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Chapter 2

A physician’s guide for the management of hypertriglyceridemia: the etiology of hypertriglyceridemia determines treatment strategy

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Abstract

Hypertriglyceridemia is a common lipid disorder associated to different, highly prevalent metabolic derangements like diabetes mellitus, the metabolic syndrome and obesity. The choice of treatment depends on the underlying pathogenesis and the consequences for atherosclerosis or pancreatitis. A family history, physical examination and analysis of the lipid profile including measurement of apolipoprotein B or non-HDL-C are necessary to establish the underlying primary or secondary cause. Due to physiological diurnal variations of triglycerides (TG), the time of measurement (fasting or postprandial) should be taken into account when evaluating TG values. Increased awareness arises concerning the impact of postprandial hypertriglyceridemia on the development of atherosclerosis. Hypertriglyceridemia is strongly associated to postprandial hyperlipidemia, remnant accumulation, increased small dense LDL concentrations, low HDL-C, increased oxidative stress, endothelial dysfunction, leukocyte activation and insulin resistance. All these factors are strongly linked to the development of atherosclerosis. Treatment should be aimed at reducing the secretion of triglyceride-rich lipoproteins, increasing intravascular lipolysis and reducing the number of circulating remnants. The main intervention is a change of lifestyle with decreased alcohol consumption, increased physical activity, dietary changes and, if applicable, adaptation of used medication. Fibrates, fish oil and nicotinic acid are the first choice of treatment in sporadic and familial hypertriglyceridemia to reduce the risk of pancreatitis, whereas high dose statins, sometimes in combination with fibrates, nicotinic acid, or fish oil capsules, are indicated for familial combined hyperlipidemia. Statins are necessary to reach low LDL-C concentrations in patients with type 2 diabetes mellitus and statin dosage should be increased when hypertriglyceridemia is present to reach secondary treatment targets for apolipoprotein B or non-HDL-C. Finally, family screening is mandatory to detect familial lipid disorders for early intervention in other family members.
Introduction

Hypertriglyceridemia is a common lipid disorder associated with an increased risk for cardiovascular disease and pancreatitis, especially at higher triglyceride (TG) concentrations. Approximately one third of the adult US population has TG concentrations above 1.70 mmol/l (150 mg/dl) and a total of 18% of the population showed marked hypertriglyceridemia with TG concentrations above 2.25 mmol/l (200 mg/dl) [1]. Nevertheless, only 3.6% percent of the population with TG concentrations above 2.25 mmol/l used medication for hypertriglyceridemia [1]. Treatment strategies for hypertriglyceridemia strongly depend on the etiology of the hypertriglyceridemia and the relation to complications. Plasma TG concentrations are determined by the production of TG-rich lipoproteins (VLDL, chylomicrons and their respective remnants), the intravascular lipolysis of TG-rich lipoproteins (TRLs) and, finally, the hepatic uptake of TRLs. Hypertriglyceridemia can be subdivided into primary and secondary causes. Therefore, physicians should search for the underlying cause(s) in patients with hypertriglyceridemia, because it influences treatment strategy, cardiovascular risk assessment and, potentially, the necessity to screen families for familial lipid disorders [2]. This review provides an overview of the current evidence how to correctly diagnose hypertriglyceridemia, to search for the underlying etiology in individual cases and how to choose the appropriate treatment strategy.

Triglyceride metabolism

A schematic overview of TG metabolism is shown in Figure 1. TG are a major energy source for the body. After ingestion of food containing fat, TG are hydrolyzed in the intestinal lumen into free fatty acids (FFA) and 2-monoacylglycerols (MAG) and taken up by enterocytes through passive diffusion and specific proteins, like CD36 and various fatty acid transport proteins [3]. Once inside the endoplasmatic reticulum of the enterocyte, FFA and MAG are assembled into TG again and packed with cholesterol, phospholipids and apolipoproteins (apo) B48 and A-IV to form chylomicrons [4,5]. In this process, the microsomal triglyceride transfer protein and the editing enzyme complex are paramount factors [6,7]. Especially the latter is crucial for the synthesis of apo B48, the structural protein of chylomicrons. After assembling, the chylomicrons are secreted into the lymphatics and finally enter the circulation through the thoracic duct. Within the circulation apo A-IV is exchanged for two other apolipoproteins, namely apo C-II and apo E [8].

