Hypertriglyceridemia: A Guide to Assessment and Treatment

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The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines recommend that a fasting lipid profile be obtained and repeated every 5 years in all adults beginning at age 20 years.[1] Based on these guidelines, hypertriglyceridemia is defined as a fasting plasma triglyceride level that exceeds 200 mg/dL and can be further classified as borderline-high (150–199 mg/dL), high (200–499 mg/dL), and very high (≥ 500 mg/dL).[1] When triglyceride levels exceed 500 mg/dL, patients may develop acute pancreatitis. Levels exceeding 1000 mg/dL define chylomicronemia, which may result in lipemia retinalis, eruptive xanthomas, hepatomegaly, and potentially fatal acute pancreatitis.

In the United States, the 90th percentile for triglyceride levels historically has been estimated at approximately 250 mg/dL,[2] 100 mg/dL above the currently recommended target. Hypertriglyceridemia is associated with an increased risk for coronary artery disease (CAD) and can be a marker for other lipid and nonlipid cardiovascular risk factors (ie, small low-density lipoprotein [LDL] particles, low high-density lipoprotein [HDL] cholesterol, hypertension, insulin resistance). Overweight/obesity and insulin resistance have been found to be associated with elevated triglyceride levels, and hypertriglyceridemia is a component of the metabolic syndrome.[3,4] Given the rising incidence of diseases associated with overweight/obesity and insulin resistance, including the metabolic syndrome and diabetes mellitus,[5–7] identification and treatment of hypertriglyceridemia is becoming increasingly important.

Hypertriglyceridemia is often clinically silent and is typically detected by lipid screening in asymptomatic patients. Treatment of hypertriglyceridemia should be individualized based on triglyceride level, family history of CAD, presence of CAD risk factors (eg, smoking, hypertension, HDL cholesterol levels < 40 mg/dL), and age. This article reviews the pathogenesis, classification, clinical evaluation, and rationale for treatment of hypertriglyceridemia. Treatment recommendations are outlined based on severity of triglyceride elevations.

TAKE HOME POINTS

- Hypertriglyceridemia is defined by the National Cholesterol Education Program Adult Treatment Panel III as a fasting plasma triglyceride level exceeding 200 mg/dL and is further classified according to severity of triglyceride elevation as borderline-high (150–199 mg/dL), high (200–499 mg/dL), and very high (≥ 500 mg/dL).
- Although genetic influences predispose patients to hypertriglyceridemia, clinicians must be aware that common medical disorders, such as diabetes mellitus, liver disorders, and hypothyroidism, as well as medications can exacerbate triglyceride levels.
- Triglyceride-lowering is important for reducing coronary artery disease risk and for reducing the risk of pancreatitis among patients with chylomicronemia.
- Therapeutic lifestyle changes are recommended for all patients with elevated triglyceride levels.
- Triglyceride-lowering agents, including fibrates, nicotinic acid, and n-3 polyunsaturated fatty acids, can be used in patients with high triglyceride levels to achieve recommended therapeutic goals.

PATHOGENESIS

Hypertriglyceridemia results from increased production of very low-density lipoprotein (VLDL), reduced VLDL clearance, or more commonly the dual effect of both processes.[8] Triglyceride-rich lipoprotein particles are derived from both endogenous and exogenous sources. The liver (endogenous) produces triglyceride-rich VLDL particles that are secreted into the blood, which are then delivered to peripheral tissues where they are metabolized by lipoprotein lipases

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Table 1. Fredrickson Classification of Lipid Disorders

Type	Elevated Particles	Associated Clinical Disorders	Serum Total Cholesterol/Triglycerides
I	Chylomicrons	Lipoprotein lipase deficiency, apolipoprotein C-II deficiency	Normal/very elevated
IIa	LDL	Familial hypercholesterolemia, polygenic hypercholesterolemia, nephrosis, hypothyroidism, familial combined hyperlipidemia	Very elevated/normal
IIb	LDL, VLDL	Familial combined hyperlipidemia	Very elevated/elevated
III	IDL	Dysbetalipoproteinemia/broad beta disease	Elevated/elevated
IV	VLDL	Familial hypertriglyceridemia, familial combined hyperlipidemia, sporadic hypertriglyceridemia, diabetes mellitus	Normal, elevated/very elevated
V	Chylomicrons, VLDL	Diabetes mellitus	Elevated/very elevated

IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein.

and used for energy by muscle tissue or stored in adipose tissue. Dietary fats (exogenous) are absorbed from the gastrointestinal tract and form triglyceride-rich chylomicron particles in the intestinal wall that are secreted into the blood and cleared by the liver. Both VLDL and chylomicron particles are cleared by a common pathway that involves tissue lipases.[9] When lipoprotein lipase activity is decreased, the clearance of both VLDL and chylomicron particles is impaired, resulting in an accumulation of triglyceride-rich lipoprotein particles in the blood (ie, underutilization). This susceptibility is modulated by genetic influences that reduce VLDL utilization, such as inherited syndromes that impair lipoprotein lipase activity. Exogenous factors such as overweight/obesity,[10] diets high in saturated fats and rich in carbohydrates,[11,12] and alcohol consumption[13] can increase chylomicron and VLDL production (ie, overproduction) and lead to hypertriglyceridemia as well.

CLASSIFICATION AND ETIOLOGY

Lipid disorders were previously defined according to the Fredrickson classification, which is based on 6 phenotypes related to the presence of hypercholesterolemia (total cholesterol, ≥ 250 mg/dL), hypertriglyceridemia (triglyceride level, ≥ 250 mg/dL), and/or chylomicronemia (triglyceride level, ≥ 1000 mg/dL; **Table 1**).[2] Currently, the NCEP ATP III classification based solely on triglyceride level is more commonly used (ie, normal [triglyceride level, < 150 mg/dL]), borderline-high, high, very high).[1]

Hypertriglyceridemia can be grouped into primary or secondary types. Of the primary types of hypertriglyceridemia, pure chylomicronemia (type I based on the Fredrickson classification) is a rare autosomal recessive disorder resulting from a deficiency of lipoprotein lipase or apolipoprotein C-II. More frequently encountered primary causes of hypertriglyceridemia include inherited syndromes such as (1) familial hypertriglyceridemia (types IV and V), which can be aggravated by exogenous factors that increase VLDL production; (2) familial combined dyslipidemia (types IIa, IIb, and IV), which can present with elevations of VLDL, LDL, or both and is associated with a family history of premature CAD; (3) polygenic hypercholesterolemia (type IIa), which commonly presents in CAD patients with concomitantly elevated LDL levels; and (4) broad beta disease (type III), which results from an apolipoprotein E–binding defect that impedes VLDL clearance.

Conditions that secondarily cause or contribute to hypertriglyceridemia are outlined in **Table 2**. Obesity is a well-recognized secondary cause of hypertriglyceridemia.[10] Excessive adiposity impairs triglyceride clearance (underutilization), resulting in hypertriglyceridemia. Clinical disorders related to insulin resistance, including diabetes mellitus, increase the risk for hypertriglyceridemia.[14] Insulin resistance leads to decreased triglyceride clearance (underutilization) as well as increased triglyceride release from adipocytes (overproduction), which elevates triglyceride levels in the blood. Some liver disorders (eg, nonalcoholic fatty liver disease) can increase triglyceride levels as a result of triglyceride overproduction by hepatocytes.[15] Hypothyroidism can affect lipid metabolism, reducing triglyceride clearance and causing hypertriglyceridemia.[16] The prevalence of hypertriglyceridemia is increased among HIV-infected patients as well as those receiving antiretroviral therapy.[17,18] Specifically, the protease inhibitors can both impair triglyceride removal and increase triglyceride production.[19] As mentioned previously, diets high in saturated fats and carbohydrates and excessive alcohol consumption can increase triglyceride production and lead to hypertriglyceridemia.[11–13] Hence, monounsaturated fats, which are more lipid-neutral, have been suggested as a better replacement for dietary saturated fats than carbohydrates.[20]

Table 2. Secondary Causes of and Contributors to Hypertriglyceridemia

Overweight/obesity
Diet (high in saturated fats and carbohydrates)
Physical inactivity
Excessive ethanol consumption
Hypothyroidism
Lipodystrophies (including the metabolic syndrome)
HIV infection
Renal disease (including the nephrotic syndrome and renal dialysis)
Acute spinal cord injury
Anorexia nervosa
Cushing's syndrome
Organ transplant
Sarcoidosis
Systemic lupus erythematosus
Myeloma
Medications (antiretroviral therapy, glucocorticoids, estrogens, tamoxifen, 13-cis-retinoic acid, some antihypertensive agents [hydrochlorothiazide, nonselective β-blockers]) and some antipsychotic medications [clozapine, olanzapine])

