RISK ASSESSMENT AND GUIDELINES FOR THE MANAGEMENT OF HIGH TRIGLYCERIDES

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Received 1July, 2015

ABSTRACT

Cardiovascular disease (CVD) remains a major cause of mortality in the Western world. In spite of the reduction of CVD risk by the use of lipid lowering agents per current treatment goals, there remains substantial residual and absolute risk of CVD in high risk populations. Focus on elevated triglyceride (TG) levels deserves renewed attention, particularly as one-third of all adults in the United States suffer from elevated TG and a growing number of people are diagnosed with the metabolic syndrome or type 2 diabetes mellitus (T2DM). The dyslipidemia of metabolic syndrome and T2DM is characterized by raised TG concentrations, low high density lipoprotein (HDL-c) concentrations and marked elevation in triglyceride rich lipoproteins (TRL). This triad is now known as atherogenic dyslipidemia. In addition small dense LDL and small HDL are frequently observed. There has been growing data that points towards an association of fasting and non-fasting triglycerides with CVD. However, the association of TG as an independent risk faster in CVD is confounded by its inverse metabolic relationship with high density lipoprotein (HDL-c) and the heterogeneity of TG lipoproteins. Current guidelines suggest diagnosis of hypertriglyceridemia based on fasting levels where length of fast is recommended to be 9-12 hours. Although non-fasting TG levels may be a better indicator of risk, the lack of standardization of non-fasting TG measurements, lack of specific reference ranges, and the variability of postprandial lipid measurements have hampered their routine clinical use. Current guidelines focus mainly on LDL-c levels; however, lowering TG may provide additional benefit for CVD prevention. Lifestyle changes including dietary changes and exercise play an important role in the treatment of hyperlipidemia. Pharmacological agents used in the treatment of hypertriglyceridemia include niacin, fibrates, fish oil, and statins. Most guidelines recommend treating elevated TG for prevention of pancreatitis. This article will discuss the role of elevated TG in pancreatitis and CVD risk. For complete coverage of this and related topics, please visit www.endotext.org.

INTRODUCTION

Cardiovascular disease (CVD) remains a major cause of mortality in the Western world, especially in individuals with obesity, metabolic syndrome, and type 2 diabetes mellitus (T2DM). With increasing incidence of metabolic syndrome and T2DM worldwide, the global burden of CVD will also increase [1]. In spite of the reduction of CVD risk by 25-35% with the use of lipid

lowering agents, especially statins, there remains substantial residual and absolute risk of CVD in high risk populations such as T2DM [2]. Elevated low-density lipoprotein (LDL-c) is a well-established CVD risk factor and has been the primary target for lipid lowering treatment. However, growing evidence suggests that an elevated triglyceride (TG) level is also an independent risk factor [3, 4] Borderline- high TGs or high TGs defined by National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) as TG concentration (150 – 199 mg/dl) and (200 – 499 mg/dl) respectively are present in 30% of the US adult population [5] and these levels have been associated with increased CVD. The dyslipidemia of metabolic syndrome and T2DM is characterized by raised TG concentrations, low high density lipoprotein (HDL-c) concentrations, and marked elevation in triglyceride rich lipoproteins (TRL). This triad is termed mixed or atherogenic dyslipidemia [6]. In addition small dense LDL and small HDL are frequently observed. Impaired metabolism of TRLs in the postprandial state have been observed in insulin resistant states such as visceral obesity and metabolic syndrome and T2DM and this has been linked to the development of atherosclerosis [7].

Severe hypertriglyceridemia and very severe hyperlipidemia are defined by Endocrine Society Clinical Practice Guideline on Evaluation and Treatment of Hypertriglyceridemia as TG concentration (1000 – 1999 mg/dl) and ($\geq$ 2000 mg/dl) carries an increased risk for pancreatitis [8]. Case series and uncontrolled studies have shown that severely elevated TG levels are associated with chylomicronemia syndrome and an increased risk of pancreatitis. Serum TG levels of 1000 mg/dl and higher have been observed in 12% to 38% of patients with acute pancreatitis [9]. Hence, understanding the role of hypertriglyceridemia in CVD, chylomicronemia syndrome, and the risk of pancreatitis is important.

METABOLISM OF TRIGLYCERIDE RICH LIPOPROTEINS

Metabolism of triglyceride rich lipoproteins

Triglyceride rich lipoproteins (TRL) consist of chylomicrons carrying triglycerides from the diet, VLDLs synthesized in the liver, and their respective remnant particles. After a fatty meal, dietary triglycerides are hydrolyzed in the intestine to free fatty acids and monoglycerides. Fatty acids and monoglycerides are then absorbed by enterocytes and resynthesized to form triglycerides. Triglycerides within the intestinal enterocytes are assembled with apolipoprotein (apo) B-48 into large chylomicrons which are released from the cells into the lymphatic system. They access the plasma via the thoracic duct and are rapidly metabolized by lipoprotein lipase (LPL) to yield chylomicron remnants. These are taken up by remnant receptors and by LDL receptors in the liver. Free fatty acids liberated by the action of LPL are available to adipose tissue for storage and to other tissues (e.g., skeletal muscle, heart) for use as energy substrates. Lipids derived from de novo synthesis, chylomicron remnants, and from lipolysis of adipose tissue are reassembled in the liver as very-low-density lipoprotein (VLDL) particles, which are secreted into the plasma. VLDL particles are metabolized by LPL to yield intermediate density lipoprotein (IDL) particles, which are metabolized by LPL and hepatic lipase to yield low density lipoprotein (LDL) particles. IDL can be taken up by the liver through an apoE-dependent process, and LDL is taken up by the liver through the binding of apoB100 to LDL receptors. Small VLDL particles,

IDL particles, and LDL particles may be taken up by peripheral tissues to deliver nutrients, cholesterol, and fat-soluble vitamins [10, 11].

