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Treatment options for hypertriglyceridemia: from risk reduction to pancreatitis

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Abstract

While there has been considerable focus on the role and treatment of LDL cholesterol levels, a definitive role of triglycerides in the management of cardiovascular disease has been uncertain. Notably, with increasing triglyceride levels, there is a parallel increase in cholesterol levels carried by triglyceride-rich lipoproteins, which has prompted interest in the use of non-HDL cholesterol levels as a tool guiding interventions. Recent studies have provided evidence for an independent role of triglyceride levels as a cardiovascular risk factor, and recently, an Endocrine Society guideline was published for treatment of hypertriglyceridemia. In contrast to the relative uncertainty regarding triglycerides and cardiovascular disease, a role of very high triglyceride levels as a risk factor for pancreatitis has been well known. The present paper summarizes the underlying evidence for a risk role for triglyceride levels in cardiovascular disease and pancreatitis, current treatment recommendations and areas of future research.

Keywords

Dyslipidemia; Lipoproteins; coronary heart disease; hypolipidemic therapy; lifestyle intervention

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Introduction

The role of triglycerides as a cardiovascular risk factor has been uncertain. Until recently, recommendations for treatment and prevention of atherosclerotic cardiovascular disease (CVD) have been focused on LDL cholesterol levels in relation to long-term risk. This has largely been driven by the well-documented association between cholesterol levels and CVD or mortality at the population level, with considerable variability between different geographical areas ^{1, 2}. As LDL is the dominating cholesterol carrier, treatment and prevention efforts have focused on levels of LDL cholesterol, and many clinical trials have demonstrated that lowering LDL cholesterol reduces CVD events or mortality ³. However, an increased triglyceride and not LDL cholesterol level is a component of the metabolic syndrome, associated with CVD in many studies ⁴⁻⁶. Although the Framingham score, widely used to assess CVD risk does not specifically include triglyceride levels, its use of total cholesterol implicates a contribution by VLDL cholesterol and therefore triglyceride-rich lipoproteins in the calculation ⁷. There is growing support for elevated triglyceride levels as an independent cardiovascular risk factor. A recent summary from the International Atherosclerosis Society suggested that the current Framingham risk scoring system underestimates risk associated with the metabolic syndrome, perhaps because triglyceride is undervalued as a risk factor ⁸. However, the extent to which elevated triglycerides constitute a direct risk for cardiovascular disease or represent a marker for other lipoprotein abnormalities associated with CVD risk is unknown and remains a focus for future investigations. Aside from CVD, very high triglyceride levels are a well-established risk factor for pancreatitis.

Triglycerides – Pathophysiology and metabolism

Triglycerides are an important source of energy and generally constitute a major portion of an individual's caloric intake. After partial hydrolysis, dietary fat is resynthesized into triglycerides in the gut mucosa and secreted into the lymphatic circulation as chylomicrons. Through interaction with lipoprotein lipase (LpL), present on the luminal surface of capillary endothelial cells, triglycerides are lipolyzed to free fatty acids, which are then taken up by tissues. However, the hydrolysis of chylomicron triglycerides is incomplete and some fraction circulates in the form of chylomicron remnants. Chylomicrons and their remnants contain apolipoprotein (apo)B48, representing the N-terminal portion of the full length apoB protein which lack the LDL-receptor binding motif. A number of other apolipoproteins impact on LpL activity and lipoprotein clearance from the plasma. ApoC-II is necessary for the function of LpL. ApoC-III may inhibit LpL and also blocks lipoprotein uptake by the liver, and apoE is important for the uptake of triglyceride-rich remnants by the liver.

In response to the uptake of lipoprotein triglycerides or free fatty acids and/or endogenous production of fatty acids from carbohydrates, the liver produces triglyceride-rich VLDL particles, containing the full length apoB-100. Similar to chylomicron triglycerides, triglycerides in VLDL particles are metabolized to free fatty acids by the action of LpL, with subsequent tissue uptake. The lipolytic process leads to production of VLDL remnants, also referred to as intermediate-density lipoproteins (IDL), and eventually to conversion to LDL

particles. Depending on the relative presence of apo C-III and apoE, VLDL subfractions differ in their metabolic properties and the propensity to hypertriglyceridemia⁹. Notably, hypertriglyceridemic VLDL particles are heterogeneous and often have a high apoC-III/apoE ratio, causing reduced clearance and increased conversion to LDL.

The plasma triglyceride level is a marker for the concentration of triglyceride-carrying lipoproteins (VLDL and chylomicrons). As the relative proportion of lipoprotein components differ, the VLDL cholesterol and apoB concentration is substantially higher than the corresponding chylomicron concentrations¹⁰. It is noteworthy that these lipoproteins contain at least as much cholesterol per particle as LDL and it has been suggested that cholesterol carried in triglyceride-rich particles might contribute to plaque development¹¹. Thus, a narrow focus on LDL cholesterol may not take the full amount of atherogenic risk carried by lipoproteins into consideration.

