Review Article

Hypertriglyceridemia: A Practical Review Artical for Assessment and Treatment

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Abstract

The incidence of hypertriglyceridemia is increasing worldwide. Although low-density lipoprotein (LDL) is the first treatment target for lipid lowering therapy, some patients still have increased risk of cardiovascular disease (CVD) events, even after lowering LDL. Moreover, recent studies showed an association between triglyceride (TG) and residual cardiovascular risk especially due to remnant cholesterol in triglyceride-rich lipoproteins (TGRL). The current review aimed to summarize the classification and measurement of TG, the role of TG in the pathogenesis of CVD, the association between TG and CV events, and management of hypertriglyceridemia in clinical practice.

INTRODUCTION

Cardiovascular disease (CVD) is an important cause of mortality and morbidity worldwide. Dyslipidemia is one of the major risk factor for CVD. Current guidelines focus on reducing low-density lipoprotein cholesterol (LDL), and statins have become the drug of choice to reduce the LDL as well as CV risk. The role of triglyceride (TG) as a CVD risk factor remains uncertain partially because the association between TG levels and adverse outcomes becomes nonsignificant after multivariate adjustment particulary the level of high-density lipoprotein cholesterol (HDL) [1]. Moreover, there is a strong association between TG and other known metabolic risk factors, such as hypertension, smoking, type 2 diabetes mellitus, and obesity [2]. However, even after lowering LDL, there is still increased risk for CVD which can be explained by elevated remnant cholesterol levels [3-5]. Remnant cholesterol can be defined as the cholesterol content of triglyceride-rich liporoteins (TGRL) such as chylomicron remnants in the non-fasting state, very-low density lipoproteins (VLDL), and intermediate-density lipoproteins (IDL) in the fasting state [4,5].

The current review summaries the classification and measurement of TG, the role of TG in the pathogenesis of CVD, the association between TG and CV events, and management of hypertriglyceridemia.

CLASSIFICATION AND MEASUREMENT OF TRIGLYCERIDES

Classification of hypertriglyceridemia is a matter of debate as there are numerous primary (genetic disorders) and secondary causes of hypertriglyceridemia such as lifestyle and diet, alcohol consumption, metabolic disorders such as renal disease, non-alcholic fatty liver disease, endocrine disorders, autoimmune disorders, pregnancy, and certain medications (Table 1) [6]. This results two different phenotypes of hypertriglyceridemia: chylomicronemia in patients with genetic conditions and atherogenic dyslipidemia. Moreover, TG levels can be effected from the measurement conditions. TG levels are increased up to 10-15% by longer venous occlusion times, reduced by 10% after movement from standing to sitting position. Therefore, it is recommended to measure TG levels within one minute of venous occlusion, and to standardize the blood sampling conditions to minimize variability in TG measurements [6]. Daily, annual, and seasonal changes can also cause 24-36% changes in TG levels and TG levels vary more on daily basis than other lipoprotein fractions [7,8]. In addition, there has been debate about the measurement state of TG levels [8]. TG levels remain elevated up to six hours after a high-fat meal, but only increase clinically unimportant by 0.2-0.4 mmol/L 2-6 hours after eating normal meals. Traditionally, fasting for nine to twelve hours is recommended to measure TG levels [6,9]. However, individuals generally stay in non-fasting state during their daily-life which indicates TG levels rise progressively over the day due to repeated consumption of fat-containing meals. Moreover, there is no evidence that shows fasting concentrations are better predictor of CV events than non-fasting concentrations and recent studies showed that non-fasting TG levels may be a better predictor of CV events [2]. In Women's Health Study, the authors found that in contrast to fasting TG levels, non-fasting TG levels were independently associated with an increased risk of CV events [10]. Moreover, in Copenhagen City Heart Study non-fasting TG levels were associated with MI and ischemic heart disease (IHD) after adjustment for other CV risk

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Table 1: Possible causes of hypertriglyceridemia.