In fasting physiological conditions, plasma TG are mainly determined by VLDL concentrations synthesized in the liver. VLDL synthesis is a continuous process, which
Figure 1: A schematic representation of triglyceride (TG) hydrolysis. Very low density lipoproteins (VLDL) are secreted by the liver and contain apolipoprotein (apo) B100. In contrast, the small intestine secretes chylomicrons, which contain apo B48. Both VLDL and chylomicrons contain high concentrations of TG and hydrolysis is necessary for the delivery of free fatty acids (FFA) to muscular and adipose tissue for energy expenditure or storage. Lipoprotein lipase (LPL) has a central role in the hydrolysis of TG. LPL is mainly produced by myocytes and adipocytes and transported to the subendothelial space by heparan sulphate proteoglycans (HSPG). Finally, LPL is transported towards the capillary lumen by glycosylphosphatidylinositol-anchored high-density-binding protein 1 (GPIHBP1). LPL becomes activated by apo C-II, which is available on both chylomicrons and VLDL. In addition, apo A-V is involved in the TG hydrolysis as well. The TG are hydrolyzed into FFA, which are taken up from the circulation by specific receptors like CD36 or via non-specific proteins like albumin. Chylomicrons and VLDL shrink in size and become denser as hydrolysis continues. The remaining remnants are taken up by the liver via multiple receptors like the LDL-related protein receptor (LRP), several proteoglycans (HSPG) and a small proportion by the LDL-receptor (LDL-R).

Within the circulation, chylomicrons and VLDL interact with HDL by cholesterylester-transfer protein (CETP), which exchanges cholesterylesters (CE) for TG. In case of hypertriglyceridemia, CETP increases cholesterol content of TG-rich lipoproteins in combination with a decrease in HDL-cholesterol. This explains the inverse relationship between TG and HDL-C. Moreover, apo E is transferred from HDL to chylomicrons and VLDL, which is necessary for the hepatic removal of the remnants.
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increases postprandially when food derived TG and FFA reach the liver. The VLDL assembly resembles chylomicron synthesis, but in this case, apoB100 is the structural protein of VLDL [7].

Both, chylomicrons and VLDL are essential for the delivery of FFA to mainly the heart, skeletal muscle and adipose tissue for energy expenditure or storage. Hydrolysis of TG in the circulation is the main determinant of FFA delivery to tissues. Many proteins are involved in the hydrolysis of TG and lipoprotein lipase (LPL) and its co-factor apo C-II are the most important. LPL is mainly synthesized by myocytes and adipocytes, which secrete LPL into the surrounding interstitial spaces. LPL is transported from the interstitial space to the capillary lumen by binding to heparan sulphate proteoglycans. Recently it was discovered that LPL anchors on glycosylphosphatidylinositol-anchored high-density-binding protein 1 (GPIHBP1) at the endothelial cell surface of small capillaries, where LPL serves as a docking station for TG-rich lipoproteins [9-11]. Apo C-II, which is carried by chylomicrons and VLDL, serves as a co-factor for LPL activity, whereas apoC-III serves as an inhibitor of LPL [10,12,13]. Furthermore, apo A-V is also a major determinant of TG hydrolysis [14]. FFA are internalized by the endothelium via cell surface receptors like CD36 and via other processes such as non-specific carriers like albumin [15,16]. Lipolysis results in TG depleted chylomicrons and VLDL, which shrink in diameter and become enriched with cholesterol due to the action of cholesterol ester transfer protein (CETP) and other transfer proteins [17], resulting in chylomicron and VLDL remnants, respectively. Finally, the remnants are taken up by the liver via multiple receptor pathways including the LDL-receptor, heparan sulphate proteoglycans and the LDL receptor-related protein [12].

Within the circulation TG-rich lipoproteins interact with HDL by CETP, which exchanges cholesterylesters for TG (Figure 1). Therefore, cholesterol content of TG-rich lipoproteins increases, HDL-C decreases and small dense LDL become more abundant in the case of hypertriglyceridemia [17]. This close metabolic connection between TRLs and HDL, reflects the difficulty to distinguish hypertriglyceridemia as a cardiovascular risk factor independently from low HDL-C concentrations [18]. Apo E is transferred from HDL to chylomicrons and VLDL, where apoE is involved in multiple processes. Apo E has an inhibitory effect on the hydrolysis of TG within the circulation and secondly apo E binds to the LDL receptor, LDL receptor-related protein and heparan sulfate proteoglycans for adequate hepatic removal of remnants [12,19,20].

