Evaluation and Treatment of Hypertriglyceridemia: An Endocrine Society Clinical Practice Guideline

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Objective: The aim was to develop clinical practice guidelines on hypertriglyceridemia.

Participants: The Task Force included a chair selected by The Endocrine Society Clinical Guidelines Subcommittee (CGS), five additional experts in the field, and a methodologist. The authors received no corporate funding or remuneration.

Consensus Process: Consensus was guided by systematic reviews of evidence, e-mail discussion, conference calls, and one in-person meeting. The guidelines were reviewed and approved sequentially by The Endocrine Society's CGS and Clinical Affairs Core Committee, members responding to a web posting, and The Endocrine Society Council. At each stage, the Task Force incorporated changes in response to written comments.

Conclusions: The Task Force recommends that the diagnosis of hypertriglyceridemia be based on fasting levels, that mild and moderate hypertriglyceridemia (triglycerides of 150–999 mg/dl) be diagnosed to aid in the evaluation of cardiovascular risk, and that severe and very severe hypertriglyceridemia (triglycerides of $>$ 1000 mg/dl) be considered a risk for pancreatitis. The Task Force also recommends that patients with hypertriglyceridemia be evaluated for secondary causes of hyperlipidemia and that subjects with primary hypertriglyceridemia be evaluated for family history of dyslipidemia and cardiovascular disease. The Task Force recommends that the treatment goal in patients with moderate hypertriglyceridemia be a non-high-density lipoprotein cholesterol level in agreement with National Cholesterol Education Program Adult Treatment Panel guidelines. The initial treatment should be lifestyle therapy; a combination of diet modification and drug therapy may also be considered. In patients with severe or very severe hypertriglyceridemia, a fibrate should be used as a first-line agent. **(*J Clin Endocrinol Metab* 97: 2969–2989, 2012)**

Summary of Recommendations

1.0. Diagnosis and definitions

1.1. Severe and very severe hypertriglyceridemia increase the risk for pancreatitis, whereas mild or moderate hypertriglyceridemia may be a risk factor for cardiovascular disease. Therefore, similar to the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III guideline committee's recommendations, we recommend screening adults for hypertriglyceridemia as part of a lipid panel at least every 5 yr (1/⊕⊕◯◯).

1.2. We recommend basing the diagnosis of hypertriglyceridemia on fasting triglyceride levels and not on nonfasting triglyceride levels (1/⊕⊕⊕◯).

1.3. We recommend against the routine measurement of lipoprotein particle heterogeneity in patients with hy-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2011-3213 Received November 23, 2011. Accepted March 8, 2012.

Abbreviations: apoB, Apolipoprotein B; CI, confidence interval; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FCHL, familial combined hyperlipidemia; FHA, familial hypoalphalipoproteinemia; FHTG, familial hypertriglyceridemia; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); LpL, lipoprotein lipase; NEFA, nonesterified fatty acid; VLDL, very low-density lipoprotein.

pertriglyceridemia (1/⊕⊕◯◯). We suggest that measurement of apolipoprotein B (apoB) or lipoprotein(a) [Lp(a)] levels can be of value, whereas measurement of other apolipoprotein levels has little clinical value (2/⊕⊕◯◯).

2.0. Causes of elevated triglycerides—primary and secondary

2.1. We recommend that individuals found to have any elevation of fasting triglycerides should be evaluated for secondary causes of hyperlipidemia including endocrine conditions and medications. Treatment should be focused on such secondary causes (1/⊕⊕◯◯).

2.2. We recommend that patients with primary hypertriglyceridemia be assessed for other cardiovascular risk factors, such as central obesity, hypertension, abnormalities of glucose metabolism, and liver dysfunction (1/⊕⊕◯◯).

2.3. We recommend that clinicians evaluate patients with primary hypertriglyceridemia for family history of dyslipidemia and cardiovascular disease to assess genetic causes and future cardiovascular risk (1/⊕⊕◯◯).

3.0. Management of hypertriglyceridemia

3.1. We recommend lifestyle therapy, including dietary counseling to achieve appropriate diet composition, physical activity, and a program to achieve weight reduction in overweight and obese individuals as the initial treatment of mild-to-moderate hypertriglyceridemia (1/⊕⊕◯◯).

3.2. For severe and very severe hypertriglyceridemia (>1000 mg/dl), we recommend combining reduction of dietary fat and simple carbohydrate intake with drug treatment to reduce the risk of pancreatitis (1/⊕⊕⊕⊕).

3.3. We recommend that the treatment goal for patients with moderate hypertriglyceridemia be a non-high-density lipoprotein (HDL) cholesterol level in agreement with NCEP ATP guidelines (1/⊕⊕◯◯).

3.4. We recommend that a fibrate be used as a first-line agent for reduction of triglycerides in patients at risk for triglyceride-induced pancreatitis (1/⊕⊕⊕◯).

3.5. We suggest that three drug classes (fibrates, niacin, n-3 fatty acids) alone or in combination with statins be considered as treatment options in patients with moderate to severe triglyceride levels (2/⊕⊕◯◯).

3.6. We recommend that statins not be used as monotherapy for severe or very severe hypertriglyceridemia. However, statins may be useful for the treatment of moderate hypertriglyceridemia when indicated to modify cardiovascular risk (1/⊕⊕◯◯).

Method of Development of Evidence-Based Recommendations

The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation group (1). A detailed description of this grading scheme has been published (2). In brief, strong recommendations use the phrase "we recommend" and the number 1, and weak recommendations use the phrase "we suggest" and the number 2. The Task Force has confidence that patients who receive care according to the recommendations will derive, on average, more good than harm. Suggestions require more careful consideration of the patient's circumstances, values, and preferences. *Cross-filled circles* indicate the quality of the evidence: ⊕◯◯◯ denotes very low quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, high quality. The quality of the evidence indicates the panel's confidence that the estimates of risks and benefits associated with the recommended course of action compared with an alternative course of action are correct and unlikely to change importantly with new research.

In developing the recommendations for the management of hypertriglyceridemia, the Task Force acknowledges the observational nature of the available evidence and the dependence on epidemiological studies. Yet, the Task Force made several strong recommendations based on several assumptions of patients' values and preferences. These values include that lifestyle therapy/modification is preferred over pharmacological interventions and that laboratory screening of hyperlipidemia, which includes screening for hypertriglyceridemia, is acceptable by patients, is feasible, and may be cost-effective if it leads to the prevention of cardiovascular events. The Task Force also considered that the majority of at-risk patients will likely place higher value on preventing clinically important cases of cardiovascular events and pancreatitis than on the burden of long-term pharmacological treatment, which may include side effects, cost, and the need for long-term monitoring.

The Endocrine Society maintains a rigorous conflict of interest review process for the development of clinical practice guidelines. All Task Force members must declare any potential conflicts of interest, which are reviewed before they are approved to serve on the Task Force and periodically during the development of the guideline. The conflict of interest forms are vetted by the Clinical Guidelines Subcommittee (CGS) before the members are approved by the Society's Council to participate on the guideline Task Force. Participants in the guideline development must include a majority of individuals without conflict of interest in the matter under study. Participants with conflicts of interest may participate in the development of the guideline but they have disclosed all conflicts. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined by remuneration in any amount from the commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (*e.g.*, stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers' bureaus, advisory boards, or boards of directors; or other financial benefits. Completed forms are available through The Endocrine Society office.

Funding for this guideline was derived solely from The Endocrine Society and thus the Task Force received no funding or remuneration from commercial or other entities.

1.0. Diagnosis and definitions

To date, treatment of hyperlipidemia has centered on the management of plasma total and low-density lipoprotein (LDL) cholesterol levels. Although there is robust evidence for an association between LDL cholesterol levels and cardiovascular disease (CVD), there has been more uncertainty regarding the meaning of the association between triglyceride levels and CVD. A high triglyceride level is one of the components of the metabolic syndrome. The latter is associated with risk for CVD, and there is growing support for unadjusted elevated triglyceride levels as an independent CVD risk factor. However, the extent to which elevated triglycerides constitute a direct risk for CVD or more likely represent a marker for other lipoprotein abnormalities associated with CVD risk is unknown and under extensive investigation.

Recommendation

1.1. Severe and very severe hypertriglyceridemia increase the risk for pancreatitis, whereas mild or moderate hypertriglyceridemia may be a risk factor for cardiovascular disease. Therefore, similar to the NCEP ATP III guideline committee's recommendations, we recommend screening adults for hypertriglyceridemia as part of a fasting lipid panel at least every 5 yr (1/⊕⊕◯◯).

