Hypertriglyceridemia

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KEYWORDS

• Hypertriglyceridemia • Cardiovascular disease • Chylomicronemia
• Acute pancreatitis • Lipoprotein lipase • Apolipoprotein C3
• Angiopoietin-like protein 3

KEY POINTS

- Hypertriglyceridemia can be either genetic, usually due to multiple small variants in genes affecting triglyceride metabolism, or secondary to several conditions or medications, including the metabolic syndrome.
- Severe hypertriglyceridemia (triglycerides levels <1000–1500 mg/dL) is most commonly due to the multifactorial chylomicronemia syndrome, which usually results from the coexistence of genetic and secondary forms of hypertriglyceridemia, much less commonly due to familial partial lipodystrophy, and very rarely due to nonfunctioning mutations in lipoprotein lipase or related proteins.
- The main consequences of hypertriglyceridemia are increased risk of cardiovascular disease and acute pancreatitis when triglyceride levels are severely elevated.
- Prevention of cardiovascular disease in hypertriglyceridemia requires attention to treatable cardiovascular risk factors and the addition of a statin.
- Triglyceride-induced pancreatitis can be prevented by keeping triglyceride levels less than 500 mg/dL.

INTRODUCTION

During the past several decades, the major focus on lipids has been on low-density lipoproteins (LDL), largely as a result of LDL-lowering therapeutic advances that have led to a reduction in cardiovascular disease (CVD). During much of this time hypertriglyceridemia has been considered a putative risk factor and has taken somewhat of a backseat. However, with the current evidence indicating that hypertriglyceridemia clearly is a CVD risk factor, and as a result of LDL-lowering medications, there has been a renewed interest in this group of disorders.

Brief Overview of Triglyceride Metabolism

Triglyceride metabolism has been extensively reviewed elsewhere.[1,2] However, a brief review is included here as a preamble to disorders of triglyceride metabolism.

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Abbreviations	
LPL	lipoprotein lipase
APOC3	apolipoprotein C3
ANGPTL3	angiopoeitin-like protein 3
CVD	cardiovascular disease
FCS	familial chylomicronemia syndrome
MFCS	multifactorial chylomicronemia syndrome
FPLD	familial partial lipodystrophy

Triglyceride-rich lipoproteins (TRLs) enter plasma either as chylomicrons following the ingestion of dietary fat (exogenous pathway) or after synthesis of very-low-density lipoproteins (VLDL) by the liver (endogenous pathway). A large portion of the triglyceride component of these lipoproteins is hydrolyzed by lipoprotein lipase (LPL), an enzyme that is synthesized by several tissues, including adipose tissue and skeletal and cardiac muscle, after which it is transported by glycosylphosphatidylinositol-anchored high-density lipoprotein (HDL)–binding protein 1 (GPIHBP1) to the luminal side of the endothelium, where it is available to hydrolyze triglycerides.[3] Several other proteins regulate LPL activity.[4] LPL is activated by apolipoprotein (APO)C2 and inhibited by APOC3. Other LPL activators include APOA4[5] and APOA5,[6,7] whereas angiopoietin-like protein 3 (ANGPTL3) and ANGPTL4 inhibit LPL. Triglyceride-depleted remnants of chylomicrons and VLDL are enriched in APOE and are taken up by the liver by the interaction of APOE on remnant particles with the LDL receptor, LDL receptor-related protein 1,[8] and syndecan 1, a heparin sulfate proteoglycan,[9] after which some of the VLDL but not chylomicron remnants are converted to LDL.