Fasting versus non-fasting triglycerides

Fasting TG levels below 1.70 mmol/l are considered desirable and hypertriglyceridemia is present when TG levels are above 1.70 mmol/l [18,21]. Current guidelines recommend to
measure TG in the fasting state since TG concentrations increase during the day [18,21]. However, most patients visit the hospital in the non-fasting state and it would be more convenient for both, patients and doctors, to measure non-fasting lipid profiles. Prospective studies have shown that also non-fasting TG predict cardiovascular disease in the non-fasting state [22,23] and it has been suggested that non-fasting TG are even a stronger predictor of cardiovascular disease than fasting TG [24,25]. Moreover, non-fasting TG are strongly correlated to fasting TG concentrations [26] and increase approximately 0.5 mmol/l in females and 1.0 mmol/l in males during the day [27,28]. These values can be used to compose normal ranges for non-fasting TG levels since mean diurnal increase in TG is similar between normotriglyceridemic and hypertriglyceridemic individuals [28]. Intra-individual variability of TG does not significantly increase in females during the day and not in males during daylight hours [28]. In summary, non-fasting TG can be used in clinical practice as long as an average TG increase of 0.5 mmol/l in females and 1.0 mmol/l in males is considered.

One of the inconveniences of measuring non-fasting lipid profiles is the fact that LDL-C calculations need fasting samples to be accurate. Non-fasting samples can lead to lower LDL-C values. It has been suggested that LDL-C is approximately 0.3-0.6 mmol/l lower in the non-fasting state [29]. In our opinion, the falsely decreased LDL-C is probably negligible in non-fasting normotriglyceridemic subjects.

Apo B and non-HDL-C can be used as an alternative for LDL-C. Apo B represents the number of circulating atherogenic lipoproteins containing apo B (LDL, VLDL, chylomicrons and their respective remnants) [30]. In contrast, non-HDL-C reflects the cholesterol concentration of both LDL and TRLs [31]. A post-hoc analysis of two combined prospective studies has shown that non-HDL-C and apo B are better predictors for future cardiovascular events than LDL-C in subjects receiving statin therapy [32]. High non-HDL-C levels predict cardiovascular disease independently from LDL-C concentrations [33]. In addition, apoB and non-HDL-C levels remain unchanged in the non-fasting state [34]. Normal values for non-HDL-C are 0.8 mmol/l above the normal ranges for LDL-C and the normal value for apoB ranges from 0.8-1.0 g/l [21].

The evaluation of the patient with hypertriglyceridemia

Whether hypertriglyceridemia alone initiates and accelerates atherosclerosis is an ongoing discussion, but hypertriglyceridemia surely is a marker of metabolic abnormalities [13]. Hypertriglyceridemia is often secondary to inappropriate dietary habits, obesity, diabetes, chronic kidney disease, end-stage liver disease or use of certain medications [2,30,35-37]. Besides secondary causes, hypertriglyceridemia can be caused by monogenic or polygenic diseases, which can have different associations with cardiovascular
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A list of diseases and factors causing hypertriglyceridemia is shown in Table 1. An adequate diagnosis for the cause of hypertriglyceridemia is of importance to determine the exact treatment strategy for each individual patient.

The evaluation of the hypertriglyceridemic patient starts with the family history, specifically aimed to identify lipid disorders and premature cardiovascular disease in first degree relatives. Secondly, potential secondary causes of hypertriglyceridemia should be identified. Therefore, other factors like the patient’s medical history, use of medication, dietary pattern and smoking history are also relevant. Physical examination should at least include the body mass index and waist circumference. The presence of xanthomas, which are usually not present in moderate hypertriglyceridemia, does not help to identify the underlying hypertriglyceridemic cause [2]. Laboratory screening should include a lipid profile (fasting or non-fasting) containing total cholesterol, LDL-C, HDL-C, TG and preferably apo B. Non-HDL-C concentrations can be easily calculated without additional costs as an alternative for apo B. In addition, creatinine levels reflecting kidney function, TSH levels, and glucose or glycated haemoglobin A1c and “liver function” tests should be measured to search for renal failure, hypothyroidism, diabetes and liver disease, respectively. An apo E genotyping can be performed when the diagnosis of familial dysbetalipoproteinemia is considered.

### Table 1: Primary and secondary causes of hypertriglyceridemia

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<th>Primary hypertriglyceridemia</th>
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<td>Familial hypertriglyceridemia</td>
<td>Diabetes mellitus</td>
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<td><em>Very rare primary causes:</em></td>
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<td>Tangier disease</td>
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<td>Lipoprotein lipase deficiency</td>
<td>Hypothyroidism</td>
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<td>GPIHBP1 deficiency</td>
<td>End stage kidney disease</td>
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<td>Apolipoprotein A-V deficiency</td>
<td>End stage liver disease</td>
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<td>Apolipoprotein C-II deficiency</td>
<td>Human Immunodeficiency Virus</td>
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<td></td>
<td>cyclosporines, tacrolimus, β-blockers, thiazide</td>
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<td>diuretics, synthetic retinoids, valproate and related</td>
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<td></td>
<td>drugs[2,35,37]</td>
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GPIHBP1 = glycosylphosphatidylinositol-anchored high-density-binding protein 1
Primary causes of hypertriglyceridemia