1.1. Evidence

Serum triglycerides are routinely measured under fasting conditions to obtain more stable concentrations and to enable the physician to calculate LDL cholesterol levels. In addition, hypertriglyceridemia and postprandial lipemia may affect the measurement of HDL cholesterol and therefore the calculation of non-HDL cholesterol. The NCEP ATP III arbitrarily divided fasting serum triglycerides into four different classes (3) as outlined in Table 1. Classification of serum triglyceride levels greater than 150 mg/dl (1.7 mmol/liter) as elevated is mainly based on large prospective observational studies. However, the exact level at which serum triglycerides start to confer risk or become a marker for CVD is unknown, but it may be even lower than 150 mg/dl (1.7 mmol/liter) (4). Serum triglycerides are higher in men and increase with age in both sexes (5). A serum triglyceride level of 150 mg/dl (1.7 mmol/liter) usually falls below the 75th percentile in various populations, although there have been well-established differences identified between racial and ethnic groups (6–9).

To focus attention on the very high triglyceride levels that are a risk factor for pancreatitis, we have modified the NCEP ATP III triglyceride classification to include an additional classification of very severe hypertriglyceridemia, *i.e.* levels above 2000 mg/dl (Table 1). Severe hypertriglyceridemia, defined as 1000–1999 mg/dl, although not causative of pancreatitis, indicates risk for development of very severe hypertriglyceridemia (10, 11). Notably, the presence of mild and moderate hypertriglyceridemia as a consequence of treated severe

TABLE 1. Criteria proposed for clinical diagnosis of elevated triglyceride levels under fasting conditions

NCEP ATP III (3)			The Endocrine Society 2010[a]		
Normal	<150 mg/dl	<1.7 mmol/liter	Normal	<150 mg/dl	<1.7 mmol/liter
Borderline-high triglycerides	150–199 mg/dl	1.7–2.3 mmol/liter	Mild hypertriglyceridemia	150–199 mg/dl	1.7–2.3 mmol/liter
High triglycerides	200–499 mg/dl	2.3–5.6 mmol/liter	Moderate hypertriglyceridemia	200–999 mg/dl	2.3–11.2 mmol/liter
Very high triglycerides	≥500 mg/dl	≥5.6 mmol/liter	Severe hypertriglyceridemia	1000–1999 mg/dl	11.2–22.4 mmol/liter
			Very severe hypertriglyceridemia	≥2000 mg/dl	≥22.4 mmol/liter

[a] The criteria developed for the present guidelines focus on the ability to assess risk for premature CVD *vs.* risk for pancreatitis. The designations of *mild* and *moderate* hypertriglyceridemia correspond to the range of levels predominant in risk assessment for premature CVD, and this range includes the vast majority of subjects with hypertriglyceridemia. Severe hypertriglyceridemia carries a susceptibility for intermittent increases in levels above 2000 mg/dl and subsequent risk of pancreatitis; very severe hypertriglyceridemia is indicative of risk for pancreatitis. In addition, these levels suggest different etiologies. Presence of mild or moderate hypertriglyceridemia is commonly due to a dominant underlying cause in each patient, whereas severe or very severe hypertriglyceridemia is more likely due to several contributing factors.

hypertriglyceridemia may represent a cardiovascular risk factor.

Elevated triglyceride levels usually are seen with other metabolic abnormalities associated with increased CVD risk. Factors contributing to elevated serum triglycerides are overweight, physical inactivity, excess alcohol intake, presence of the metabolic syndrome or type 2 diabetes mellitus, as well as certain genetic disorders [familial hypertriglyceridemia (FHTG), familial combined hyperlipidemia (FCHL), and familial dysbetalipoproteinemia] (Table 2). Frequently, hypertriglyceridemia is a result of a combination of genetic factors and other causes of increased secretion or impaired clearance of triglyceride-rich lipoproteins. Based on the NCEP ATP III classification, the prevalence of hypertriglyceridemia is high in adults as well as in youth and adolescents, reflecting a population increase in body weight and obesity during the past several decades. In the National Health and Nutrition Examination Survey (NHANES), 1999–2004, 33% of the nearly 6000 participants (37% men, 30% women) had serum triglycerides of at least 150 mg/dl (≥1.7 mmol/liter) (5). In subjects aged 60 yr or older, the percentage was 42% (5). Of subjects with hypertriglyceridemia, about 14% had mild hypertriglyceridemia (150–200 mg/dl), whereas 16% had triglyceride levels of 200–500 mg/dl, and about 2% had levels above 500 mg/dl. Recent surveys of youth and adolescents in the United States (NHANES cycle 1996–2006) and Germany revealed abnormal lipid levels in 20–25% of the participants (12, 13). Lastly, a systematic review and meta-analysis of observational studies commissioned by The Endocrine Society found that hypertriglyceridemia is associated with increased risk of cardiovascular events and pancreatitis (14).

TABLE 2. Causes of hypertriglyceridemia

Primary hypertriglyceridemia
FCHL
FHTG
Familial dysbetalipoproteinemia
FHA
Familial chylomicronemia and related disorders
Primary genetic susceptibility
Metabolic syndrome
Treated type 2 diabetes
Secondary hypertriglyceridemia
Excess alcohol intake
Drug-induced (*e.g.* thiazides, β-blockers, estrogens, isotretinoin, corticosteroids, bile acid-binding resins, antiretroviral protease inhibitors, immunosuppressants, antipsychotics)
Untreated diabetes mellitus
Endocrine diseases
Renal disease
Liver disease
Pregnancy
Autoimmune disorders

Recommendation

1.2. We recommend basing the diagnosis of hypertriglyceridemia on fasting triglyceride levels and not on nonfasting triglyceride levels (1/⊕⊕⊕○).

1.2. Evidence

Prospective studies have indicated that, compared with fasting levels, nonfasting serum triglyceride levels may be a better or similar predictor of CVD events in the general population (15–18). In a number of studies using standardized meals on the association of postprandial lipemia with CVD, greater CVD risk was found to be associated with increased hypertriglyceridemia (19, 20).

Investigators of the Multiple Risk Factor Intervention Trial (MRFIT) concluded that average fasting [187 mg/dl (2.11 mmol/liter)] and nonfasting [284 mg/dl (3.21 mmol/liter)] triglyceride levels were similarly predictive for nonfatal or fatal coronary heart disease with hazard ratios of 1.64 and 1.46, respectively (21). Two recent population-based studies have addressed CVD risk and nonfasting triglyceride levels. The Copenhagen City Heart Study (15) comprised 7587 women and 6394 men, aged 20 to 93 yr, recruited from the general population and followed for a mean of 26 yr. After adjustment for other cardiovascular risk factors (age, total cholesterol, body mass index, hypertension, diabetes, smoking, alcohol consumption, physical inactivity, lipid-lowering therapy, postmenopausal status, and hormone replacement therapy in women), hazard ratios for quintiles of nonfasting triglyceride levels *vs.* the reference level of less than 89 mg/dl (<1.0 mmol/liter) were as follows: between 1.7 and 5.4 for women and 1.4 to 2.4 for men for myocardial infarction; between 1.2 and 2.6 for women and 1.1 to 1.5 for men for ischemic heart disease; and between 1.3 and 3.3 for women and 1.2 to 1.8 for men for total death. All results were significant for trend with increasing triglyceride level. Limitations of this analysis include a small number of subjects with high triglycerides, no adjustment for HDL cholesterol, and a lack of fasting triglyceride levels for comparison.

The Women's Health Study (16) followed 26,509 initially healthy U.S. women older than 45 yr of age for a median of 11.4 yr; testing was done in 20,118 fasting and 6,391 nonfasting participants. The overall rate of cardiovascular events was 3.46/1000 person-years of follow-up. Although fasting triglyceride levels predicted cardiovascular events, the authors did not find an independent association with cardiovascular events after adjusting for potential confounders. In contrast, higher nonfasting triglyceride levels were independently associated with an increased risk of future events with hazard ratios for increasing tertiles of 1.0 (reference group, <104 mg/dl), 1.44 [95% confidence interval (CI), 0.90–2.29; 105–170

mg/dl], and 1.98 (95% CI, 1.21–3.25; >171 mg/dl) (P = 0.006 for trend). Associations were strongest among individuals who had their blood drawn 2 to 4 h after a meal and weakened with increasing time after the participants' last meal. Triglyceride levels and event rates were lower among the healthy U.S. women than those reported in the Copenhagen City Heart Study (15).