CLINICAL EVALUATION

Typically, patients with hypertriglyceridemia are asymptomatic. Awareness for hypertriglyceridemia should be raised in patients with CAD, diabetic patients with or without CAD, and patients presenting with acute pancreatitis. Patients with hypertriglyceridemia often have cardiovascular disease. This is especially relevant for patients with diabetes or insulin resistance, as these patients frequently present with atherogenic dyslipidemia,[21] a triad of hypertriglyceridemia, low HDL cholesterol, and increased levels of small, dense LDL particles. The presence of low HDL cholesterol, small LDL particles, and/or remnant lipoproteins strongly predict CAD, and thus patients presenting with this "lipid triad" can be considered at risk for premature CAD.[1,22] Small, dense LDL particles have a high apolipoprotein B-100 concentration as compared with large, buoyant LDL particles with normal apolipoprotein B-100 content, which are less atherogenic.

The evaluation should always include a detailed personal, family, and medication history. Information that should raise suspicion for hypertriglyceridemia includes a positive family history for lipid disorders and diabetes mellitus; a personal history of vascular disease, diabetes mellitus, and/or pancreatitis; and prescribed medications known to increase triglyceride levels (ie, glucocorticoids, estrogens, tamoxifen, hydrochlorothiazide, nonselective β-blockers, clozapine, olanzapine). Information regarding a patient's lifestyle is relevant because sedentary behavior coupled with a high-calorie, fat-rich diet can promote hypertriglyceridemia, especially in the setting of overweight/obesity. Overweight/obesity (body mass index, > 27 kg/m^2) is an important clinical sign given its well-established association with hypertriglyceridemia.[10]

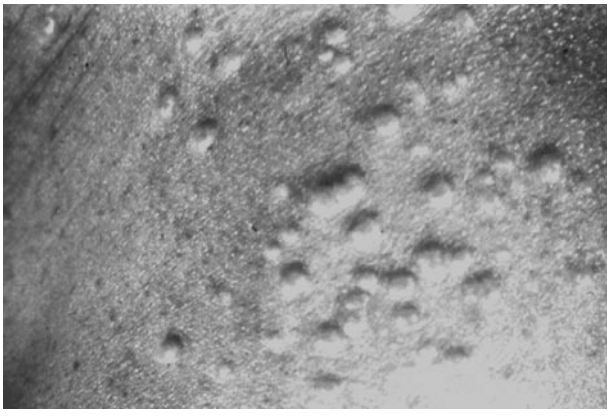

Figure. Eruptive xanthoma.

Patients with chylomicronemia may present with abdominal pain, a result of organomegaly caused by organ distention from fat infiltration that can trigger acute pancreatitis. Clinical findings pathognomonic for chylomicronemia include eruptive xanthoma and lipemia retinalis. Eruptive xanthoma consists of small yellowish papules frequently surrounded by an erythematous base that appear predominantly on the buttocks and elbows and other pressure-sensitive areas and are caused by large amounts of chylomicron triglycerides deposited in cutaneous histiocytes (**Figure**).[23] Lipemia retinalis is characterized by a creamy, salmon-colored retina and white retinal vessels on ophthalmoloscopic examination. Diffuse lymphadenopathy resulting from chylomicronemia has been reported.[24] Although chylomicronemia is uncommon (found in 1.79/10,000 patients in 1 study[25]), it is an important clinical entity to diagnose and treat given the associated mortality risk.

