant side effects such as flushing, mostly involving the face, and hot flushes. Fibrates may be combined with nicotinic acid in SHTG. Of note, nicotinic acid worsens glycaemic control which may be of particular importance in diabetic patients.

It should be mentioned however that nicotinic acid is included into standards but its use may be questioned by some lipidologists after disappointing results of AIM-HIGH [25] and HPS2-THRIVE [26] trials. They do not support the use of extended release nicotinic acid to improve (in addition to statin) cardiovascular outcomes.

As mentioned above, MCT may be a source of energy in patients with chylomicronaemia, as they enter the liver with portal venous blood without chylomicron formation. Special MCT preparations may be used for preparation of meals. Long-term safety of MCT use is unknown and they are usually not used chronically but only temporarily when chylomicronaemia becomes severe and there is a risk of acute pancreatitis, particularly in a patient with a history of pancreatitis.

Statins also decrease TG level, affecting VLDL triglycerides, with the strongest effect exerted by the most potent drugs of this class, i.e. atorvastatin and rosuvastatin. However, in SHTG they are not recommended as first-line drugs but only as a part of combined treatment, mostly together with a fibrate and/or an n-3 fatty acid preparation. Additional statin therapy is essential in patients at high or very high cardiovascular risk [22]. In such patients with moderate hypertriglyceridaemia, statins

Table 2. Management of severe hypertriglyceridaemia

If severe hypertriglyceridaemia is detected (serum triglyceride level ≥ 5.6 mmol/L [500 mg/dL]), recommendations include:

1. Detailed history regarding:
   a) lipid disorders in close family members
   b) diseases that may reveal or exacerbate hypertriglyceridaemia (diabetes, hypothyroidism, chronic kidney disease)
   c) alcohol intake
   d) use of drugs increasing triglyceride level (e.g., oral estrogens, glycocorticosteroids, thiazide diuretics, nonselective beta-blockers, immunosuppresive drugs, vitamin A derivatives, some antipsychotic drugs)
   e) attacks of abominal pain, pancreatitis
2. Physical examination: body mass index, xanthomas and hepatosplenomegaly
3. Visual assessment of serum kept for 10–12 h at +4°C to check whether chylomicrons are present
4. Laboratory testing: plasma glucose, HbA1c (diabetes control), thyroid-stimulating hormone, creatinine, alanine transaminase (increased activity may indicate hepatic steatosis, also baseline evaluation before initiation of lipid-lowering drugs)
5. Appropriate treatment of diseases that may reveal or exacerbate hypertriglyceridaemia, withdrawal of drugs increasing triglyceride level
6. If chylomicrons are present, prompt institution of a very low-fat diet (practically a fat-free diet), alcohol abstinence, consideration of medium-chain triglycerides use if triglyceride level very high, reduction of simple carbohydrate intake to lower very low-density lipoproteins triglyceride level. Specialist dietary advice needed
7. If chylomicrons are not present, institution of a diet with reduced carbohydrate intake (particularly simple sugars), alcohol abstinence, substitution of unsaturated fat for saturated fat. Specialist dietary advice needed
8. Body weight reduction in obese patients
9. Increased physical activity
10. Drug therapy: fibrate and an n-3 polyunsaturated fatty acid preparation; add statin if high or very high cardiovascular risk (established cardiovascular disease, diabetes, chronic kidney disease)
11. Triglyceride level lowering below 11.0 mmol/L and preferably below 5.6 mmoL to avoid acute pancreatitis. For prevention of cardiovascular disease, target non-high-density lipoproteins cholesterol level < 3.3 mmol/L (< 130 mg/dL) in high risk patients and < 2.5 mmol/L (< 100 mg/dL) in very high risk patients

are used as the first-line therapy, and if their TG-lowering effect is not sufficient, the above mentioned drugs are added.

In summary, management of SHTG with TG levels > 1000 mg/dL (with fasting chylomicronaemia) includes an extremely low-fat diet (< 25 g/day), alcohol abstinence, reduced intake of simple carbohydrates (due to their VLDL-TG-increasing effect), treatment with fibrates and n-3 fatty acids, and statin treatment in patients at high or very high cardiovascular risk. Those patients require specialist dietary advice.

In "acute" SHTG, i.e. with a very largely increased TG level (attention should be paid to drugs that increase TG levels), particularly with complaints of abdominal pain and a risk of acute pancreatitis, total fast for 1–2 days is recommended. Plasmapheresis can be used to induce a rapid decrease in serum TG level. However, this is a costly and not widely available therapy which is in fact rarely required. After prompt reduction of TG level by fasting, MCT may be used in combination with other treatment as described above. Obviously, drugs that that increase hypertriglyceridaemia must not be used in these patients.

Recently, the U.S. Food Drug Administration and European Medicines Agency approved intramuscular administration of the LPL gene transferred using a viral vector for the treatment of chylomicronaemia syndrome (SHTG due to lacking or deficient LPL). This beneficial LPL gene variant is present in 20% of the Caucasian population and is associated with increased plasma clearance of apo B-containing lipoproteins, including chylomicrons, VLDL, their remnants, and LDL. This drug has been marketed under the trade name Glybera.

SUMMARY

Diagnostic approach to and management of SHTG are not always straightforward and specialist knowledge is required, particularly with the expected increase in the rates of SHTG associated with obesity and diabetes epidemics. We hope that this article will prove helpful for physicians caring for such patients. Their management may be guided by our recommendations that are shown in Table 2.

Conflict of interest: *none declared*

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