Management of hypertriglyceridemia

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ABSTRACT

Hypertriglyceridemia is one of the most common lipid abnormalities encountered in clinical practice. Many monogenic disorders causing severe hypertriglyceridemia have been identified, but in most patients triglyceride elevations result from a combination of multiple genetic variations with small effects and environmental factors. Common secondary causes include obesity, uncontrolled diabetes, alcohol misuse, and various commonly used drugs. Correcting these factors and optimizing lifestyle choices, including dietary modification, is important before starting drug treatment. The goal of drug treatment is to reduce the risk of pancreatitis in patients with severe hypertriglyceridemia and cardiovascular disease in those with moderate hypertriglyceridemia. This review discusses the various genetic and acquired causes of hypertriglyceridemia, as well as current management strategies. Evidence supporting the different drug and non-drug approaches to treating hypertriglyceridemia is examined, and an easy to adopt step-by-step management strategy is presented.

Introduction

Hypertriglyceridemia is a fairly common clinical condition, but it continues to evoke considerable debate about its ramifications and management. Consider the clinical vignette in box 1. Even as the diagnosis of hypertriglyceridemic acute pancreatitis (HTG-AP) seems relatively straightforward, the clinician is confronted by quite a few conundrums. Is hypertriglyceridemia a cause or a consequence of acute pancreatitis? Are previous non-fasting serum triglyceride values valid for diagnosing hypertriglyceridemia and assessing future risk? What is the cause of the patient’s hypertriglyceridemia: primary genetic abnormality or secondary to uncontrolled diabetes and estrogen use? Would genetic testing have any benefit? What is the optimal treatment plan for the elevated triglycerides, both acutely to relieve pancreatitis and in the long term to prevent its recurrence? Does hypertriglyceridemia increase her long term risk of atherosclerotic cardiovascular disease (ASCVD)? What is the optimal diet that should be recommended, especially in view of her preference for a “ketogenic” diet? Which drug treatment will benefit her the most: statins, fibrates, omega-3 fatty acids, niacin, or a combination?

This review summarizes relevant data to help to answer some of these questions. The target audience is general internists, hospital based physicians, endocrinologists, and cardiologists. It outlines the epidemiology and changing trends of dyslipidemia in the general population, the different classifications of the severity of hypertriglyceridemia, and the pathophysiology of hypertriglyceridemia and its complications. The role of hypertriglyceridemia as an independent risk factor for ASCVD and optimal drug treatment, including novel and emerging therapies, to mitigate this will be examined in greater detail.

Sources and selection criteria

I searched PubMed for English language articles published in peer reviewed journals over the past two decades. Search terms used included hypertriglyceridemia management, hypertriglyceridemic pancreatitis, hypertriglyceridemia and cardiovascular risk, drug-induced dyslipidemia, and genetic hypertriglyceridemia. I included consensus statements, guidelines, and systematic reviews from 2010 to 2020 and also considered randomized controlled trials (RCTs) and human pathophysiology studies from earlier (from 1970). I prioritized RCTs, systematic reviews with meta-analyses, and large case series, in that order, when evaluating treatment effects. Case reports were excluded, but some observational studies detailing the epidemiology and pathophysiology of the disease were included.

Diagnosis and classification

The mean age adjusted serum triglyceride concentrations of US adult men and women were reported to be 128 (5th-95th percentile 52-361) mg/dL and 110 mg/dL (48-270), respectively, in the 1999-2008 National Health and Nutrition Examination Survey (NHANES). Serum triglycerides tend to increase with age and are lower in children. Hypertriglyceridemia is commonly defined as fasting serum triglycerides of 150 mg/dL (1.7 mmol/L) or above, although the “optimal” fasting triglyceride concentration, which confers the lowest risk of incident
State of the Art Review

Box 1: Clinical vignette

A 46 year old woman with recently diagnosed type 2 diabetes was admitted with severe abdominal pain, nausea, and vomiting. Abdominal imaging and elevated serum lipase concentrations confirmed the diagnosis of acute pancreatitis. At presentation, her plasma glucose was 306 mg/dL and her serum triglycerides were 1850 mg/dL. Two months previously, her fasting plasma glucose was 155 mg/dL, her hemoglobin A1c was 7.6%, and she had been treated with metformin monotherapy. She had also been given hormone replacement therapy for menopausal symptoms and moderate intensity statin therapy for primary prevention of atherosclerotic cardiovascular disease. She had generalized obesity with a body mass index of 35. Review of previous medical records showed serum triglyceride concentrations ranging from 265 to 440 mg/dL, although some measurements were obtained in a non-fasting state. Her family history was significant for hypercholesterolemia and premature coronary artery disease but not for pancreatitis or severe hypertriglyceridemia.

and recurrent ASCVD, may be below 100 mg/dL. Different guidelines and expert committees have designated different cut-off values for classification of the severity of hypertriglyceridemia (table 1). The US National Cholesterol Education Program (NCEP) Adult Treatment Panel, and the subsequent American Heart Association/American College of Cardiology (AHA/ACC) guidelines on lipid treatment, considered serum triglycerides of 500 mg/dL or above as severe hypertriglyceridemia indicative of risk for pancreatitis, with lesser elevations (borderline and borderline high) associated with increased ASCVD risk. They note that patients with triglycerides in the 500-999 mg/dL (5.6-11.2 mmol/L) range are at risk of developing unrecognized marked increases in triglycerides, leading to pancreatitis. As pancreatitis is rarely seen with serum triglycerides below 1000 mg/dL, the Endocrine Society and European Atherosclerosis Society/European Society of Cardiology classify severe hypertriglyceridemia as concentrations of at least 1000 mg/dL or 10 mmol/L (880 mg/dL), respectively.

The above classifications are based on fasting serum triglyceride concentrations, but non-fasting serum triglycerides are perhaps more indicative of health risk. Many large epidemiologic studies including the Women’s Health Initiative study and the Copenhagen City Heart Study have identified serum triglycerides, but non-fasting serum triglycerides as a more robust marker for ASCVD than fasting serum triglycerides.

Furthermore, non-fasting serum triglycerides have also been shown to be associated with risk of acute pancreatitis, with a hazard ratio exceeding that for ASCVD. Non-fasting triglycerides may better reflect the postprandial accumulation of atherogenic triglyceride-rich remnant lipoprotein particles and thus better predict the risk for ASCVD than do fasting triglyceride concentrations. Accordingly, the European and Canadian guidelines do not advocate a fasting lipid profile, and the recent AHA/ACC guidelines recommend either a fasting or a non-fasting lipid profile for screening, although a follow-up fasting lipid profile is recommended if serum triglycerides are above 400 mg/dL. These recommendations are intended to simplify screening procedures, as an elevation of only 15-20% in serum triglycerides is seen after a regular low fat meal (about 15 g fat), which would be inconsequential in people with normal triglyceride concentrations. However, in the absence of established normal standards for postprandial triglyceride concentrations, fasting triglycerides are still recommended for the diagnosis and classification of hypertriglyceridemia. The postprandial triglyceride response to a standardized test meal that would best predict future ASCVD or pancreatitis remain to be determined.

Epidemiology

Hypertriglyceridemia is the most common form of dyslipidemia observed in the general population. On the basis of the NHANES 2003-06 data, an estimated 53% of US adults have dyslipidemia, 27% have elevated low density lipoprotein (LDL) cholesterol, 23% have low high density lipoprotein (HDL) cholesterol, and 30% have elevated serum triglycerides (>150 mg/dL). However, encouraging trends have been noted, with a steady decline in the prevalence of hypertriglyceridemia from 33.3% in the 2001-04 survey to 25.1% in the 2009-12 survey. According to the 2007-14 NHANES data, the overall prevalence of hypertriglyceridemia is 25.9%, and the prevalence in people treated with statins is 31.6%. The overall prevalence is still higher in men than in women (28.7% and 21.5%, respectively), with the highest prevalence in the 40-59 year age group in men and in the over 60 year age group in women.