A 12-hour fast is recommended to optimally assess triglyceride values. A fasting plasma triglyceride level greater than 200 mg/dL on laboratory testing is diagnostic of hypertriglyceridemia. A fasting triglyceride level in excess of 500 mg/dL is suggestive of chlyomicronemia because nonfasting triglyceride levels will often exceed 1000 mg/dL in these patients. Acute physiologic stress, such as infections and the acute coronary syndrome, can raise triglyceride levels by twofold in some patients.[26] Routine laboratory tests, including measurement of

serum glucose, serum creatinine, and blood urea nitrogen as well as thyroid and liver function testing, should be performed to rule out secondary causes of hypertriglyceridemia (Table 2). Thyroid-stimulating hormone levels will be elevated in patients with hypothyroidism. Hyperglycemia may be noted in the setting of diabetes mellitus. Serum creatinine and blood urea nitrogen are elevated in the setting of renal failure, while albumin is reduced in the nephrotic syndrome. Transaminitis occurs in the setting of acute liver disease. Although not part of the routine evaluation of hypertriglyceridemia, serum protein electrophoresis is abnormal in patients with myeloma and systemic lupus erythematosus.

RATIONALE FOR TREATMENT

Recommendations for treatment of hypertriglyceridemia have been debated because data from epidemiologic studies have been inconclusive regarding whether triglycerides are an independent risk factor for CAD.[27,28] At present, hypertriglyceridemia has become more generally accepted as a risk factor for atherosclerosis and vascular disease.[29] Still, epidemiologic studies have inherent methodologic issues that limit the ability to conclusively demonstrate that hypertriglyceridemia is independently associated with CAD risk.[27] For instance, wide biologic variations in triglyceride levels weaken the statistical power in correlation analyses. Additionally, because hypertriglyceridemia is not a single clinical entity, its presence can reflect different dyslipidemic entities (eg, familial combined dyslipidemia, which is atherogenic) that are associated with varying degrees of CAD risk. Furthermore, triglyceride levels are inversely related to plasma HDL cholesterol levels, which are a more powerful predictor of CAD risk.

Multiple logistic regression analysis cannot effectively demonstrate that triglycerides are a CAD risk factor independent of plasma HDL cholesterol levels. However, several recent studies support the relationship between hypertriglyceridemia and increased CAD risk. A recent meta-analysis of 17 epidemiologic studies including 46,413 men and 10,864 women indicates that triglyceride levels are associated with a 30% and 75% increased risk of CAD in men and women, respectively, independent of plasma HDL cholesterol.[30] A prospective Danish study involving 7587 women and 6394 men found that nonfasting triglyceride levels were associated with increased risk of CAD and overall mortality during a 26-year period.[31] Similarly, the Women's Health Study, which compared fasting versus nonfasting triglyceride levels in 26,509 initially healthy women, found that fasting and nonfasting triglyceride levels were associated with an increased CAD risk during an 11.4-year follow-up.[32] Although the association weakened after adjusting for confounding variables (eg, measurements of insulin resistance and plasma HDL cholesterol levels) in the fasting triglyceride analysis, the strength of the associations persisted in the nonfasting triglyceride analysis.[32]

The Bezafibrate Infarction Prevention study showed that elevated triglyceride levels were associated with a small independent risk of increased mortality in men and women with CAD, especially among those with elevated total and LDL cholesterol levels.[33] In addition, randomized controlled trials of primary and secondary prevention of CAD with gemfibrozil, which has powerful HDL cholesterol–raising and triglyceride-lowering effects, have shown that gemfibrozil therapy reduced CAD-related mortality without lowering LDL cholesterol.[34,35] The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, a 5-year randomized prospective study of fenofibrate versus placebo in 9795 diabetic men and women, showed that patients receiving fenofibrate experienced a reduction in total cardiovascular events (a composite of CAD death, myocardial infarction, stroke, and cardiac and cerebrovascular revascularization procedures) as compared with placebo-treated patients.[36] Although fenofibrate had no significant effect on total CAD death alone, this may be due to the use of statin medications in the placebo group, which would have offset the ability to demonstrate a larger benefit from using fibrates.

TREATMENT RECOMMENDATIONS

The NCEP ATP III treatment guidelines[1,37] recommend achieving non-HDL cholesterol targets for patients with triglyceride levels less than 500 mg/dL. Non-HDL cholesterol is the sum of triglyceride and plasma LDL cholesterol levels.[5] These non-HDL cholesterol targets are individualized according to the presence of CAD risk factors, which include cigarette smoking, hypertension, a plasma HDL cholesterol level less than 40 mg/dL, a family history of premature CAD (a first-degree male relative aged < 55 yr, a first-degree female relative aged < 65 yr), and age (men aged ≥ 45 yr and women aged ≥ 55 yr).