The three most common primary causes of hypertriglyceridemia are familial combined hyperlipidemia (FCH), familial hypertriglyceridemia and familial dysbetalipoproteinemia, which all affect approximately 1% of the population [2,35,38-40]. Besides the three most common primary hypertriglyceridemias, severe hypertriglyceridemia can already present during childhood due to very rare genetic disorders like LPL deficiency, apo A-V deficiency or apo C-II deficiency. Recently, the first human case with a GPIHBP1 deficiency showing marked hypertriglyceridemia was published [41]. However, these rare disorders are beyond the scope of this review.

FCH is characterized by increased TG, LDL-C and apo B in combination with the presence of premature cardiovascular disease in at least one first degree relative [42,43]. Multiple genes are involved in FCH leading to an increased hepatic production of VLDL together with a decreased clearance of circulating remnants [43-50]. Insulin resistance often coincides with FCH [51]. The presence of small, dense LDL is another characteristic of FCH [52]. Cardiovascular risk is substantially increased in FCH [38-40] and it has even been suggested that approximately 10% of the patients with a myocardial infarction below the age of 60 years have FCH [53].

In contrast, familial hypertriglyceridemia (FHTG) is not associated with an increased risk of cardiovascular disease [38] and is characterized by an impaired catabolism of TRLs [35]. The exact genetic disorder is unknown, but several candidate genes have been postulated [54]. Lipid profiles from patients with FHTG typically show increased TG concentrations above 5.0 mmol/l, with decreased LDL-C and normal apo B concentrations. FHTG may not be accompanied by premature atherosclerosis, but chylomicronemia syndrome (TG > 20.00 mmol/l) can develop when FHTG is accompanied by other factors, which can raise TG levels substantially. Highly increased TG levels can cause acute pancreatitis, making treatment imperative [55-57].

Familial dysbetalipoproteinemia (FD), also called “remnant removal disease” or type III hyperlipoproteinemia according to the Fredrickson classification, is most frequently caused by homozygosity for an isoform of apo E, namely apo E2 [12]. Additional genetic or environmental factors such as obesity or diabetes are needed besides the apo E2/E2 genotype for the development of hyperlipidemia, since only 10% of the subjects with the apo E2/E2 genotype develop hyperlipidemia [12]. For example estrogens may protect subjects with the apo E2/E2 genotype, since women do not develop type III hyperlipoproteinemia before the menopause, whereas males are already susceptible after adolescence [58]. Apo E2 has less affinity for the LDL-receptor, heparan sulfate proteoglycans and LDL receptor-related protein compared to the wild type apo E3, which leads to decreased hepatic removal of remnants [12,59]. In addition, the wild type apo E3 enhances the hydrolysis of TG compared to an inhibitory effect on the hydrolysis
by apo E2 [60,61]. FD is typically characterized by TG levels above 3.5 mmol/l and total cholesterol levels above 7.5 mmol/l in combination with normal ranges for apo B and LDL-C and is associated with an increased cardiovascular risk [12,18,62].

**Secondary causes of hypertriglyceridemia**

Genetic defects can cause hypertriglyceridemia, but dietary habits and other abnormalities can also contribute (Table 1). The most frequent cause of hypertriglyceridemia is obesity, a growing problem in Western countries [63]. Obesity has been associated with an increased mortality, largely by an increased risk of cardiovascular disease, which can be attributed by an increment of obesity related risk factors like hypertriglyceridemia [64]. Mildly obese subjects already have an impaired postprandial TG response, despite having normal fasting TG concentrations [65]. The mechanism of hypertriglyceridemia in the case of obesity has been linked to insulin resistance with an increased flux of FFA from the abdominal fat to the liver leading to increased hepatic VLDL production [51,66]. Triglyceridemia increases even more because competition for clearance between VLDL and chylomicrons occur, since both share the same catabolic processes [65,67]. However, not all obese subjects develop hypertriglyceridemia, which is the main lipid disorder in obesity. A recent study has shown that increased plasma apo C-III, which inhibits hydrolysis, significantly contributes to the development of the hypertriglyceridemic waist [68,69]. Obesity can lead to insulin resistance and subsequently to type 2 diabetes mellitus (T2DM). Lipid abnormalities are common in T2DM, which significantly add to the increased cardiovascular risk of patients with T2DM [70]. Very often TG are increased in patients with T2DM despite adequate treatment of the T2DM, probably because T2DM coexists with other disorders like obesity, smoking, alcohol consumption or the apo E2/E2 genotype [35].