Recently, there has been much interest in understanding the wider metabolic consequences of hypertriglyceridemia. Increased tissue accumulation of triglycerides can result from increased triglyceride uptake, greater de novo formation of triglyceride, or reduced utilization or secretion of triglyceride. Excess tissue triglyceride has become the signature of a number of metabolic diseases that are termed lipotoxicities; these include non-alcoholic fatty liver disease (NAFLD), type 2 diabetes mellitus and some forms of cardiomyopathy, and patients with acquired generalized lipodystrophy and extensive fat loss often have hepatic steatosis as circulating triglyceride is unable to be stored in adipose tissue^{12,13}. Secondly, an increased ectopic fat deposition may lead to insulin resistance associated with type 2 diabetes mellitus and metabolic syndrome¹⁴. This defect in insulin signaling is thought to be due not to triglyceride itself, but to the associated accumulation of signaling lipids such as diacylglycerol and ceramides.

Although the association of central obesity and insulin resistance with dyslipidemia is well established, underlying mechanisms remain unclear. An increase in the level of portal vein long-chain non-esterified fatty acids (NEFAs) has been suggested as an underlying factor that would potentially inhibit hepatic apoB-100 degradation and increase the likelihood of secretion of triglyceride-containing lipoproteins. Secondly, this could contribute to increased triglyceride levels with a higher number of VLDL and LDL particles in patients with insulin resistance¹⁵. Because hypertriglyceridemia, increased intra-abdominal fat, and NAFLD occur with insulin resistance and excess caloric intake, a cause-and-effect relationship is difficult to conclude. The increased use of imaging tools coupled with metabolic and genetic studies may provide novel insights.

Hypertriglyceridemia – what is a relevant definition?

The definition of normal vs. elevated triglyceride levels under fasting conditions has been subject to revision over time. Earlier versions of the NCEP Adult Treatment Panel (Panel I and II) defined elevated triglycerides as a level >200 mg/dL¹⁶. The current NCEP Adult Treatment Panel III (ATP III) has classified fasting serum triglycerides into 4 different classes with an elevated serum triglyceride level in adults classified as >150 mg/dL (>1.7 mmol/L)⁵. Although to some extent an arbitrary cutoff, the level is based on findings from

large prospective observational studies. However, the exact level at which serum triglycerides start to confer risk or become a marker for cardiovascular disease is unknown, but could be lower than a level of 150 mg/dL¹⁷. Age, gender and race/ethnicity impact the averages (normal) within the population. Serum triglycerides are higher in men and increase with age in both men and women; these changes parallel the frequency of the metabolic syndrome with age¹⁸. In support of the current definition of hypertriglyceridemia, serum triglyceride levels <150 mg/dL (<1.7 mmol/L) usually are <75th percentile at a population level, although there are well-established inter-ethnic differences, with generally lower levels among African Americans¹⁹. The more stringent definition of increased triglycerides, together with a higher frequency of overweight and obesity, has resulted in a high hypertriglyceridemia prevalence²⁰. Thus, a third of the NHANES 1999–2004 participants were hypertriglyceridemic. Hypertriglyceridemia was greatest with higher ages, however, a quarter of younger subjects had increased triglyceride levels²¹.

The recently published Endocrine Society guidelines specifically addressed the risk for pancreatitis in subjects with very high triglyceride levels²². The guidelines classified triglyceride levels in four hypertriglyceridemic categories, where the two lowest categories, together spanning triglyceride levels of 150–999 mg/dL, were considered as mild and moderate hypertriglyceridemia, respectively. The focus for this group is primarily on reducing CVD risk, while the highest category level, defined as very severe hypertriglyceridemia (>2,000 mg/dL), is associated with risk for pancreatitis. Triglyceride levels of 1000 – 1999 mg/dL, classified as severe hypertriglyceridemia, indicate risk for development of very severe hypertriglyceridemia, causative of pancreatitis^{23, 24}. A recent meta-analysis, classifying increased triglyceride levels as >500 mg/dL, confirmed an association between hypertriglyceridemia and pancreatitis²⁵. Although this new categorization attempts to provide a more clear association between triglyceride levels and pancreatitis, it adheres to the same treatment guidelines used in NCEP-ATP III. Triglyceride levels over 500 mg/dL approach and exceed the saturation level for triglyceride removal, are associated with rapid increases in post-prandial triglyceride levels, and are an indication for dietary and pharmacologic treatment.

Measurement of hypertriglyceridemia - Fasting vs. non-fasting triglyceride levels in clinical practice

Historically, lipid and lipoprotein levels, including triglycerides, have been routinely measured under fasting conditions. While this has allowed comparisons across studies and populations, it brings an element of inconvenience with regard to the practical clinical situation. The possibility that the postprandial status would represent an atherogenic condition was initially suggested by Zilversmit²⁶ and has been substantiated in many subsequent studies, primarily using a heavy lipid load with standardized blood sampling²⁷. Results from several recent prospective studies indicate that compared to fasting levels, non-fasting serum triglyceride levels may be a better or similar predictor of CVD events in the general population^{28–30}. The potential ability to make treatment decisions based on non-fasting lipid levels has therefore attracted interest. In one recent study, results showed a similar ability to predict nonfatal or fatal coronary heart disease by average fasting and non-

fasting triglyceride levels³¹. However, an important factor in using fasting conditions is the ability for the treatment provider to calculate LDL-cholesterol levels, the keystone in many cardiovascular risk reduction guidelines for intervention decisions regarding lipid risk factors⁵. Further, given the close and frequently inverse association between triglyceride and HDL cholesterol levels, hypertriglyceridemia and postprandial lipemia may affect measurement of HDL cholesterol and therefore the calculation of non-HDL cholesterol, an alternative treatment goal beyond LDL cholesterol⁵.

