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Hypertriglyceridemia:
A review of the evidence

Abstract: Elevated triglycerides are independently associated with increased atherosclerotic cardiovascular disease risk. Hypertriglyceridemia is often a polygenic condition that can be affected by numerous interventions. Primary care NPs are well positioned to appropriately evaluate and manage hypertriglyceridemia, improving overall health outcomes.

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High triglyceride (TG) levels are becoming increasingly common in the US and are associated with an increased risk of cardiovascular disease and life-threatening pancreatitis.[1,2] Clinical practice guidelines for the evaluation and treatment of hypertriglyceridemia have been published by a number of organizations, including the American Heart Association (AHA), the National Lipid Association (NLA), and the Endocrine Society (ES); a joint guideline was published by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE).[3-6]

Observational, randomized clinical, and genetic studies all support the causal relationship between elevated TG levels and atherosclerotic cardiovascular disease (ASCVD).[3,4] High levels are found to be a biomarker of atherogenesis. However, the complexity of lipid metabolism and the confounding effects of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) have made the direct correlation with ASCVD a research challenge.[3,4] TG levels are also greatly impacted by lifestyle and genetics, which further muddle the risk relationship.

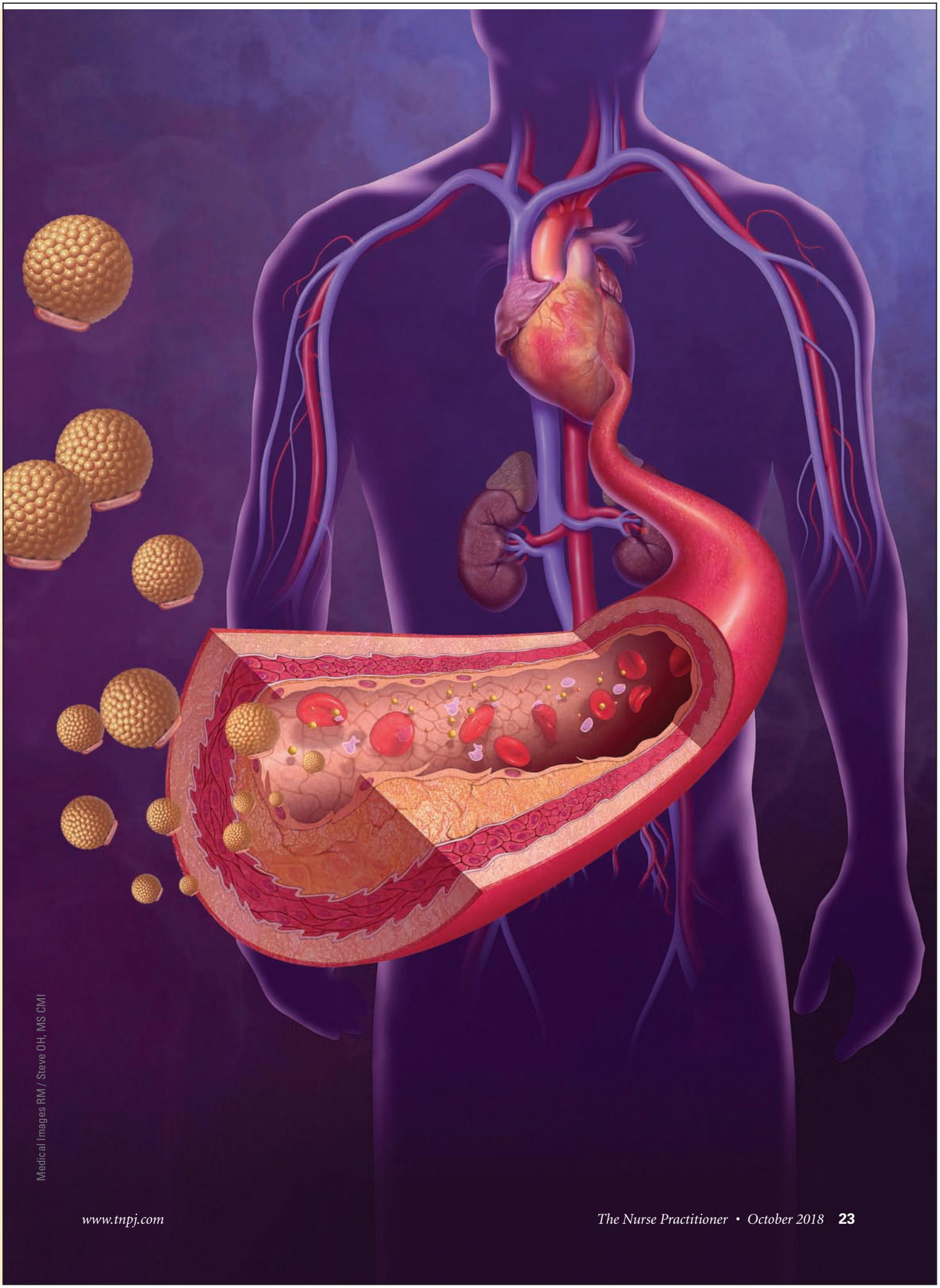
Diagnosis and screening

Hypertriglyceridemia is often clinically silent and is most often found while screening patients presenting without any symptoms. According to the most recent guidelines from the AHA and NLA, TG levels are considered normal if they are less than 150 mg/dL, borderline high if they are 150 to 199 mg/dL, high if they are 200 to 499 mg/dL, and very high if they are 500 mg/dL or greater.[3,5] The ES defines severe hypertriglyceridemia as TG levels of 1,000 to 1,999 mg/dL and very severe hypertriglyceridemia as 2,000 mg/dL or greater.[6]

Hypertriglyceridemia is classified as primary when there are no secondary causes identified. Patients with hypertriglyceridemia should always be evaluated further for secondary causes, and treatment should target this diagnosis. Lab tests to exclude secondary causes include fasting blood glucose (diabetes mellitus), serum creatinine (kidney disease or nephrotic syndrome), thyroid-stimulating hormone (hypothyroidism), gamma glutamyl transferase, and mean cell volume (alcohol abuse), in addition to non-HDL cholesterol.[6]