Although these studies provide some support for the hypothesis that nonfasting or postprandial lipid levels may be a more potent predictor of CVD risk than fasting levels, the lack of standardization and reference levels impedes a general implementation of nonfasting triglyceride or remnant particle levels (22). Further work is needed on determining the most informative procedure of collecting postprandial lipids and characterization of postprandial effects on triglyceride measurements (23). Thus, at present, the diagnosis of hypertriglyceridemia is suggested to be based on fasting levels where the length of fast is recommended to be 12 h. During this time period, intake of liquids without caloric content is acceptable.

Recommendation

1.3. We recommend against the routine measurement of lipoprotein particle heterogeneity in patients with hypertriglyceridemia (1/⊕⊕◯◯). We suggest that measurement of apoB or Lp(a) levels can be of value, whereas measurement of other apolipoprotein levels has little clinical value (2/⊕⊕◯◯).

1.3. Evidence

In most hypertriglyceridemic patients, the distribution of both LDL and HDL sizes is shifted to smaller particles (24). In patients with the metabolic syndrome, treated type 2 diabetes mellitus, or FCHL, the number of small, dense LDL and HDL particles and the apoB levels are increased (25, 26). Hepatic lipase and cholesterol ester transfer protein contribute to the remodeling processes; whether hepatic lipase or cholesterol ester transfer protein has the predominant effect on the size and density of LDL and HDL particles depends on the triglyceride content of very low-density lipoproteins (VLDL) (27, 28). Although the LDL cholesterol level is frequently normal in patients with these conditions, the concentration of LDL particles is generally increased because of the presence of a higher number of cholesterol-poor, small, dense LDL particles. It is not necessary to measure LDL size or density; however, measurement of non-HDL cholesterol and/or apoB levels can indicate the presence of increased numbers of LDL particles (3, 29).

Epidemiological studies vary as to the independent association between large or small LDL and atherosclerotic cardiovascular disease (30). Several prospective studies suggest that circulating levels of small, dense LDL particles are better predictors of coronary atherosclerosis, carotid atherosclerosis, and response to therapy than are levels of large, buoyant LDL particles (28, 31–33). There is wide agreement, however, that the concentration of LDL, regardless of the particle size, predicts coronary heart disease (3). An increase in small, dense LDL particles is not reflected in the LDL cholesterol concentration. Statins reduce the concentration of all sizes of LDL, and their benefits to CVD are universal across population groups that have large or small LDL (3, 34). Neither LDL size nor the concentration of small, dense LDL particles adds to CVD prediction in multiple variable analysis beyond the standard lipid risk factors, although small LDL particles predict cardiovascular risk in univariate analysis (35–37). Prospective multivariate studies demonstrate that large LDL predicts atherosclerosis and coronary heart disease (35, 38, 39). Several reports also show that measurement of apoB is superior to measurement of LDL or even non-HDL cholesterol as an indicator of global CVD risk (40, 41).

Lp(a) has many properties in common with LDL but contains a unique protein, apolipoprotein(a), which is linked to apoB-100 by a single disulfide bond (42). Recently, interest in Lp(a) has increased because studies over the past decade have confirmed and more robustly demonstrated a risk factor role of Lp(a) for cardiovascular disease (43–46). However, there are limited treatment options to alter its level and a current lack of outcome evidence supporting its use as a specific therapeutic target.

Small HDL in hypertriglyceridemia is associated with hypercatabolism of apolipoprotein A-I (47, 48), and it seems to be related to elevated hepatic lipase activity in central obesity and insulin resistance (49). This property may impair the ability of HDL to take up sufficient cholesterol from peripheral cells. Epidemiological studies have not provided conclusive evidence that measurement of HDL size contributes to risk prediction (36, 50–55). For these reasons, assessment of lipoprotein heterogeneity is not recommended in the assessment of hypertriglyceridemia.

2.0. Causes of elevated triglycerides—primary and secondary

Pathophysiology

Triglycerides are the most dense form of calories and serve as an important source of energy. Dietary triglycerides are assembled in the gut into chylomicrons. Their interaction with lipoprotein lipase (LpL) located on the luminal surface of capillary endothelial cells leads to liberation of free fatty acids from triglyceride; free fatty acids are able to traverse cell membranes. Only 50% of chylo-

micron triglyceride is estimated to be lost in this process, and the remainder of the lipoprotein, called a chylomicron remnant, contains lipids such as cholesteryl esters, retinyl esters, and apoB-48. Several proteins, called apolipoproteins (apo), regulate LpL actions and lipoprotein clearance from the liver. apoC-II is the necessary cofactor for LpL actions. apoC-III blocks the uptake of lipoproteins by receptors in the liver and may impair LpL. apoE is the ligand for hepatic uptake of triglyceride-rich remnants. VLDL particles are produced by the liver, and the VLDL triglyceride content is derived from a variety of substrates including lipoprotein triglyceride, free fatty acids, and *de novo* fatty acids synthesized from carbohydrates. VLDL triglycerides lose free fatty acids by the action of LpL, leading to production of VLDL remnants, also referred to as intermediate-density lipoproteins (IDL), and eventually to conversion to LDL.

The plasma triglyceride level reflects the concentration of the triglyceride-carrying lipoproteins (VLDL and chylomicrons). The concentration of VLDL cholesterol and apoB is at least 10 times higher than the corresponding chylomicron concentration, even after consumption of a large amount of fat (56–59). These lipoproteins contain at least as much cholesterol per particle as does LDL. Although triglyceride itself is not a component of arterial plaque, it is thought that cholesterol within triglyceride-rich particles may contribute to plaque development (60, 61).

Hypertriglyceridemia results from increased triglyceride production, or reduced triglyceride catabolism, or both. The common forms of hypertriglyceridemia emerge as adults get older and become overweight and sedentary and develop insulin resistance. The most common setting of hypertriglyceridemia is that found with metabolic syndrome, FCHL, and type 2 diabetes. The increase in triglyceride production may be due to excess free fatty acids returning to the liver, particularly in the setting of visceral obesity and insulin resistance, and increased *de novo* triglyceride production due to hyperinsulinemia (24, 62, 63). In hypertriglyceridemia, more VLDL particles, as measured by apoB, and larger and more triglyceride- and apoC-III-enriched lipoproteins are found (39, 64, 65). Hepatic insulin resistance may contribute to a high production rate of VLDL because insulin reduces apoB synthesis and VLDL secretion in the liver (66, 67). Although insulin resistance is associated with high triglycerides, VLDL and triglyceride concentrations can be similar in patients with widely divergent insulin sensitivity (68, 69). Acute or chronic elevation of insulin in response to a high carbohydrate diet did not lower serum triglyceride levels in healthy subjects (70, 71). In African-Americans, low triglyceride levels occur in the context of severe insulin resistance (72). Thus, in an individual patient, the contribution of insulin resistance to overproduction of triglycerides and VLDL may be variable.

Clearance of VLDL from the circulation is reduced in many patients with hypertriglyceridemia (64, 65, 73), in part due to saturation of triglyceride clearance (74). This saturation might occur owing to defective triglyceride hydrolysis by LpL and/or reduced clearance of VLDL and chylomicron remnants by the liver. Defective lipolysis occurs with genetic defects in LpL; defects in apoC-II; defective association of LpL with the vascular wall due to antibodies to heparin or defects in glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1, an LpL-binding protein (75, 76); or defective intracellular LpL processing due to mutated lipase maturation factor 1 (77). Severe hyperchylomicronemia also occurs when a secondary cause of hypertriglyceridemia such as diabetes or pregnancy is superimposed on an underlying genetic defect (78). A number of additional genetic factors influence human triglyceride levels, including mutations in apoC-III, apoE, apoA-V, and angiopoietin-like protein 4. apoE is the main protein that mediates binding of VLDL and chylomicron remnants to hepatic receptors and proteoglycans; it is antagonized by apoC-III. Hypertriglyceridemic VLDL particles are heterogeneous and often have a high apoC-III/apoE ratio, causing reduced clearance and increased conversion to LDL. Recent studies have underscored the difference in metabolism of VLDL subpopulations containing apoC-III, with or without apoE, and how these apolipoproteins are involved to establish hypertriglyceridemia and cause the formation of dense LDL (79).

Moderate hypertriglyceridemia, *i.e.* 200–999 mg/dl, is due to excess circulating VLDL, the principal triglyceride carrier in the circulation. Defective clearance of triglyceride-rich VLDL by LpL can contribute to this condition, and many patients have overproduction of VLDL triglyceride in the liver with an increased secretion (24, 62, 63).