Several large population-based studies have addressed the association of non-fasting triglyceride levels with CVD risk. One of these studies, including more than 26,000 US women healthy at baseline and followed for about 11 years, tested fasting levels in 20,118 subjects and non-fasting in 6,391 women²⁹. Fasting triglyceride levels predicted CVD events but no independent association with cardiovascular events was seen after adjustment for potential confounders. Non-fasting triglyceride levels were independently associated with an increased risk of future events with a significant trend with increasing tertiles of triglyceride levels. Notably, the associations weakened with increasing time after the participants' last meal and there was some concern regarding compliance.

Another study, undertaken in Copenhagen and representing the general population, enrolled both women (n=7,587) and men (n=6,394) over a broad age range, with a mean follow-up of 26 years²⁸. After adjustment for other CVD risk factors, associations with myocardial infarction, ischemic heart disease, and total death were significant for trend with increasing triglyceride level for both men and women. Some limitations to note were the limited number of subjects with high triglycerides, lack of adjustment made for HDL-cholesterol, and no comparison with fasting triglyceride levels. Triglyceride levels and event rates in this study were higher compared to the healthy US women²⁹. While non-fasting conditions represent an advantage with regard to patient convenience and compliance, a number of issues remain to be resolved allowing a more general use. Lack of standardization and reference levels impede a general implementation of non-fasting triglyceride or remnant particle levels, requiring further studies to recommend an optimal procedure for postprandial sampling³². Finally, any postprandial effects on triglyceride measurement needs to be addressed³³.

Hypertriglyceridemia – causes

Hypertriglyceridemia can result from increased production, reduced catabolism, or a combination thereof. A common cause of hypertriglyceridemia is seen in conditions with insulin resistance, such as metabolic syndrome and type 2 diabetes mellitus. An increase in triglyceride production under these conditions may be due to excess free fatty acids returning to the liver, as well as an increased de novo triglyceride production^{15,34}. Although insulin resistance is associated with high triglycerides, VLDL and triglyceride concentrations can be similar in patients with widely divergent insulin sensitivity, and in African Americans, low triglyceride levels may occur in the context of severe insulin resistance^{35,36}. Thus, the contribution of insulin resistance to overproduction of triglycerides and VLDL may be variable. Foods that contain potent substrates for

triglyceride production such as free carbohydrates, fructose, and alcohol can substantially increase triglyceride levels in susceptible individuals ³⁷.

Mechanisms underlying a reduced catabolism contributing to hypertriglyceridemia include defective triglyceride hydrolysis and reduced hepatic clearance of VLDL and chylomicron remnants. Defective lipolysis can result from a variety of genetic defects, such as defects in LpL, apoC-II, glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1 (GPIHBP1, an LpL-binding protein), or mutated lipase maturation factor 1 (LMF1), leading to defective intracellular LpL processing ^{38, 39}. Other causes may be defective association of LpL with the vascular wall due to heparin antibodies ⁴⁰. In addition, a number of additional genetic factors influence human triglyceride levels, including mutations in apoC-III, apoE, apoA-V, and angiopoietin-like protein 3, 4 and 8. Reduced VLDL clearance may in part be due to saturation of clearance pathways ⁴¹. For this reason, there is concern that triglyceride levels >1,000 mg/dL can rapidly increase following a fat-rich meal.

As hypertriglyceridemia frequently constitute a component of metabolic abnormalities, many of which are associated with an increased risk for CVD, triglyceride levels may be seen as a canary in a mine. Beyond the presence of the metabolic syndrome, as mentioned above, elevated serum triglyceride levels are seen in overweight or obese people, a sedentary lifestyle, excess alcohol intake, and presence of endocrine or metabolic diseases. In addition, there are several genetic conditions with hypertriglyceridemia, including familial hypertriglyceridemia (FHTG), familial combined hyperlipidemia (FCHL), and familial dysbetalipoproteinemia (Type III hyperlipidemia). A combination of environmental and genetic factors underlying a hypertriglyceridemic condition is therefore not uncommon.

Genetic causes of hypertriglyceridemia

Elevated triglycerides can occur in the absence or presence of other lipid or lipoprotein disturbances. Patients with elevations in the levels of both total plasma cholesterol and triglyceride can be divided into three categories. In the first category, VLDL and/or LDL cholesterol levels are elevated, as in familial combined hyperlipidemia. In the second category VLDL and chylomicron remnant cholesterol are elevated, as in familial dysbetalipoproteinemia. The third category consists of patients with severe and very severe hypertriglyceridemia, such as chylomicronemia.

Familial Combined Hyperlipidemia (FCHL)

FCHL is a relatively common condition with a prevalence of about 1% to 2%. Notably, it is more common in patients with coronary artery disease, where the frequency has been reported to be at least 10% ⁴², highlighting the importance of diagnosis and treatment. The FCHL phenotype is variable, within families and in single individuals, and ranges from isolated hypertriglyceridemia to isolated hypercholesterolemia suggesting an environmental modulating impact ⁴². However, elevated apoB levels and small, dense LDL particles are always seen ⁴³. In addition, patients with FCHL frequently have other cardiovascular risk factors (i.e. central obesity, hypertension, insulin resistance, and impaired glucose tolerance), highlighting the need for comprehensive risk factor treatment.