Hypertriglyceridemia is a normal physiological state that occurs post ingestion of a meal where lipids undergo the above mentioned metabolism. In insulin- resistant states there is an exaggerated lipid response leading to pathological hypertriglyceridemia which is thought to be atherogenic. In insulin-resistant states there is an increase in the production of VLDL by the liver and decreased hepatic uptake of VLDL, IDL and LDL. There is a reduction in LPL activity resulting in high triglyceride concentrations, especially in the postprandial state. The over secretion of VLDL, which competes with chylomicron remnants for clearance through the common pathway, can exacerbate the post prandial response. The large amount of TRLs and their prolonged residence time in the circulation leads to increased exchange of cholesteryl ester for triglycerides between TRL and LDL or HDL particles mediated by cholesteryl ester transfer protein (CETP). This process enriches LDL and HDL with triglyceride, and these particles are subsequently more readily hydrolyzed by hepatic lipase resulting in smaller, denser LDL particles and lower concentrations of HDL [12]. These abnormalities result in a characteristic dyslipidemia in insulin resistant states, which is now recognized to be atherogenic.

In severe or very severe TG levels (> 1000 mg/dl), which occur as a result of defective lipolysis or excessive production of endogenous triglyceride the LPL removal system is saturated. There is decreased degradation of dietary TGs incorporated into chylomicrons and a rapid increase of TG levels post fat-rich meals (simple sugars, fructose, alcohol stimulate hepatic VLDL production enhancing the increase in TG) in susceptible individuals causing pancreatitis. The mechanism by which hypertriglyceridemia causes pancreatitis is not understood, but could include local accumulation of free fatty acids and serum hyperviscosity [8, 13].

HYPERTRIGLYCERIDEMIA AND RISK OF PANCREATITIS AND CHYLOMICRONEMIA SYNDROME

Severe hypertriglyceridemia (> 1000 mg/dl) is a rare laboratory finding and is generally associated with genetic disorders of lipid metabolism or TG levels exacerbated by secondary causes. Chylomicronemia syndrome is defined as presence of chylomicronemia (TG > 1000 mg/dl) along with one or more of the following: eruptive xanthomas, lipemia retinalis, or abdominal findings of pain, acute pancreatitis and/or hepatosplenomegaly [14]. Individuals with severe hypertriglyceridemia may present with these classic findings and pancreatitis or may be asymptomatic. The mechanisms by which hypertriglyceridemia may lead to acute pancreatitis are not known. Possible mechanisms include intra-pancreatic hydrolysis of high triglycerides by pancreatic lipase leading to accumulation of fatty acids in the pancreas which may be toxic and lead to inflammation and ischemia. Another proposed mechanism is increased viscosity by high chylomicron levels leading to ischemia [15]. A study looking at the frequency of signs and symptoms of hypertriglyceridemia including pancreatitis found that the incidence of pancreatitis and eruptive xanthomas was low unless TG levels were significantly elevated, e.g. > 1700 mg/dl (20 mmol/l); patients with extreme hypertriglyceridemia had a combination of primary and secondary factors (T2DM, obesity, alcohol intake, pregnancy) contributing to their high TG

levels [16]. Murphy et al. in their cohort study estimated the risk of pancreatitis with differing degrees of TG elevations and showed that the crude incidence of pancreatitis was 0.91 per 1000 person years (95% CI, 0.76 – 1.09) in individuals with TG levels ≤ 150 mg/dl, 1.24 (95% CI, 1.07 – 1.44) with TG levels 150 – 499 mg/dl and 2.48 (95% CI, 1.79 – 3.42) with TG levels ≥ 500 mg/dl [17]. Increased incidence is seen with increased TG levels. The level of TG at which pancreatitis can be attributed to hypertriglyceridemia is not well defined nor is the level of TG reduction that is associated with reduced risk known. A study by Lindkist et al. [15] looked at the association of moderately elevated serum TG levels and acute pancreatitis. In this study, 33,260 individuals were followed for median 25.7 years where overall incidence of acute pancreatitis in the cohort was 35.5/100,000 person years. There was a statistically significant association between TG levels and risk of pancreatitis with adjusted HR for pancreatitis of 1.21 (95% CI, 1.07 – 1.36) per 1 mmol/l (~88.5 mg/dl) increment in TG and a significant increased risk for acute pancreatitis in individuals with TG levels > 1.64 mmol/l (145 mg/dl). The analysis in this study was restricted to individuals with TG levels < 6 mmol/l (530 mg/dl) producing statistically significant results and showing that TG level much lower than previously believed can be associated with increased risk of acute pancreatitis. Another study evaluated the association between lower follow-up TG levels and the incidence of recurrent clinical events for patients with severe hypertriglyceridemia (>500 mg/dl). This study included 41,210 individuals with < 1% having a history of pancreatitis. Individuals with severe hypertriglyceridemia with follow up TG levels <200 mg/dl experienced a lower rate of recurrent pancreatitis episodes, with an adjusted rate ratio of 0.45 (95% CI, 0.34 – 0.60) compared to those with TG levels ≥ 500 mg/dl[18]. There is an increased risk of pancreatitis with severe hypertriglyceridemia and in individuals with elevated TG levels dietary and in some cases pharmacological intervention is necessary to prevent severe complications such as pancreatitis.