Triglyceride concentrations are lower in children, with values of 100 mg/dL (1.1 mmol/L) or higher considered abnormal in those aged 0-9 years and values of 130 mg/dL (1.1 mmol/L) or higher considered abnormal in those aged 10-19 years. Mexican Americans have nearly twice as high a prevalence of hypertriglyceridemia as non-Hispanic black people (34.9% vs 15.6%). When considering only people with serum triglycerides greater than 500 mg/dL, the overall prevalence of this degree of hypertriglyceridemia is estimated to be 1.7%. The DECODE study, based on analysis of nine European population cohorts in the 1990s, found the prevalence of hypertriglyceridemia (serum triglycerides >1.7 mmol/L) to be 36.4% in men and 24.8% in women.

Table 1 | Classification of hypertriglyceridemia

<table>
<thead>
<tr>
<th>Society</th>
<th>Category</th>
<th>Serum triglyceride concentration mg/dL (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Heart Association/American College of Cardiology: ATP III</td>
<td>Normal</td>
<td>&lt;150 (1.7)</td>
</tr>
<tr>
<td></td>
<td>Borderline high</td>
<td>150-199 (1.7-2.3)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>200-699 (2.3-5.6)</td>
</tr>
<tr>
<td></td>
<td>Very high</td>
<td>≥500 (≥5.6)</td>
</tr>
<tr>
<td>Endocrine Society</td>
<td>Normal</td>
<td>&lt;150 (1.7)</td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>150-199 (1.7-2.3)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>200-999 (2.3-11.2)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>1000-1999 (11.2-22.4)</td>
</tr>
<tr>
<td></td>
<td>Very severe</td>
<td>≥2000 (≥22.4)</td>
</tr>
<tr>
<td>European Atherosclerosis Society, European Society of Cardiology</td>
<td>Normal</td>
<td>&lt;150 (1.7)</td>
</tr>
<tr>
<td></td>
<td>Hypertriglyceridemia</td>
<td>150-880 (1.7-9.9)</td>
</tr>
<tr>
<td></td>
<td>Severe hypertriglyceridemia</td>
<td>≥880 (≥10)</td>
</tr>
</tbody>
</table>
**Metabolism of triglyceride-rich lipoproteins**

To facilitate transport in the aqueous extracellular medium inside the body, the hydrophobic triglycerides (and cholesteryl esters) are packaged into the core of lipoproteins, the surface of which is composed of amphipathic lipids and proteins. The two principal triglyceride-rich lipoproteins (TGRL) are chylomicrons and very low density lipoproteins (VLDL), secreted respectively by the intestine and liver for the purpose of transporting exogenous (dietary) and endogenous lipids to peripheral tissues (fig 1 and table 2). Apolipoprotein B is the primary apolipoprotein in both TGRLs, with chylomicrons carrying the smaller, truncated apolipoprotein B-48 and VLDL the larger apolipoprotein B-100. They also contain other apolipoproteins, such as apolipoprotein A-V, apolipoprotein C-II, apolipoprotein C-III, and apolipoprotein E, some of which are obtained from HDL in the circulation. Lipoprotein lipase is the critical enzyme mediating hydrolysis of TGRL, releasing free fatty acid (FFA) and remnant lipoproteins. Abundant lipoprotein lipase expression is seen in adipose tissue and muscle tissue (both skeletal and cardiac), which use the released FFA either for energy storage after re-esterification or as an energy source for muscle contraction, respectively. Activity of lipoprotein lipase is regulated by many key proteins including activators such as insulin, apolipoprotein C-II, and apolipoprotein A-V and inhibitors such as apolipoprotein C-III and angiopoietin-like proteins 3 and 4 (ANGPTL 3/4). Chylomicron remnants are taken up by the liver through LDL receptors and related proteins using apolipoprotein E as a ligand. VLDL remnants are also cleared in a similar manner, but some are further hydrolyzed by the hepatic lipase to yield LDL composed entirely of cholesteryl ester and apolipoprotein B. Remnant uptake by the liver serves as a source of lipid for subsequent VLDL triglyceride synthesis, the other sources being FFA released from adipose tissue under the action of hormone sensitive lipase and de novo hepatic lipogenesis, which is often driven by consumption of simple sugars. Although remnant lipoproteins are generally cleared by hepatic uptake, they can also be taken up by the vascular endothelium where they promote inflammation and atherosclerosis by a variety of mechanisms including abnormal endothelial cell secretion and impaired flow mediated dilatation.25 This would be especially relevant when generation of TGRL is increased and clearance is decreased in certain pathologic conditions as discussed below.

**Causes of hypertriglyceridemia**

Most patients with hypertriglyceridemia do not have a recognizable genetic cause, and the elevated triglycerides likely stem from a combination of multiple genetic variations with small effects and environmental influences. Even when an apparent familial clustering of hypertriglyceridemia occurs, a monogenic cause is rarely identified. Table 3 summarizes the well recognized primary hypertriglyceridemic disorders, and box 2 lists common secondary factors contributing to elevated serum triglycerides.

**Familial chylomicronemia syndrome**

Familial chylomicronemia syndrome (FCS) is a rare autosomal recessive disorder with an estimated prevalence of one in a million. Bi-allelic mutations in lipoprotein lipase account for most of these cases, followed by mutations in apolipoprotein A5, which is thought to stabilize the dimeric structure of lipoprotein lipase.20 Similar presentation has been reported in a few rare pedigrees with mutations in apolipoprotein C2,21 which is a cofactor for lipoprotein lipase. Homozygous mutations in genes encoding other proteins critical for lipoprotein lipase processing and function such as lipase maturation factor, glycerol-3-phosphate dehydrogenase-1, and glycosylphosphatidylinositol-anchored high density lipoprotein binding protein-1 have also been implicated in causing FCS.22-25

These defects result in impaired hydrolysis of chylomicron triglycerides, leading to excessive accumulation of these large lipoprotein particles, a major consequence of which is pancreatitis. The exact mechanism by which chylomicromenia causes pancreatitis is not clear, but it likely involves triglyceride hydrolysis by pancreatic amylase leading to high levels of FFA, leading to inflammatory changes and capillary injury. Hyperviscosity due to chylomicromenia accentuates hypoxic damage and leakage of pancreatic enzymes and further FFA release.26 The role of FFA in initiating tissue damage has been demonstrated, and although other inflammatory cytokines such as interleukins and tumor necrosis factor-α are known to be involved in the pathogenesis of chronic pancreatitis including fibrogenesis, their role in HTG-AP has not been studied. A affected person usually have recurrent pancreatitis from childhood and may show eruptive xanthoma and lipemia retinalis when serum triglyceride concentrations are above 2000 mg/dL. However, most patients with HTG-AP do not have a monogenic disorder. Instead, their presentation is more consistent with “multifactorial chylomicronemia syndrome,” which is caused by either a heterozygous defect in one the aforementioned genes or cumulative small effect variations in other genes with secondary exacerbating factors such as uncontrolled diabetes or alcohol misuse.29

**Familial hypertriglyceridemia**

Familial hypertriglyceridemia is a fairly common disorder characterized by moderate elevations in serum triglycerides (200-1000 mg/dL) due to increased secretion of triglyceride-rich VLDL particles. Familial clustering is noted, but no genetic cause has been identified. It is sometimes referred to as “benign hypertriglyceridemia,” as increased risk for ASCVD has not been observed. However, superimposed metabolic syndrome has been noted to...
increase ASCVD risk.\textsuperscript{31} Similarly, other exacerbating factors can lead to severe hypertriglyceridemia and pancreatitis.

**Familial combined hyperlipidemia**

Familial combined hyperlipidemia is another fairly common disorder with variable lipid phenotypic expression. Affected people may have elevated cholesterol, triglycerides, or both, which segregates with first degree relatives. Elevation in apolipoprotein B concentrations (>90th percentile or 120 mg/dL) is characteristic, and a strong predisposition to premature ASCVD is observed.\textsuperscript{32} These findings of elevated apolipoprotein B and family history of premature ASCVD may help in differentiating familial hypertriglyceridemia and familial combined hyperlipidemia and in identifying patients who need more aggressive treatment for ASCVD risk reduction. Despite the strong familial predilection, a genetic basis of this disorder has not been identified. Variants in the \textit{ApoA1/C3/A4/A5} cluster and \textit{USF1} have been associated with this phenotype,\textsuperscript{33} but a monogenic cause is unlikely.