In patients with severe or very severe triglyceride levels ($\geq$1000 mg/dl), the LpL removal system is saturated (74). This saturation occurs whether hypertriglyceridemia is primarily due to defective lipolysis or excessive production of endogenous triglyceride, and it leads to reduced catabolism of dietary triglyceride incorporated into chylomicrons. For this reason, there is concern that triglyceride levels above 1000 mg/dl can rapidly increase after a fat-rich meal. Foods that contain potent substrates for triglyceride production such as simple sugars, fructose, and alcohol can substantially increase triglyceride levels in susceptible people (80, 81). Very severe triglyceride levels ($>$2000 mg/dl) are associated with lipemic serum and risk of pancreatitis in the chylomicronemia syndrome (82).

Recommendation

2.1. We recommend that individuals found to have any elevation of fasting triglycerides should be evaluated for secondary causes of hyperlipidemia including endocrine conditions and medications. Treatment should be focused on such secondary causes (1/⊕⊕◯◯).

2.1. Evidence

An isolated elevation in triglyceride levels may be caused by a primary disorder of lipid metabolism, *e.g.* FHTG or FCHL. It may also arise secondary to a number of conditions as outlined in Table 2, including a number of medications, a high-carbohydrate diet with intake of simple sugars, 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 may lead to severe and very severe triglyceride levels and the risk of pancreatitis.

Endocrine disorders

Patients with untreated diabetes mellitus and insulin deficiency commonly have hypertriglyceridemia; this condition occurs more frequently in type 2 than in type 1 diabetes mellitus. Appropriate diabetes management reduces triglyceride levels. Mild hypertriglyceridemia, typically seen in treated type 2 diabetes, is probably related to the presence of central obesity and insulin resistance (83).

Hypertriglyceridemia related to increased insulin resistance and to decreased activity of both hepatic lipase and LpL occurs in some acromegalic patients (84).

Owing to estrogen-induced stimulation of the secretion of hepatic triglyceride-rich lipoprotein, triglyceride levels increase progressively during pregnancy, with levels in the third trimester increased by 200% or more over levels before pregnancy. In women with underlying disorders of triglyceride metabolism or overproduction, an estrogen-induced increase in triglycerides during pregnancy can result in a risk of pancreatitis with potential fetal loss (85, 86). Oral estrogen in the form of estrogen replacement therapy or oral contraceptives has a triglyceride-increasing effect due to increased hepatic VLDL production. This effect does not occur with transdermal estrogen due to its lesser exposure to the liver (87, 88). Tamoxifen, a selective estrogen receptor modulator, can also increase triglyceride levels. The effect is less pronounced with raloxifene, but that drug can increase levels in women with an underlying propensity to hypertriglyceridemia (89, 90).

Thyroid hormone deficiency is associated with increased LDL cholesterol levels; this increase has been postulated to be due to decreased function of LDL receptors. There can also be an increase in triglyceride levels. Hypothyroidism can lead to the expression of dysbetalipoproteinemia (91–93).

Glucocorticoids have several effects on lipoprotein metabolism including increased cholesterol production from induction of hydroxymethylglutaryl coenzyme A reductase, increased fatty acid synthesis due to increased expression of fatty acid synthase, and decreased clearance of triglyceride-rich lipoproteins (94). Because weight gain and insulin resistance are major effects of both exogenous and endogenous glucocorticoid excess, elevated triglycerides can be seen in Cushing's syndrome as well as during glucocorticoid treatment.

Rare genetic disorders

Inherited and congenital lipodystrophies are associated with moderate-to-severe hypertriglyceridemia and are characterized by loss of adipose tissue and either autosomal recessive or dominant inheritance (95). The loss of adipose tissue is selective and variable and may be partial or complete. Some forms manifest at birth, whereas others become evident later in life with loss of fat beginning in childhood and puberty (96). Varieties of familial partial lipodystrophy, which are rare autosomal disorders, involve fat loss from the extremities more than the trunk. The Kobberling variety is more common, but the defect is unknown (97). Hypertriglyceridemia is also seen in several types of glycogen storage disease in children (98).

Other conditions

Acquired lipodystrophy can be seen in patients with HIV infection who are being treated with highly active antiretroviral therapy (99). Other acquired forms of lipodystrophy are seen in patients with autoimmune diseases such as juvenile dermatomyositis. Patients with acquired generalized lipodystrophy lose fat from large areas of the body during childhood and adolescence and often have hepatic steatosis (100).

Hypertriglyceridemia has been reported in multiple myeloma and in autoimmune diseases such as systemic lupus erythematosis involving autoantibodies to LpL, apoC-II, or heparin. Hypertriglyceridemia can also be seen with infections including inflammation and sepsis, apparently due to increased production of VLDL (101). Hypertriglyceridemia in severe stress may be related to possible catecholamine induction of adipose tissue lipolysis and reduced LpL activity (102).

Renal and hepatic disease can be associated with hypertriglyceridemia. Nephrotic syndrome causes increased production of apoB-containing lipoproteins, including VLDL, by the liver (103). Hypertriglyceridemia is common in patients with renal failure and may be related to decreased clearance of triglyceride-rich lipoproteins via

reduced LpL and hepatic lipase activities (104). Acute hepatitis may be associated with increased VLDL production and hypertriglyceridemia (105).

Drugs

Many drugs raise triglyceride levels. One of the most commonly used is alcohol. Alcohol intake increases hepatic fatty acid synthesis and decreases fatty acid oxidation, with a net effect to stimulate hepatic VLDL triglyceride secretion. The effects of alcohol vary interindividually, tend to be amplified in subjects with underlying lipid disorders, are dose-dependent (106), and may be related to the mode of intake (107).

Antihypertensive drugs with a potential to increase triglyceride levels are thiazide (and furosemide) diuretics and β-adrenergic blocking agents. The hypertriglyceridemic effect of β-adrenergic blocking agents is greater for atenolol, metoprolol, and propranolol than for carvedilol. These effects are most relevant in patients with underlying genetic hypertriglyceridemia (94).

Oral estrogens increase the hepatic secretion of VLDL, leading in turn to an increase in serum triglyceride levels (108). In patients with familial hypertriglyceridemia or LpL deficiency, the use of oral estrogens can provoke severe pancreatitis (109). An increase in hepatic VLDL and apoC-III production and perhaps a decrease in LpL leading to increased triglyceride levels are also seen during use of retinoids such as isotretinoin and the anticancer drug bexarotene (110–112).

Bile acid sequestrants (cholestyramine, colestipol, colesevelam) can worsen hypertriglyceridemia and are contraindicated in patients with severe hypertriglyceridemia (>1000 mg/dl) and in patients with dysbetalipoproteinemia. Patients with normal baseline triglyceride levels experience minimal triglyceride increases with bile acid sequestrant therapy, but those with moderate hypertriglyceridemia (triglycerides > 200 mg/dl) may experience substantial further elevation (113).

Dyslipidemia is a frequent complication of antiretroviral therapy for HIV infection. In particular, the protease inhibitors ritonavir and lopinavir can increase plasma triglyceride levels (114).

Immunosuppressants such as sirolimus also increase triglyceride levels (115).

Certain second-generation antipsychotic medications such as clozapine, olanzepine, risperidone, and quetiapine can be associated with hypertriglyceridemia, but this effect has not been seen for aripiprazol or ziprasidone. Those that are associated with weight gain, insulin resistance, and worsening of the metabolic syndrome are particularly important contributors to secondary hyperlipidemia. Among selective serotonin reuptake inhibitors, sertraline may raise triglycerides (116).

Recommendation

2.2. We recommend that patients with primary hypertriglyceridemia be assessed for other cardiovascular risk factors, such as central obesity, hypertension, abnormalities of glucose metabolism, and liver dysfunction (1/⊕⊕◯◯).

2.2. Evidence

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 FCHL. 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 in whom the increase in plasma cholesterol is a result of increased VLDL and chylomicron cholesterol.