Drugs	Lifestyle	Metabolic Disorders	Genetics loss of function
Beta blockers Thiazide diüretics Oral estrogens Glucocorticoids Retinoic acid Cyclophosphamide Tamoxifen Rosiglitazone Interferon L-Asparginase Protease inhibitors	High calorie intake High glycemic load Alcohol concumption Reducel physical activity Weight gain	Diabetes Mellitus Chronic kidney disease Nephrotic syndrome Hypothyroidism Metabolic syndrome Autoimmune disorders Polycystic ovary sysndrome HIV infection	LPL APOA5 APOC2 GPD1 CIHBP1 LMF1

factors [11]. The current discussion rises from the knowledge of more stable TG levels in fasting state than non-fasting state, and usage of Friedewald equation to calculate LDL levels was developed with fasting individuals, and non-fasting state may affect the measurement of HDL and the calculation of non-HDL.

Current guidelines classify TG levels differently (Table 2). However, the common point is a level of fasting TG level should be below <150 mg/dL [12-14]. ACC/AHA 2013 guideline on the treatment for blood cholesterol recommends measuring non-fasting TG levels, and recheck levels if they exceed ≥ 200 mg/dL, whereas EAS-EFLM consensus paper recommends assessing lipid profile routinely in non-fasting state, and consider fasting sampling when non-fasting TG levels >440 mg/dL [13,15]. EAS-EFLM consensus paper also defines high TG levels in a patients with a TG level of >175 mg/dL in non-fasting state [15].

METABOLISM AND THE ROLE OF TRIGLYSERIDES IN THE PATHOGENESIS OF CVD

In 1979, Zilversmit defined the raised concentrations of TG and remnant cholesterol are the main cause of atherosclerosis [16]. However, the independent relationship between TG and the risk of future CVD has long been controversial. Whether TG causes CVD is a matter of debate two hypothesis are in concern: remnant hypotesis and lipolytic toxin hypothesis [17].

Intestines and liver are the primary sources of plasma TG. Lipoprotein lipase (LpL) is the main enzyme in the TG metabolism which is found primarily on the luminal surface of endothelium within muscles (cardiac and skeletal) and adipose tissue. TG both in chylomicrons and VLDL are hydrolyzed by LpL, and the lypolytic products free fatty acids (FFAs) and monoacylglycerol occur. LpL also facilitates cholesterol transfer from these lipoproteins to HDL. Insulin and heparin increases the activity of LpL. FFAs can be taken up by fat cells and reincorped into TG or into muscle cells, where they can be used for energy [1,17,18].

Dietary TG enter the circulation through the thoracic duct within chylomicrons. Chylomicrons lose TG after lipolysis by LpL and cholesterol-enriched chylomicron remnants occurs. Chylomicron remnants are removed by the liver by binding to the LDL receptor, the LDL receptor-related protein, hepatic TG lipase, and cell-surface proteoglycans. VLDL is the main endogenous TG carrier lipoprotein and produced by liver. VLDL TG derives from the combination of glycerol with fatty acids that have been taken up from plasma or newly synthesized in the liver. In the plasma, LpL mediated VLDL lypolysis leads the production of smaller and denser VLDL and subsequently IDL called as VLDL remnants. IDL particles can undergo futher cathabolism to become LDL. Remnant cholesterol is the cholesterol content of triglyseride-rich lipoproteins (TGRL) (chylomicron remnants, VLDL, and IDL) [1,17,18]. Although chylomicrons and VLDL are too large to enter into the arterial intima, remnants are small enough to enter the arterial wall, which would lead the accumulation of intimal cholesterol and atherosclerosis [18,19]. Remnants have been identified within human atherosclerosis plaques [20]. Moreover, TGRL may not need to be oxidized to be taken up by macrophages to cause foam cell formation and atherosclerosis [21].