The clearance of triglycerides from plasma is saturable. When plasma triglyceride levels exceed approximately 500 to 700 mg/dL, additional chylomicrons and VLDL entering plasma cannot readily be removed and hence accumulate.[10]

Hypertriglyceridemia

Cut points for the diagnosis of hypertriglyceridemia are provided in most major guidelines related to hyperlipidemia. However, the biological basis for these cut points is often not supported by a strong rationale. Guidelines such as those from the American Heart Association/American College of Cardiology (AHA/ACC) and National Lipid Association regard values of less than 150 mg/dL as normal, 150 to 199 mg/dL as borderline elevated, 200 to 499 mg/dL as high, and greater than 500 mg/dL as very high. Roughly similar cut points are provided by societies such as the Endocrine Society, although they regard values of 1000 to 1999 mg/dL as severe and greater than 2000 mg/dL as very severe. Summaries of the definitions for the various grades of hypertriglyceridemia are reviewed in Refs.[2,11,12] However, a more rational approach might consider the upper limit of normal as values greater than which complications of hypertriglyceridemia occur, which may differ depending on the specific complication. For example, the value at which the risk of CVD increases is much lower than the level for the development of pancreatitis. As regards CVD risk, the associated lipid and lipoprotein abnormalities, and other CVD risk factors, may be more important determinants of CVD risk than the triglyceride level per se. Thus, establishing a normal range is actually more complicated than simply applying statistical approaches or arbitrary cut points.

Causes of Hypertriglyceridemia

Mild to moderate hypertriglyceridemia occurs commonly as part of the metabolic syndrome, can result from multiple small-effect genetic variants, and can be secondary to

several diseases and drugs. Severe hypertriglyceridemia with plasma triglyceride levels greater than 1000 to 1500 mg/dL can result from 3 groups of conditions: (1) rare mutations in the LPL complex, which is termed the familial chylomicronemia syndrome (FCS); (2) the coexistence of genetic and secondary forms of hypertriglyceridemia, termed the multifactorial chylomicronemia syndrome (MFCS), which is a much more common cause of severe hypertriglyceridemia; and (3) familial partial lipodystrophy (FPLD). Each of these is discussed in more detail in later sections.

Genetic causes

Studies in the 1970s suggested that a variable pattern of lipid abnormalities was present in families of survivors of myocardial infarction that was termed familial combined hyperlipidemia (FCHL)[13] or multiple-type familial hyperlipoproteinemia.[14] These disorders were originally believed to be monogenic.[13] However, genome-wide association studies (GWAS) have identified single-nucleotide polymorphisms in at least 45 loci associated with plasma triglyceride levels, affecting triglycerides alone or in combination with other lipoproteins,[15,16] with some common variants in several genes being strongly associated with susceptibility to hypertriglyceridemia. It is now believed that most clinically relevant genetic abnormalities that result in mild to moderate elevations of plasma triglyceride levels are due to the presence of multiple common gene variants,[17,18] each with small effects. These gene variants also can interact with lifestyle measures and secondary forms of hypertriglyceridemia (see later). These minor gene variants, each having small phenotypic effects, can be quantified using a polygenic score,[19–21] but such gene scores are not yet in widespread clinical use. Monogenic causes of severe hypertriglyceridemia are discussed later.

Although FCHL is no longer believed to be a monogenic disorder,[20] there is some utility in making a *clinical* diagnosis of "FCHL" based on elevated APOB levels in combination with elevated triglycerides in subjects with premature CVD and lipoprotein abnormalities in their families,[22] because it identifies individuals and families at markedly increased risk for developing premature CVD who likely would benefit from lipid-lowering therapy.[23] Such individuals often also have features such as visceral obesity and insulin resistance, that is, features of the metabolic syndrome. In other words, some patients with FCHL have the metabolic syndrome, and vice versa (see later).

Genetic forms of hypertriglyceridemia often result from increased VLDL secretion, which can be associated with increased levels of APOB.[24] Increased residence time of VLDL in plasma favors the accumulation of small dense LDL particles,[25] which frequently are found in the presence of hypertriglyceridemia.

Remnant removal disease

Remnant removal disease, dysbetalipoproteinemia or type III hyperlipoproteinemia, is a rare autosomal recessive genetic form of hypertriglyceridemia in which remnants of chylomicrons and VLDL accumulate in plasma, resulting in mild to moderate elevations of triglyceride levels together with elevated cholesterol levels. This disease usually results from homozygosity for the APOE2 genotype plus a disorder resulting in VLDL overproduction,[26] which results in impaired hepatic uptake of APOE-containing lipoproteins[27] and impaired conversion of VLDL remnants to LDL.[28]

Hypertriglyceridemia as a component of the metabolic syndrome

Hypertriglyceridemia is a component of the metabolic syndrome. Some consider this to be a secondary form of hypertriglyceridemia. Because up to one-quarter to one-third of the US population have been estimated to have the metabolic syndrome,[29] it is worth considering the hypertriglyceridemia that occurs as a component of this syndrome as a separate category. Although the term "hypertriglyceridemic waist"

has been used to describe patients with hypertriglyceridemia and central obesity who are at increased risk of developing CVD,[30] there is likely to be considerable overlap between these individuals and those classified as having the hypertriglyceridemia as part of the metabolic syndrome.