For patients with borderline-high triglycerides (150–199 mg/dL), levels of VLDL are not sufficiently elevated to warrant a non-HDL cholesterol target goal (higher serum VLDL reflects atherogenic potential). For patients with a high triglyceride level (200–499 mg/dL) with 0 or 1 CAD risk factor (low CAD risk) or 2 or more CAD risk factors (average CAD risk), the non-HDL cholesterol goals are less than 190 mg/dL and less than 160 mg/dL, respectively. Patients with a triglyceride level between 200 and 499 mg/dL and known CAD or CAD

Table 3. Summary of Treatment Recommendations Based on Triglyceride Level, Risk of Coronary Artery Disease, and Non-HDL Cholesterol Goals

Triglyceride Level/CAD Risk	Treatment
High (200–499 mg/dL)	
Low CAD risk; non-HDL cholesterol goal < 190 mg/dL	Single agents: statins, nicotinic acid, fibrates, n-3 PUFAs
Average CAD risk; non-HDL cholesterol goal < 160 mg/dL	Combination therapy: statin/nicotinic acid, ezetimibe/fibrate, ezetimibe/statin, fibrate/n-3 PUFAs, n-3 PUFAs/nicotinic acid
High CAD risk; non-HDL cholesterol goal < 130 mg/dL (< 100 mg/dL in some patients)	
Very high (≥ 500 mg/dL)	Fibrates and/or n-3 PUFAs
Chylomicronemia (> 1000 mg/dL) with abdominal pain	Hospitalization with insulinization, fibrates, and/or n-3 PUFAs

CAD = coronary artery disease; HDL = high-density lipoprotein; PUFA = polyunsaturated fatty acid.

Table 4. Medications Approved by the US Food and Drug Administration for Management of Hypertriglyceridemia

Medication	Recommended Dose
Lovastatin	10–80 mg orally at bedtime
Pravastatin	10–80 mg orally at bedtime
Simvastatin	5–80 mg orally at bedtime
Fluvastatin	20–80 mg orally at bedtime
Atorvastatin	10–80 mg orally at bedtime
Rosuvastatin	5–40 mg orally at bedtime
Nicotinic acid (immediate release)	1.5–3 g orally daily in divided doses
Nicotinic acid (extended release)	1–2 g orally at bedtime
Ezetimibe	5–10 mg orally daily
Gemfibrozil	600 mg orally twice daily
Fenofibrate micronized	Titrate to 200 mg/day
Fenofibrate regular	Titrate to 400 mg/day
Omega-3-acid ethyl esters (fish oil)	Six 1-g capsules daily in single or divided doses

risk equivalents, including diabetes mellitus, cerebrovascular accident, peripheral arterial disease, abdominal aortic aneurysm, or a Framingham CAD risk score of 20 or greater (high CAD risk), the non-HDL cholesterol goal is less than 130 mg/dL (< 100 mg/dL is optimal for some patients). In patients with a triglyceride level of 500 mg/dL or greater, the ideal goal is to lower triglyceride levels to less than 150 mg/dL to reduce the risk of acute pancreatitis, although this target is often not feasible due to the presence of genetic syndromes that affect triglycerides. Patients with a triglyceride level greater than 1000 mg/dL in the setting of the chylomicronemia syndrome with acute pancreatitis should be managed in an inpatient setting with the immediate goal of resolving chylomicronemia. **Table 3** provides an overall conceptual summary of treatment considerations based on triglyceride level, CAD risk, and non-HDL cholesterol targets. **Table 4** lists agents currently approved by the US Food and Drug Administration for reducing non-HDL cholesterol and triglyceride levels.