Epidemiologic evidence is inconsistent on the effects of chronic alcohol consumption on TG concentrations. In the fasting state, both unchanged and increased TG have been described in relation to increased alcohol consumption [71-74]. However, in postprandial studies high alcohol intake has been related to elevated TG in contrast to low and moderate consumption [26,74-76]. It has been proposed that alcohol impairs oxidation of FFA by mitochondria, which accelerates TG synthesis leading to an increased hepatic secretion of VLDL [77,78]. Low to moderate alcohol consumption (1-3 consumptions per day) would probably not have major effects on TG, whereas excessive intake can cause hypertriglyceridemia. Besides alcohol, smoking has especially an effect on postprandial lipemia [26]. Smokers showed a postprandial increase in chylomicrons and their respective remnants characterized by increased postprandial apo B48 concentra-
tions. The increased number of chylomicrons and chylomicron remnants is probably due to a decreased clearance of chylomicron remnants [79].

Untreated hypothyroidism is frequently accompanied by hypercholesterolemia and possibly hypertriglyceridemia with increased concentrations of VLDL, LDL and also HDL [80]. Hypothyroidism leads to a reduced number of LDL receptors, which decreases the catabolism and turnover of mainly LDL and in part TRLs [81]. Hormone replacement therapy resulted in normalisation of total cholesterol and LDL-C, but TG concentrations remained unchanged [82,83]. However, it should be noted that the study groups were small and mean TG concentrations were normal at baseline.

Increased TG concentrations also occur in poorly controlled HIV infections together with decreased LDL-C and HDL-C concentrations. HIV-associated hypertriglyceridemia is caused by a combination of hepatic VLDL overproduction and reduced TG clearance [84]. In addition, antiretroviral therapy leads to lipodystrophy in 10 to 80 percent of the treated patients. The lipodystrophy impairs the storage of FFA in adipose tissue, which further increases the HIV-related hypertriglyceridemia [84].

TG concentrations are also frequently elevated in patients with end stage kidney disease, but cholesterol levels are mostly normal or even decreased. Secondly, the composition of the lipoproteins is also altered in end stage kidney disease. For example VLDL contains relatively more cholesterol and less TG in patients with end stage kidney disease. Moreover, clearance and hydrolysis of TRLs is altered by multiple mechanisms, which are reviewed in detail elsewhere [85,86].

### Treatment of hypertriglyceridemia by diet and lifestyle

The non-pharmacological treatment with diet and increased physical activity is the most important strategy in reducing hypertriglyceridemia and is applicable on all patients with hypertriglyceridemia regardless the cause. In recent years, it has become clear that lifestyle factors including type of dietary fats, proteins, fibers, micronutrients, alcohol consumption, exercise, obesity and smoking have a strong impact on triglyceridemia [36]. Since all these factors can be altered via improved lifestyle behaviour, hypertriglyceridemia and subsequently reducing cardiovascular risk can be partly reduced by non-pharmacological strategies [87].

The average Western style meal contains 20-40 g of fat and a postprandial rise in TG is already evident after the ingestion of 30 g of fat. Postprandial triglyceridemia is likely to be present most of the day, because people typically eat 3 to 4 meals a day [26]. The amount of dietary fat remains the most important determinant of postprandial lipemia [36], but the type of dietary fat influences triglyceridemia as well. Postprandial lipemia is most pronounced after ingestion of saturated fatty acids (SFA), which are found in high
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amounts in animal fat, followed by monounsaturated fatty acids (MUFA), the main fatty acids in olive oil. In contrast, dietary polyunsaturated fatty acids (PUFA), which are mainly found in vegetables (n-6 PUFA) and fish oils (n-3 PUFA), show the smallest postprandial increase in TG [36,88]. Obese subjects probably experience more beneficial effects of a diet rich in PUFA and MUFA and low on SFA compared to lean subjects. Chylomicron remnant concentrations were reduced after a meal with olive oil (22% SFA, 38% MUFA, 4% PUFA) compared to a meal with butter (35% SFA, 22% MUFA, 4% PUFA), but only in obese subjects and not in lean subjects [89].