Secondary forms of hypertriglyceridemia

Hypertriglyceridemia can be present secondary to many other diseases and drugs. The most common of these is diabetes, particularly type 2 diabetes, in which up to 20% to 25% have increased triglyceride levels.[31] Hypertriglyceridemia in type 1 diabetes occurs mainly in those in poor glycemic control and in those who also have features of the metabolic syndrome.[32,33] As mentioned earlier, hypertriglyceridemia is a feature of the metabolic syndrome even in the absence of diabetes. Other common conditions that are associated with increased triglyceride levels include alcohol excess, chronic kidney disease, nephrotic syndrome, and hypothyroidism. These and rarer secondary causes are shown in **Box 1**. The most common medications that cause hypertriglyceridemia are beta-adrenergic blockers and diuretics. Other medications include drugs such as oral estrogen and estrogen receptor agonists, glucocorticoids, protease inhibitors, some antipsychotics, and antidepressants and retinoids. A more complete list is given in **Box 1**.

Treatment of some but not all these secondary causes of hypertriglyceridemia can result in normalization of the elevated triglyceride levels. Examples include treatment of diabetes and hypothyroidism, whereas hypertriglyceridemia secondary to chronic renal disease is not easily reversed. Discontinuation of drugs leading to hypertriglyceridemia often results in reduction in triglyceride levels. Substitution of lipid-neutral antihypertensive agents for beta-blockers or diuretics can lead to normalization of triglyceride levels.

The coexistence of secondary forms of hypertriglyceridemia with genetic forms of hypertriglyceridemia can result in saturation of triglyceride removal mechanisms, leading to severe hypertriglyceridemia and features of the chylomicronemia syndrome, which is discussed next.

Severe hypertriglyceridemia and the chylomicronemia syndrome

As noted earlier, hypertriglyceridemia is designated as being severe when values exceed 1000 to 1500 mg/dL, depending on which guidelines are used. If left untreated, triglyceride levels of this magnitude can result in recurrent episodes of acute pancreatitis. Such high levels are usually due to one of the following 3 conditions.

Familial chylomicronemia syndrome

FCS, originally termed type I hyperlipoproteinemia[34] and later, primary LPL deficiency,[35] is by far the least common cause of severe hypertriglyceridemia and results from rare mutations in LPL or associated proteins. Causes include nonfunctioning mutations of LPL itself,[36–38] loss-of-function mutations in APOC2[39,40] and APOA5,[39,41,42] and mutations leading to defective or absent GPIHBP1[39,43] or LMF1,[5] a protein responsible for maturation of LPL. These mutations result in impaired clearance of TRLs from plasma, and accumulation of chylomicrons and VLDL in plasma.

Multifactorial chylomicronemia syndrome

MFCS is by far the most common cause of severe hypertriglyceridemia (reviewed in Ref.[44]) and likely describes the same conditions that have previously been termed type V hyperlipoproteinemia[34] and polygenic late-onset chylomicronemia.[18,42] MFCS nearly always is the result of the coexistence of a genetic predisposition to hypertriglyceridemia with one or more of the secondary forms of hypertriglyceridemia