Familial Hypertriglyceridemia (FHTG)

FHTG is another variant of genetic hypertriglyceridemia with triglyceride levels ranging from about 250 to 1,000 mg/dL where the CVD risk is low⁴⁴. Determination of whether an individual patient with hypertriglyceridemia is at increased risk for CVD is challenging. Family history and associated other risk factors that contribute to the metabolic syndrome are useful guides, and a concomitant increased apoB or LDL cholesterol concentration is suggestive of greater CVD risk and might assist in differentiating FCHL from more benign FHTG^{42,45}.

Many, if not most, patients with hypertriglyceridemia have a concomitant reduction in HDL cholesterol levels, and most forms of severe genetic HDL deficiency, such as Tangier's Disease, apoA-I deficiency, and lecithin cholesterol acyl transferase (LCAT) deficiency, are associated with mild-to-moderate hypertriglyceridemia. It has been suggested that familial hypoalpha-lipoproteinemia (FHA) might be a separate disorder with elevated triglyceride and low HDL cholesterol associated with premature coronary artery disease⁴⁶.

Chylomicronemia Syndrome

Severe hyperchylomicronemia is associated with very severe hypertriglyceridemia and abdominal pain, eruptive xanthomas on the buttocks and the extensor surfaces of the upper limb, and transient memory loss. If uncorrected, the chylomicronemia syndrome may result in acute, recurrent pancreatitis. The risk of pancreatitis markedly increases with triglyceride levels >2,000 mg/dL, and can be prevented by maintaining triglyceride levels <1,000 mg/dL. To reduce risk for acute, recurrent pancreatitis, patients must be treated with moderate to severe dietary fat restriction to reduce plasma triglyceride levels⁴². Although underlying mechanisms need to be resolved, a release of excess fatty acids and lysolecithin from chylomicrons, exceeding the binding capacity of albumin in pancreatic capillaries may contribute. Importantly, severe hyperchylomicronemia may be due to a secondary cause of hypertriglyceridemia, such as diabetes or pregnancy, in combination with an underlying genetic defect⁴². Attention should also be directed to any use of drugs that could raise triglyceride levels. Occasionally, chylomicronemia may occur together with a genetic defect in the LpL-related triglyceride clearance system, such as LpL deficiency or rarely, as apoC-II, apoA-V, or GPIIIBP 1 deficiency (see above).

Type III hyperlipidemia or Dysbetalipoproteinemia

Dysbetalipoproteinemia, also called type III hyperlipoproteinemia or remnant removal disease, is seen when an apoE genetic variant resulting in a reduced lipoprotein clearance (almost always the E2/E2 genotype) is present together with another condition (genetic or acquired, such as intake of steroids or estrogen or following surgery) resulting in VLDL overproduction (e.g. FCHL) or reduced LDL receptor activity (e.g. heterozygous FH or hypothyroidism). The net result is an impaired hepatic uptake of apoE-containing lipoproteins and a reduction in the conversion of VLDL and IDL to LDL particles, with concomitant elevations in both cholesterol and triglyceride levels⁴⁷. VLDL particles in patients with dysbetalipoproteinemia are cholesterol-enriched, as determined after isolation of VLDL by ultracentrifugation. In the absence of a second contributing factor beyond apoE, the accumulation of remnant lipoproteins is generally not sufficient to cause hyperlipidemia

under fasting conditions. It can be useful to confirm the diagnosis by demonstrating the presence of the E2/E2 genotype.

Due to the accumulation of triglyceride-rich lipoprotein remnants, patients with dysbetalipoproteinemia are at increased risk for premature coronary artery disease and peripheral vascular disease. Clinical characteristics include palmar xanthomas, orange lipid deposits in the palmar creases, which are pathognomonic but not always present, and tuberoeruptive xanthomas occasionally seen at pressure sites on the elbows, buttocks, and knees. The presence of dysbetalipoproteinemia should be suspected in a person with elevated total cholesterol and triglyceride levels that range from 300 to 1,000 mg/dL and are roughly equal.

Secondary causes of hypertriglyceridemia

An isolated elevation in triglyceride levels may arise secondary to the use of various drugs, a high carbohydrate diet, or as a component of endocrine and other diseases, inflammation, or some rare genetic diseases. In the setting of common, underlying genetic dyslipidemias, such secondary causes can lead to severe and very severe elevations of triglyceride levels and risk of pancreatitis.

Metabolic Syndrome and Endocrine Disorders

Hypertriglyceridemia is one of the components of the metabolic syndrome, a constellation of metabolic risk factors including triglycerides >150 mg/dL, HDL cholesterol <40 mg/dL in men or <50 mg/dL in women, blood glucose >100 mg/dL, blood pressure >130 mm Hg systolic or >85 mm Hg diastolic, and waist circumference >102 cm in men or >88 cm in women, recognized as conferring cardiovascular risk⁶. Although criteria for defining the metabolic syndrome have differed among health organizations and some cutoff levels differ across ethnicities, leading cardiovascular and diabetes organizations have agreed on a harmonized definition⁴⁸. Notably, presence of endocrine conditions such as type 2 diabetes mellitus, polycystic ovary syndrome, and FCHL may account for up to 50% of premature coronary artery disease in some populations with metabolic syndrome⁴⁹. Importantly, in normal, randomly selected healthy populations, isolated visceral obesity and insulin resistance were associated with only modest increases in triglyceride and decreases in HDL cholesterol levels⁵⁰. Increased waist circumference and plasma triglyceride levels together confer greater cardiovascular risk in these patients⁵¹.