Besides dietary fats, carbohydrates may influence TG concentrations as well. Reduced postprandial TG responses have been observed with lean red meat, soy protein, casein and whey protein [36,90,91]. In addition, indigestible carbohydrates like oat bran, wheat fiber, wheat germ and psyllium husk also have beneficial effects on TG concentrations [36,92,93]. In contrast, fructose, which is abundant in soft drinks, may enhance postprandial lipemia when consumed more than 50 g per day [94]. Moreover, micronutrients like vitamins and polyphenols found in fruit and beverages like green tea are believed to reduce postprandial lipemia [95,96]. It was recently shown for the first time that a high intake of fruit and vegetables was indeed significantly associated with a reduced risk of cardiovascular disease [87].

Obesity is a strong determinant for hypertriglyceridemia as well and obese patients should be urged to lose weight regardless of the hypertriglyceridemic cause. Moderate weight loss induced by a diet low on carbohydrates and SFA combined with a slight increase in physical activity resulted in a 27%-46% reduction in postprandial TG responses [97]. Moderate weight loss normalized postprandial lipemia, despite persisting obesity. Regular physical activity does reduce weight, but acute exercise bouts alone also reduced postprandial lipemia by 24% to 35% by an increase in LPL activity [36]. However, exercise needs to be done on a regular basis, because the improved clearance of TG-rich lipoproteins already attenuates after 2 to 3 days [98].

In addition to weight loss and exercise, smoking increases TG, postprandial chylomicrons and their remnants suggesting a beneficial effect of smoking cessation on TG. However, a meta-analysis could not confirm a TG lowering effect from cessation of smoking [99]. Nevertheless, smoking cessation should be promoted for improving cardiovascular health and many other reasons [36].

Mechanisms of triglyceride lowering pharmacotherapy

Isolated hypertriglyceridemia can be present, but hypertriglyceridemia is more frequently present in combination with other lipid abnormalities like increased LDL-C or decreased HDL-C depending on the underlying etiology. The four main pharmacological
agents used to treat hypertriglyceridemic disorders, either isolated or in combination with other lipid abnormalities, are fibrates, statins, nicotinic acid and omega-3 fatty acids. Each of them has different mechanisms of action to modify TG synthesis and clearance of TRLs (Figure 2).

Figure 2: Schematic representation of triglyceride (TG) lowering mechanisms by different pharmacological agents: fibrates, nicotinic acid, statins and omega-3 fatty acids (Ω-3). Fibrates increase transcription of LPL and decrease transcription of apo C-III, which all improves TG clearance from plasma. Nicotinic acid reduces the lipolysis of adipocytes leading to reduced hepatic TG synthesis. Moreover, niacin has the potential to increase apoB100 degradation in hepatocytes. Statins have only a modest effect on TG and inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is the rate limiting step of the hepatic cholesterol synthesis. Reduction in the endogenous cholesterol synthesis leads to upregulation of the LDL receptor (LDL-R) and subsequently increased hepatic uptake of LDL. Omega-3 fatty acids have multiple effects on TG metabolism. First of all, omega-3 fatty acids lower gene transcription of sterol regulatory element-binding protein-1c leading to decreased hepatic synthesis of fatty acids and thus TG synthesis. In addition, TG clearance from VLDL and chylomicrons is stimulated by omega-3 fatty acids, because it is a ligand for the farnesoid X receptor, which suppresses apo C-III gene expression and induces apo C-II gene expression. Hydrolysis of VLDL and chylomicrons is also increased by omega-3 fatty acids, potentially via increased lipoprotein lipase (LPL) gene expression in adipose tissue.
Fibrates (fibric acid derivatives) are synthetic ligands that bind to the peroxisome proliferator-activated receptor (PPAR)-α and are known for their TG-lowering and HDL-C increasing effect. Activation of PPAR-α modulates many genes affecting TG metabolism including LPL, APOC3 and APOA5 [100]. Fibrates increase transcription of LPL and decrease transcription of apo C-III, which favours TG clearance from plasma [101,102]. Most studies investigating the effect of fibrates on apo B metabolism reported increased VLDL apo B100 clearance and in some subjects reduced VLDL apo B100 secretion in patients with hypertriglyceridemia [100]. Treatment with fenofibrate also resulted in reduced apo B48 secretion in two subjects with a rare combination of heterozygous familial hypercholesterolemia combined with dysbetalipoproteinemia [103]. In addition, the catabolic rate of chylomicrons is increased by fenofibrate in hypertriglyceridemic subjects with T2DM [104].

Statins mainly reduce LDL-C, non-HDL-C and apoB concentrations, but statins modestly lower TG levels in hypertriglyceridemic subjects as well [105]. The TG lowering effect of the different statins is comparable with the percentage of cholesterol lowering effect and is probably a reflection of reduced cholesterol content of the TRLs since TG strongly correlate with cholesterol concentrations in the TRLs [25]. Statins inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is the rate limiting step of the hepatic cholesterol synthesis. Reduction of the endogenous cholesterol synthesis leads to upregulation of the LDL receptor and subsequently increased hepatic uptake of LDL. When hepatic uptake of LDL is increased, LDL-C and apo B concentrations decrease.