During lipolysis of TGRL, production of FFAs and lysolecithin triggers endothelial dysfunction, and coagulation due to increased inflammatory response and secretion of tissue factor, fibrinogen, coagulation factors VII, XII, and plasminogen activator inhibitor–1 secretion [17,18]. Moreover, accumulation of FFAs in non-adipose tissues such as in liver, muscle and pancreas influence both insulin action and secretion leading insulin resistance and diabetes, a state that may be named as ''Diabetes Lipidus'' [1]. In addition, elevated levels of remnant cholesterol were causally

Table 2: Classification of Triglyceride Levels according to the guidelines.

2011 ESC/EAS		2013 ACC/AHA		2012 Endocrine Society	
Triglyceride level	Classification mg/dL	Triglyceride level	Classification mg/dL	Triglyceride level	Classification mg/dL
Normal	<150	Normal	<150	Normal	<150
High	150-884	Borderline high	150-199	Mild	150-199
Very High	>885	High	200-499	Moderate	200-999
		Very high	≥500	Severe	1000-1999
				Very severe	>2000

associated with low grade inflammation whereas elevated levels of LDL were not causally associated with low-grade inflamation [22]. Moreover, lipolysis causes increased permeability of blood vessels leading greater infiltration of LDL [23].

Based on the data from Copenhagen General population study, low HDL levels were highly correlated with remnant cholesterol [3]. Hypertriglyceridemia stimulates the enzymatic activity of cholesteryl ester transfer protein (CEPT). CEPT facilitates the transfer of TG from TGRL to HDL. TG-enriched HDL have short plasma life-time as they are propone to increased catabolism [1]. Moreover, elevated TG levels is associated with small dense LDL (sdLDL) which are also considered very atherogenic as CEPT also mediates exchange of LDL cholesteryl esters for TG [1,17,24]. TG-enriched LDL undergoes hydrolysis via LpL or hepatic lipase, thereby reducing LDL particle size.

Taken together, elevated TG represents the level of TGRL and remnant cholesterol and TGRL can cause plaque formation and progression. Moreover, hypertriglyceridemia is associated with low HDL, and is a predictor of increased sdLDL. Since there is no direct measurement assay for remnant cholesterol, it can simply be calculated from a non-fasting lipid profile as total cholesterol minus HDL minus LDL.

TRIGLYCERIDES, TRIGLYSERIDE-RICH LIPOPRO-TEINS AND CARDIOVASCULAR EVENTS

Recent evidence from epidemiologic, observational and genetic studies indicates that elevated levels of TG and TGRL are independently associated with CV events. Prospective Cardiovascular Münster Study (PROCAM) has demonstared that elevated levels of TG are an indicator of increased risk of major coronary events in middle-aged men, regardless of their HDL, LDL, and glucose levels [25]. Meta-analysis of data from population-based prospective studies has demonstared that elevated TG level is associated with a 14 % increase in risk of CVD in men, and 37% increase in risk of CVD in women after adjustment for HDL [26]. Recently, the meta-analysis of 26 prospective studies in Asian, and Pasific populations showed that TG is independent determinant of CVD [27]. Moreover, meta-analysis of 29 Western prospective studies including Reykjavik and the European Prospective Investigation of Cancer (EPIC)-Norfolk studies with a total of 262525 participants and 10158 cardiovascular disease cases, showed that moderated but significant association between TG and coronary heart disase risk which was attenuated after adjustment for HDL [28].

Emerging Risk Factors Collaboration study showed that elevated fasting and non-fasting TG levels were associated with an increased risk of CHD, however this association was attenuated after adjustment for HDL and non-HDL raising the question that remnant cholesterol in TGRL is causative for CVD rather than raised TG itself [29]. Population based studies suggest that increased non-fasting TG and TGRL are associated with increased risk of CVD even after adjusting for non-HDL in general population [10,11]. Nordestgaard et al demonstrated that risk of myocardial infarction (MI), ischemic heart disease, and death is increased with 88.41 mg/dL increase in non-fasting TG [11]. Women's Health Study showed that non-fasting TG levels were independently associated with an increased risk of CV events [10].