HYPERTRIGLYCERIDEMIA AS A CARDIOVASCULAR RISK FACTOR

Epidemiological data supporting TG as a CVD risk factor

The association of elevated TG values with CVD remains controversial. Establishing TG level as an independent risk factor for CVD is confounded by its inverse metabolic relationship with HDL-c and the heterogeneity of TG risk lipoproteins. In addition, high TG levels are associated with small dense LDL, an atherogenic lipoprotein. Growing evidence suggests that an elevated TG level is an independent risk factor for CVD and represents an important biomarker of CVD risk because of their association with atherogenic remnant particles. A meta-analysis by Hokanson and Austin [4], showed increased plasma TG level is associated with a significant increase in risk of CVD independent of HDL-c level. An overall relative risk (RR) for CVD of 1.32 for men and 1.76 for women per 1 mmol/L (~88.5 mg/dl) increase in TGs was noted. However, this analysis was limited to Caucasian study subjects. A non-overlapping meta-analysis involving data from 26 prospective studies in Asian and Pacific populations reported a RR for CVD of 1.8 (95% CI, 1.49 – 2.19), comparing subjects in the top fifth with the bottom fifth of triglyceride levels [19]. Sawar et al. [20] reported data from two prospective cohort studies: the Reykjavik study and the European Prospective Investigational of Cancer (EPIC) - Norfolk study, which together comprised 44,237 western middle-aged men and women and total of 3582

incident cases of CVD. Comparing individuals with TGs in the top tertile with the bottom tertile, the adjusted odds ratio for CVD was 1.76 (95% CI, 1.39 – 2.21) in the Reykjavik study and 1.57 (95% CI, 1.10 – 2.24) in the EPIC-Norfolk study. However, adjustment for HDL-c substantially attenuated the magnitude of association of TG level with CVD. They also performed an updated meta-analysis of the Western population studies adding information to include a total of >10,000 CVD cases from 29 Western prospective studies involving a total of > 260,000 participants, and report an adjusted odds ratio of 1.72 (95% CI, 1.56 – 1.90) comparing top and the bottom tertiles of TG values [20]. A more recent meta-analysis by Murad, et al. [9], included 35 studies with total of 927,218 subjects who suffered 132,460 deaths and 72,654 cardiac events, myocardial infarctions or pancreatitis; with odds ratio of 1.80 (95% CI, 1.31 – 2.49) for cardiac events, 1.31 (95% CI, 1.15 – 1.49) for myocardial infarctions and 3.96 (95%, CI 1.27 – 12.34) for pancreatitis.

Genetic data linking TG to CVD

Recent human genetic studies show that elevated TGs and TRLs are causal risk factors for CVD. A Mendelian randomization study based on several genetic variants affecting remnant cholesterol and/or HDL showed that a 1 mmol/l (39 mg/dl) increase in non-fasting remnant cholesterol is associated with a 2.8-fold causal risk for ischemic heart disease, independent of reduced HDL cholesterol [21]. A meta-analysis of 46 lipid genome-wide-association studies (GWAS) together comprising >100,000 individuals of European descent identified four novel loci associated with CVD that were related to HDL-c and TG levels suggesting elevated TG metabolism may also be associated with CVD risk [22]. Another large Mendelian randomization study based on a single APOA5 variant (-1131T>C) that regulates TG showed an association with CVD risk. The odds ratio for coronary heart disease was 1·18 (95% CI 1·11–1·26; $p=2{\cdot}6\times10^{-7}$) per C allele, which was concordant with the hazard ratio of 1·10 (95% CI 1·08–1·12) per 16% higher triglyceride concentration recorded in prospective studies [23]. This finding is similar to that seen in the study by Jorgensen et al. [24], where doubling of genetically raised remnant cholesterol and TG levels due to APOA5 genetic variants was associated with an increased risk of myocardial infarctions. In addition, a study using individuals from the Copenhagen City Heart Study with genetic variants in lipoprotein lipase (LPL), tested whether low concentrations of non-fasting triglycerides were associated with reduced all-cause mortality in observational analyses (n = 13,957). The results showed that each genetically-derived 1 mmol/l (~88.5 mg/dl) reduction in TG levels was associated with a halved risk of all-cause mortality [25]. Two large studies examining the relationship between the gene encoding apolipoprotein C3 (APOC3) found that loss of function mutations in APOC3 were associated with low levels of triglycerides and reduced risk of CVD [26, 27]. These studies strongly point to a causal effect of elevated TG and TRLs with CVD.

Clinical trial evidence supporting lowering TG reduces CVD

Results from clinical outcomes trials of fibrate therapy have been variable but primarily indicate a reduction in CV events. Post hoc analysis of several of these trials provides consistent evidence showing a clinical benefit in subgroups with elevated TG levels. A meta-analysis of the effect of TG lowering in 18 trials providing data for 45,058 participants showed that fibrate