**Familial (type III) dysbetalipoproteinemia**

Both a genetic predisposition and environmental factors are needed for this rare disorder to manifest. Hepatic clearance of chylomicron remnants and VLDL remnants requires apolipoprotein E, which serves as the ligand for receptor mediated uptake. This uptake is slowed in the presence of the E2/E2 phenotype, but most patients with the e2/e2 genotype do not necessarily have significant dyslipidemia as alternate
pathways help in remnant clearance.\textsuperscript{35} However, when secondary factors increase the generation of TGRL (for example, obesity, excess of dietary calories, alcohol consumption, estrogen) or decrease their clearance (for example, hypothyroidism), the alternate pathways are overwhelmed, leading to accumulation of remnants. Identification and management of the “second hit” that contributes to the disease phenotype is therefore critical. Rarely, dominant mutations in apolipoprotein E may independently cause disease manifestation.\textsuperscript{36,37} The characteristic features of this condition are similar elevations in serum cholesterol and triglycerides along with palmar xanthomas. Various diagnostic criteria based on VLDL composition have been proposed. One of these is a ratio of VLDL cholesterol to serum triglyceride above 0.3, with cholesterol and triglyceride concentrations expressed as mg/dL. This requires ultracentrifugation to isolate VLDL, a procedure generally limited to research laboratories.\textsuperscript{38} An alternative recommended by Sniderman and associates that does not require ultracentrifugation is a total cholesterol to apolipoprotein B ratio above 6.2 with simultaneous triglyceride to apolipoprotein B ratio below 10, with cholesterol and triglyceride concentrations expressed as mmol/L and apolipoprotein B as mg/mL.\textsuperscript{39} Recognizing this rare disorder is important, as it is associated with a significantly increased risk (odds ratio 5-10) of premature coronary artery disease.\textsuperscript{40}

### Lipodystrophy
Lipodystrophies are a heterogeneous group of rare inherited and acquired disorders characterized by selective loss of adipose tissue.\textsuperscript{41,42} Fat loss can either involve the whole body (generalized) or be restricted to some regions (partial). Despite phenotypic and genotypic differences, they share similar metabolic complications including hypertriglyceridemia, diabetes with severe insulin resistance, steatohepatitis, and polycystic ovarian disease in women. The severity of metabolic abnormalities correlates with extent of fat loss, highlighting the critical importance of adipose tissue in maintaining lipid and glucose homeostasis.\textsuperscript{43} Genetic lipodystrophies, both generalized and partial, are an important cause of monogenic hypertriglyceridemia. Management of metabolic complications with traditional glucose and lipid lowering therapies in these patients is challenging. Leptin replacement therapy has been shown to significantly decrease hyperlipidemia, hyperglycemia, and hepatic steatosis, especially in patients with generalized lipodystrophy.\textsuperscript{44,45}

### Glycogen storage disorders
Severe hypertriglyceridemia is commonly seen in some forms of glycogen storage disorders (GSD), notably GSD type 1a which is due to deficiency of glucose-6 phosphatase. The resultant accumulation of glycolytic products increases de novo lipogenesis, leading to severe hypertriglyceridemia and hypercholesterolemia.\textsuperscript{46}

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**Table 2 | Key molecules involved in metabolism of triglyceride-rich lipoproteins**

<table>
<thead>
<tr>
<th>Molecules</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lipoproteins</strong></td>
<td></td>
</tr>
<tr>
<td>Chylomicrons</td>
<td>Transport of exogenous lipids</td>
</tr>
<tr>
<td>Very low density lipoproteins</td>
<td>Transport of endogenous lipids</td>
</tr>
<tr>
<td>Chylomicron remnants</td>
<td>Delivery of lipids to liver</td>
</tr>
<tr>
<td>Very low density lipoprotein remnants</td>
<td>Delivery of lipids to liver; generation of LDL</td>
</tr>
<tr>
<td>Intermediate density lipoproteins</td>
<td>Delivery of lipids to liver; generation of LDL</td>
</tr>
<tr>
<td><strong>Apolipoproteins</strong></td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein B-48</td>
<td>Structural protein of chylomicron</td>
</tr>
<tr>
<td>Apolipoprotein B-100</td>
<td>Structural protein of VLDL; ligand for LDLR</td>
</tr>
<tr>
<td>Apolipoprotein A-V</td>
<td>Enhances LPL function</td>
</tr>
<tr>
<td>Apolipoprotein C-II</td>
<td>Cofactor for LPL</td>
</tr>
<tr>
<td>Apolipoprotein C-III</td>
<td>Inhibitor of LPL</td>
</tr>
<tr>
<td>Apolipoprotein E</td>
<td>Ligand for remnant uptake through LDLR and LRP</td>
</tr>
<tr>
<td><strong>Lipids</strong></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Energy storage</td>
</tr>
<tr>
<td>Cholesteryl esters</td>
<td>Membrane synthesis; precursor for many hormones</td>
</tr>
<tr>
<td>Free fatty acids</td>
<td>Energy source for muscle</td>
</tr>
<tr>
<td><strong>Enzymes</strong></td>
<td></td>
</tr>
<tr>
<td>Lipoprotein lipase</td>
<td>Hydrolysis of triglyceride-rich lipoproteins facilitating FFA delivery to adipose tissue and muscle</td>
</tr>
<tr>
<td>Hormone sensitive lipase</td>
<td>Hydrolysis of adipose tissue triglyceride releasing FFA</td>
</tr>
<tr>
<td>Hepatic lipase</td>
<td>Hydrolysis of IDL leading to generation of LDL</td>
</tr>
<tr>
<td><strong>Other proteins</strong></td>
<td></td>
</tr>
<tr>
<td>Low density lipoprotein receptor</td>
<td>Hepatic uptake of LDL through apolipoprotein B-100</td>
</tr>
<tr>
<td>LDLR related protein</td>
<td>Hepatic uptake of chylomicron remnants and other remnants through apolipoprotein E</td>
</tr>
<tr>
<td>Glycosylphosphatidylinositol-anchored high density lipoprotein binding protein-1</td>
<td>Anchors LPL to capillary endothelium</td>
</tr>
<tr>
<td>Lipase maturation factor</td>
<td>Maturation of LPL</td>
</tr>
<tr>
<td>Angiopoietin-like protein 3 and 4</td>
<td>Inhibitors of LPL</td>
</tr>
</tbody>
</table>

FFA=free fatty acid; IDL=intermediate density lipoprotein; LDL=low density lipoprotein; LDLR=low density lipoprotein receptor; LPL=lipoprotein lipase; LRP=LDLR related protein; VLDL=very low density lipoprotein.
Secondary causes of hypertriglyceridemia
As listed in box 2, a variety of lifestyle factors, medical conditions, and drugs can cause or worsen hypertriglyceridemia. Lifestyle factors that promote obesity, such as caloric excess and decreased physical activity, can worsen hypertriglyceridemia from any other cause.

Alcohol
Alcohol consumption causes the most profound effect on serum triglycerides and seems to be primarily related to increased VLDL production. However, this may be dependent on both the amount of alcohol ingested and other factors such as obesity and simultaneous caloric intake. Acute alcohol ingestion also decreases lipoprotein lipase activity, although chronic consumption may restore or increase lipoprotein lipase activity and be responsible for elevated HDL cholesterol concentration. Moderate alcohol consumption (30 g) only transiently exacerbates postprandial lipemia, whereas chronic excess alcohol consumption can lead to elevated fasting serum triglycerides as well. Most of these changes are modest (about 15%) in people with normal triglyceride concentrations but can lead to severe elevations with increased risk of pancreatitis in patients with underlying hypertriglyceridemia.