Patients with Borderline-High Triglycerides

The therapeutic lifestyle changes (TLC) intervention is aimed at promoting weight loss by reducing the intake of dietary saturated fats (< 7% of total calories) and cholesterol (< 200 mg/day) and increasing physical activity. TLC should be a part of the management strategy for all patients with elevated triglyceride levels and is a first-line option in patients with borderline-high triglycerides (150–199 mg/dL). Physical activity has a well-demonstrated role in reducing body fat and triglyceride levels.[38] In the Diabetes Prevention Study, patients randomized to TLC (7% weight loss, ≥ 150 min of physical activity/wk) had a 58% reduced risk of obesity and new-onset diabetes mellitus during a 3-year period compared with placebo-treated patients.[39] In the setting of acute pancreatitis, a more aggressive nonfat diet (rice/fruit diet) is recommended[40] in addition to hospitalization for insulinization to eliminate chylomicronemia. In patients undertaking TLC, progress should be monitored with plasma lipid level testing every 6 weeks by a primary care provider on a long-term basis or until triglycerides become high enough to warrant pharmacologic treatment. A period of 3 to 6 months of TLC is recommended in patients at low and average CAD risk before considering pharmacologic therapy. However, in patients at high risk for CAD, medications (ie, hydroxymethylglutaryl coenzyme A reductase inhibitors [statins] in patients with triglycerides < 500 mg/dL) should be initiated in combination with TLC. Of note, because hypertriglyceridemia frequently occurs in the setting of diabetes mellitus, adequate insulinization and adjustment of hyperglycemic agents is of paramount importance in managing hypertriglyceridemia in diabetic patients.

Patients with High Triglycerides

For patients at low and average risk for CAD with a high triglyceride level (200–499 mg/dL), first-line medications can be initiated if target non-HDL cholesterol levels are not achieved after 3 to 6 months of participation in a TLC program. Medications should

be initiated immediately in patients at high risk for CAD with triglycerides less than 500 mg/dL. Elevated non-HDL cholesterol levels in patients with triglycerides from 200 to 499 mg/dL are typically the result of either prominent LDL cholesterol or triglyceride elevations. From this perspective, the initial choice of medications in these patients is based on the principle cause of non-HDL cholesterol elevation (ie, either LDL or triglycerides) to maximize non-HDL cholesterol–lowering potential. Therefore, medications can be simplistically dichotomized as primarily cholesterol-lowering or triglyceride-lowering and should be employed based upon the main contributor to non-HDL cholesterol.

Cholesterol-lowering medications. Cholesterol-lowering medications include bile acid sequestrants, statins, and ezetimibe. However, bile acid sequestrants can exacerbate hypertriglyceridemia and should not be used in this setting. When LDL cholesterol is the prominent cause of increased non-HDL cholesterol, statins constitute first-line medications given their ability to markedly reduce LDL cholesterol levels (and therefore non-HDL cholesterol levels) and their well-established effect on reducing CAD risk. Statins inhibit hepatic hydroxymethylglutaryl coenzyme A reductase, a rate-limiting enzyme in endogenous cholesterol synthesis, which results in up-regulation of LDL receptors and increased LDL clearance from plasma. Statins can lower LDL cholesterol levels by up to 60%, depending on the dose and type of statin, and can also raise HDL cholesterol by up to 20% and lower triglycerides by up to 30%.[1] Adverse events associated with statin use include transaminitis, myositis, and rhabdomyolysis,[41] but they are infrequent and are more likely to occur in older patients and when taken in conjunction with medications that inhibit cytochrome P3A4 (ie, macrolide antibiotics, azole antifungals, cyclosporine). Medication dose should be increased until patients have achieved non-HDL cholesterol target levels (ie, < 190, < 160, or < 130 mg/dL depending on CAD risk). Plasma lipid levels and liver function tests should be measured every 6 weeks for medication adjustment.

Ezetimibe impairs cholesterol absorption at the intestinal brush border, resulting in up-regulation of LDL receptors and reduced plasma LDL cholesterol levels. Ezetimibe is well-tolerated and can be used in conjunction with a statin to reduce LDL cholesterol (ie, non-HDL cholesterol) by an additional 10% to 15%, but it has little effect on triglyceride levels.[42] Adverse effects are infrequent and include transaminitis, myalgia, rhabdomyolysis, hepatitis, acute pancreatitis, and thrombocytopenia.