therapy produced a 10% RR reduction (95% CI 0-18) for major cardiovascular events (p=0.048) and a 13% RR reduction (95% CI 7-19) for coronary events (p<0.0001) [26]. The Helsinki Heart Study (HHS) , a primary prevention trial showed that in an average follow up of 5 years, there was a 34% (95% CI 8.2-52.6, P =0.02) RR reduction in CVD in those treated with gemfibrozil compared to placebo [27]. In an 18 year follow up of this study, individuals randomized to gemfibrozil had a 24% adjusted RR reduction (p=0.05) in CVD, and individuals with elevated TG and body mass index (BMI) showed significant benefit from treatment with gemfibrozil. Those with TG level in the highest tertiles had a 71% lower RR of CVD mortality (p <0.001) [28]. The Bezafibrate Infarction Prevention (BIP) study assessed the role of fibrates in secondary prevention. The initial reports showed no significant RR reductions in CVD outcomes in bezafibrate treated vs. placebo-treated subjects. However, a post-hoc analysis of individuals with TG $\geq$ 200 mg/dl demonstrated significant RR reduction by 39.5% (p=0.02); there was no significant RR in those with TG values < 200 mg/dl [29, 30]. In a subgroup analysis of patients in the BIP study by Tenebaum at al.[31], patients with CVD, metabolic syndrome and TG > 150 mg/dl experienced significant benefits from the treatment with bezafibrate. Bezafibrate was associated with a reduced risk of any MI and nonfatal MI with HRs of 0.71 (95% CI, 0.54-0.95) and 0.67 (95% CI, 0.49-0.91), respectively. The cardiac mortality risk tended to be lower in patients taking bezafibrate (HR, 0.74; 95% CI, 0.54-1.03). The Veterans Affairs High-Density Lipoprotein Intervention (VA-HIT) involved 2531 males with CVD with low HDL-c and relatively low LDL-c who were treated with gemfibrozil or placebo and monitored for 5.1 years. Gemfibrozil safely reduced the risk of death from CVD or nonfatal myocardial infarction by 22 percent [32]. For every 100 mg/dl increment in baseline TG there was a 14% increase in coronary risk (p=0.045). Further, those with highest tertile of TG values (>180 mg/dl) exhibited a more marked decrease in coronary risk with gemfibrozil compared with those in lower tertiles [33]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid study using statin + fibrate combination therapy, fenofibrate + simvastatin had no effect on the primary outcome vs. simvastatin alone for all patients. However, in the fenofibrate + simvastatin group, there was a 31% reduction in CV risk in the subgroup with baseline TG levels in the upper tertile vs. simvastatin monotherapy [1].

These studies demonstrate that fibrate therapy leading to a reduction in TG levels prevents coronary events. Many of these studies also show improvements in HDL-c levels which may contribute to the improvements in CVD seen; however, recent HDL-c raising studies (using CETP inhibitors) have not found improved cardiovascular benefits suggesting that the decrease in TG levels contributed to the reduction of CVD seen in the fibrate studies.

Post-prandial TG as a CVD risk factor

There is also growing evidence that postprandial hypertriglyceridemia may be a better indicator of the presence or development of CVD than fasting hypertriglyceridemia. In the Women's Health Study, a prospective cohort of 26,330 initially healthy women with over 11 years of follow up, it was observed that higher non-fasting TG levels were strongly associated with an increased risk of future cardiovascular events independent of baseline cardiac risk factors, levels of other lipids, and markers of insulin resistance. The concentrations of lipids and

apolipoproteins differed minimally when measurements were performed on non-fasting compared to fasting blood samples, except for TG, which were higher when non-fasting. There was a > 4 fold increased risk of a cardiovascular event among individuals with postprandial TG concentrations peaking at 2-4 hours following a meal. This study showed that HDL-c, TG, total cholesterol/HDL-c ratio, and apolipoprotein predict CVD when measured in non-fasting samples. By contrast, total cholesterol, LDL, and non-HDL cholesterol, in addition to apolipoprotein B-100 and B-100/A-I ratio, may provide less useful CVD risk information when measured non-fasting [34, 35]. In a Norwegian study which included 42,600 women and 43,641 men ages 20 – 50 years at inclusion, with a mean follow-up of 27 years, non-fasting TG were positively associated with CVD death in both genders, with hazard ratios being higher in women than in men. However, after adjustment for cholesterol, systolic blood pressure and smoking, and in a sub-sample also HDL-c, the associations were distinctly attenuated [36]. In another study, the Copenhagen City Heart Study, a prospective cardiovascular study of the Danish general population initiated in 1976, 7581 women and 6391 men who had lipids measured at baseline in 1976-1978, were followed for up to 31 years without losses to follow-up, and most were not taking lipid-lowering therapy. The study found that the cumulative incidence of myocardial infarction, ischemic heart disease, and death increased with increasing levels of non-fasting TG levels. Non-fasting TG level were a better predictor of coronary heart disease in women whereas non-fasting cholesterol level was a better predictor in men. However, non-fasting cholesterol levels were not found to be associated with total mortality [37, 38]. Data from these studies provide evidence for a link between non-fasting TG and cardiovascular disease and support the concept that non-fasting TG levels may strongly predict the risk of cardiovascular events.

Mechanisms by which TG are a CVD risk factor

The exact mechanism by which TG may promote vascular disease remains to be elucidated. A possible explanation for TG being associated with increased CVD is that elevated levels of postprandial TG may indicate a high content of TRLs derived from chylomicrons and VLDL. Given their relatively small size, these TRLs can enter the arterial wall, and contribute to the formation of foam cells and thus cause atherosclerosis. The remnant particles under normal conditions are rapidly taken up by the liver. However in people with metabolic syndrome or T2DM, hepatic clearance of remnant particles can be delayed and thus there is a predisposition towards increased production of remnant particles and small dense LDL and HDL particles. Thus, increased production along with prolonged exposure of circulating remnant particles enhances the possibility for the particles to be trapped in the arterial wall. Accordingly, remnant lipoproteins have been shown to increase the risk of atherosclerotic heart disease. This suggests a need to direct attention towards diagnosis and treatment of high TG levels in conjunction with treating high cholesterol levels.[39]. These studies also draw importance to further investigate independent association of fasting and non-fasting hypertriglyceridemia in CVD.