Screening guidelines for dyslipidemia vary by age-group but should be based on clinical judgment.

Keywords: ASCVD, atherosclerotic cardiovascular disease, dietary modification, hypertriglyceridemia, pharmacologic intervention, physical activity



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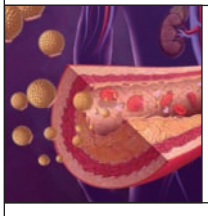
According to the clinical practice guidelines from ES, adults should be screened for high TG levels once every 5 years because of the potential risk of cardiovascular disease and pancreatitis associated with hypertriglyceridemia.[6] These guidelines also recommend that the diagnosis of hypertriglyceridemia be made using fasting lipid levels and not nonfasting levels.

The most recent guidelines from AACE/ACE (2017) recommend that adults older than 20 years should be evaluated for dyslipidemia every 5 years as part of a global risk assessment.[4] More frequent screenings are justified for this age-group with a family history of premature ASCVD (definite myocardial infarction or sudden death before age 55 years in first-degree male relative, or before age 65 years in first-degree female relative). All young adults with diabetes mellitus should be screened with a lipid profile at the time of diagnosis.[4]



Hormonal imbalances and fluctuations may lead to secondary causes of hypertriglyceridemia.

If LDL-C values are within the accepted risk level (less than 100 mg/dL), a lipid profile repeated every 3 to 5 years is reasonable. Males 45 years of age or older and women 55 years of age or older should be screened for dyslipidemia at least every 1 to 2 years. More frequent lipid testing is recommended when multiple ASCVD risk factors are present. The AACE/ACE advocates screening for dyslipidemia in all adults up to age 75 years regardless of ASCVD risk status and in adults older than age 75 years who have multiple ASCVD risk factors.[4]

Primary and secondary causes

Hypertriglyceridemia can stem from a variety of causes, including familial and genetic syndromes, metabolic disease, and medications. Elevated TG levels are commonly seen with conditions such as metabolic syndrome, type 2 diabetes mellitus (T2DM), and familial combined hyperlipidemia. The latter, a primary cause, is an inherited disorder of lipid metabolism that is also greatly affected by secondary causes of dyslipidemia.[3] However, primary genetic dyslipidemia cases are rare; therefore, the focus in primary care is on secondary sources, including lifestyle, endocrine conditions, and medications.