Familial combined hyperlipidemia

The lipid phenotype in FCHL varies from isolated hypertriglyceridemia to isolated hypercholesterolemia within families and in single individuals, suggesting that the variation in the lipid phenotype is affected by environmental factors (78). In some subgroups, such as those with half-normal LpL activity, the lipoprotein phenotype seems to be more stable as hypertriglyceridemia and less stable as hypercholesterolemia. In patients with FCHL, increases in triglycerides and LDL cholesterol are often found, whereas elevated apoB levels and small, dense LDL particles are always seen (25). It has been suggested that measurement of apoB and non-HDL cholesterol levels, in addition to assessment of LDL and HDL cholesterol levels, will serve as a basis by which to identify these FCHL individuals at risk for premature CVD (117). In addition, patients with FCHL frequently have nonlipid cardiovascular risk factors (*i.e.* central obesity, hypertension, insulin resistance, and impaired glucose tolerance). The prevalence of FCHL in the population is estimated to be 1–2% and in CVD populations to be at least 10% (78). It should be underscored that regardless of the etiology, the combination of hypertriglyceridemia and elevated LDL cholesterol, with small, dense LDL particles, appears to increase the risk associated with elevated LDL cholesterol alone.

Familial hypertriglyceridemia

FHTG is a common inherited disorder, thought to be autosomal dominant, which affects about 1% of the population. It is characterized by an increased triglyceride synthesis, which results in very large triglyceride-enriched

VLDL particles, secreted in normal numbers. Affected people have elevated VLDL levels, but low levels of LDL and HDL cholesterol, and are generally asymptomatic unless very severe hypertriglyceridemia develops. FHTG does not appear to be associated with an increased risk of premature CVD (118). However, subjects are at increased risk for the development of the chylomicronemia syndrome and pancreatitis when secondary forms of hypertriglyceridemia are present, such as untreated diabetes or use of triglyceride-raising drugs. A diagnosis is made by family history and examination of fasting lipoprotein profiles of the patient and relatives. The triglyceride level ranges from about 250 to 1000 mg/dl in approximately one half of first-degree relatives. A strong family history of premature CVD usually is lacking, and elevated LDL cholesterol levels are not present.

It is important to distinguish FHTG, which seems to confer no risk of premature CVD, from FCHL, which is associated with a high incidence of premature CVD (78). It is often difficult to distinguish these disorders when FCHL is associated with hypertriglyceridemia. Concomitant increased apoB or LDL cholesterol concentration indicates FCHL. FCHL is also strongly suggested by a positive personal or family history of premature atherosclerosis with hypertriglyceridemia (78).

Chylomicronemia syndrome

Chylomicronemia is associated with pancreatitis, but the mechanism is unclear. Pancreatitis may result from the release of excess fatty acids and lysolecithin from chylomicrons, exceeding the binding capacity of albumin in pancreatic capillaries. The chylomicronemia syndrome occasionally occurs with a genetic defect in the LpL-related triglyceride clearance system. More commonly, chylomicronemia is caused by the coexistence of a common genetic form of hypertriglyceridemia combined with an acquired disorder of plasma triglyceride metabolism, the most common being untreated diabetes (82). Another condition that may be implicated is the use of drugs that raise triglyceride levels.

The chylomicronemia syndrome is associated with abdominal pain, eruptive xanthomas on the buttocks and the extensor surfaces of the upper limb, transient memory loss, and the risk for artifactual alterations in laboratory analyses. If uncorrected, the chylomicronemia syndrome may result in acute, recurrent pancreatitis. The risk of pancreatitis markedly increases with very severe triglyceride levels above 2000 mg/dl (82), but it can be prevented by maintaining triglyceride levels below 1000 mg/dl. Severe hypertriglyceridemia can present in childhood as a result of LpL deficiency or, extremely rarely, as apoC-II, apoA-V, or glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 deficiency. These patients are at risk for acute, recurrent pancreatitis with severe hypertriglyceridemia, and they must be treated with moderate to severe dietary fat restriction to reduce plasma triglyceride levels (78). In patients with severe and very severe triglyceride elevations, the increase in total plasma cholesterol is a result of the cholesterol in VLDL and chylomicrons.

Familial hypoalphalipoproteinemia with high triglycerides

In 1992, Genest *et al*. (119, 120) proposed that familial hypoalphalipoproteinemia (FHA), a disorder with elevated triglyceride and low HDL cholesterol, was a common genetic dyslipidemia associated with premature CVD. Many, if not most, patients with hypertriglyceridemia have a concomitant reduction in HDL cholesterol levels. It is not known whether FHA is a discrete genetic disorder. Low HDL cholesterol is commonly seen with premature CVD and may be related, in part, to mutations in proteins of HDL metabolism. However, mutations in these candidate genes are rare and account for few FHA cases. FHA is often confused with FHTG, and more studies are needed to characterize this condition.

Almost all forms of severe genetic HDL deficiency are associated with mild-to-moderate hypertriglyceridemia. These include Tangier's disease, apoA-I deficiency, and lecithin cholesterol acyl transferase deficiency.

Dysbetalipoproteinemia

Dysbetalipoproteinemia, also called type III hyperlipoproteinemia or remnant removal disease, is caused in part by a mutation in the APOE gene, resulting in impairment in the hepatic uptake of apoE-containing lipoproteins and reduction in the conversion of VLDL and IDL to LDL particles (121). In the absence of additional genetic, hormonal, or environmental factors, remnants do not accumulate to a degree sufficient to cause hyperlipidemia in fasting blood. Dysbetalipoproteinemia results when an apoE defect (almost always the E2/E2 genotype) occurs in conjunction with a second genetic or acquired defect that causes either overproduction of VLDL (such as FCHL) or a reduction in LDL receptor activity (such as occurs in heterozygous FH or hypothyroidism). Other rare apoE variants such as apoE3-Leiden and apoE2(Lys146→Gln) can also cause dysbetalipoproteinemia (122, 123). Patients with dysbetalipoproteinemia have elevations in both cholesterol and triglyceride levels (124). They are likely to develop premature CVD and are at increased risk for peripheral vascular disease. Clinical dyslipidemia usually does not develop before adulthood in men or before menopause in women. Palmar xanthomas, orange lipid

deposits in the palmar creases, are pathognomonic, but are not always present. Tuberoeruptive xanthomas are occasionally found 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 1000 mg/dl and are roughly equal. VLDL particles are cholesterol-enriched, which can be determined by isolation of VLDL by ultracentrifugation. It can be useful to confirm the diagnosis by demonstrating the presence of the E2/E2 genotype.

Metabolic syndrome

Hypertriglyceridemia is one of the components of the metabolic syndrome, a constellation of metabolic risk factors including a central distribution of adiposity or visceral obesity, insulin resistance, impaired glucose tolerance, hypertension, and high triglycerides and/or low HDL-C, associated with an atherogenic, procoagulant, and proinflammatory state (125). Although criteria for defining the metabolic syndrome have differed among health organizations, recently a harmonized definition has been agreed to by leading cardiovascular and diabetes organizations including the National Heart, Lung, and Blood Institute, the International Diabetes Federation, and the American Heart Association (126). The five components that form the criteria for defining the metabolic syndrome are triglycerides above 150 mg/dl; HDL-C below 40 mg/dl in men or below 50 mg/dl in women; blood glucose above 100 mg/dl; blood pressure above 130 mm Hg systolic or above 85 mm Hg diastolic; and waist circumference greater than 102 cm in men or greater than 88 cm in women. A lower criterion for waist circumference is recommended for Asian populations. Three of these five criteria are needed to make the diagnosis of metabolic syndrome. Genetic and environmental factors appear to affect the distribution of these variables in both normal individuals and those with the metabolic syndrome. Type 2 diabetes mellitus, polycystic ovary syndrome, and FCHL may account for at least 40–50% of premature coronary artery disease in some populations with metabolic syndrome, and they need to be considered in assessing the risk of CVD in patients who have the metabolic syndrome (26).

Although the association of central obesity and insulin resistance with dyslipidemia is well established, the underlying mechanisms remain unclear. An increase in the level of portal vein long-chain nonesterified fatty acids (NEFA, or free fatty acids) has been suggested as an underlying factor. Increased visceral fat is associated with insulin resistance, hyperinsulinemia, low plasma adiponectin levels, and elevations in plasma NEFA levels (127). An increase in portal NEFA would potentially inhibit apoB-100 from undergoing degradation in the hepatic proteosome and would increase the likelihood of secretion of triglyceride-containing lipoproteins, contributing to increased triglyceride levels and an increased number of VLDL and LDL particles seen in patients with insulin resistance (24). Importantly, in normal, randomly selected healthy populations, isolated visceral obesity and insulin resistance were associated with only a slight increase in triglyceride levels and only a slight decrease in HDL cholesterol levels (127). Increased waist circumference and plasma triglyceride levels together confer greater CVD risk in these patients (128).