PREVELENCE AND ASSESMENT OF HYPERTRIGLYCERIDEMIA

There is high prevalence of hypertriglyceridemia in the US which necessitates periodic assessment of TG levels, especially in individuals with increased risk. A study looking at 5680 subjects, greater than or equal to 20 years of age who participated in the National Health and Nutrition Examination Survey from 2001 and 2006 evaluated the epidemiology of adults with hypertriglyceridemia. This study reports about 67.8% of the study participants had a normal TG level (<150 mg/dl), 14.2% had borderline high TG levels (150 – 200 mg/dl) and 16.3% had high TG levels (200 - 500 mg/dl). The prevalence of severe high TG (500 – 2000 mg/dl) was noted to be 1.7% equating to about 2.4 million Americans. Three participants were noted to have TG levels > 2000 mg/dl. The participants with severe high TG tended to be men (75.3%), non-Hispanic whites (70.1%), and aged 40 to 59 years (58.5%), and more than 14% of those reported having diabetes mellitus, and 31.3% reported having hypertension [40].

Assessment of Hypertriglyceridemia

Plasma lipids and lipoproteins are generally measured in the fasting state and guidelines for therapy for CVD prevention are based on these measurements. The Endocrine Society clinical practice guidelines on evaluation and treatment of hyperlipidemia suggest diagnosis of hypertriglyceridemia based on fasting levels where length of fast is recommended to be 12 hours [8]. In insulin resistant states postprandial TG may be more relevant to CVD risk. To assess postprandial TG there is a need to identify an accurate and standardized methodology to measure postprandial triglycerides and TRLs. Currently, the lack of standardization of non-fasting TG measurements, lack of specific reference ranges, and the variability of postprandial lipid measurements have hampered their routine clinical use [41]. A Fat Tolerance Test (FTT) has been used to assess post prandial lipoproteins. An expert panel suggests that individuals with fasting TG concentrations between 1-2 mmol/l (89-180 mg/dl) would have better risk assessment by being tested with a FTT than with just fasting TG. Individuals with fasting TG concentration of less than 1 mmol/l (88.5 mg/dl) commonly do not have exaggerated and delayed response of TGs to a FTT, whereas individuals with elevated fasting TG values above 2 mmol/l (180 mg/dl) are expected to have an exaggerated and delayed response of TG to a FTT. These two patient populations would not benefit from a FTT for better risk assessment [42].

Given that humans spend most of their awake time in a post prandial state, various factors including fasting concentrations of serum TGs, time of the day when test is undertaken, the fat content and quality of FTT need to be considered. An expert panel statement recommends measuring total TGs to evaluate the post prandial lipemia response 4 hours after a standardized FTT performed after an 8 hour fast. There has been significant variability in the fat- rich meal used for FTT ranging from dairy products, eggs, oils, to liquid formulations. An expert panel suggests a FTT meal consists of 75 g fat including both saturated and unsaturated fatty acids [42]. ApoB-48 is an alternative marker for the assessment of post prandial hypertriglyceridemia as it measures the number of circulating chylomicrons and their remnants after a meal (there is one ApoB-48 per chylomicron particle). The level of ApoB-48 is very low compared to ApoB-100 in the fasting state but it increases after a FTT. However, the lack of internationally recognized standardized assays and reference ranges, limited availability of the ApoB-48 assay, and high costs limit the utilization of ApoB-48 in clinical settings [41, 43].

Individuals found to have any elevation of fasting TG should be evaluated for secondary causes including endocrine conditions and medications (Table 1). Patients with untreated diabetes, obesity and insulin resistant states commonly have elevated TG levels. Other endocrine disorders such as hypothyroidism, Cushing's disease and growth hormone deficiency can also be associated with elevated TG levels [8]. TG levels can also significantly increase during pregnancy owing to estrogen-induced stimulation of the secretion of hepatic TRLs. In women with underlying disorders of TG metabolism, this increase in TG levels during pregnancy can be associated with pancreatitis and fetal loss. Alcohol intake increases hepatic fatty acid synthesis and decreases breakdown resulting in hepatic VLDL secretion and hypertriglyceridemia. Lipodystrophies, either primary or as seen in HIV treated patients as well associated with other diseases is also associated with hypertriglyceridemia [8]. There are several genetic disorders that lead to hypertriglyceridemia (table 1). LPL deficiency, apo CII deficiency and GPIHBP1 loss of mutations are associated with impaired LPL activity and present in young patients with increased risk of chylomicronemia and pancreatitis. Additional genetic syndromes in the differential diagnosis of hypertriglyceridemia include mixed or familial combined hyperlipidemia (FCHL), type III dysbetalipoproteinemia, and familial hypertriglyceridemia (FHTG) [44]. Many drugs also raise triglyceride levels (table 1). Oral estrogens increase the hepatic secretion of VLDL causing an increase in serum TG levels [45]. Other medications include Tamoxifen/Raloxifene, retinoids, beta blockers, thiazide inhibitors, corticosteroids, immunosuppressants, antipsychotics, and antiretroviral protease inhibitors [8]. If possible, individuals with secondary hypertriglyceridemia should have the secondary cause addressed, and such individuals may then not need primary, TG-lowering therapy. However, secondary causes of hypertriglyceridemia cannot always be addressed, in which case providers should consider TG-lowering therapy.