As adults get older, excess weight can shift to visceral (central) adiposity, which is evidenced by an increase in waist circumference. This, in combination with a more sedentary lifestyle, leads to insulin resistance and metabolic syndrome. Research findings associate metabolic syndrome with an atherogenic, procoagulant, and proinflammatory state contributing to endothelial dysfunction and increased ASCVD risk.[6]

A systematic review and meta-analysis of the cardiovascular risk associated with the metabolic syndrome showed a two-fold increase in cardiovascular outcomes and a one-and-a-half-fold increase in all-cause mortality.[4] The five components of metabolic syndrome include increased waist circumference, elevated TG levels, elevated blood glucose, low HDL-C, and elevated BP (see *Cardiovascular risk components of metabolic syndrome*).[3] Only three of the five criteria are needed to make the diagnosis of metabolic syndrome.[3]

Hormonal factors. Hormonal imbalances and fluctuations may lead to secondary causes of hypertriglyceridemia. Estrogen can be a potent stimulator of TGs produced by the liver.[7] During pregnancy, particularly the third trimester, these levels can increase up to 200% or more over prepregnancy baseline.[6] In women with an underlying genetic disorder of lipid metabolism, this estrogen-induced increase can put these patients at risk for pancreatitis and potential fetal demise.[6]

In addition, estrogen in the form of oral hormone replacement therapy or oral contraceptives can increase TG levels by the same mechanism.[6] Topical transdermal or vaginal estrogen does not have the same effect because of its decreased exposure to the liver.[6] Tamoxifen, a selective estrogen receptor modulator (SERM), mainly used for its ability to inhibit growth in estrogen receptor-positive breast cancer, can also increase TG levels. The SERM raloxifene seems to have a lesser effect on this mechanism.[6]

Thyroid and kidney disorders. Deficiencies in thyroid hormone can also affect lipid metabolism by decreasing the clearance of TG-rich lipoproteins.[8] Checking a thyroid panel and screening for hypothyroidism in patients with high TGs is prudent during a patient workup. Elevations in serum TG levels greater than 200 mg/dL are seen in approximately 40% to 50% of patients with chronic kidney disease caused by defective removal of these particles from the circulation,

and should also be an important consideration in the clinical workup.[3]

Effects of alcohol. Alcohol ingestion causes an increase in the synthesis of TGs and TG-rich lipoproteins in the liver and can produce substantial elevations in TGs, particularly if combined with other secondary and/or primary factors.[9] The effect of alcohol on TG levels is dose dependent, and when combined with a high-fat meal and conditions such as metabolic syndrome and T2DM, the risk becomes synergistic.[9]

Medications. Certain medications can have a significant impact on plasma TG levels, so therefore, a detailed medication review during the office visit is essential. Common medications known to increase TG levels include diuretics, beta-blockers, oral estrogens, corticosteroids, antiretroviral therapy for HIV infection, isotretinoin used to treat acne, immunosuppressants, antipsychotic medications, as well as bile acid sequestrants used to treat cholesterol disorders associated with elevated LDL.[6]

Antihypertensive drugs such as thiazide diuretics, furosemide, and beta-adrenergic blockers should be reassessed in patients with high TGs.[6] The TG effect is greater for atenolol, metoprolol, and propranolol than for carvedilol.[6] Also, certain second-generation antipsychotic medications such as clozapine, risperidone, and quetiapine have been associated with hypertriglyceridemia and other components of the metabolic syndrome.[6] This effect has not been seen with aripiprazole or ziprasidone.[6]

Among selective serotonin reuptake inhibitors, sertraline has been shown to increase TG levels.[6] An individualized approach is recommended for patients who are being treated with antidepressants and often involves collaboration with a mental health specialist. When evaluating the potential interaction of certain medications on the patient's lipid profile, it is also important to consider the cost and efficacy of replacement options.

If the TG level is only modestly elevated, it is usually more practical to educate the patient on the impact of diet and exercise on decreasing the lipid parameters rather than changing the medication. However, if levels are high enough to put the patient at risk for pancreatitis, aggressive management should be initiated.