Other conditions with hypertriglyceridemia include acromegaly, oral estrogen treatment, tamoxifen therapy (less pronounced with raloxifene), and pregnancy⁵². These changes relate to increased insulin resistance, to decreased activity of both hepatic lipase and LpL, or estrogen-induced stimulation of the secretion of triglyceride-rich lipoproteins⁵³. This latter effect does not occur with transdermal estrogen⁵⁴. In patients with familial hypertriglyceridemia or LpL deficiency, the use of oral estrogens can provoke severe pancreatitis⁵⁵. Glucocorticoids lead to increased fatty acid synthesis due to increased expression of fatty acid synthase, and decreased clearance of triglyceride-rich lipoproteins⁵⁶. Patients with untreated diabetes mellitus commonly have hypertriglyceridemia, more frequently seen in type 2 than in type 1, and appropriate diabetes management reduces

triglyceride levels. One of the most commonly used triglyceride-increasing agents is alcohol, which increases hepatic VLDL secretion due to increased hepatic fatty acid synthesis and decreased fatty acid oxidation. The effects of alcohol are dose-dependent and tend to be amplified in subjects with underlying lipid disorders ⁵⁷.

Rare Diseases

Loss of adipose tissue as seen in inherited and congenital lipodystrophies is associated with moderate-to-severe hypertriglyceridemia ⁵⁸. Some forms are present already at birth while others become clinically apparent in childhood and puberty ⁵⁹. In some rare varieties of familial partial lipodystrophy, such as the Kobberling variety, fat loss is more prominent from the extremities ⁶⁰. Hypertriglyceridemia is also seen in several types of glycogen storage disease in children ⁶¹.

HIV, Autoimmune disease, Renal and Hepatic disease

The finding of hypertriglyceridemia and acquired lipodystrophy in patients with HIV infection treated with highly active antiretroviral therapy has attracted much attention and a large number of studies have addressed potential mechanisms. At present, the HIV condition in itself as well as some antiretroviral regimens, such as combinations including ritonavir or lopinavir, have been associated with hypertriglyceridemia and decreased HDL cholesterol levels ^{62, 63}. Some autoimmune or malignant diseases show presence of lipodystrophy or hypertriglyceridemia, including systemic lupus erythematosus involving autoantibodies to LpL, apoC-II, or heparin, juvenile dermatomyositis, and multiple myeloma. Further, immunosuppressants such as sirolimus increase triglyceride levels ⁶⁴. Hypertriglyceridemia with increased VLDL production has been reported in infections including inflammation and sepsis ⁶⁵, and hypertriglyceridemia in severe stress may be related to possible catecholamine induction of adipose tissue lipolysis and reduced LpL activity ⁶⁶. Interestingly, acute hepatitis may be associated with increased VLDL production and hypertriglyceridemia ⁶⁷. Hypertriglyceridemia due to varying mechanisms is seen in some conditions of kidney disease. Nephrotic syndrome causes increased hepatic production of apoB-containing lipoproteins, including VLDL ⁶⁸, and hypertriglyceridemia is common in patients with renal failure, possibly related to decreased clearance of triglyceride-rich lipoproteins ⁶⁹.

Drugs

The association between bile acid sequestrants (cholestyramine, colestipol, colesevelam) and triglyceride levels is well established. While patients with normal baseline triglyceride levels experience minimal triglyceride increases, those with moderate hypertriglyceridemia may experience substantial further elevation ⁷⁰. Bile acid sequestrants are contraindicated in patients with severe hypertriglyceridemia (>1,000 mg/dl) and in patients with dysbetalipoproteinemia.

Antihypertensive drugs with a potential to increase triglyceride levels are thiazide and furosemide diuretics and β -adrenergic blocking agents and the effects are most relevant in patients with underlying genetic hypertriglyceridemia ⁵⁶. Retinoids (e.g. isotretinoin and bexarotene) are associated with increased triglyceride levels, and mechanisms may involve both increased hepatic VLDL and apoC-III production and decreased LpL ⁷¹.

Hypertriglyceridemia can be seen with certain second-generation antipsychotic medications associated with weight gain, insulin resistance and worsening of the metabolic syndrome ⁷².

Hypertriglyceridemia and lipoprotein composition – clinical practice applications

Triglyceride is a component of all lipoproteins, and triglyceride metabolism has a major impact on lipoprotein distribution and properties. In particular, triglyceride and HDL cholesterol levels are often inversely related, and HDL particles are closely involved in the catabolism of triglyceride-rich lipoproteins. Further, triglyceride-rich lipoproteins contain cholesterol, and under hypertriglyceridemic conditions, the amount of cholesterol carried in triglyceride-rich lipoproteins and their remnants can be substantial. These particles have an atherogenic potential. In addition, hypertriglyceridemia affects LDL and HDL particle properties, with a shift to smaller particle sizes ¹⁵. Thus, in patients with hypertriglyceridemic conditions due to the metabolic syndrome, treated type 2 diabetes mellitus, or familial combined hyperlipidemia, the number of small, dense LDL and HDL particles are increased ^{43, 49}. Whether measurement of these changes in particle size is of clinical value is debated.