Ectopic fat accumulation

Excess tissue triglyceride accumulation results from increased uptake of circulating triglycerides (*e.g.* in LpL deficiency), greater production of triglyceride from carbohydrates or free fatty acids (*e.g.* in type 2 diabetes mellitus), or reduced utilization or secretion of triglyceride (*e.g.* in familial hypobetalipoproteinemia). Excess triglyceride stores are found in livers of patients with nonalcoholic fatty liver disease (129). Hepatic steatosis is often associated with increased intraabdominal fat and fat accumulation in other tissues such as skeletal muscle, heart, and perhaps pancreas, and may lead to insulin resistance associated with type 2 diabetes and metabolic syndrome (130). Cellular and animal experiments suggest that signaling lipids other than triglyceride, such as ceramides or diacylglycerols, may be pathological (131). Because hypertriglyceridemia, increased intraabdominal fat, and nonalcoholic fatty liver disease occur with insulin resistance and excess caloric intake, a cause-and-effect relationship is difficult to conclude. Recent human genetic studies have found several predisposing factors that might provide novel insights. At this time, routine assessment of hepatic fat content or intraabdominal fat content in hypertriglyceridemic patients is not indicated. An increase in hepatic fat content is associated with an increase in aminotransferase activities, in particular, alanine aminotransferase.

Recommendation

2.3. We recommend that clinicians evaluate patients with primary hypertriglyceridemia for family history of dyslipidemia and cardiovascular disease to assess genetic causes and future cardiovascular risk (1/⊕⊕◯◯).

2.3. Evidence

Whether serum triglycerides are causally related to atherosclerosis remains to be elucidated, as does the exact mechanism by which they may promote vascular disease. Factors contributing to this uncertainty are the complex metabolism of triglyceride-rich lipoproteins and the fact

that abnormal triglyceride concentrations are seen frequently in conditions associated with increased CVD risk, such as type 2 diabetes mellitus, the metabolic syndrome, and the familial forms of hypertriglyceridemia, in the presence of low HDL-cholesterol levels and small dense LDL particles. An elevated serum triglyceride level might in some cases be a marker for CVD rather than a causal factor.

Several meta-analyses from studies performed in the general population have shown a modest but independent effect of triglycerides on CVD. A meta-analysis of Western population-based prospective studies, including 46,413 men and 10,864 women, showed an overall relative risk for CVD of 1.32 for men and 1.76 for women per 1 mmol/liter (88.5 mg/dl) increase of triglycerides (132). Adjustment for HDL cholesterol and other cardiovascular risk factors attenuated the relative risk attributed to triglycerides, although they remained significant (1.14 and 1.37, respectively) (132). More recently, a report of two nested case-control comparisons from population-based cohorts [the Reykjavik study and the European Prospective Investigation of Cancer (EPIC)-Norfolk study] comprised 44,237 Western middle-age men and women of predominantly European ancestry and a total of 3,582 cases of coronary heart disease (133). In the Reykjavik study, fasting triglyceride levels in cases were 105 ± 70 mg/dl (1.19 ± 0.79 mmol/liter) *vs.* 91 ± 55 mg/dl (1.03 ± 0.62 mmol/liter) in controls. The corresponding levels in the EPIC-Norfolk study were 195 ± 107 mg/dl (2.20 ± 1.21 mmol/liter) and 168 ± 104 mg/dl (1.90 ± 1.17 mmol/liter), respectively. Comparing individuals in the top *vs.* 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. Adjustment for HDL cholesterol attenuated the effect to an odds ratio of 1.31 (95% CI, 1.06–1.62) in the EPIC-Norfolk study. In addition, an updated meta-analysis of prospective studies in Western populations, providing information in aggregate from more than 10,000 coronary heart disease cases involving more than 260,000 participants, reported an adjusted odds ratio of 1.72 (95% CI, 1.56–1.90) comparing the top and bottom triglyceride tertiles (133). These results are similar to those reported by another nonoverlapping meta-analysis based on Asian and Pacific populations, although the absolute risk in these populations was much lower (134). This latter meta-analysis calculated a relative risk for coronary heart disease, adjusted for several established risk factors, of 1.80 (95% CI, 1.49–2.19), comparing subjects in the top with those in the bottom quintile of triglyceride levels.

A third large prospective cohort study, the MELANY study, was conducted in 13,953 healthy male soldiers (aged 26 to 45 yr) in Israel (135). After multivariate adjustment (including age, body mass index, HDL cholesterol, physical activity, fasting glucose, mean arterial blood pressure, smoking), men in the top quintile of triglyceride levels had a hazard ratio for coronary heart disease of 4.05 (95% CI, 2.68–8.61) compared with the lowest quintile ($P = 0.001$ for trend) (135). Beyond fasting triglyceride levels, the change in triglyceride levels strongly predicted incident coronary heart disease (135). Finally, the Emerging Risk Factors Collaboration (ERFC) collected 112 prospective studies of cardiovascular risk factors, involving a total of 1.2 million participants in a central database with individual data records (136). This group recently assessed the association of major lipids and apolipoproteins with vascular risk based on 68 of these prospective studies, involving more than 300,000 participants with information on lipid profile and conventional risk factors (9). The hazard ratio for coronary heart disease with triglycerides was 1.37 (95% CI, 1.31–1.42) after adjustment for nonlipid factors, but was reduced to 0.99 (95% CI, 0.94–1.05) after adjustment for HDL cholesterol and non-HDL cholesterol (9).

There may be a nonlinear relationship between triglyceride levels and CVD (patients with the chylomicronemia syndrome are not always characterized by premature CVD) (82). It could be due to enrichment of these populations with patients with FHTG who are not at increased risk for premature CVD. Very large triglyceride-rich lipoproteins, perhaps equivalent to unmetabolized chylomicrons, are not atherogenic if they are too large to penetrate into the arterial wall (60, 137). Although there are a number of severely hypertriglyceridemic animals, especially genetically modified mice, these animals develop only early-stage lesions (138, 139). In contrast, there is no doubt that metabolic products of triglyceride-rich lipoproteins are atherogenic (140–142). Zilversmit (143) first postulated that atherosclerosis developed in part due to arterial infiltration of chylomicron remnants locally produced by arterial wall LpL. A variety of animal models produced using dietary or genetic manipulations have confirmed that chylomicron remnants are atherogenic (139, 144). Remnants have been identified within human atherosclerosis plaques (145). Unlike VLDL and LDL that contain full-length apoB-100, chylomicrons contain a truncated apoB, apoB-48. apoB-48 lipoproteins are clearly atherogenic as shown in a mouse model constructed with apoB-48 as the only type of apoB in VLDL and LDL (146).

Although it is cholesterol and not triglyceride that is the pathological signature of atherosclerosis and that accumulates both intracellularly in foam cells and extracellularly within the plaque, lipolysis of triglyceride-rich lipoproteins also produces fatty acids, lysolecithin, and other

reactive lipids. *In vitro* studies have implicated these lipids (and in some experiments lipolysis of triglyceride) in inflammation (147), expression of adhesion molecules (148), and promotion of coagulation (149). In addition, *ex vivo* studies have shown that lipolysis leads to increased permeability of blood vessels (150), which may allow greater infiltration of LDL. Nonetheless, because of the lack of clear human data showing that reductions of triglyceride reduce CVD, the Task Force views hypertriglyceridemia as a marker for risk in some individuals.

3.0. Management of hypertriglyceridemia

Recommendation

3.1. We recommend lifestyle therapy, including dietary counseling to achieve appropriate diet composition, physical activity, and a program to achieve weight reduction in overweight and obese individuals as the initial treatment of mild-to-moderate hypertriglyceridemia (1/⊕⊕◯◯).

3.1. Evidence

Diet

Much of the increase in serum triglycerides that occurs in adult life is caused by weight gain, lack of exercise, and a diet rich in simple carbohydrates and sugar-sweetened beverages. This may also underlie hypertriglyceridemic situations in younger ages (151). As regards diet quality, in the weight-stable condition, even in overweight or obese people, reduced carbohydrate intake and increased fat intake lower fasting triglycerides. There is a quantitative linear relation between replacement of dietary carbohydrate with fat and reduction in serum triglycerides (152). Saturated, monounsaturated, and n-6 polyunsaturated fatty acids all lower serum triglycerides when they replace carbohydrate, with no clear difference between fatty acid classes in this action. However, diet affects other cardiovascular risk factors beyond triglycerides, and such effects need to be taken into account. Thus, there is a large body of evidence clearly indicating that both dietary saturated fat and trans fatty acids increase LDL cholesterol levels. Replacing these atherogenic fatty acids with monounsaturated or polyunsaturated fat lowers LDL cholesterol; n-6 polyunsaturated fats have a stronger LDL-lowering effect than monounsaturated fats (152). n-3 Polyunsaturated fat lowers serum triglycerides uniquely among the fatty acids, as discussed in the section on drug treatment below.