Mendelian randomization studies have provided further evidence linking TGRL and CVD. Data from Copenhagen including Copenhagen General population Study, Copenhagen City Heart Study, and the CIHDS study with 73513 subjects of whom 11984 had ischemic heart disease showed that a 39 mg/dL increase in non-fasting remnant cholesterol was associated with a 2.8 fold causal risk for ischemic heart disease independent of HDL levels. In other words, incidence of CVD is increased with a 88.41 mg/dL increase in non-fasting remnant cholesterol [4]. Additionally, in patients with APOA5 genetic variant remnant cholesterol doubling in concentration was associated with 2.2 times increased risk of MI, and TG doubling in concentration was associated with 1.9 times increased risk of myocardial infarction [30]. Furthermore, every 1 mmol/L TG level increase due to LpL genetic variant was associated with 2.0 times increased risk of all-cause mortality [31].

Elevated levels of TG are associated with low HDL levels as discussed above. HDL serves as an antiatherogenic lipoprotein with its reverse cholesterol transport, anti-oxidative, anti-inflammatory and endothelium-dependent vasodilatation properties [1,32]. However, 2 major HLD-raising studies failed to show that HDL raising drugs did not improve CV events despite increasing HDL levels [33,34]. Moreover, mendelian randomization studies showed that genetically low HDL was not associated with CVD risk [35,36]. These results demonstrated that a low HDL level is not causally associated with CVD and it may be the HDL function not HDL level that has a causal relation for atheroprotection. Moreover, remnant cholesterol may be a more likely causal factor for CVD than reduced HDL. Therefore, low HDL may be an innocent bystander that shows a long-term marker of raised TG and remnant cholesterol [1].

TREATMENT

The 2016 ESC/EAS guideline recommends drug treatment for hypertriglyceridemia in high-risk patients with TG >200 mg/dL with class IIa endication and a level evidence of B [37]. For the past few decades, the primary target of lipid lowering therapy has been LDL and statins have become the established drug of choice to lower LDL and CVD risk. However, terauputic targeting of elevated TRLP may offer the possibility of incremental reduction in CV risk in high-risk populations. Recently, guidelines recommends non-HDL as a secondary treatment target which is a measure of all atherogenic lipoproteins [13,37].

Hypertriglyceridemia is the most complex lipid disorder to treat as it is associated with numerous conditions, methabolic disorders and medications. The therapeutic strategy for hypertriglyceridemia can be summarized as lifestyle modifications and drug therapy. However, secondary causes of hypertriglyceridemia and medications that have potential to cause hypertriglyceridemia should be diagnosed, treated or ruled out.

Lifestyle management

Lifestyle management including weight loss, diet modification, reducing alcohol consumption, and increasing physical activity is the cornerstone of hypertriglyceridemia treatment. Reducing calories from carbohydrates by 45-60% of total calorie intake can help to lower TG [6]. Patients should be advised to reduce

consumption of carbohyrates especially those with a high glycemic index, avoid to refined sugar (including fruit juice) and fructose (causes higher TG levels than sucrose or glucose). Intake of dietary fiber to more than 30 g/day is also recommended. Saturated fatty acid consumption should be restricted to <7% if TG level is 150-199 mg/dL and 5% if TG level is ≥ 200 mg/dL. Alcohol consumption should be reduced to 10 g/day ethanol for women, 20 g/day for men. Reducing body weight by 5-10% can reduce TG by 20%, and increasing physical activity can reduce TG by up to 20% [6].