Box 1
Secondary causes of hypertriglyceridemia

- Common conditions
  - Hypothyroidism
  - Uncontrolled diabetes
  - Pregnancy
  - Nephrotic syndrome
  - Chronic renal failure
  - Acute hepatitis
  - Weight regain after weight loss
  - Sepsis
  - Autoimmune chylomicronemia
    - Systemic lupus erythematosus
    - Anti-LPL antibodies
    - Anti-GPIHPD1 antibodies
- Rare genetic causes
  - Glycogen storage disorders
  - Lipodystrophies
    - Congenital generalized or partial
    - Acquired: HIV or autoimmune
- Drugs
  - Alcohol
  - Beta-blockers
  - Diuretics
  - Oral estrogens
  - Selective estrogen reuptake modulators: tamoxifen, raloxifene
  - Androgens
  - Glucocorticoids
  - Atypical antipsychotics
  - Sertraline
  - Bile acid resins
  - Sirolimus, tacrolimus
  - Cyclosporine
  - RXR agonists: bexarotene, isotretinoin
  - HIV protease inhibitors
  - L-Asparaginase
  - Alpha-interferon
  - Propofol
  - Lipid emulsions

HIV, human immunodeficiency virus; RXR, retinoid X receptor.

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shown in **Box 1**.[12,45] The coexistence of these disorders leads to saturation of triglyceride removal systems, such that additional input of chylomicrons from the diet or endogenously synthesized triglycerides from the liver are unable to be removed and hence accumulate in plasma (**Fig. 1**).

Familial partial lipodystrophy

Several forms of FPLD can be associated with severe hypertriglyceridemia and severe insulin-resistant diabetes.[46] The 2 most common forms are the Köbberling variety, in