Table 1: Secondary Causes of Hypertriglyceridemia

Conditions
Hypothyroidism
Uncontrolled Diabetes
Obesity
Chronic renal failure
Nephrotic syndrome
Pregnancy
HIV
Cushing's syndrome
Lipodystrophy
Inflammatory disease – rheumatoid arthritis, lupus, psoriasis, etc
Drugs
Alcohol
Estrogens

Beta blockers
Tamoxifen/Raloxifene
Glucocorticoids
Atypical anti-psychotics
Cyclosporine
Protease inhibitors

Genetic conditions
Lipoprotein lipase deficiency
Apolipoprotein CII deficiency
Apolipoprotein AV deficiency
GPIHBP1 deficiency

GUIDELINES FOR TRIGLYCERIDE EVALUTION AND MANAGEMENT

The Endocrine Society Clinical Guidelines

The Endocrine Society Guidelines recommends that the diagnosis of hypertriglyceridemia be based on fasting serum triglyceride levels and defines TG levels of 150 to 199 mg per dL as mild hypertriglyceridemia; 200 to 999 mg per dL as moderate; 1,000 to 1,999 mg per dL as severe; and 2,000 mg per dL or greater as very severe hypertriglyceridemia. The screening for elevated triglyceride levels for all adults is recommended as part of a lipid panel at least every five years. These guidelines recommend against the routine measurement of lipoprotein particle heterogeneity. The guidelines also recommend screening patients with hypertriglyceridemia for secondary causes (medications, alcohol use, endocrine diseases, renal disease, liver disease) and that patients with primary hyperlipidemia be evaluated for family history of dyslipidemia and CVD. The guidelines recommend the use of non-HDL-c (goal 30 mg/dl higher than the LDL-c goal) for both risk stratification and as a target for therapy in patients with moderate hypertriglyceridemia. Initial treatment of patients with mild to moderate hypertriglyceridemia should include lifestyle therapy. For patients with severe to very severe hypertriglyceridemia, dietary modifications in combination with drug treatment should be considered. A fibrate is recommended as a first-line agent in patients with severe or very severe hyperlipidemia [8].

American Association of Clinical Endocrinologists (AACE) Guidelines

Similar to other guidelines, the AACE clinical practice guidelines recommend evaluating all adults >20 years of age for dyslipidemia every 5 years for risk assessment with a fasting (9 to 12 hour fast) lipid profile. In addition, it recommends more frequent assessments for patients with a family history of premature CVD. However, unlike other guidelines, AACE also recommends Apo B measurements to assess for residual risk in patients with increased TG levels (>150 mg/dl) or low HDL-c levels (< 40 mg/dl). TG levels less than 150 mg/dl are defined

as normal, 150 – 199 mg/dl as borderline high, 200 – 499 mg/dl as high, and levels >500 mg/dl or greater as very high, and AACE recommends maintaining TG levels less than 150 mg/dl. Fibrates are recommended for the treatment of severe hypertriglyceridemia (>500 mg/dl) and lifestyle changes including physical activity, weight loss, and smoking cessation are recommended as first line therapy in moderate hypertriglyceridemia [46].

American Heart Association (AHA) Statement on Triglycerides and Cardiovascular Disease

In 2011, AHA published a scientific statement addressing TG and CVD; however this statement is not intended to serve as a specific guideline. In this statement optimal fasting TG level is defined as < 100 mg/dl as a parameter of metabolic health and they suggest screening for non-fasting TG for those with high fasting TG levels. A non-fasting level of <200 mg/dl corresponds with a normal (<150 mg/dl) or optimal (<100 mg/dl) fasting TG level and requires no further testing. The AHA statement uses fasting TG levels to define levels between 150 – 199 mg/dl as borderline high, 200 – 499 mg/dl as high and levels $\geq$ 500 mg/dl as very high. Intensive lifestyle changes are recommended to be most crucial in the management of hypertriglyceridemia and reductions of 50% or more in TG levels may be attained through intensive therapeutic lifestyle change [44].

National Lipid Association (NLA)

The National Lipid Association guidelines recommend obtaining a fasting or a non-fasting lipoprotein profile in all adults ($\geq$ 20 years) every 5 years. It defines TG level of <150 mg/dl as normal, 150 – 199 mg/dl borderline high, 200 – 499 mg/dl as high and levels of $\geq$ 500 mg/dl as very high. The NLA Expert Panel views non-HDL-c as a better primary target for medication than LDL-c and recommends levels of non-HDL-c < 130 mg/dl as the desirable level of atherogenic cholesterol for primary prevention of CVD. An elevated TG level is not a target of therapy, except when very high ($\geq$500 mg/dl). NLA recommends that when TG levels are between 200 – 499 mg/dl, the targets of therapy are non-HDL-c and LDL-c to reduce risk of CVD events and when TG levels are very high ($\geq$ 500 mg/dl, and especially if $\geq$1000 mg/dl), reducing the concentration to <500 mg/dl to prevent pancreatitis becomes the primary goal. The NLA recommends lifestyle interventions as first step in efforts to reduce triglycerides. If drug therapy is indicated NLA guidelines recommend using fibric acids, omega-3 fatty acids, or nicotinic acid as first line agents if fasting TG level is $\geq$ 1000 mg/dl. For patients with TG levels of 500 – 999 mg/dl a triglyceride-lowering agent or a statin is considered reasonable and for TG level between 200 – 499 mg/dl a statin generally is considered fist-line drug therapy with addition of a triglyceride-lowering agent if non-HDL-c is not at goal post initiation of statin [47].

European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines

Similar to the above mentioned guidelines, ESC/EAS guidelines also recommend checking lipid levels in fasting state. The specific target for non-HDL-c is recommended to be 0.8 mmol/L (~30

mg/dl) higher than the corresponding LDL-c target and TG level < 1.7 mmol/L (~ 150 mg/dl). TG levels above 10 mmol/L (~ 880 mg/dl) are considered to be clinically significant for the risk of pancreatitis and treatment is recommended. In patients with hypertriglyceridemia the ESC/EAS guidelines recommend that the first step is to consider possible causes of hypertriglyceridemia and to evaluate for total CVD risk; the primary goal is to achieve LDL-c target based on the total CVD risk. The use of pharmacologic agents is recommended in patients with TG levels > 2.3 mmol/L (~ 200 mg/dl) who cannot lower them by lifestyle changes and/or if the subject is at high risk of CVD. Statins are recommended as the first choice to reduce both total CVD risk and moderately elevated TG levels [48].