Complications

The majority of modest hypertriglyceridemia cases are diagnosed through a routine lipid panel. Most patients are completely asymptomatic until levels reach severe or very severe. Often, it is the accompanying conditions of T2DM or metabolic syndrome and/or low levels of HDL-C that bring attention to the abnormal TG level; the same holds true with the elevated TG level, prompting further workup and diagnosis of other metabolic disorders.

Cardiovascular risk components of metabolic syndrome

Metabolic syndrome criteria	Parameters
Elevated waist circumference	≥40 in for non-Asian men >34 in for Asian men ≥35 in for non-Asian women >31 in for Asian women
Elevated TGs	≥150 mg/dL
Reduced HDL-C	<40 mg/dL in men <50 mg/dL in women
Elevated BP	Systolic BP ≥130 mm Hg, and/or diastolic BP ≥85 mm Hg, or taking antihypertensive medications in a patient with hypertension
Elevated fasting glucose	≥100 mg/dL or taking medications to control blood glucose

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When TG levels exceed 500 to 1,000 mg/dL, the presentation can change drastically. Severe hypertriglyceridemia may cause pancreatitis, xanthomas (eruptive skin lesions), and lipemia retinalis, which is the visualization of lipemic blood in the retinal blood vessels of the eye.[10] Eruptive xanthomas are yellow papules 1 to 3 mm in size that can erupt anywhere but are usually seen on the back, chest, and proximal extremities.[11]

A history of recurrent episodes of acute pancreatitis is common in patients with severe and uncontrolled hypertriglyceridemia. TG levels often exceed 2,000 mg/dL at the onset of pancreatitis.[12] The cardinal symptom in the clinical presentation of acute pancreatitis is abdominal pain, and although characteristically the pain is generalized to the upper abdomen, it can localize to the right upper quadrant and/or epigastric area.

With the retroperitoneal location of the pancreas, the pain is often described as deep or boring and tends to be moderately to intensely severe and lasts for several days. Patients will often find relief when leaning

forward because of the decreased tension on the pancreas in this position. Upon physical exam, patients will have tenderness and guarding localized to the upper abdomen. Hypoactive bowel sounds, epigastric distension, and low-grade fever are also characteristic findings in pancreatitis.

Lifestyle interventions

Dietary modifications. Optimization of nutrition-related modifications (weight loss; reducing simple carbohydrate, alcohol, trans and saturated fat, and fructose intake; and increasing fiber and omega-3 fatty acids) can result in 20% to 50% TG level reduction (see *Effects of nutritional practices on TGs*).[13]

Adherence to the Mediterranean diet is associated with a 10% to 15% reduction in TG level.[13] This results from the combination of increased omega-3 fatty acid, whole grains, fruits, vegetables, legumes, and nuts. High alcohol intake is associated with elevated TG level.[14] Therefore, patients with hypertriglyceridemia should be instructed to reduce or eliminate alcohol intake. Patients with TG levels greater than 500 mg/dL should be instructed to abstain from alcohol intake to reduce the risk of pancreatitis.[13,14]

Dietary modifications for patients with TG levels 500 mg/dL or greater differ from those with lower TG levels. These patients require a total dietary fat reduction. In patients with TG levels 1,000 mg/dL or greater, dietary fat is restricted to no more than 15% of daily caloric intake (20 g to 40 g) to reduce the presence of chylomicronemia, an accumulation of fat within the blood.

These patients should limit consumption of sugar, refined grains, and alcohol. When fasting TG levels have decreased to less than 500 mg/dL, total dietary fat consumption may slowly be increased while monitoring fasting TG levels. If patients remain on very low-fat diets for an extended period, essential fatty acids should be supplemented, such as by using walnut or sunflower oil.[15,16]

Physical activity. TG levels frequently decline with physical activity to a degree positively correlated with baseline value and energy expenditure.[13] Fasting TG levels have been lowered 4% to 37% by increasing physical activity.[13] TG usually declines immediately after endurance exercise and remain lower for up to 48 hours. A reduction of weight by 5% to 10% is expected to lower the TG level by approximately 20%.[13]