Several plasma proteins or enzymes, such as hepatic lipase and cholesterol ester transfer protein (CETP) contribute to the lipoprotein particle remodeling processes, and their relative impact depends on the VLDL triglyceride content ^{73, 74}. There has been much interest in the potential impact of variability of LDL size and density ⁷⁵. However, while there is wide agreement that the LDL concentration predicts coronary heart disease, epidemiological studies assessing any independent association between large or small LDL and atherosclerotic CVD have yielded variable results ^{5, 76}. Statins reduce the concentration of all sizes of LDL, and their benefits to reducing cardiovascular disease are universal across population groups that have large or small LDL ^{5, 77}. Further, as for LDL, epidemiological studies have not provided conclusive evidence that measurement of HDL size contributes to risk prediction ⁷⁸.

As pointed out above, the amount of cholesterol carried in triglyceride-rich lipoproteins may significantly contribute to atherogenic risk in some patients, and measurement of non-HDL cholesterol and/or apoB levels can indicate the presence of increased numbers of atherogenic particles, including LDL and triglyceride-rich lipoproteins ⁵. An advantage of non-HDL-cholesterol (total serum cholesterol minus HDL-cholesterol) is that this level reflects the amount of cholesterol in all atherogenic lipoprotein particles, including lipoprotein remnants and lipoprotein(a), [Lp(a)]. Lp(a) contains apoB and has many properties in common with LDL. As recent studies have underscored the importance of Lp(a) as a CVD risk factor, measurement of Lp(a) may inform CVD risk assessment ^{79, 80}. In addition to measurement of LDL and non-HDL cholesterol, the apoB level has been suggested as a useful tool. Not unexpectedly, there is a good correlation between apoB and non-HDL-cholesterol levels, as one apoB molecule is present on the surface of each chylomicron, VLDL, IDL, LDL and Lp(a) particle and resides with the particle during its metabolism. Elevated levels of apoB often occur in FCHL and might assist in differentiating it from more benign familial hypertriglyceridemia. Non-HDL cholesterol can then be

followed as the therapeutic target. Regarding overall measurement of lipoprotein heterogeneity, the Endocrine Society guidelines recommended against a routine measurement of lipoprotein particle heterogeneity in patients with hypertriglyceridemia, but stated that measurement of apoB or Lp(a) levels could be of value.

Management of Hypertriglyceridemia

There is general agreement that lifestyle therapy, including appropriate diet composition, physical activity and a program to achieve weight reduction is the foundation of treatment for mild-to-moderate hypertriglyceridemia. In some cases, such as more severe forms, addition of hypolipidemic drugs may be needed.

Lifestyle therapy

The increase in serum triglycerides with aging is likely driven by changes in lifestyle, such as weight gain, lack of exercise, and a high calorie diet rich in simple carbohydrates and sugar-sweetened beverages. There has been much debate regarding diet approaches in hyperlipidemia. Under weight-stable conditions, the combination of reduced carbohydrate intake and increased fat intake lowers triglyceride levels, with a linear relation between replacement of dietary carbohydrate with fat and a reduction in serum triglycerides⁸¹. There is no clear difference between fatty acid classes with regard to triglyceride-lowering effect. However, dietary saturated fat and trans-fatty acids increase LDL cholesterol levels, while monounsaturated or polyunsaturated fat lower LDL cholesterol levels⁸¹. Notably, the ability of n-3 polyunsaturated fat to uniquely lower serum triglycerides has been used in drug development.

Recently, studies have focused on the type of carbohydrate that may affect serum triglyceride levels, and in particular on the role of fructose³⁷. However, while a reduced intake of sugar-sweetened beverages is recommended as an important part of lowering serum triglycerides, more information is needed to ascertain whether fructose as a component of sugar-sweetened beverages is more detrimental than sucrose or glucose⁸². Following intake of carbohydrate-rich foods, a correlation between an increase in triglyceride levels and the glycemic index, i.e. the rise in blood glucose provided by 50 g of carbohydrate in a specific food compared with either 50 g glucose or white bread, has been observed⁸³.

Diet modification may vary across ethnicity as diet modification had less effect on triglyceride levels in African Americans compared to Caucasians, matched for baseline triglyceride levels⁸⁴. For conditions where triglyceride clearing mechanisms are compromised (triglyceride levels >500 mg/dL) as well as in severe and very severe hypertriglyceridemia (triglyceride levels >1,000 mg/dL), combining reduction of dietary fat and simple carbohydrate intake with drug treatment is recommended to reduce the risk of pancreatitis²².

Exercise

Although benefits may be transient, there is some support for a hypotriglyceridemic effect of exercise. Thus, exercise the day before ingestion of a high-fat meal is associated with a

marked dampening of the postprandial triglyceride increase. Further, a period of 30–60 minutes of intermittent aerobic or mild resistance exercise is reported to be effective in lowering plasma and VLDL triglycerides⁸⁵. However, a recent meta-analysis comparing aerobic exercise programs showed favorable effects only for high-intensity programs with an increase in the HDL cholesterol, while triglyceride reductions appeared less often⁸⁶.