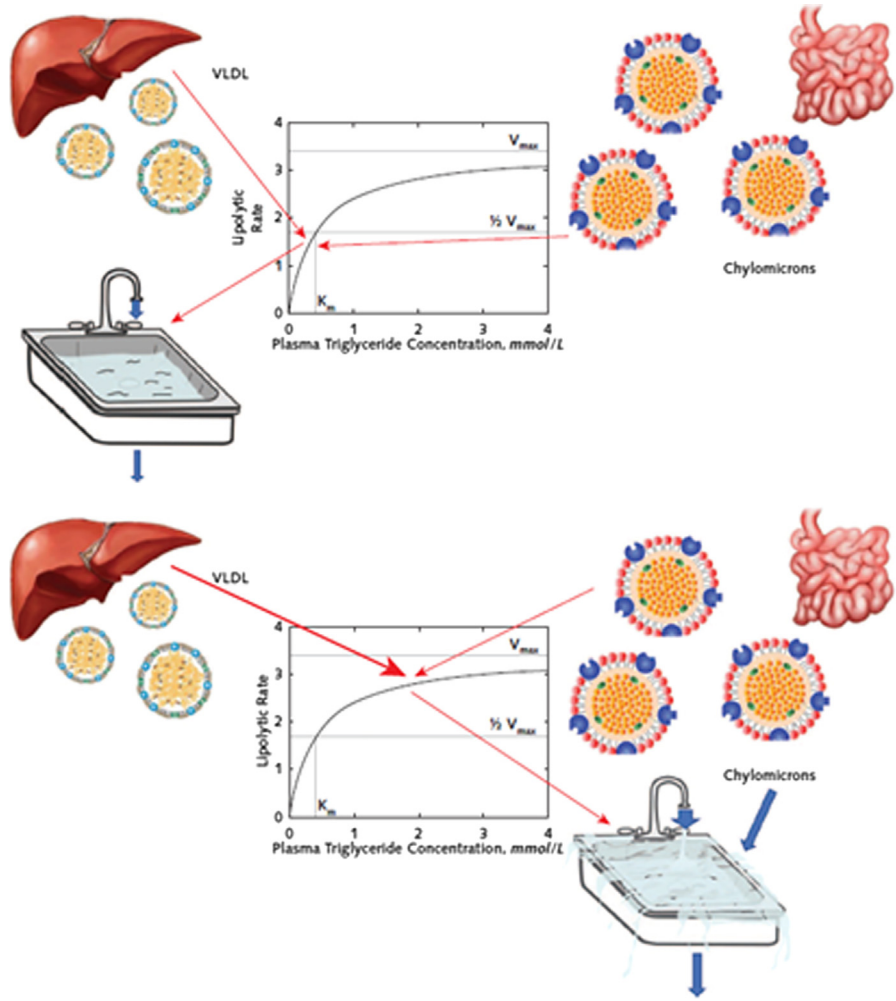

Fig. 1. Pathophysiology of hypertriglyceridemia. K_m = Michaelis constant; VLDL = very-low-density lipoprotein; V_{max} = maximum velocity. Top. When triglyceride removal mechanisms are not saturated (central graph), outflow from plasma equals inflow and plasma triglyceride levels are stable, as depicted by the level in the sink. Bottom. When increased hepatic input of VLDL leads to saturation of triglyceride removal mechanisms, inflow from VLDL and chylomicrons exceeds outflow, leading to a marked increase in the plasma triglyceride pool, depicted as the overflowing sink. (*From* Chait A, Eckel RH. The chylomicronemia syndrome is most often multifactorial: a narrative review of causes and treatment. Ann Intern Med 2019;170(9):626–34.)

which subcutaneous adipose tissue is absent in the limbs but not the trunk, and the Dunnigan variety, in which adipose tissues also are reduced in the visceral compartment. Mutations in LMNA gene (encoding A-type lamins) is commonly seen with the Dunnigan phenotype, whereas no single-gene mutations have been found to date with the Köbberling variety. The Köbberling form of FPLD is likely vastly underdiagnosed, due to its phenotypic resemblance to the metabolic syndrome, including the presence of central obesity, diabetes, hypertension, and hypertriglyceridemia.

However, a classical shelf above which subcutaneous fat is present and below which it is absent is observed by careful clinical examination of the buttocks.[44,47]

Consequences of Hypertriglyceridemia

Atherosclerotic cardiovascular disease

There has been a longstanding acceptance of the causal relationship between LDL and CVD. However, although hypertriglyceridemia has long been considered a CVD risk factor by some, recent studies have put this beyond doubt. Epidemiologic studies were the first to suggest that hypertriglyceridemia is a CVD risk factor,[48–52] which has been reconfirmed in a meta-analyses.[53] Although the association of triglycerides with CVD risk is attenuated when adjusted for HDL and non-HDL cholesterol, it, nonetheless, remains significant.[53] Moreover, a strong relationship also exists between nonfasting triglyceride levels and CVD.[52]

GWAS have shown that some genetic variants that influence triglyceride levels are also associated with increased CVD risk,[54–56] even after adjusting for their effects on other lipid traits.[57] Heterozygous deletion and other types of mutations of LPL also have been associated with increased CVD risk.[58] Variants in APOC3[59,60] and ANGPTL4[61,62] that are associated with reduced triglyceride levels are associated with reduced CVD risk, whereas variants in APOA5 that are associated with increased triglyceride levels are associated with increased CVD risk.[63,64] These genetic studies strongly support a role for triglycerides in CVD risk. However, the strongest evidence for triglycerides playing a causal role in the development of CVD comes from Mendelian randomization studies that focus on variants in genes encoding triglyceride-related proteins such as LPL, APOC2, APOA5, and ANGPTL3 and 4.[58,61,64,65] Confounding variables are equally distributed in such studies. When 185 common variants for plasma lipids were mapped, loci with a strong association with triglycerides also were associated with CAD, even after adjusting for LDL and HDL cholesterol levels.[57] Collectively these studies provide convincing evidence that triglycerides play a causal role in atherosclerotic CVD.

The exact mechanism by with TRLs cause CVD is not known. It is noteworthy that atherosclerotic plaques are not rich in triglycerides. Moreover, chylomicrons are too large to traverse the endothelial barrier and enter the subendothelial space. However, the cholesterol-enriched remnants of chylomicrons and VLDL are small enough to enter the arterial intima, where they can be retained by arterial wall proteoglycans and undergo various modifications that render them proinflammatory and atherogenic.[2,66–70] Chylomicrons also can enter endothelial cells in an SRB1-dependent manner, after which lysosomal hydrolysis generates lipid-rich exosomes, which might contain toxic and proinflammatory lipids.[71] Hypertriglyceridemia also often is accompanied by the presence of small, dense LDL particles and low levels of dysfunctional HDL,[2] both of which may play a role in the atherogenesis.