The type of carbohydrate may affect serum triglycerides. Fructose as contained in sweetened beverages may have stronger triglyceride-raising effects than glucose. This point of view, that fructose as a component of sugar-sweetened beverages, is more detrimental than sucrose or glucose is controversial, however, and more information is needed from randomized comparative trials. Nonetheless, it is recommended that reduced intake of sugar-sweetened beverages, whether composed mainly of high-fructose corn syrup or sucrose, is an important part of lowering serum triglycerides (151). Some carbohydrate-rich foods such as potatoes, white bread, and rice increase blood glucose more quickly and to a higher concentration than other carbohydrate-rich foods such as apples, legumes, nuts, pasta, and densely-baked whole grain breads. This difference is expressed by the glycemic index, which is the rise in blood glucose of 50 g of carbohydrate in a specific food compared with either 50 g glucose or white bread (153). The glycemic index may correlate with the extent of rise of serum triglyceride after eating carbohydrate-rich foods (154).

There has been much less attention paid to the effects of dietary protein on serum triglycerides. Low-carbohydrate diets are mainly high in fat, but protein content usually increases as well. Thus, the triglyceride-lowering effects of low-carbohydrate diets may be partly caused by protein. The OmniHeart study compared the effects of healthful dietary patterns based on the DASH diet that lowered blood pressure and LDL cholesterol. These dietary patterns all emphasize fruits, vegetables, and low-fat dairy products; include whole grains, poultry, fish, and nuts; use unsaturated vegetable oils; and contain smaller amounts of red meat, sweets, and sugar-containing beverages than typical diets in the United States (155, 156). Compared with a diet that emphasized carbohydrate, a similar diet that emphasized protein decreased triglyceride levels further, and this decrease was about twice the effect of a diet that emphasized unsaturated fat (155).

African-Americans have lower serum triglyceride levels than other racial or ethnic groups. The OmniHeart study, in which 50% of the population was African-American, found that diet modification had less effect on triglyceride levels in this ethnic group than in a Caucasian population when matching baseline triglyceride levels (157). Further studies addressing variability across population subgroups are needed.

Exercise

It has been reported that exercise the day before ingestion of a high-fat meal is associated with a marked dampening of the postprandial triglyceride increase. The mechanisms for this are not clear, and the exercise benefits are relatively short-lived. The minimum exercise required to reduce a postprandial triglyceride increase has not been determined, but a period of 30–60 min of intermittent aerobic exercise or mild resistance exercise has been shown to be effective in lowering plasma and VLDL triglycerides. These findings suggest a benefit from an active lifestyle that does not require intense or prolonged exercise

(158, 159). A recent meta-analysis comparing aerobic exercise programs showed favorable effects only for high-intensity programs. The most frequently observed alteration was an increase in the HDL cholesterol, whereas reductions in triglycerides, total cholesterol, and LDL cholesterol appeared less often (160). Furthermore, in a recent large, community-based study, a combination of aerobic and resistance exercise was associated with lower triglyceride levels in men as compared with aerobic exercise alone (161).

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-yr duration did not find differences in effects on triglyceride levels between low-fat, high-carbohydrate diets and low-carbohydrate diets (162, 163). Many studies have shown that ongoing counseling by dietitians and behavioral therapists, as well as support from peers, is important to most people who are successful in losing weight and maintaining weight loss.

Recommendation

3.2. For severe and very severe hypertriglyceridemia (>1000 mg/dl), we recommend combining reduction of dietary fat and simple carbohydrate intake with drug treatment to reduce the risk of pancreatitis (1/⊕⊕⊕⊕).

3.2. Evidence

Determination and treatment of underlying causes of very severe hypertriglyceridemia should be considered first. Restriction of both saturated and unsaturated dietary fat, particularly at initiation of therapy and in LpL deficiency, assists in lowering triglyceride acutely. Design of the dietary intervention may benefit from input from nutrition specialists. Regain of weight loss might exacerbate pancreatitis risk (82).

Recommendation

3.3. We recommend that the treatment goal for patients with moderate hypertriglyceridemia be a non-HDL cholesterol level in agreement with NCEP ATP guidelines (1/⊕⊕◯◯).

3.3. Evidence

Non-HDL cholesterol (total serum cholesterol minus HDL cholesterol) reflects the amount of cholesterol in all atherogenic lipoprotein particles. In the case of an increase in VLDL, commonly seen in hypertriglyceridemia, measurement of LDL cholesterol alone would underestimate the risk associated with atherogenic lipoproteins. Therefore, measurement of non-HDL cholesterol is recommended in subjects with hypertriglyceridemia both for risk stratification and as a secondary target for therapy (3, 164). Alternatively, the blood level of atherogenic lipoprotein particles can be assessed by measuring the concentration of apoB. Not unexpectedly, there is a good correlation between apoB and non-HDL cholesterol because 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 in the plasma compartment. Therefore, the apoB concentration reflects the concentration of atherogenic lipoprotein particles. Because measurement of apoB is helpful in the differentiation of FCHL from FHTG, apoB levels may be measured during an initial evaluation of a hypertriglyceridemic patient. Non-HDL cholesterol can then be followed as the therapeutic target.

Recommendations

3.4. We recommend that a fibrate be used as a first-line agent for reduction of triglycerides in patients at risk for triglyceride-induced pancreatitis (1/⊕⊕⊕◯).

3.5. We suggest that three drug classes (fibrates, niacin, n-3 fatty acids) alone or in combination with statins be considered as treatment options in patients with moderate to severe triglyceride levels (2/⊕⊕◯◯).

3.4.–3.5. Evidence

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. It is uncertain whether we should treat moderate hypertriglyceridemia or other lipoprotein abnormalities associated with this degree of hypertriglyceridemia. If the primary goal is to lower triglyceride levels, fibrates and perhaps n-3 fatty acids are best. If the primary goal is to modify the size and density of LDL and HDL particles, niacin is best.

Fibrates

Fibrates should be strongly considered in patients with severe and very severe hypertriglyceridemia and should be considered in patients with moderate hypertriglyceridemia. Fibrates decrease triglyceride levels by 30–50% and sometimes increase HDL cholesterol (165–168). In patients with high triglyceride levels, LDL cholesterol levels may increase, whereas in mild hypertriglyceridemia, LDL cholesterol levels may decrease. In patients with triglyceride-induced pancreatitis, treatment of underlying causes

and concomitant fibrate therapy to maintain triglyceride levels below 2000 mg/dl is beneficial to prevent recurrent disease (82). Due to a large excursion of triglyceride levels in the setting of very severe hypertriglyceridemia, a treatment goal of less than 1000 mg/dl is recommended. Below this level, the main effort should be directed toward prevention of premature atherosclerosis. We do not recommend the use of heparin infusions or plasmapheresis in the treatment of very severe hypertriglyceridemia with pancreatitis. The treatment of underlying causes including dietary fat restriction and use of long-term fibrate therapy should suffice (82).

Studies to date have not demonstrated an overall benefit of fibrates for reduction of cardiovascular or total mortality (165–169). An *a priori* analysis demonstrated that a decrease in triglyceride and elevation of HDL cholesterol levels was associated with a decrease in primary events, while at the same time, there was an increase in death in females (169). *Post hoc* subgroup analyses of all of these trials show that the use of fibrates in patients with moderate hypertriglyceridemia results in a decrease in composite cardiovascular events, but not a decrease in mortality (170–172). However, these studies also indicate that treatment of patients with triglycerides below 200 mg/dl does not confer benefit.

Fibrates increase fatty acid oxidation, increase LpL synthesis, and reduce expression of apoC-III, all of which decrease VLDL triglyceride production and increase LpL-mediated catabolism of triglyceride-rich lipoproteins (170). Side effects include gastrointestinal discomfort and possibly an increased incidence of cholesterol gallstones. Fibrates are contraindicated in patients with liver and gall bladder disease. Fibric acid derivatives should be used with great caution in the setting of renal insufficiency because the drugs are excreted in the urine and may reversibly increase serum creatinine levels— especially fenofibrate, although the significance of this effect is unknown. Fenofibrate, which does not interfere with statin metabolism and has a lower risk of causing myopathy, is the preferred fibrate to use in combination with a statin. Due to effects on protein binding, there is a potential interaction with warfarin requiring careful monitoring. Gemfibrozil can be considered in very severe hypertriglyceridemia beginning in the second trimester in pregnant women who are at risk of pancreatitis (86).