Weight loss

Treatment of excess weight is critical to reduce triglyceride levels. The macronutrient composition of a weight-loss diet is considerably less important for lowering triglycerides than the amount of weight lost. Two recent large-scale clinical trials of 2 years duration did not find differences in effects on triglyceride levels between low-fat, high-carbohydrate diets and low-carbohydrate diets^{87, 88}. Many studies have shown that ongoing counseling by dietitians and behavioral therapists, and support from peers, is important to most people who are successful in losing weight and maintaining weight loss.

Drug therapy

Three drug classes are clinically available for treatment of hypertriglyceridemia, fibrates, niacin and n-3 fatty acids. Each of these classes has limitations. There is inconsistency in the evidence base for cardiovascular risk reduction using fibrates, the use of niacin is associated with significant side effects, and there are limited data on the use of n-3 fatty acids to reduce cardiovascular risk. Considering that elevated triglycerides may be a marker for metabolic disease and/or other lipoprotein abnormalities, it is uncertain whether we should treat moderate hypertriglyceridemia in itself or other lipoprotein abnormalities associated with this degree of hypertriglyceridemia. A reasonable approach may be that if the primary goal is to lower triglyceride levels, fibrates and perhaps n-3 fatty acids are best. On the other hand, if the primary goal is to modify the size and density of LDL and HDL particles, niacin might be best. As statin treatment is becoming common in patients with elevated cholesterol levels, it is likely that in most cases with hypertriglyceridemia, many patients will already be on statins. A hypotriglyceridemic drug might then be added to a statin-based regimen. In view of differences in underlying mechanisms for the three hypotriglyceridemic drug classes described above, there is a considerable potential for use of drug combinations based on complementary mechanisms⁸⁹.

Statins—While HMG-CoA reductase inhibitors, or statins, are potent cholesterol-lowering drugs, their triglyceride-lowering effect is modest, typically about 10–15 %, and dose-dependent. At higher doses (e.g. atorvastatin 80 mg or rosuvastatin 40 mg), plasma triglyceride levels can be lowered by 25–30%. Therefore, statin monotherapy is unlikely to be effective in severe or very severe hypertriglyceridemia. However, statins can be considered to reduce cardiovascular risk in patients with mild-to-moderate hypertriglyceridemia and elevated non-HDL cholesterol. Side effects of statins include muscle symptoms ranging from leg cramps to aching to weakness, present in about 10% of patients, while rhabdomyolysis is rare⁹⁰. Conditions predisposing to severe myopathy include advanced age, renal failure, drug interactions and acute illness.

Fibrates—Fibrates reduce triglyceride levels through several mechanisms, including increased fatty acid oxidation, increased LpL synthesis, and reduced apo C-III expression. The net effect is a decrease in VLDL triglyceride production and an increase in catabolism of triglyceride-rich lipoproteins⁹¹. Fibrates should be considered in patients with moderate and severe hypertriglyceridemia as they generally decrease triglyceride levels by 30–50% and sometimes increase HDL cholesterol⁹². In patients with high triglyceride levels, LDL cholesterol levels may increase during therapy, likely due to an increased conversion of VLDL to LDL particles, while LDL cholesterol levels may decrease in mild hypertriglyceridemia. In patients with triglyceride-induced pancreatitis, treatment of underlying causes and concomitant fibrate therapy to maintain triglyceride levels <2,000 mg/dL is beneficial to prevent recurrent disease. Due to a large excursion of triglyceride levels in the setting of severe and very severe hypertriglyceridemia, a treatment goal of <500–1,000 mg/dL is recommended. Below this level, the main effort should be directed towards prevention of premature atherosclerosis.

Studies to date have not shown a reduction in total mortality in response to fibrate treatment. However, studies have demonstrated that fibrate treatment resulted in a decrease in composite cardiovascular events, including nonfatal coronary events in patients with moderate hypertriglyceridemia. A recent meta-analysis showed a significant benefit of fibrate treatment in subjects with hypertriglyceridemia and low HDL cholesterol^{88, 91, 93}. Therefore, it is reasonable to expect that fibrate treatment of patients with at least moderate hypertriglyceridemia will produce some cardiovascular benefit. However, these studies also indicate a lack of benefit in patients with mild hypertriglyceridemia, i.e. triglycerides <200 mg/dL. Due to a possible increase in the incidence of cholesterol gallstones, fibrates are contraindicated in patients with liver and gall bladder disease. Further, due to their renal excretory pathway, fibrates should be used with great caution in the setting of renal insufficiency. In view of the likely combination therapy of fibrates with a statin, it should be noted that fenofibrate does not interfere with statin metabolism and has a lower risk of causing myopathy. Other potential interactions include warfarin due to effects on protein binding, requiring careful monitoring.