CVD risk in those with severe hypertriglyceridemia and the chylomicronemia syndrome depends on the cause of the syndrome and is discussed in more detail later.

Acute pancreatitis and other features of the chylomicronemia syndrome

The chylomicronemia syndrome describes a constellation of findings that occur with severe elevations of plasma triglyceride levels, usually greater than 1500 mg/dL. The most serious complication of severe hypertriglyceridemia is acute pancreatitis, which has a mortality rate of about 2% to 5%.[72,73] The mechanisms by which severe hypertriglyceridemia leads to acute pancreatitis remains somewhat speculative. Local liberation of lysolecithin and free fatty acids by the hydrolysis of lecithin and triglycerides by lipases in the pancreas are believed to play a role, because lysolecithin and

free fatty acids result in chemically induced pancreatitis in animal models.[74,75] Inflammation in the pancreas liberates more pancreatic lipases, thereby establishing a vicious cycle.[74,75] Triglyceride-induced hyperviscosity leading to ischemic damage to the pancreas also is believed to play a role.[75]

Severe hypertriglyceridemia is the third most common cause of acute pancreatitis after alcohol and gallstones, and often is recurrent if triglyceride levels remain markedly elevated. Moreover, triglyceride-induced pancreatitis has a worse prognosis than other forms of pancreatitis, with an approximate doubling of renal and respiratory failure, a nearly 4-fold increase in shock, and a near doubling of mortality.[76]

Other features of the chylomicronemia syndrome include eruptive xanthomas, characterized by yellow-red papules on the buttocks, back, and extensor surfaces of the upper limbs; fatty liver, which is associated with an increased risk of CVD; and a whitish appearance of the optic fundus and retinal vessels termed lipemia retinalis, which is a curiosity and of no pathophysiological consequence. Acute memory loss for recent events and mental fogginess also have been reported.[77] These features are obviously of much less importance than acute pancreatitis but can help in the diagnosis of the chylomicronemia syndrome.

The chylomicronemia syndrome can be associated with an increased risk of CVD, depending on the cause. CVD risk usually is not increased in FCS unless there are other CVD risk factors such as cigarette smoking and diabetes.[78,79] However, individuals with the MFCS, the commonest cause of the chylomicronemia syndrome, often have polygenic mutations of triglyceride-raising genes that are associated with CVD, as well as other CVD risk factors, such as diabetes and hypertension. FPLD also is associated with increased CVD risk.[47,80,81]

Treatment of Hypertriglyceridemia

The approach to treating hypertriglyceridemia depends to a large extent on the cause and what the goals of treatment are. The major goal of treating mild to moderate hypertriglyceridemia is to prevent CVD, whereas the goal of management of individuals with severe hypertriglyceridemia is prevention of pancreatitis, as well as prevention of CVD in susceptible individuals.

Treatment of secondary forms of hypertriglyceridemia

Before instituting lifelong therapy for hypertriglyceridemia, it is essential to rule out and treat reversible secondary disorders that can elevate plasma triglyceride levels, including appropriate management of diabetes and hypothyroidism and substituting drugs that can elevate triglyceride levels with lipid-neutral alternatives, particularly with respect to the management of hypertension where beta-adrenergic blocking agents and diuretics should be replaced by agents such as calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and alpha-adrenergic blockers. If triglyceride levels fall and remain normal after such strategies, no additional therapy may be needed, other than statins to reduce CVD risk in appropriate individuals, such as those with diabetes.

Approach to the prevention of cardiovascular disease in individuals with hypertriglyceridemia

Lifestyle measures are an important starting point for the prevention of CVD. Many individuals with hypertriglyceridemia are overweight or obese, and there is good evidence that triglyceride levels decrease with weight loss. However, weight loss has proved difficult to maintain. When triglyceride levels remain elevated, CVD risk should be assessed using one of the several risk calculators, such as that from the AHA/ACC. Statins are the initial drug therapy to reduce CVD risk in all high-risk individuals

independent of triglyceride levels. However, their effect in reducing triglycerides is moderate.