Niacin

Clinical trials using niacin, alone or in combination with other lipid medications, have shown benefits in decreasing cardiovascular event rates and atherosclerosis (173–176). However, the recently concluded AIM-HIGH study did not report any further benefits with regard to cardiovascular events when niacin was added to a statin in patients with median triglyceride level of about 160 mg/dl in the mild hypertriglyceridemia range and average LDL cholesterol levels below 80 mg/dl (177). At doses of 500-2000 mg/d, niacin lowers triglycerides by 10–30%, increases HDL cholesterol by 10–40%, and lowers LDL cholesterol by 5–20%. Although higher doses of immediate-release (crystalline) niacin have been used, the maximum dose of the prescription extended-release formulation is 2000 mg/d; doses this high are reached by increasing the dose slowly over time. Niacin contributes to the release of prostaglandin D2 from cells in the skin leading to vasodilatation. The most common side effect is cutaneous flushing, which is most significant with the first few doses. It occurs 15 to 60 min after ingestion and typically lasts 15 to 30 min. Ingestion after a meal and administration of uncoated aspirin before the meal minimizes flushing. The most serious complication of niacin therapy is hepatotoxicity (which is dose dependent), and therapy should be accompanied by monitoring of liver function tests (178). Other side effects of niacin therapy include impairment or worsening of glucose tolerance and hyperuricemia. Niacin can be used safely in patients with glucose intolerance and can be considered in diabetic patients on oral medications or insulin who have moderate to good glycemic control but could cause conversion of borderline glucose intolerance to meet diabetes criteria in some patients. Niacin can increase blood levels of uric acid by blocking its excretion and can precipitate or worsen gout unless the patient is treated with allopurinol. Niacin is contraindicated in patients with active peptic ulcer disease.

n-3 Fatty acids

The long-chain marine omega-3 fatty acids [eicosapentaenoic acid, C20:5n-3 (EPA) and docosahexaenoic acid, C22:6n-3 (DHA)] lower fasting and postprandial triglyceride levels in a dose-dependent fashion. Approximately 3 to 4 g/d of EPA plus DHA are necessary to reduce hypertriglyceridemia by 20–50% (179). HDL cholesterol is mildly increased by about 5%. With reductions of triglyceride levels, there can be increased levels of LDL cholesterol due to increased conversion of VLDL to LDL. To date, no studies using high-dose n-3 fatty acids in hypertriglyceridemia patients have shown a beneficial cardiovascular outcome. EPA added to statin therapy in subjects with cholesterol levels above 250 mg/dl in an open-label study resulted in a 19% relative reduction in major coronary events (180). Omega-3 fatty acids (*e.g.* Lovaza) may be considered for treatment of triglyceride levels above 1000 mg/dl. Over-the-counter preparations of omega-3 fatty acids have variable quantities of EPA and DHA ranging from 20–50%, depending on products. The nutrition

labels must be studied to calculate the number of capsules required to obtain a dose of 3–5 g of n-3 fatty acids. Omega-3 acid ethyl esters are available by prescription in capsules that contain 80% EPA and DHA. Thus, a dose of four capsules is needed to lower triglycerides by 30–50% (181). Side effects with large doses of omega-3 fatty acids include fishy taste and burping. Beyond an impact of omega-3 fatty acid supplements on triglyceride levels, intake of diets rich in n-3 fatty acids have resulted in positive outcomes with regard to cardiovascular disease (182–184).

Recommendation

3.6. We recommend that statins not be used as monotherapy for severe or very severe hypertriglyceridemia. However, statins may be useful for the treatment of moderate hypertriglyceridemia when indicated to modify cardiovascular risk (1/⊕⊕◯◯).

3.6. Evidence

Hydroxymethylglutaryl coenzyme A reductase inhibitors, or statins, have a modest triglyceride-lowering effect, typically about 10–15%, which is dose-dependent. High doses of statins that have strong efficacy, such as atorvastatin 80 mg or rosuvastatin 40 mg, can lower plasma triglyceride by 25–30%. Statin monotherapy should not be first-line therapy to reduce triglyceride levels in patients with severe or very severe hypertriglyceridemia (>1000 mg/dl). Addition of statins can be considered to reduce cardiovascular risk in patients with mild-to-moderate hypertriglyceridemia (>150 mg/dl and <1000 mg/dl) and elevated non-HDL cholesterol. Side effects of statins occur in about 5–10% of patients. Muscle symptoms ranging from leg cramps to aching to weakness occur in about 10% of patients, whereas rhabdomyolysis is rare (185). Conditions predisposing to severe myopathy include advanced age, renal failure, polypharmacy, and acute illness.

Combination therapy and other drugs

Because the four drug classes described above (fibrates, niacin, n-3 fatty acids, and statins) have different underlying mechanisms in reducing triglyceride levels, as well as correcting other associated dyslipidemias, there is a considerable potential for use of drug combinations based on complementary mechanisms (169, 186). Examples include a combination of niacin and statins or fibrates and statins. Attention needs to be paid to potential drug-drug interaction. To minimize such risks, combination treatment should be initiated carefully, and advice should be sought from clinicians familiar with these types of interactions.

Pioglitazone, a peroxisome proliferator-activated receptor-γ agonist, has a mild triglyceride-lowering effect, whereas rosiglitazone does not lower triglycerides (188, 189). Side effects reported include weight gain and risk of heart failure and macular edema (190). Of note, some data suggest an association between the use of pioglitazone and an increased risk of bladder cancer (191). Orlistat, an inhibitor of intestinal lipase that is used as a weight-loss drug, can lower postprandial triglyceride levels. It is a pharmacological method to reduce fat absorption, which may be helpful in patients with fasting hyperchylomicronemia (187). Orlistat has been used in combination with fibrates with additive effects. Side effects include bloating, diarrhea, incontinence, and oily leakage and are related to the amount of fat ingested in the diet. Furthermore, cases of severe liver injury have been reported to occur rarely with the use of orlistat.

Acknowledgments

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Cosponsoring Associations: American Heart Association, European Society of Endocrinology.

Financial Disclosure of Task Force

Lars Berglund, M.D., Ph.D. (chair)—Financial or Business/Organizational Interests: NIH, AHA, Pfizer, AstraZeneca, Danone; Significant Financial Interest or Leadership Position: AHA, Pfizer, Astra-Zeneca. **John D. Brunzell, M.D.**—Financial or Business/Organizational Interests: American Diabetes Association, Endocrine Society, Amsterdam Molecular Therapeutics, Lexicon Genetics, Merck Research Laboratories, Daiichi Sankyo, University of Washington; Significant Financial Interest or Leadership Position: none declared. **Anne Carol Goldberg, M.D., F.A.C.P.**—Financial or Business/Organizational Interests: AHA, NIH/NHLBI, National Lipid Association, Foundation of the National Lipid Association, Washington University, Merck, Sanofi-Aventis, Roche, ISIS/Genzyme; Significant Financial Interest or Leadership Position: National Lipid Association, Foundation of the National Lipid Association. **Ira Jay Goldberg, M.D.**—Financial or Business/Organizational Interests: American Heart Association, American Diabetes Association, Astra-

Zeneca, GSK, Merck, Medcom, Amylin, Schering; Significant Financial Interest or Leadership Position: none declared. **Frank Sacks, M.D.**—Financial or Business/Organizational Interests: NIH/NHLBI, R3i Foundation, Metabolic Syndrome Institute, American Society of Nutrition, Sherborne-Gibbs, WebMD, Abbott, AstraZeneca, Aegerlan, Pfizer, Lilly, Isis, Genzyme, Roche, Genentech; Significant Financial Interest or Leadership Position: R3i Foundation, Metabolic Syndrome Institute, American Society of Nutrition. **Mohammad Hassan Murad, M.D.***—Financial or Business/Organizational Interests: KER Unit (Mayo Clinic); Significant Financial Interest or Leadership Position: none declared. **Anton F. H. Stalenhoef, M.D., Ph.D., F.R.C.P.**—Financial or Business/Organizational Interests: Dutch Heart Foundation, Merck, Genzyme, Roche; Significant Financial Interest or Leadership Position: Dutch Journal of Medicine, Current Opinion Lipidology.

* Evidence-based reviews for this guideline were prepared under contract with The Endocrine Society.

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