Nicotinic acid has multiple effects on serum lipoprotein levels by raising HDL-C, lowering LDL-C and decreasing TG by 13-50% [106-108]. Nicotinic acid inhibits the lipolysis in adipocytes accompanied by a drop in FFA by binding of nicotinic acid to the nicotinic acid receptor [109]. This reduces the supply of FFA and subsequently hepatic TG synthesis and VLDL formation [110,111]. In addition, an in vitro study has shown the potential of nicotinic acid to degrade intracellular apo B100 [112]. The HDL-C raising property of nicotinic acid is probably a result of decreased TG concentrations. When TG levels are lowered, cholesterylesters are less transferred from VLDL to HDL in exchange for TG by CETP.

Omega-3 fatty acids are PUFA obtained from fatty fish or fish-oil supplements and consist of α-linoleic acid (ALA, 18:3n-3), eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) [113]. Humans are unable to synthesize omega-3 fatty acids and only a small percentage of ALA is converted to EPA [113]. Therefore, supply of EPA and DHA depends on dietary intake. Fatty acids with multiple double bonds, like omega-3 fatty acids, are essential to increase cell membrane fluidity for improved receptor functions and signalling pathways [113]. Studies have shown that omega-3 fatty acids lower TG by reducing hepatic TG synthesis and VLDL secretion and enhancing TG
clearance from circulating chylomicrons and VLDL. However, animal studies investigating the exact mechanisms were not always consistent or physiologically relevant [114]. It has been shown that omega-3 fatty acids lower gene transcription of sterol regulatory element-binding protein-1c (SREBP-1c), which stimulates the hepatic synthesis of fatty acids and thus TG synthesis [115]. In addition, TG clearance from VLDL and chylomicrons is stimulated by DHA, because it is a ligand for the farnesoid X receptor (FXR), which suppresses apo C-III gene expression and induces apo C-II gene expression [113,116,117]. Hydrolysis of TRLs is even more stimulated by omega-3 fatty acids via increased LPL gene expression in adipose tissue [118,119].

**Treatment targets**

Treatment of hypertriglyceridemia is complex due to the multifactorial basis of this lipid abnormality. Lifestyle changes including weight loss, physical exercise and a healthy diet should be advised to all patients with hypertriglyceridemia. The importance of lifestyle changes is clear, but different opinions exist about the pharmacological treatment of hypertriglyceridemia. Some pharmacological agents are more appropriate than others in certain cases of hypertriglyceridemia but evidence is often lacking (Table 2). The recent ESC/EAS guidelines advise treatment targets of LDL-C < 1.8 mmol/l and < 2.5 mmol/l in subjects with very high and high cardiovascular risk, respectively [21]. Non-HDL-C is advised as a secondary treatment target in case of hypertriglyceridemia, which treatment target is 0.8 mmol/l higher than the corresponding LDL-C target [21]. Moreover, apo B can be used as a treatment target, because it reflects the number of

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<td>High dose statins, sometimes in combination with fibrates, niacin or fish oil</td>
<td>- Weight loss&lt;br&gt;- Physical exercise</td>
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<tr>
<td>Familial hypertriglyceridemia</td>
<td>Fibrates, nicotinic acid</td>
<td>- Diet low on fat and SFA and rich in dietary fibres, soy, casein, whey and lean red meat and PUFA.</td>
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<td>Familial dysbetalipoproteinemia</td>
<td>Statins + fibrate when lifestyle changes are insufficient</td>
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<tr>
<td>Obesity</td>
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<td>- Reducing alcohol&lt;br&gt;- Cessation of smoking</td>
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<td>Type 2 diabetes mellitus</td>
<td>High dose statins</td>
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<td>Hypothyroidism</td>
<td>Adequate treatment with thyroid hormone</td>
<td></td>
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</table>

Table 2: Choosing the right pharmacological agent depends on the underlying hypertriglyceridemic cause. Lifestyle changes are always important besides pharmacological therapy.

Note: do not combine gemfibrozil with a statin. Instead ciprofibrate, bezafibrate or fenofibrate can be combined with a statin.
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atherogenic particles. Treatment targets of apo B are 0.8 g/l and 1.0 g/l for subjects with very high and high cardiovascular risk, respectively [21]. No specific treatment targets are available for TG or for the addition of a secondary agent on top of statin therapy to treat the residual cardiovascular risk associated with hypertriglyceridemia. However, more evidence is becoming available on efficacy and safety concerning combination therapies [120].