TG assessment strategies

The different guidelines in general recommend screening for lipids using a fasting lipid profile, screening for secondary causes of dyslipidemia, and focusing on lifestyle interventions as the first approach to lower elevated TG. A practical approach is to request fasting lipid panels on patients, but to obtain non-fasting (random) panels if fasting samples are not provided. For any patient with a TG level that is elevated (for example, > 200 mg/dl), screen for secondary causes and address these if possible. For significantly elevated TG (eg > 500 mg/dl) consider the addition of TG-lowering therapy, with the goal of preventing any further elevations increasing risk for pancreatitis. For individuals with moderately elevated TG (eg 150-500mg/dl) then we recommend consideration of TG-lowering therapy on an individual basis. For example, individuals with existing CVD or at high CVD risk, or those with very low HDL levels might be candidates for therapy; whereas in those with low CVD risk, or desirable HDL levels, additional focus on lifestyle interventions to lower TG may be the appropriate first line of therapy.

MANANGEMENT OF HYPERTRIGLYCERIDEMIA

Lifestyle Intervention

Studies have shown that the consumption of a Western diet which includes highly processed, calorie-dense and nutrient poor foods leads to an exaggerated lipemia. In addition factors such as physical inactivity, cigarette smoking, excessive alcohol intake, and obesity worsen lipemia [42]. Hence, the control of secondary factors and lifestyle changes are considered to be the first line approach of the clinical management of both fasting hypertriglyceridemia and postprandial hyperlipidemia. Appropriate dietary changes include limiting fat content, caloric restriction resulting in weight loss, restriction of alcohol intake and increased exercise are fundamental for management of hypertriglyceridemia [41, 42]. The type of carbohydrate consumed may affect serum triglycerides and a diet rich in simple carbohydrates and sugar-sweetened beverages is associated with hypertriglyceridemia. As compared with starches, sugars, particularly sucrose and fructose, tend to increase serum triacylglycerol concentrations by about 60%. Because fructose bypasses a major rate-determining step in glycolysis, a high influx of fructose to the liver promotes triacylglycerol synthesis and VLDL production [49]. The effects of sucrose or fructose on fasting TG may be more pronounced in men, sedentary overweight individuals, or those with the metabolic syndrome. Sucrose and fructose also increase postprandial TG levels

and may augment the lipemia associated with fat-containing meals [50]. There is mounting evidence that physical activity lowers risk for CVD [51]. Mestek et al. [52] reported that aerobic exercise lowered the postprandial triglyceride response to a high fat meal in subjects with metabolic syndrome. The effects of exercise in reducing postprandial lipemia are seen both in an acute setting right after exercise as well as delayed effects through the next day. Additionally, exercise does not need to be a single continuous bout but instead could be spread out throughout the day. Accumulated physical activity appears to be as effective in lowering postprandial TGs concentrations [53] as a single bout. The mechanisms leading to decreased triglyceride levels post meals are not completely understood and need further investigation.

Statins

Statins are the most widely used lipid lowering agents and have beneficial effects on cardiovascular morbidity and mortality. Statins are effective in lowering non HDL-c, mainly because of their LDL lowering action and to a certain extent lowering TG levels. The higher the baseline TG levels, the greater the TG lowering effect. Available data also indicate that statins can reduce postprandial TG values [42]. Statins inhibit HMG-CoA reductase, hence up-regulate the LDL receptor due to the intracellular depletion of cholesterol. Increased numbers of LDL receptors may improve removal of TRL remnants in postprandial state. It is also postulated that statins inhibit VLDL synthesis [54]. Parhofer et al [55] showed that 10 mg of atorvastatin per day for 4 weeks improves, but does not normalize, postprandial lipoprotein metabolism in hypertriglyceridemic patients. Other studies have also shown that atorvastatin improved fasting as well as postprandial lipemia [56, 57].

Fibrates

Fibrates have the most pronounced effect on lowering plasma TG levels of currently available lipid lowering therapies. Through activation of peroxisomal proliferator activated receptor (PPAR) alpha, fibrates decrease triglycerides by increasing LPL activity and decreasing apolipoprotein CIII production, an inhibitor of LPL, leading to increased catabolism of TG rich lipoproteins. Fibrates also increase fatty acid oxidation in the liver leading to a decrease in VLDL secretion [42]. The Endocrine Society Clinical Practice Guidelines on Evaluation and Treatment of Hypertriglyceridemia recommend that a fibrate be used as a first line agent for reduction of TGs in patients at risk for triglyceride- induced pancreatitis [45]. The ACCORD trial evaluated the benefit of adding fenofibrate to simvastatin therapy concluded that the addition of fenofibrate in patients with diabetes did not reduce the rate of CVD events. However, in the fenofibrate + simvastatin group there was a significant reduction in cardiovascular risk in the subgroup with clinically significant dyslipidemia marked by elevated TG levels and low HDL levels [58]. Rosenson et al. reported that fenofibrate treatment for 6 weeks significantly decreased both postprandial hypertriglyceridemia and the inflammatory response after the ingestion of a test meal consisting of a milkshake including standardized fat content (68% of energy) that was adjusted to body surface area (50 g/m^2) in patients with hypertriglyceridemia and the metabolic syndrome [59]. In a small study (n = 10), bezafibrate was shown to significantly decrease postprandial endothelial dysfunction and elevations of both exogenous and endogenous

triglycerides in patients with metabolic syndrome [60]. The effects of fibrates in decreasing postprandial TRLs may play a role in their vascular protective effects.