Pharmacologic management

Statins, fibrates, omega-3 fatty acids and niacin are commonly used agents to treat hypetriglyceridemia that may reduce TG levels by 20 to 50% [38]. Statins are the first drug of choise for reducing CVD risk in high-risk patients with elevated TG levels [37]. However, in statin monotherapy era, major lipid lowering therapies showed that the higher TG levels on-treatment arm was associated with a higher CV risk [39,40]. The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) showed that the risk of CV events is reduced by 27% if TG levels reduced to <150 mg/dL [41]. Moreover, LIPID trial demonstrated that although baseline TG levels were not associated with CV risk, CVD risk was reduced by 11% for each 89 mg/dL decrease in TG levels [42].

Randomised clinical trials that evalute the effects of fibrates on CV events are Helsinki Heart Study (HHS), Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), the Bezafibrate Infarction Prevention (BIP) study, Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, and Action to control Cardiovascular Risk in Diabetes (ACCORD) study [43-47]. In HHS and VA-HIT trials gemfibrozil treatment statistically reduced the CVD [43,44]. However, in FIELD trial fenofibrate did not demonstrate a benefit on MI, sudden death, and coronary events which may be due to greater use of statins in the placebo group than in fibrate group [46]. In addition, the ACCORD trial and the ACCORDION trial which is the extended post-trial of ACCORD trial showed the benefical effects of fibrates in combination with statin were the greatest in patients with both hypertriglyseridemia (>204 mg/dL) and low HDL (<34 mg/dL) [47,48]. Recently, the metaanalysis of 10 major TG lowering trial including six trial of fibrates, 2 of niasin, 1 of fibrate plus niacin, and 1 of omega–3 fatty acids showed 12% risk reduction overall the study population. However, subgroup analysis showed there was a 18% risk reduction in patients with elevated TG levels and 29% risk reduction in patients with elevated TG and low HDL [49]. Therefore, the 2016 ESC/EAS guideline recommends avoidance gemfibrozil in combination with statins due to increased risk of myopathy, and fenofibrate as the fibrate of choise in fibrate-statin combination [37].

Benefical effects of omega-3 fatty acids on cardiovascular outcomes of were limited and inconsistent. In JELIS trial there was a 19% risk reduction in major CV events in general population and greater lowered risk of major cardiac event compared to statin alone in patients with elevated TG and low HDL [50]. Patients with documented coronary heart disease should consume approximately 1 g of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) daily preferably from oily fish and the 2016 ESC/EAS guideline defines prescription of n-3 fatty acids to decrease TG in combination with statins or fibrates safely and well tolerated [37]. The results of upcoming two large, omega-3 fatty acid trials (the reduction of Cardiovascular Events with EPA-Intervention Trial – REDUCE-IT, NCT01492361, and the Long-Term Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia – STRENGTH, NCT02104817) will evaluate the safety and efficacy of high dose omega-3 fatty acids added on statin treatment for the CV outcomes in high-risk patients [19].

Large scaled randomised clinical trials of niacin such as AIM-HIGH, HPS2-THRIVE failed due to safety concerns and did not show an additional CV benefit when compared combination with statin and statin alone [33,34].

CONCLUSION

Over the 30 past years, the independent relationship between TG and the risk of CVD as well as timing of the treatmen has been long controversial. However, it is well known that the CV risk is increased if TG >150 mg/dL even in patients with statin treatment. Just to remember diabetes lipidus once again, a patient with a fasting TG ≥ 150 mg/dL may be an insulin resistant patient. The TG lowering therapy is beneficial in patients with hypertriglyceridemia and low HDL (TG>204 mg/dL; HDL<34 mg/dL). The furher question should be it may be remnant cholesterol in TGRL not TG itself that has a relation for atherosclerosis. We can simply think TGRL can also be calculated as non-HDL minus LDL as non-HDL level which is calculated as total cholesterol minus HDL, and TGRL is calculated as as total cholesterol minus HDL minus LDL. Therefore, we have to keep our treatment goals tight for both LDL and non-HDL levels especially in high risk patients.

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