Pharmacological treatment for different causes of hypertriglyceridemia

Statins are the first choice of treatment for FCH since it is characterised by increased hepatic VLDL production, small dense LDL and substantially increased cardiovascular risk [52,121]. Although no specific studies exist on the long-term effects of treatment of FCH, results can be extrapolated from subjects with combined hyperlipidemia. High dosages of statins are advised to further reduce apo B and non-HDL-C, because of the increased remnant cholesterol in subjects with FCH. Lowering non-HDL-C results in a linear reduction of cardiovascular risk [122] and non-HDL-C is the strongest predictor of the residual cardiovascular risk in subjects already on statin therapy [32]. When statin related myopathy occurs, a combination of fenofibrate and ezetimibe, an intestinal cholesterol absorption inhibitor, can be prescribed. This combination decreases cholesterol in both VLDL and LDL and reduces the amount of small dense LDL particles [123].

Treatment of FHTG should not be aimed at reducing cardiovascular risk, but to reduce the risk of hypertriglyceridemia associated pancreatitis [120]. Medical treatment with a fibrate should be initiated when TG are > 10.00 mmol/l to reduce the risk of pancreatitis [2], but the threshold for developing pancreatitis could be much higher [2,57]. A common side effect of fibrates is an increase in serum creatinine, which is often reversible [124]. Nicotinic acid can be used as an alternative when fibrates can not be prescribed, because nicotinic acid has a strong TG lowering capacity of 30-50% as well [125]. Patients receiving nicotinic acid should be warned for the frequent occurring side effect of severe flushing, which lasts for approximately 30 to 90 minutes after intake [109].

The most optimal pharmacological treatment of FD is controversial since FD seems to improve by all available interventions. It should be noted that most subjects with the apo E2/E2 genotype have normal lipid parameters. Pharmacological treatment is indicated when lifestyle changes and treatment of other secondary causes have not improved the combined hyperlipidemia [126]. Both statins and fibrates have been investigated in relation to FD, but studies on clinical outcomes are unavailable. Statins reduce mainly LDL-C, whereas fibrates lower mainly TG in subjects with FD [62,127]. In
addition, both bezafibrate 400 mg daily and atorvastatin 10 mg show both a reduction in non-HDL-C of approximately 45% [62]. Combination therapy with a statin and fibrate may be considered in therapy refractory subjects [126,128,129].

Post hoc subgroup analyses showed that fibrates reduce cardiovascular risk substantially in subjects with characteristics of the metabolic syndrome [130-132]. However, results could not always be replicated. Treatment of patients with T2DM with fenofibrate alone or on top of statin therapy did not result in a reduction of cardiovascular events [133,134]. It seems that gemfibrozil has more potential to reduce cardiovascular risk in subjects with the metabolic syndrome compared to bezafibrate, possibly by decreased concentrations of small dense LDL particles [135,136]. However, statins are the first choice of treatment for diabetic dyslipidemia and gemfibrozil should not be combined with a statin, because of an increased risk of rhabdomyolysis [102,120]. Targets for patients with T2DM are LDL-C concentrations < 1.8 mmol/l, but often diabetic patients have elevated TG as well [21]. In the case of hypertriglyceridemia, statin therapy should be intensified to further reduce non-HDL-C concentrations < 2.6 mmol/l [21].

Omega-3 fatty acids reduce TG levels but are insufficient as monotherapy. However, they can be safely combined with other drugs to further decrease TG concentrations [113]. Drugs like cholesterol absorption inhibitors (ezetimibe) or bile acid sequestrants, have no place in the specific treatment of hypertriglyceridemia and the latter are even contraindicated since these agents can increase TG concentrations.

Conclusion

Hypertriglyceridemia is common and can be caused by primary lipid disorders like familial combined hyperlipidemia, familial hypertriglyceridemia and familial dysbetalipoproteinemia or by secondary causes, mainly obesity and T2DM. It is often possible to diagnose the underlying hypertriglyceridemic cause with a family history, physical examination and lipid profile including apo B. Treatment should always include lifestyle changes and different pharmacological treatment options exist aiming at different pathways within the vast lipid metabolism. Pharmacological agents reduce the TG-rich lipoprotein secretion, increase lipolysis of TG-rich lipoproteins or reduce remnant cholesterol levels. Multiple agents can be used when monotherapy is insufficient to reach treatment targets. In addition, families should be screened for lipid abnormalities in case of a familial lipid disorder.
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