Obesity and uncontrolled diabetes
Among medical disorders contributing to hypertriglyceridemia, obesity and uncontrolled diabetes are the most common causes. Hypertriglyceridemia has been noted in more than 80% of people who are overweight or obese. In a recently reported cohort of 160 patients with serum triglycerides above 2000 mg/dL, uncontrolled diabetes was the contributing factor in nearly 75% of the patients. Both obesity and type 2 diabetes are characterized by insulin resistance, which leads to VLDL overproduction as a result of increased hepatic lipogenesis from excess FFA delivery to the liver, as well as decreased apolipoprotein B degradation. In the absence of suppression of hormone sensitive lipase by insulin, excessive release of FFA from adipocytes occurs, which fuels triglyceride synthesis and VLDL secretion from the liver. Insulin deficiency, as occurs in poorly controlled type 1 diabetes, decreases lipoprotein lipase activity and thereby impairs clearance of TGRL. Insulin infusion has been shown to stimulate adipocyte lipoprotein lipase activity, an effect mediated by both increased gene transcription and regulation of posttranscriptional and post-translational mechanisms. Insulin treatment has also been shown to restore impaired lipoprotein lipase activity in both adipocytes and skeletal muscle of patients with untreated type 1 diabetes, leading to reduction in serum triglycerides. Decreased clearance of TGRL is also noted in type 2 diabetes despite no decrease in lipoprotein lipase activity and is an important contributor to hypertriglyceridemia in diabetes.51

Drug induced dyslipidemia
Another common secondary cause of hypertriglyceridemia is drug induced dyslipidemia. A wide variety of drugs can cause adverse effects on lipid metabolism, leading to dyslipidemia. These\

Table 3 | Primary (genetic) disorders causing severe hypertriglyceridemia

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
<th>Inheritance</th>
<th>Genetic basis</th>
<th>Pathophysiology</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial chylomicronemia syndrome</td>
<td>1 in 1 million</td>
<td>Autosomal recessive</td>
<td>Biallelic mutations in LPL, APOC-II, APOA-V, LMFI, GPHB1P1, or GPD1</td>
<td>Defective LPL mediated clearance of chylomicrons</td>
<td>Serum triglycerides generally &gt;1000 mg/dL with triglyceride to total cholesterol ratio around 10:1; recurrent pancreatitis from childhood, eruptive xanthoma, lipemia retinalis, hepatosplenomegaly</td>
</tr>
<tr>
<td>Familial hypertriglyceridemia</td>
<td>5-10%</td>
<td>No clear mendelian pattern</td>
<td>Polygenic with environmental influence</td>
<td>Increased production of triglyceride-rich VLDL particles</td>
<td>Serum triglycerides in 200-1000 mg/dL range with normal total cholesterol and apolipoprotein B concentrations; generally not associated with increased risk of ASCVD or pancreatitis in absence of other risk factors</td>
</tr>
<tr>
<td>Familial combined hyperlipidemia</td>
<td>1-2%</td>
<td>No clear mendelian pattern</td>
<td>Polygenic with environmental influence</td>
<td>Increased production of apolipoprotein B and associated lipoproteins</td>
<td>Elevated serum triglycerides, total cholesterol, or both, with elevated apolipoprotein B in patients and first degree relatives; high risk of ASCVD</td>
</tr>
<tr>
<td>Familial (type 3) dysbetalipoproteinemia</td>
<td>1 in 10 000</td>
<td>Usually autosomal recessive; rarely autosomal dominant</td>
<td>APOE2/E2 genotype (AR), or rare APOE2 mutations (AD)</td>
<td>Defective apolipoprotein E mediated clearance of VLDL and chylomicron remnants</td>
<td>Near equivalent elevations in serum total cholesterol and triglycerides (usually 300-500 mg/dL), palmar and tuberous xanthomas, secondary factors often present</td>
</tr>
<tr>
<td>Inherited lipodystrophy syndromes:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital generalized lipodystrophy</td>
<td>1 in 10 million</td>
<td>Autosomal recessive</td>
<td>Biallelic mutations in AGPAT2, BSCL2, CAV2, or PTPR</td>
<td>Defective adipocyte development and differentiation leading to loss of subcutaneous fat and tendency for hepatic steatosis and VLDL overproduction</td>
<td>Generalized loss of body fat from birth with features of extreme insulin resistance</td>
</tr>
<tr>
<td>Familial partial lipodystrophy</td>
<td>1 in 1 million</td>
<td>Autosomal dominant; rarely autosomal recessive</td>
<td>Mutations in LMNA, PPARG, PLIN1, CIDEC, LIPE, AKT2, or ADRA2A</td>
<td></td>
<td>Variable loss of subcutaneous fat from extremities and trunk starting in peripubertal period; features of insulin resistance</td>
</tr>
</tbody>
</table>

AD=autosomal dominant; ADRA2A=α2A-adrenergic receptor; AGPAT2=1-acylglycerol-3-phosphate O-acyltransferase 2; AKT2=v-akt murine thymoma viral oncogene homolog 2; APOA5=apolipoprotein A5; APOC2=apolipoprotein C2; APOE2=apolipoprotein E2; AR=autosomal recessive; ASCVD=atherosclerotic cardiovascular disease; BSCL2=Berardinelli-Seip congenital lipodystrophy 2; CAV1= Caveolin 1; CIDEC=cell death-inducing DFFA-like effector C; GPHB1P1=glycosylphosphatidylinositol-anchored high density lipoprotein binding protein 1; GPD1=glycerol-3-phosphate dehydrogenase 1; LIPE=hormone sensitive lipase; LMF1=lipase maturation factor; LMNA=lamin A/C; LPL=lipoprotein lipase; PLIN1=perilipin; PPARG=peroxisome proliferator-activated receptor gamma; PTPR=protein-tyrosine phosphatase receptor-type; VLDL=very low density lipoprotein.
include antihypertensives such as thiazide diuretics and non-specific β adrenergic blockers; various steroid hormones including glucocorticoids and estrogens and their related compounds, immune-suppressive drugs, anti-neoplastic agents, atypical antipsychotics; HIV-1 protease inhibitors, anti-epileptics such as carbamazepine, and other miscellaneous drugs (Box 2).

The effect of some drugs is mild and of little clinical significance, whereas others can cause severe hyperlipidemia and acute complications such as pancreatitis. Modest triglyceride elevation is noted with use of non-selective β blockers such as atenolol, propranolol, and metoprolol, especially in people with underlying hypertriglyceridemia, but not with the selective β adrenergic blocker carvedilol. Similarly, thiazide diuretics have been associated with a 15% increase in serum triglycerides, although loop diuretics and potassium sparing diuretics seem to have a mild or neutral effect.

Second generation (atypical) antipsychotics are also associated with mild hypertriglyceridemia, often in association with obesity, but sometimes severe hypertriglyceridemia and pancreatitis can also occur. Among the different antipsychotics, clozapine and olanzapine are associated with the highest risk of metabolic complications, followed by risperidone and quetiapine, whereas ziprasidone and aripiprazole have the lowest risk. Oral estrogens can cause a 30-40% increase in serum triglycerides in a dose dependent manner, also due to increase in VLDL production. This is most prominent in people with baseline hypertriglyceridemia, and many instances of estrogen induced pancreatitis from hypertriglyceridemia in patients with underlying lipid disorders such as FCS and lipodystrophy have been reported. Unlike oral estrogen, transdermal estrogens, which do not undergo first pass metabolism in the liver, have only minimal effects on lipid concentrations. Related compounds such as tamoxifen and clomiphene have also been rarely associated with severe hypertriglyceridemia and pancreatitis. Severe but reversible hypertriglyceridemia has also been observed during treatment with retinoid derivatives including isotretinoin, acitretin, and bexarotene, which inhibit hepatic fatty acid oxidation and increase apolipoprotein C-III concentrations. Other drugs rarely associated with severe hypertriglyceridemia include L-asparaginase, which inhibits lipoprotein lipase, capcetabine, and propofol.

Management
The goal of all triglyceride lowering therapies must be to reduce the risk of either HTG-AP or ASCVD. The nature of this risk largely depends on accumulation of which type of TGRL is responsible for the hypertriglyceridemia. Accumulation of the large chylomicron particles, and to a lesser extent VLDL particles, increases the risk of pancreatitis, whereas accumulation of the smaller remnant particles increases the risk for ASCVD. A variety of drug and non-drug measures helps to either reduce the generation or improve the clearance of these TGRL particles, and these will be discussed in the different clinical contexts.