Niacin—Niacin lowers triglyceride levels and increases HDL cholesterol levels. At doses of 500 to 2,000 mg/d, niacin lowers triglycerides by 10–30%, increases HDL cholesterol by 10–40%, and lowers LDL cholesterol by 5–20%. Further, it is one of the few agents to date with a Lp(a)-lowering effect. Although higher doses of immediate-release (crystalline) niacin have been used, the maximum dose of the prescription extended-release formulation is 2,000 mg/day, achieved by a slow dose increase over time. Clinical trials using niacin go back more than 40 years, and administration of niacin, alone or in combination with other lipid medications, have been shown to provide benefits in decreasing cardiovascular event rates and atherosclerosis^{94, 95}. However, two recent placebo-controlled studies have not shown any incremental benefit of adding niacin to statin therapy. Both of these studies included patients with normal triglyceride levels or mild hypertriglyceridemia. Probably most important was that the subjects were taking statins and had low LDL cholesterol levels. In the AIM-HIGH study, mean triglyceride levels at baseline were about 165 mg/dL and in the HPS2-THRIVE study, so far reported as a press release, mean baseline triglycerides

were in the normal range (125 mg/dL) ⁹⁶. The latter study, addressing a combination of statin and extended-release niacin with laropiprant, a prostaglandin receptor blocker included to reduce vasodilatation and cutaneous flushing, was stopped early due to lack of benefit and increased side-effects in the niacin/laropiprant arm. Other approaches to reduce niacin-induced flushing include postprandial intake of niacin or pre-meal administration of uncoated aspirin, e.g. 325 mg. Complications of niacin therapy include hepatotoxicity, impaired glucose tolerance or hyperuricemia requiring laboratory monitoring ⁹⁷. Niacin is contraindicated in patients with active peptic ulcer disease, but can be used safely in patients with glucose intolerance and can be considered in diabetic patients with moderate to good glycemic control.

N-3 Fatty Acids—Many studies have demonstrated a dose-dependent triglyceride-lowering effect of long chain marine omega-3 fatty acids (eicosapentaenoic acid, C20:5n-3; or EPA and docosahexaenoic acid, C22:6n-3; or DHA). However, no studies using high-dose n-3 fatty acids in hypertriglyceridemic patients have demonstrated any beneficial cardiovascular outcomes to date. Omega-3 fatty acids may be considered for treatment of severe and very severe hypertriglyceridemia (>1,000 mg/dL), and to achieve a reduction of hypertriglyceridemia by 20–50%, administration of 3 to 4 g/d of EPA plus DHA is required ⁹⁸. With reductions of triglyceride levels, there can be increased levels of LDL cholesterol due to increased conversion of VLDL to LDL, while HDL cholesterol levels commonly are mildly increased. Omega-3 acid ethyl esters are available by prescription while over-the-counter preparations of omega-3 fatty acids have variable quantities of EPA and DHA ⁹⁹. Side effects of large doses of omega-3 fatty acids include fishy taste and burping.

Summary

Hypertriglyceridemia is common and present in about a third of the population. In recent meta-analyses, triglyceride levels have been associated with cardiovascular events but not with mortality. The majority of hypertriglyceridemic patients have mild or moderate triglyceride levels (<1,000 mg/dL) and treatment should be focused on reduction of cardiovascular risk. Patients with severe or very severe hypertriglyceridemia (>1,000 mg/dL) are at risk for pancreatitis. Cholesterol is a constituent of triglyceride-rich lipoproteins and contributes to overall plasma cholesterol levels. Through the lipolytic cascade, triglyceride-rich lipoproteins are converted to remnant particles with an atherogenic potential. As remnant cholesterol levels are not captured through measurement of LDL cholesterol, non-HDL cholesterol levels as defined by the NCEP-ATP III guidelines should be considered as treatment goal in patients with moderate hypertriglyceridemia. Although results are suggestive of an association between non-fasting triglyceride levels and cardiovascular risk, diagnosis of hypertriglyceridemia is best based on fasting levels until standardized sampling conditions are established. Given the frequent combination of genetic and environmental factors underlying hypertriglyceridemia, patients with hypertriglyceridemia should be evaluated for secondary causes of hyperlipidemia. Subjects with primary hypertriglyceridemia should be evaluated for family history of dyslipidemia and cardiovascular disease. Treatment for hypertriglyceridemia should be initiated as lifestyle therapy, while addition of hypotriglyceridemic drugs may be considered if patients

do not reach treatment goals. In patients with severe or very severe hypertriglyceridemia, a fibrate should be used as a first-line agent, while in patients with moderate hypertriglyceridemia, a statin-based combination therapy is more common.

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Practice points

- Patients with mild-moderate hypertriglyceridemia should be assessed for cardiovascular risk
- The use of fibrates is recommended in patients with severe or very severe hypertriglyceridemia
- Patients with hypertriglyceridemia should be evaluated for secondary causes
- FCHL is differentiated from FHTG by increased apo B levels and presence of small, dense LDL
- With the exception of apoB or Lp(a) levels, there is limited value of measuring lipoprotein subfractions or heterogeneity

Research agenda

- Trials are needed directly comparing the cardiovascular risk associated with fasting vs. non-fasting triglycerides
- The pro-inflammatory action of triglycerides needs to be investigated
- Factors regulating fatty acid oxidation and mitochondrial capacity need to be explored in relation to hypertriglyceridemia
- The importance of ectopic tissue triglyceride accumulation for cardiovascular risk needs to be investigated