However, repeated exercise, if not accompanied with reduced visceral adiposity, does not produce a persistent reduction in TG concentration beyond that which occurs immediately after the exercise session. Higher-intensity exercise (greater than 60% of maximum aerobic capacity) reduces postprandial TG more effectively than moderate-intensity exercise.[17]

Effects of nutritional practices on TGs

Nutritional practice	TG-lowering response
Weight loss (5%-10% of body weight)	20%
Implement Mediterranean-style diet versus low-fat diet	10%-15%
Add marine-derived polyunsaturated fatty acids (per gram)	5%-10%
Decrease carbohydrates (1% energy replacement with monounsaturated or polyunsaturated fatty acids)	1%-2%
Eliminate transfat (1% energy replacement with monounsaturated or polyunsaturated fatty acids)	1%
Total optimal TG-lowering effect	49%

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Medical interventions

Although lifestyle modifications are the primary treatment for hypertriglyceridemia, many patients require pharmacologic intervention to appropriately treat their condition and mitigate the risks associated with elevated TG levels (see *Effect of lipid-lowering medications on TG*). There are several interventions that are indicated to primarily reduce TG levels, others that tangentially reduce TG, and many drugs in development aimed primarily at TG reduction.

Statins. HMG-CoA reductase inhibitors (statins) reduce LDL-C by inhibiting hydroxymethylglutaryl coenzyme A reductase, which results in up-regulation of the LDL receptor and reduced circulation of LDL-C.[16] There is significant evidence supporting the substantial ASCVD risk reduction observed when statin therapy is initiated.[18] Although statins are primarily indicated to lower LDL-C, their use in patients with borderline hypertriglyceridemia is justified because statins have demonstrated their ability to reduce cardiovascular disease along with their variable ability to reduce plasma TG concentrations (up to 30%) based on the dose and potency of the statin used.[19]

High-dose high potency statins (atorvastatin 80 mg and rosuvastatin 40 mg) are required to achieve the greatest level of serum TG reduction and may alter the risk–benefit profile.[18] Commonly known adverse reactions of statins, such as myalgia and elevated liver enzymes, are often attributed to high-potency statins. If elevated levels of TG persist despite intensive lifestyle interventions and the use of maximum tolerated statin dosing, the addition of TG-lowering agents, such as long-chain omega-3 fatty acids may aid in achieving appropriate goals.[18]

Fibrates. The ability of fibric acid derivatives, as a monotherapy, has been demonstrated in numerous placebo-controlled trials to significantly lower TG levels.[16-18] Fibrates decrease TG levels by activating peroxisome proliferator-activated receptor (PPAR)-alpha, which is part of a group of nuclear receptor proteins that act as transcription factors, leading to lipid modifying gene expression via three separate mechanisms: suppressed production of the lipoprotein lipase (LPL) inhibitor apolipoprotein C-III (ApoC-III), reduced hepatic secretion of very low density lipoprotein cholesterol (VLDL-C), and reduced hepatic TG production via beta-oxidation.[16] This increases catabolism of TG-rich lipoproteins, consequently increasing LDL particle size and decreasing LDL particle density.[18] Gemfibrozil was shown to increase the number of HDL particles and reduce HDL particle size, which was shown to be associated with cardiovascular benefit.[18]

Fibrates are often one of the first-line treatment options to mitigate the risk of pancreatitis in patients with very high TG levels. They have the ability to significantly lower TGs dependent on the baseline TG level.[16-18] The average TG-lowering effect of gemfibrozil was 48%, whereas fenofibrate reduced TG levels by an average of 40%.[16] Fibrates have been demonstrated to reduce TG levels by up to 62% in patients with isolated hypertriglyceridemia.[14]

Myopathy, cholelithiasis, and elevations in creatinine levels are the most common adverse reactions associated with fibrate therapy.[18] Fibrate-induced elevations in creatinine are increased by an average of 12%, are reversible upon discontinuation, and are not thought to indicate intrinsic renal damage.[18] Myopathy is the most serious adverse reaction associated with fibrates and is more prevalent when administered concomitantly with statins.[18]