Management of severe hypertriglyceridemia in patients with acute hypertriglyceridemic pancreatitis
Although significant elevations in triglyceride concentrations can occur in patients with acute pancreatitis of any cause as an epiphenomenon, HTG-AP is a distinct entity accounting for 2-10% of all cases of acute pancreatitis; it usually results from serum triglyceride elevation over 2000 mg/dL. In a systematic review of 1340 patients with HTG-AP the median serum triglyceride concentration at presentation was 2622 (range 1160-9769) mg/dL. Risk of pancreatitis increases progressively with higher serum triglycerides, but whether higher triglycerides also correlates with greater severity of pancreatitis is not entirely clear. Nevertheless, prompt reduction of triglycerides is essential in this setting. In the absence of food intake, further generation of chylomicrons is halted, and a gradual decline in serum triglycerides is noted even with conservative measures (fasting, intravenous

### Box 2: Secondary causes of hypertriglyceridemia

<table>
<thead>
<tr>
<th>Lifestyle factors</th>
<th>Medical conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Alcohol</td>
<td>• Obesity, metabolic syndrome</td>
</tr>
<tr>
<td>• Diet:</td>
<td>• Uncontrolled diabetes mellitus</td>
</tr>
<tr>
<td>○ High saturated fat intake</td>
<td>• Hypothyroidism*</td>
</tr>
<tr>
<td>○ High refined sugar intake</td>
<td>• Nephrotic syndrome</td>
</tr>
<tr>
<td>○ Excess caloric consumption</td>
<td>• Cushings’s syndrome</td>
</tr>
<tr>
<td>• Decreased physical activity</td>
<td>• HIV associated lipodystrophy</td>
</tr>
<tr>
<td>• Smoking</td>
<td>• Pregnancy</td>
</tr>
</tbody>
</table>

**Drugs**

**Mild to moderate elevation**

- Thiazide diuretics
- β blockers (non-selective)
- Atypical antipsychotics
- Glucocorticoids

**Severe elevation**

- Oral estrogen
- Tamoxifen, raloxifene, clomiphene
- Isotretinoin, acitretin, bexoreten
- Ciclosporin*, sirolimus
- L-asparaginase, capecitabine
- Propofol
- Protease inhibitors
- Interferon

*Increase in serum cholesterol may be more prominent
Therapeutic plasma exchange (TPE) involves the extracorporeal removal of plasma, which is then replaced by equivalent amounts of fresh plasma or albumin. Observational studies and case reports have shown that this procedure results in rapid reduction in serum triglycerides. In one of the largest case series of more than 100 patients, a nearly 60% reduction in serum triglycerides was noted compared with 27% in the conservatively treated group. Most patients (56%) needed a single plasma exchange procedure, and the reported complications, including hypotension (2.6%), gastrointestinal hemorrhage (1%) and hypocalcemia (3.6%), were few. However, whether it significantly affects overall patient outcomes is not clear, as no controlled trials have been reported. A retrospective review of 10 patients who underwent TPE in a single center showed no significant reduction in APACHE II scores despite the median reduction in triglyceride concentration from 2625 mg/dL to 415 mg/dL. Similar to the single-center comparison, no differences in mortality or complications were noted in another single center study comparing patients before and after the institution of TPE. A small randomized trial of high volume hemofiltration, which like TPE achieves emergent triglyceride reduction, also showed no improvement in morbidity and mortality compared with heparin and insulin treatment. The American Society of Apheresis has a category III recommendation for TPE in patients with HTG-AP, implying that the optimal role of TPE in this situation is not established.

Intravenous insulin infusion also promotes rapid reduction in serum triglycerides by activating lipoprotein lipase, thereby enhancing the clearance of TGRL. In addition, it reduces the activity of hormone sensitive lipase, thus decreasing the release of FFA from adipocytes and subsequent hepatic triglyceride synthesis and VLDL generation. Insulin treatment has been frequently used in the management of HTG-AP, in patients both with and without diabetes. However, no controlled trials have been done, and a recent retrospective review showed similar triglyceride lowering with insulin infusion compared with conventional therapy. The optimal insulin infusion dose is also not clear, with infusion rates usually ranging from 0.1 to 0.3 units/kg/h with simultaneous glucose infusion to avoid hypoglycemia.

In summary, the role of adjuvant triglyceride lowering therapies beyond fasting and intravenous hydration in patients with HTG-AP is not clear. Intravenous insulin should certainly be considered when concomitant hyperglycemia is present, especially with metabolic decompensation such as ketoacidosis, but may be beneficial in patients without diabetes as well. TPE may be considered in patients with markedly diminished lipoprotein lipase activity such as those with FCS or with features of hyperviscosity. It is often used in patients presenting with marked elevation of serum triglycerides or severe pancreatitis associated with acidosis and multi-organ failure, although little evidence of benefit exists. Clinical trials to examine the comparative benefits of TPE and intravenous insulin infusion are needed.

Management of severe hypertriglyceridemia to prevent pancreatitis

The risk of pancreatitis increases with increasing serum triglyceride concentrations. In the general population, acute pancreatitis is seen in about 0.5-1% of the population, which increases to about 5% in people with chronic alcohol misuse. By contrast, an estimated 10% of patients with serum triglycerides greater than 1000 mg/dL have history of previous pancreatitis, and the proportion increases to 20% and 50% in those with serum triglycerides greater than 2000 mg/dL and 5000 mg/dL, respectively. As serum triglycerides can rise precipitously after triglyceride hydrolysis enzymes are close to saturation at a triglyceride concentration of 500 mg/dL, this has been the traditional “goal” of triglyceride lowering therapies to reduce the risk of pancreatitis. Primary triglyceride lowering drugs such as fibrates, omega-3 fatty acids, and niacin are recommended when serum triglycerides are greater than 500 mg/dL, but they should be started in conjunction with therapeutic lifestyle changes and after correction of potential secondary exacerbating factors discussed below.

**Weight loss**

Serum triglycerides are much more responsive than serum cholesterol to weight changes. Even modest weight loss of 5% by caloric restriction alone has been shown to significantly reduce serum triglycerides by about 10% despite minimal change in other lipid parameters. A meta-analysis of 70 studies examining weight loss by dietary intervention alone estimated that for each kilogram of weight loss, serum triglycerides declined by 1.5 mg/dL. Any diet that results in weight loss, irrespective of macronutrient composition, helps to reduce serum triglycerides. In a randomized trial of 811 overweight adults assigned to one of four diets with varying macronutrient content (carbohydrates 35-65%, fats 20-40%, and protein 15-25%), similar weight loss (about 4 kg) and serum triglyceride reduction (12-17%) was seen at the end of two years. Another meta-analysis that included studies using drugs and surgery for weight loss in addition to lifestyle changes also showed similar beneficial effects. Targeting at least a 5-10% weight loss should be reasonable in all overweight patients with hypertriglyceridemia, which would be expected to decrease serum triglycerides by about 20%.

**Dietary changes**

Caloric restriction has been recognized as the most important step in management of hyper-
triglyceridemia, but multiple investigations have tried to determine the optimal macronutrient mix, with most favoring a moderate to high fat diet rich in monounsaturated fatty acids (MUFA). The mechanisms by which a MUFA rich diet lowers serum triglycerides are not clear but may involve increased secretion of VLDL particles containing both apolipoprotein E and apolipoprotein CIII, which are more effectively cleared from the circulation.108

A meta-analysis of nine RCTs in patients with type 2 diabetes comparing an iso-energetic high carbohydrate, low saturated fat diet with a diet high in MUFA found 19% lower triglyceride concentrations with the high fat diet.109 Another meta-analysis of 30 controlled feeding studies comparing a low fat (18-30% of total energy) diet with a moderate fat (32-50% of total energy) diet also found lower triglycerides by about 10 mg/dL in patients without diabetes and 25 mg/dL in those with diabetes, although no difference in LDL cholesterol concentrations was seen.110 Replacement of every 1% of energy intake from a carbohydrate source by a fat source has been estimated to reduce serum triglycerides by 1-2%.111 In overweight patients with metabolic abnormalities, a low fat diet (12-30% of total energy intake) has been consistently associated with higher triglycerides compared with higher fat (>30%) intake.112 113 Meta-analyses of the increasingly popular low carbohydrate diets have also shown consistent reduction of serum triglycerides by 15-22 mg/dL.114 115 However, higher serum triglycerides were not seen in the low fat diet group in two large randomized trials, the Women’s Health Initiative Dietary Modification Trial and the Dietary Approaches to Stop Hypertension (DASH) trial.116 117 The low fat diet group in both of these studies had increased consumption of fruits, vegetables, and whole grains, with a total dietary fiber intake of about 30 g/day in the DASH diet. Simple carbohydrates, especially fructose, are responsible for the triglyceride elevating effect of high carbohydrate diets.