Triglyceride-lowering medications. Triglyceride-lowering agents are especially important in the setting of low plasma HDL cholesterol levels and include nicotinic acid (niacin), fibrates, and n-3 polyunsaturated fatty acids (PUFAs). Although nicotinic acid can be used as monotherapy, it is more commonly used in combination with statins, especially in patients with low HDL cholesterol.[43] Nicotinic acid can raise HDL cholesterol by up to 30% and lower LDL cholesterol and triglycerides by 15% to 20% and 15% to 35%, respectively.[43] Prostaglandin-mediated flushing is the most common side effect, occurring in approximately 80% of patients receiving the immediate-release (shorter-acting) form, but it is generally not an issue for patients taking the extended-release form. Flushing can be reduced by pretreatment with acetylsalicylic acid 30 minutes prior to dosing. Other adverse effects include pruritus, paresthesias, and nausea. Some studies suggest nicotinic acid can exacerbate insulin resistance;[44] hence, clinicians should monitor blood glucose levels in diabetic patients and may need to initiate or intensify hyperglycemic therapy.

Fibrates can reduce triglycerides by 50% and concomitantly raise plasma HDL cholesterol by 20%.[45] Their use is contraindicated in the setting of hepatic or renal dysfunction. Important potential side effects include increased lithogenicity of bile (ie, increased risk for cholelithiasis) and potentiation of the effects of oral anticoagulants. Combination therapy with fibrates and statins should generally be avoided due to concerns of muscle and liver toxicity, but, if necessary, statins can be given in low doses with close patient monitoring. Fibrates can be safely combined with ezetimibe. A recent study showed that fenofibrate combined with ezetimibe resulted in significantly lower triglyceride and non-HDL cholesterol levels as compared with ezetimibe alone.[46]

N-3 PUFAs (fish oil) can reduce triglycerides by 50% with little effect on other lipid fractions.[47] Major adverse effects include gastrointestinal complaints of eructation. N-3 PUFAs can be safely combined with other medications including statins, fibrates, and nicotinic acid to reduce triglyceride levels by up to an additional 50%.[47,48]

Patients with Very High Triglycerides

For patients with very high triglycerides (≥ 500 mg/dL), first-line agents include fibrates and/or n-3 PUFAs, initiated immediately. Although the ideal goal is to lower triglycerides to less than 150 mg/dL, this is typically not realistic and a more reasonable goal is to maintain fasting triglyceride levels less than 500 mg/dL to reduce the risk for acute pancreatitis. Fibrates and n-3 PUFAs are usually used in combination to reduce triglycerides by an additional 50%.[49] If target triglyceride levels can be achieved, LDL cholesterol–lowering medications can

be considered in high-risk patients to achieve non-HDL cholesterol target goals as described previously.

Patients with Triglycerides Exceeding 1000 mg/dL and Experiencing Abdominal Pain

Patients who present with chylomicronemia (ie, triglyceride levels > 1000 mg/dL) and abdominal pain should be considered a medical emergency because of the concern for acute pancreatitis. Typically, this occurs in the setting of uncontrolled diabetes mellitus. The initial goal of resolving chylomicronemia is best accomplished in a hospital setting. The patient should be given nothing by mouth and hydrated with intravenous fluids and administered insulin to reduce triglyceride levels. If the patient does not have diabetes, intravenous glucose is required to prevent hypoglycemia. Once chylomicronemia has resolved (triglycerides < 1000 mg/dL), symptoms of chylomicronemia syndrome (ie, lipemia retinalis, eruptive xanthomas, hepatomegaly) will begin to diminish and the patient can then be instructed to adopt a nonfat diet such as the rice/fruit diet.[40] This diet can be nutritionally tolerated on a short-term basis to control triglyceride levels while the patient is advanced to a long-term TLC program. Fibrates and n-3 PUFAs can be initiated prior to discharge.

Triglyceride levels should be monitored every 6 weeks until the therapeutic target is achieved, and once triglyceride levels are stable, monitoring can take place every 3 to 6 months. Liver function tests should be obtained before initiating statins, fibrates, and nicotinic acid and should be rechecked each time the medication dose is adjusted. Once the patient is on a stable dose, liver function testing can be performed on a 3- to 6-month basis. Diabetic patients will need close long-term attention to their treatment regimen for diabetes to achieve and maintain adequate glucose control.

CONCLUSION

With the increasing incidence of overweight/obesity and diabetes mellitus, management of triglyceride levels is assuming greater clinical relevance. Practitioners have an important role in evaluating patients with hypertriglyceridemia and implementing therapeutic lifestyle and pharmacologic interventions. Treatment should be individualized based on triglyceride level, patient risk factors, and family history of CAD. TLC is recommended for all patients regardless of risk factors/family history. **HP**

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