There remains some controversy as to how to approach the patient on statins with residual triglycerides greater than 150 mg/dL, who have either CVD or diabetes plus 2 additional risk factors. Fibrates are peroxisome proliferator-activated receptor (PPAR) alpha agonists that are effective in reducing triglyceride levels. However, their effect on reducing CVD risk remains controversial. Early studies such as the Helsinki Heart Study and VA HDL Intervention Trial (VA-HIT) showed a reduction in CVD events with the use of gemfibrozil,[82,83] but these studies were performed before the widespread use of statins. Several subsequent studies such as BIP (bezafibrate infarction prevention study), FIELD (Fenofibrate Intervention and Event Lowering in Diabetes), and ACCORD (Action to Control Cardiovascular Risk in Diabetes, also with fenofibrate) have failed to show a significant overall CVD benefit of fibrates in the entire cohort studied, possibly because hypertriglyceridemia was not a prespecified inclusion criterion. However, subgroup analyses, which were not prespecified with the exception of the ACCORD trial, did show benefit in patients with triglyceride levels greater than 200 mg/dL and low levels of HDL.[84] A PPAR alpha polymorphism had been shown to influence the benefit of fenofibrate in the ACCORD study.[85] However, a cardiovascular outcome study of a novel PPAR alpha agonist added to a statin in individuals with hypertriglyceridemia and low HDL-C,[86] Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients With Diabetes (PROMINENT), recently was discontinued due to a low likelihood of the primary endpoint being met, thereby essentially ending the debate about potential cardiovascular benefits of adding a fibrate to a statin in individuals with hypertriglyceridemia.

Fish oils also reduce plasma triglyceride levels. Multiple studies and a meta-analysis have failed to show a CVD benefit of mixed eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).[87] However, a landmark randomized controlled trial, Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT), showed significant benefit of adding EPA ethyl ester to statins in reducing the risk of CVD in patients with residual high triglyceride levels and CVD or diabetes and 2 or more risk factors.[88] The risk reduction was unrelated to either the baseline triglyceride level or to the magnitude of triglyceride reduction. This study confirmed an earlier study from Japan, which was open label and termed Japan EPA Lipid Intervention Study (JELIS), which showed that a lower dose of EPA also reduced CVD events.[89] However, a subsequent study, Outcomes Study to Assess Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia (STRENGTH), which used a combined EPA/DHA preparation, was stopped earlier due to futility.[90] Thus, despite a wide range of formulations and doses of omega-3-fatty acids in various trials, the current consensus is that EPA, but not DHA, affects CVD events. Potential mechanisms for the beneficial outcome of the REDUCE-IT study have been proposed.[91] In addition, proresolving mediators generated from EPA may also be playing a role (see Goldberg and colleagues' article, "Big Fish or No Fish; EPA and Cardiovascular Disease," in this issue on omega-3 fatty acids). Therefore, although some have suggested that the benefit seen in the REDUCE-IT trial might be attributable to adverse effects of the mineral oil control used, the current American Diabetes Association's recommendation is to consider adding EPA ethyl ester to a statin in patients with diabetes who have atherosclerotic CVD or other CV risk factors and have controlled LDL cholesterol levels but persistently elevated triglyceride levels. The role of fish oils in the prevention of atherosclerosis and CVD is discussed in more detail in Goldberg and colleagues' article, "Big Fish or No Fish; EPA and Cardiovascular Disease," in this issue.

A similar approach to CVD prevention should be applied to individuals with the MFCS and FPLD after their triglyceride levels have been lowered sufficiently to reduce their risk of pancreatitis (see later).

Several other protein targets that affect triglyceride metabolism are being evaluated in ongoing clinical trials. The rationale for these targets is based on genetic studies that indicate that individuals with genetically low levels of APOC3 and ANGPTL3 have protection against CVD. Antisense oligonucleotide (ASO) inhibitors of APOC3 and both ASO and monoclonal antibody inhibitors of ANGPTL3 have been shown to reduce plasma triglyceride levels,[92–94] but their effect on CVD events remains to be determined; these are discussed in more detail in Zambon and colleagues' article, "New and Emerging Therapies for Dyslipidemia," in this issue. However, the development of Vupanorsen, an ANGPTL3 ASO inhibitor that was being tested for CVD risk reduction and treatment of severe hypertriglyceridemia, recently was discontinued due to insufficient magnitude of triglyceride reduction.