The complex metabolic pathways that link fructose and simple sugar consumption to increased lipogenesis and VLDL synthesis, including the critical role of transcription factors, sterol regulatory element binding protein-1c, and carbohydrate responsive element binding protein, have been the subject of many recent reviews.118 119 Daily consumption of fructose greater than 100 g or added sugars greater than 10% of total energy has been shown to increase serum triglycerides,120 121 whereas increased fiber consumption (>20 g/1000 kcal) has been associated with lower triglyceride concentrations.122 Lower serum triglycerides have also been reported in patients adopting the Mediterranean diet, which emphasizes liberal intake of whole grains, fruits, vegetables, nuts, and olive oil.123 In an RCT of 180 patients with metabolic syndrome, total fat consumption was lower by 1.4% and saturated fat consumption by 5.3%, whereas MUFA intake increased by 3% and fiber intake by about 16 g/day in the group randomized to the Mediterranean diet. Serum triglycerides decreased by 19 mg/dL, although this was in conjunction with 2.8 kg weight loss and 2 cm decrease in waist circumference.124

The PREDIMED (Prevencion con Dieta Mediterranea) study also showed decreased prevalence of hypertriglyceridemia and metabolic syndrome in patients randomized to the Mediterranean diet supplemented by either nuts or olive oil.125

In summary, the optimal diet for patients with hypertriglyceridemia should promote weight loss, consist of not more than 50-60% carbohydrate sources comprising mostly complex carbohydrates such as whole grain and fruits and vegetables, and be rich in fiber (20-30 g/day). Saturated fat must be restricted to below 7% of total energy intake, and increased intake of MUFA (nuts, olive oil) and marine omega-3 polyunsaturated fatty acids (oily fish) is recommended. However, these general recommendations need to be modified in patients with extreme hypertriglyceridemia due to FCS who need restriction of dietary fat to below 10-15% of total energy intake (15-20 g/day).126 Limited data also suggest a benefit of medium chain triglycerides in these patients, as they are absorbed and transported without being incorporated into chylomicrons.127 128

Exercise

Regular aerobic exercise not only promotes weight loss and physical fitness but has been shown to significantly reduce postprandial triglyceride response. A meta-analysis of 76 studies showed that previous exercise reduced postprandial lipemia, an effect that was more prominent in women than men and with high intensity interval exercise (HIIE) than aerobic and resistance training.129 HIIE has been estimated to ameliorate postprandial lipemia by 15-30%, but only when energy expenditure is high, with submaximal interval exercise offering little benefit.130 Postprandial triglyceride response decreased by 31% and 33% respectively after 45 minutes and 60 minutes of moderate intensity (60% \( \text{VO}_{2\text{max}} \)) exercise, but not after 30 minutes.131

A small randomized trial showed that 45 minutes of aerobic exercise five days a week significantly reduced fasting serum triglycerides, which correlated with reduction in apolipoprotein CIII.132 Recommending at least 45 minutes a day of moderate intensity exercise, five days a week, and possibly HIIE in those who are fit enough, therefore seems reasonable. However, these recommendations must be tempered by the patient’s ability and motivation, and clearly any effort at increasing physical activity must be encouraged.

Alcohol

As discussed earlier, moderate alcohol ingestion has modest effects on serum triglycerides in people with normal triglyceride concentrations, but chronic alcohol misuse leads to significant elevation.133 134 It can also greatly exacerbate hypertriglyceridemia in those with baseline hypertriglyceridemia, and complete abstinence is strongly recommended in such people.
**Drug treatment**

As the risk of pancreatitis increases when serum triglycerides are elevated above 500 mg/dL, most guidelines recommend treatment with fibrates, omega-3 fatty acids, or niacin to reduce this risk. However, these recommendations are largely based on observational studies. A meta-analysis of seven fibrate trials involving more than 40,000 patients failed to show a reduced risk of pancreatitis compared with placebo (risk ratio 1.39, 95% confidence interval 1.00 to 1.95). However, the baseline triglyceride concentrations in these trials ranged from 118 to 187 mg/dL, so they do not consider the risk of HTG-AP in people with more severe hypertriglyceridemia. Interestingly, the same meta-analysis showed a reduced risk of pancreatitis with statin therapy (risk ratio 0.77, 0.62 to 0.97). This may be related to decreased biliary cholesterol concentration with statin treatment, whereas fibrates increase biliary cholesterol concentration and risk of gall stones. However, the triglyceride lowering effect of fibrates in patients with severe hypertriglyceridemia is likely a bigger determinant of the risk of pancreatitis, justifying its use under these circumstances. Similarly, no clinical trials have shown a reduced risk of pancreatitis with omega-3 fatty acid therapy or niacin, although the former has been shown to improve some outcomes in acute pancreatitis, likely owing to its anti-inflammatory effect. However, as they have been shown to reduce serum triglycerides by 30-50%, the assumption that they will reduce risk of HTG-AP is reasonable.

**Management of patients with moderate hypertriglyceridemia to reduce risk of ASCVD**

As discussed above for patients with severe hypertriglyceridemia, optimizing therapeutic lifestyle changes and correcting secondary exacerbating factors is critically important in patients with moderate hypertriglyceridemia before consideration of drug treatment. The only class 1 recommendation on treating hypertriglyceridemia in the most recent AHA/ACC lipid treatment guidelines is for clinicians to “address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism) and medications that increase triglycerides.” If serum triglycerides remain elevated after optimization of these factors, consideration of drug treatment would be worth while. Hypertriglyceridemia is a “risk enhancing factor” favoring statin treatment to reduce LDL cholesterol and thereby favorably affect risk of ASCVD.

The role of hypertriglyceridemia as an independent cardiovascular risk factor has been debated. In the Emerging Risk Factors Collaboration Study, one of the largest analyses of 68 prospective studies involving more than 300,000 participants, fasting and non-fasting serum triglycerides were associated with increased risk of coronary heart disease (CHD), but not after adjustment for non-HDL cholesterol. Interestingly, other large prospective studies such as the Copenhagen City Heart Study and Women’s Health Initiative Study have identified non-fasting triglycerides as a better marker for risk of ASCVD than fasting serum triglycerides. These findings have shifted attention to the role of remnant lipoprotein cholesterol in atherogenesis. The remnants of initial hydrolysis of chylomicron and VLDL particles carry a large amount of cholesterol and are easily taken up by the arterial wall, leading to atherosclerotic plaque formation. Although the triglyceride molecule may itself not contribute to this process, high serum triglycerides, especially postprandially, may be a marker for elevated remnant lipoprotein cholesterol concentrations, which directly promote atherogenesis. Furthermore, mendelian randomization studies exploring the relation of genetic variants causing high or low serum triglycerides and remnant lipoprotein cholesterol concentrations with CHD risk have also confirmed this association. People with mutations in apolipoprotein A-V, an activator of lipoprotein lipase, resulting in elevated postprandial triglycerides and remnant lipoprotein cholesterol, have a 2.2-fold higher risk for CHD, whereas those with inactivating mutations in apolipoprotein C-III or ANGPTL4, which are inhibitors of lipoprotein lipase and lead to lower postprandial triglycerides and remnant lipoprotein cholesterol concentrations, have lesser risk for CHD. These findings have offered the possibility of novel therapies to reduce the levels of TGRL, but they also reaffirm the importance of traditional aggressive risk management in patients with hypertriglyceridemia. Drug treatment to mitigate this risk includes the use of statins, fibrates, and omega-3 fatty acids.

**Statins**

Statin therapy reduces serum triglycerides by 15-30%, and more importantly VLDL and other apolipoprotein B containing atherogenic remnant particles that are increased in hypertriglyceridemic patients. No statin trials have been done exclusively in hypertriglyceridemic patients, but subgroup analyses of major statin trials have generally shown a similar or greater benefit compared with patients with normal triglycerides. Given the large body of evidence establishing the efficacy of statins for both primary and secondary prevention, starting statin therapy in all patients with hypertriglyceridemia and elevated risk of ASCVD is reasonable.