Niacin

Niacin decreases TG levels and has pronounced effects on increasing HDL concentration. The mechanism of action of niacin remains unclear, but it is proposed that niacin decreases triglyceride synthesis and hepatic secretion of VLDL. The Coronary Drug Project was a randomized controlled trial that looked at the role of immediate-release niacin as a solo agent for coronary prevention. The Coronary Drug Project showed that niacin was associated with a significant reduction in cardiovascular events [61, 62]. Studies have shown that both immediate-release and extended-release niacin suppress postprandial hypertriglyceridemia [63, 64]. The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial showed that the addition of niacin to statin therapy in patients with CVD and LDL cholesterol levels of less than 70 mg per deciliter had no incremental clinical benefit during a 36-month follow-up period, despite significant improvements in HDL cholesterol and triglyceride levels [2]. However a trend towards benefit (hazard ratio 0.74; p=0.073) was found for the subset of patients with both the highest TG levels and lowest HDL levels (>198 and <33mg/dl respectively) [67]. Lipids in this study were measured in fasting state. Similarly the Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2 –THRIVE) study , which compared niacin + laropiprant (a prostaglandin D2 receptor antagonist used as an anti-flushing agent) + statin vs statin alone did not find added benefit of niacin. However, this lack of additional benefit may be related to the patient population studied which did not have elevated TG levels [65] and a possible benefit may be seen for subjects with both elevated TG and low HDL. Further studies are needed to access the effects of niacin on hypertriglyceridemia in metabolic syndrome and patients with T2DM.

Ezetimibe

Ezetimibe is a cholesterol lowering agent that inhibits the intestinal absorption of cholesterol [66]. Recent studies show that ezetimibe alone or in conjunction with statins also reduces postprandial hypertriglyceridemia. Masuda, et al. showed that ezetimibe significantly decreased triglycerides in the fasting state along with a decrease in postprandial elevations of cholesterol and TG levels in the chylomicrons (CM) size range, suggesting that the postprandial production of CM particles was suppressed by ezetimibe [67]. In a study by Olijhoek at al, combination therapy with low dose simvastatin and ezetimibe was shown to preserve post-fat load endothelial function when compared to treatment with high-dose simvastatin monotherapy in male metabolic syndrome patients [68]. Most recently the Improved Reduction of Outcomes: Vytorin Efficacy International trial (IMPROVE-IT), a multicenter, randomized, double blind trial of 18,144 moderate-high risk patients stabilized following ACS, was conducted to investigate if the addition of ezetimibe to a statin improves cardiovascular outcomes relative to statin monotherapy in these patients. The results from this study suggest that the addition of ezetimibe to statin therapy improves cardiovascular outcomes, but likely via further LDL-c lowering [69].

Fish Oil

Omega 3 polyunsaturated fatty acids (PUFAs) have dose dependent TG lowering effects resulting from variety of mechanisms including decreased VLDL secretion and improved VLDL TG clearance [70]. In the Japan EPA Lipid Intervention Study (JELIS) trial, 18,645 patients in Japan were recruited between 1996 and 1999 and assigned to receive either 1800 mg of eicosapentaenoic acid (EPA) daily with statin or statin only. A 19% relative reduction in major coronary events ($p = 0.011$) was seen in patients in the EPA group. Unstable angina and non-fatal coronary events were significantly reduced; however, sudden cardiac death and coronary death did not differ between the groups [71]. A few studies have examined the effects of fish oil supplementation on postprandial lipemia and found that fish oil use decreases fasting and postprandial triglyceride levels [72, 73]. A study looking at the effect of fish oil, exercise and the combined treatments on fasting and postprandial chylomicron metabolism showed that combining fish oil with chronic exercise reduced the plasma concentration of pro-atherogenic chylomicron remnants; in addition it reduced the fasting and postprandial TG response in viscerally obese insulin resistant subjects [74].

Other Treatments

Emerging evidence suggests that incretin-based therapies not only improve postprandial glucose levels in diabetic patients, but may also pay a role in postprandial lipid metabolism [75]. Further studies will help clarify whether incretin-based therapies are vasculoprotective agents. Improved understanding of the physiology and mechanism thorough which postprandial hypertriglyceridemia leads to increased cardiovascular events will help identify new targets in future.

CONCLUSION

Recent data strongly indicate that fasting as well as non-fasting hypertriglyceridemia is a risk factor for atherosclerosis and CVD. Current treatment goals aimed at lowering LDL-c still do not eliminate residual risk of CVD. Current guidelines focus mainly on LDL-c levels and correction of hypertriglyceridemia is not the aim of current treatment. However, focus on elevated hypertriglyceridemia deserves renewed attention, particularly as one-third of all adults in the United States suffer from elevated TG and growing number of people are diagnosed with metabolic syndrome or T2DM. There is need for more studies specifically testing the benefits of lowering hypertriglyceridemia. Additionally, the usefulness of “fat tolerance test” using a standardized meal, analogous to a glucose tolerance test, warrants further evaluation as potential indicator of a metabolic state identifying individuals at higher risk for cardiovascular events. Given the association with CVD, elevated postprandial TGs levels may represent a particularly attractive therapeutic target and further studies particularly looking at effect of various lipid lowering agents on postprandial along with fasting TGs are necessary.

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