Approach to the prevention of pancreatitis in individuals with severe hypertriglyceridemia

The best way to prevent the onset of triglyceride-induced pancreatitis is to keep triglyceride levels less than 500 mg/dL.[95–97] The approach to so doing will depend to a large extent on the cause of the severe hypertriglyceridemia, as reviewed in Ref.[44] Although FCS is very rare, it is extremely difficult to keep levels this low. The mainstay of therapy to date has been the use of a very-fat-restricted diet (<5% of calories from fat). However, this degree of fat restriction is a major burden on patients. A promising approach is the use of an APOC3 ASO, which has been shown to lower triglyceride levels in these patients by actions of APOC3 that are independent of LPL.[98,99]

The approach to triglyceride lowering in MFCS requires diagnosis and treatment of any of the reversible secondary forms of hypertriglyceridemia discussed earlier. Cessation of alcohol intake, appropriate treatment of diabetes, or substitution of beta-adrenergic blockers and diuretics for lipid-neutral antihypertensive agents often reduces triglyceride values sufficiently to reduce the risk of pancreatitis. As these individuals almost always have a genetic component to their hypertriglyceridemia, triglyceride values seldom fall to within the normal range with this approach. Residual hypertriglyceridemia should be treated with fibrates,[97] which will prevent recurrent episodes of acute pancreatitis. As APOC3 ASOs reduce triglyceride levels over a wide range of triglyceride levels,[93] with time this approach might prove to be of value in this difficult-to-treat group of patients.

The hypertriglyceridemia that can be seen with FPLD is often very severe and difficult to treat; it sometimes responds to fibrates, but levels often remain sufficiently high to put the patient at risk of recurrent pancreatitis. Thiazolidinediones and glucagonlike peptide-1–receptor analogs help reduce triglycerides in some patients with the Köbberling variety of FPLD, and leptin administration can be useful in congenital total lipodystrophy and in some cases of FPLD in patients with low leptin levels.[100] Because leptin levels are normal in Köbberling FPLD[47], there is little rationale for its use in this condition. The role of APOC3 and ANGPTL3 inhibition in the treatment of these difficult-to-treat disorders may prove to be of use with time.

Once triglyceride levels have been lowered sufficiently to prevent acute or recurrent pancreatitis, strategies to prevent CVD need to be undertaken in individuals with MFCS and FPLD. A statin should be added for CVD prevention, as well as lifestyle measures and appropriate treatment of other CVD risk factors. Because ANGPTL3 inhibition lowers LDL and HDL cholesterol levels in addition to triglycerides, and loss-of-function mutations of ANGPTL3 are associated with a reduced risk for CVD,[65]

ANGPTL3 inhibition might prove valuable in preventing CVD in addition to pancreatitis in these patients.

SUMMARY

The recent focus on hypertriglyceridemia, in large part prompted by genetic studies confirming its role as a CVD risk factor and by newer drug targets, offers lots of promise for the management of patients with hypertriglyceridemia, both from the standpoint of CVD prevention and also for the prevention of triglyceride-induced pancreatitis in severe hypertriglyceridemia.

CLINICS CARE POINTS

- Consider and exclude secondary causes of hypertriglyceridemia
- Mild to moderate hypertriglyceridemia is an established risk factor for CVD, so a careful family history is useful
- Use lifestyle measures and statins as the first-line therapy for the prevention of CVD
- Add EPA ethyl esters for residual hypertriglyceridemia with diabetes or 2 or more risk factors
- With triglyceride levels greater than 1000 mg/dL, distinguish between the 3 main causes, MFCS, FPLD, and the rare cases of FCS. Careful examination of the buttocks for a ledge above which fat is present and below which it is absent is helpful in making the diagnosis of the Köbberling form of FPLD.
- Treatment of severe hypertriglyceridemia depends on the cause. Maintaining triglyceride levels less than 500 mg/dL is necessary for pancreatitis prevention

DISCLOSURE

The author has nothing to disclose.

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