**Fibrates**

Fibrates induce the expression of peroxisome proliferator activated receptor α (PPAR-α), a key transcription factor that increases the expression of various proteins involved in lipoprotein metabolism including lipoprotein lipase, apolipoprotein A-I, apolipoprotein A-II, adenosine triphosphate binding cassette transporter-1, and scavenger receptor class B-type 1, which regulate the metabolism of TGRL and...
reverse cholesterol transport. The net effect is a 30-50% decrease in serum triglycerides and a 15-20% increase in HDL cholesterol. Placebo controlled trials have shown cardiovascular benefit for both primary and secondary prevention, although no mortality benefit was seen. In the Helsinki Heart Study, a 34% relative risk reduction for non-fatal myocardial infarction was seen. This was a primary prevention trial in more than 4000 middle aged men (40-55 years) with non-HDL cholesterol above 200 mg/dL. The average baseline serum triglyceride was about 176 mg/dL, and non-HDL cholesterol was 242 mg/dL, which decreased by 43% and 14%, respectively, with gemfibrozil therapy. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial was also an RCT of gemfibrozil in 2531 men with established CHD and HDL cholesterol less than 40 mg/dL and LDL cholesterol less than 140 mg/dL. The baseline serum triglycerides averaged about 160 mg/dL and decreased by 31% in the gemfibrozil group. A 22% relative risk reduction in the composite primary endpoint of non-fatal myocardial infarction or death from CHD was reported, despite no change in LDL cholesterol concentrations. However, two other placebo controlled fibrate trials, the Bezafibrate Infarction Prevention Study and the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study failed to show improvement in the primary composite outcome, although the FIELD study showed a significant reduction in a pre-specified composite secondary outcome of total cardiovascular events, mainly driven by reduced incidence of non-fatal myocardial infarction and revascularization procedures. Furthermore, the FIELD trial found increased statin use in the placebo group by the end of the study, which may have affected the results.

Combined statin and fibrate
The Action to Control Cardiovascular Risk in Diabetes (ACCORD) explored the benefit of combining statin and fibrate therapy for ASCVD reduction by randomly assigning 5518 patients with type 2 diabetes on background simvastatin therapy to fenofibrate or placebo. The primary composite endpoint of fatal or non-fatal cardiovascular events did not differ between the two groups (hazard ratio 0.92, 0.79 to 1.08). However, only 17% of the participants had atherogenic dyslipidemia (serum triglycerides >204 mg/dL and HDL cholesterol <34 mg/dL), which in regular clinical practice would prompt treatment with fibrates. In this subgroup, a significant 31% relative risk reduction was seen, with a nearly 5% absolute risk reduction. Subgroup analyses of other fibrate trials have also consistently shown a benefit in patients with hypertriglyceridemia and low HDL cholesterol. A large meta-analysis of 18 fibrate trials involving more than 45,000 patients showed a 10% relative risk reduction for major cardiovascular events (P=0.048) and a 13% reduction in coronary events (P<0.001) but no effect on stroke, cardiovascular mortality, or all cause mortality.

Greater effect sizes were noted in trials that recorded a higher mean basal triglyceride concentration. A registry study of 8982 patients with acute coronary syndrome showed a lower 30 day rate of major cardiovascular events in patients on statin-fibrate combination therapy compared with those on statin monotherapy. Furthermore, small mechanistic studies have shown that fibrates effectively lower remnant lipoprotein cholesterol concentrations, even when compared with statins. All these observations suggest that considering combining fibrate with statin therapy would be reasonable in patients at high risk who have elevated serum triglycerides and low HDL cholesterol.

Combination therapy with statin and fibrate significantly increases risk of myositis compared with monotherapy with either drug. This is due to inhibition of statin glucuronidation by fibrates, especially gemfibrozil, which increases statin concentrations. In a retrospective review of more than 250,000 patients on lipid lowering therapy, the incidence of rhabdomyolysis was 0.44 per 10,000 person years with statin monotherapy, 2.82 per 10,000 person years with fibrate monotherapy, and 5.98 per 10,000 person years with combination therapy. Combination of gemfibrozil with a statin was associated with a 15-fold to 20-fold higher risk of rhabdomyolysis compared with a statin-fenofibrate combination, which is therefore preferable. The safety and efficacy of this combination compared with either drug as monotherapy needs to be studied in patients with atherogenic dyslipidemia before it can be routinely adopted in clinical practice. A newly developed PPAR-α activator, pemafibrate, is being studied in an RCT of more than 10,000 patients with type 2 diabetes who are on moderate to high intensity statin therapy and have serum triglycerides 200-499 mg/dL and HDL cholesterol not exceeding 40 mg/dL. This may help to determine the role of statin-fibrate combination therapy in atherogenic dyslipidemia.

Omega-3 fatty acids
Marine long chain omega-3 polyunsaturated fatty acids, docosahexaenoic acid and eicosapentaenoic acid, effectively lower serum triglycerides by decreasing VLDL synthesis through a variety of mechanisms including increased fatty acid β oxidation, decreased hepatic lipogenesis, and increased intracellular apolipoprotein B degradation. They also enhance lipoprotein lipase mediated clearance of TGRL. Depending on the baseline triglyceride concentration, therapeutic administration of 2-4 g of docosahexaenoic acid and eicosapentaenoic acid can result in a 30-50% reduction in serum triglycerides. A simultaneous mild increase in LDL cholesterol by about 7 mg/dL has been reported with administration of docosahexaenoic acid but not eicosapentaenoic acid, the clinical significance of which is not clear. This elevation is dependent on baseline serum triglyceride concentrations. Many observational studies have shown that regular consumption of
fish reduces the risk of CHD, but the results of therapeutic trials of docosahexaenoic acid and eicosapentaenoic acid administration have not been consistent.

In the Japan EPA Lipid Intervention Study (JELIS), an open label trial of 1.8 mg/day eicosapentaenoic acid supplementation in more than 18,000 patients without CHD on baseline low intensity statin therapy, a 19% reduction in major coronary events was seen, with an even greater benefit in patients with elevated triglycerides. However, no reduction in either fatal or non-fatal myocardial infarction occurred, and the positive results were mainly due to decreased hospital admissions for unstable angina. A secondary prevention trial, GISSI Prevenzione, in more than 11,000 patients with recent myocardial infarction treated with 1 g omega-3 polyunsaturated fatty acids (eicosapentaenoic acid to docosahexaenoic acid ratio of 1:2) also showed significant benefit with a 17% reduction in deaths from CHD. However, this was an unblinded trial in which the triglyceride reduction was rather minimal, and the reduction in CHD events was largely driven by sudden cardiac deaths rather than atherothrombotic events. Other trials using 1 g or less of omega-3 polyunsaturated fatty acids did not show any clinical benefit for either primary or secondary prevention. A large meta-analysis of 10 trials involving more than 77,000 patients also showed no association with fatal or non-fatal CHD or other vascular events. However, the recent REDUCE-IT trial in 8179 patients at high risk with serum triglyceride concentrations of 135-499 mg/dL showed a 25% reduction in risk of the primary composite endpoint and a 20% reduction in risk of death from CHD. All patients were on baseline statin therapy and were randomized to receive either 4 g/day of eicosapentaenoic acid in the form of eicosapent ethyl or placebo. Whether the marked benefits observed in this trial in contrast to other previous omega-3 fatty acid trials are related to the drug dose or formulation or to baseline patient dyslipidemia is not clear. A similar trial (STRENGTH) using 4 g/day omega-3 free fatty acids (docosahexaenoic acid plus eicosapentaenoic acid) was recently halted for futility, suggesting the superiority of eicosapentaenoic acid for ASCVD risk reduction. Differences in biologic effects of docosahexaenoic acid and eicosapentaenoic acid, including differential effects on cardiometabolic risk factors, have been noted. Administration of docosahexaenoic acid has been associated with a slight increase in LDL cholesterol concentration, a simultaneous increase in LDL particle size and HDL concentration was seen, as well as a more favorable effect on heart rate, blood pressure, and vascular function compared with eicosapentaenoic acid. The cause of the discrepant trial results between REDUCE-IT and STRENGTH are not clear. The available data support the addition of eicosapentaenoic acid 4 g/day to statin therapy in patients at high risk (age >55 years and established ASCVD or age >50 years and at least one other major risk factor) who have moderate hypertriglyceridemia.

**Niacin**

Niacin is well known to reduce serum triglycerides and increase HDL cholesterol concentration, as well as reducing LDL cholesterol concentrations. Despite these favorable lipid effects, two large clinical trials did not show any benefit, and this drug has little role for additional risk reduction in patients with well controlled lipids on statin therapy.

**Emerging therapies**

Recently, interest has been growing in novel therapies aimed at increasing lipoprotein lipase mediated clearance of TGRL by decreasing the activity of proteins that inhibit lipoprotein lipase such as apolipoprotein C-III and ANGPTL 3/4. Volanesorsen is an antisense oligonucleotide that inhibits apolipoprotein C-III and has been shown in phase II trials to reduce apolipoprotein C-III concentrations by 40-80% and serum triglycerides by 31-71% in a dose dependent manner. Interestingly, this drug also reduced serum triglycerides by 56-86% in patients with FCS who are deficient in lipoprotein lipase, suggesting that it helps in clearance of TGRL through lipoprotein lipase independent pathways as well. Phase III trials in both FCS and non-FCS patients with hypertriglyceridemia have been undertaken. The US Food and Drug Administration did not approve volanesorsen for clinical use because of the risk of thrombocytopenia, but it is approved for use in Europe for patients with genetically confirmed FCS. An n-acetyl galactosamine conjugated version of this drug has been developed and shown to reduce triglyceride concentrations significantly in healthy volunteers. Both a monoclonal antibody (evinacumab) and an antisense oligonucleotide to ANGPTL3 have also been developed and are awaiting clinical trials. Gene therapy for lipoprotein lipase deficiency delivered through an adeno-associated viral vector, alipogen tiparvovec, has also been shown to be effective for triglyceride lowering in FCS patients. It was approved for clinical use in Europe but is no longer available for commercial reasons.

**Guidelines**

Various international societies, including the AHA/ACC, the European Society of Cardiology/European Atherosclerosis Society, and the Endocrine Society, have issued guidelines for the assessment and management of hypertriglyceridemia, generally as part of the broader guidelines for management of dyslipidemia and risk of ASCVD. The most consistent feature of all three guidelines is the strong emphasis on correcting secondary factors in all patients with hypertriglyceridemia. The importance of lifestyle interventions is stressed, and the European guidelines list the magnitude of benefit of each intervention, with reduction of excess weight and alcohol intake being ranked at the top. However, some differences exist in the classification of moderate and severe hypertriglyceridemia, as shown in table 1. As a result, the threshold triglyceride concentration to start drug treatment to reduce risk of pancreatitis is
also different: 500 mg/dL in the AHA/ACC guidelines, 10 mmol/L (880 mg/dL) in the ESC/EAS guidelines, and 1000 mg/dL in the Endocrine Society guidelines. The European guidelines, however, acknowledge that even patients with serum triglycerides between 5 and 10 mmol/L (440-880 mg/dL) are at risk of developing pancreatitis. All three groups recommend fibrate (preferably fenofibrate) and omega-3 fatty acids, and niacin is also included in the ESC/EAS guidelines to reduce severe hypertriglyceridemia and risk of pancreatitis. Statin therapy is also uniformly recommended by all the guidelines for ASCVD risk reduction, especially in patients with moderate hypertriglyceridemia.

Figure 2 outlines a suggested step-by-step approach to patients with hypertriglyceridemia based on these guidelines with some modifications. The suggested time intervals for repeat testing are the author’s recommendations. The AHA/ACC threshold of 500 mg/dL is used to recommend drug treatment to prevent pancreatitis.

Conclusions
In light of the preceding discussion on the causes and management of hypertriglyceridemia, we can reconsider the optimal approach to the patient presented initially in the clinical vignette (box 1). In the absence of other causes of pancreatitis, and with serum triglyceride concentrations close to 2000 mg/dL, it would be reasonable to conclude that the patient has acute pancreatitis due to hypertriglyceridemia. Her clinical features are also suggestive of underlying familial combined hyperlipidemia (family history of hypercholesterolemia and CHD), and the recent marked elevation in serum triglycerides leading to pancreatitis is likely secondary to uncontrolled diabetes and oral estrogen therapy. Genetic testing would be of little benefit, as this is not a monogenic
disorder, although she may have a heterozygous defect or minor variation in the gene for lipoprotein lipase or related genes. Genetic testing in patients with hypertriglyceridemia is generally not recommended unless FCS is strongly suspected. The best treatment option for the severe hypertriglyceridemia would be intravenous insulin infusion, especially in view of concomitant hyperglycemia. She should subsequently be transitioned to subcutaneous insulin, which should be continued for optimal control of diabetes. Good glucose control and changing oral estrogens to transdermal estrogen will help to decrease serum triglycerides. She should also receive detailed instructions on diet therapy, including calorific restriction, decreasing the intake of simple sugars and saturated fat, and increasing the consumption of monounsaturated and polyunsaturated fat sources as well as dietary fiber. A very low carbohydrate diet may also be beneficial, provided saturated fat intake is restricted, which is often difficult and therefore best avoided. Statin therapy must be continued for primary prevention of ASCVD. With adequate control of the secondary factors, maintaining serum triglycerides below 500 mg/dL should be possible to avoid further episodes of pancreatitis. Additional triglyceride lowering treatment such as fibrates or omega-3 fatty acids should be considered only if serum triglycerides remain above this threshold after optimization of diet and control of diabetes. Limited data support the addition of these therapies for ASCVD risk reduction in this patient profile.

Competing interests: I have read and understood the BMJ policy on declaration of interests and declare the following interests: none.

Provenance and peer review: Commissioned; externally peer reviewed.

GLOSSARY OF ABBREVIATIONS

- AHA/ACC—American Heart Association/American College of Cardiology
- ANGPTL 3/4—angiopoetin-like proteins 3 and 4
- ASCVD—atherosclerotic cardiovascular disease
- CHD—coronary heart disease
- FCS—familial chylomicronemia syndrome
- FFA—free fatty acid
- GSD—glycogen storage disorders
- HDL—high density lipoprotein
- HIIE—high intensity interval exercise
- HTG-AP—hypertriglyceridemic acute pancreatitis
- LDL—low density lipoprotein
- MUFA—monounsaturated fatty acids
- NCEP—National Cholesterol Education Program
- NHANES—National Health and Nutrition Examination Survey
- PPAR-α—peroxisome proliferator activated receptor α
- RCT—randomized controlled trial
- TGRL—triglyceride-rich lipoproteins
- TPE—therapeutic plasma exchange
- VLDL—very low density lipoproteins

QUESTIONS FOR FUTURE RESEARCH

- What postprandial serum triglyceride concentration can be used for the diagnosis of hypertriglyceridemia that will help to identify patients at increased risk of pancreatitis and atherosclerotic cardiovascular disease (ASCVD)?
- In patients with acute hypertriglyceridemic pancreatitis who do not have diabetes, does either intravenous insulin infusion or therapeutic plasma exchange have any benefit?
- Does the addition of fibrate or omega-3 fatty acids (docosahexaenoic acid + eicosapentaenoic acid) to statin therapy decrease the risk of ASCVD in patients with hypertriglyceridemia?
- Will potential novel therapies targeting apolipoprotein C-III and ANGPTL3/4 help to decrease residual risk of ASCVD after statin therapy?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS MANUSCRIPT

An initial draft of the manuscript was provided to a patient with familial partial lipodystrophy and another with familial hypertriglyceridemia. The patient with lipodystrophy wanted providers to realize the enormous challenge that patients face in being compliant with strict dietary requirements and the frustration with current therapies to normalize triglyceride concentrations. The patients expressed a fervent hope for novel, effective therapies. They also had reservations about being able to regularly exercise as directed. On the basis of these observations, the manuscript was modified to include a discussion on novel therapies and an acknowledgment of the difficulties faced by patients with genetic hypertriglyceridemia


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