Rhabdomyolysis can occur if fibrates are not discontinued when myopathy develops.[18] The incidence of myalgia and rhabdomyolysis is higher with gemfibrozil contrasted to fenofibrate.[18] Furthermore, gemfibrozil increases the area under the plasma concentration time curve and reduces renal clearance of statins and is associated with severe adverse reactions when combined with statins.[18]

Effect of lipid-lowering medications on TG

Drug class	Approximate TG reduction
Fibric acids	20%-50%
Nicotinic acid	20%-50%
Statins	7%-30%*
Cholesterol absorption inhibitor	5%-11%
Long-chain omega-3 fatty acid drugs	19%-44%

*high-potency statins (atorvastatin 40-80 mg and rosuvastatin 20-40 mg) can reduce TGs up to 50% in some patients

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Long-chain omega-3 fatty acids. Long-chain omega-3 fatty acids are available in the form of nonprescription dietary supplements, sold over-the-counter, and prescription drugs; both lower fasting and postprandial TG levels in a dose-dependent manner.[20] Dietary supplements are not as rigorously regulated and can contain other fats and cholesterols, inconsistent levels of long-chain omega-3 fatty acids, and levels of oxidation products that exceed international recommendations.[18]

Therefore, prescription products should primarily be used to lower elevated plasma TG levels. Currently, there are three formulations of prescription long-chain omega-3 fatty acids: eicosapentaenoic acid (EPA) ethyl ester, combination EPA and docosahexaenoic acid (DHA) ethyl esters, and EPA/DHA carboxylic acids.[16]

The exact mechanism of action by which long-chain omega-3 fatty acids reduce TG levels is unknown but is thought to be multifactorial, including increased beta-oxidation of fatty acids, increased LPL hydrolysis through activation of PPAR-alpha, and inhibition of apoC-III.[16,20]

Although long-chain omega-3 fatty acids lipid-altering effects are dose dependent and vary by drug formulation, reductions of serum TG levels up to 45% have been observed.[20] With their lipid-altering effects, they are also thought to have antiarrhythmic,

antithrombotic, antiatherosclerotic, anti-inflammatory, and antihypertensive effects as well as improved endothelial function.[20]

In clinical trials, the frequency of adverse reactions has been similar with the long-chain omega-3 fatty acids and placebo groups.[18] No serious safety issues have been identified, and treatment discontinuation has been shown to be minimal.[18] Unlike other lipid-modifying drugs, there is no effect on liver function and no serious drug-drug interactions.[18] Several studies have shown long-chain omega-3 fatty acids containing DHA are associated with increases in LDL-C up to 45%.[18] This increase in LDL-C has not been noted in agents that contain EPA alone.[18]

Niacin, also known as nicotinic acid or vitamin B3, decreases plasma TG levels by reducing hepatocyte TG synthesis by inhibiting diacylglycerol acyltransferase-2 activity, reducing free fatty acid flux from adipose tissue and enhancing TG-rich lipoprotein, apoB-100, and apoB-48 catabolism.[20] In addition to lowering TG at high doses, nicotinic acid also increases HDL-C and lowers total cholesterol, VLDL-C, LDL-C, and lipoprotein(a).[17]

Although nicotinic acid only moderately lowers LDL-C, a decrease in the presumably atherogenic, small dense LDL particles has been noted, resulting in a shift toward large buoyant LDL particles.[18] Niacin is marketed in three different forms: immediate-release and slow-release, which are both over-the-counter, and extended-release, which is only available in a prescription form. The TG-lowering effect remains consistent with the use of any of the three previously mentioned formulations. However, there are no TG-lowering benefits with the use of "flush-free" niacin.[21]

Although niacin has demonstrated an ability to significantly lower TG levels and reduce the rate of cardiovascular events in patients with hypertriglyceridemia, its use in clinical practice has been limited because of the elevated incidence of adverse reactions.[18] The most common adverse reaction is cutaneous vasodilation, or "flushing," which has been reported in up to 70% of patients taking niacin.[18] Pruritus, gastrointestinal disorders, hyperuricemia, blurred vision, myopathy, elevated liver enzymes, and hyperglycemia are all reported adverse reactions associated with niacin therapy.[18]

Other related therapies. Although proprotein convertase subtilisin/kexin type 9 inhibitors are primarily used to reduce LDL-C, they have been shown to reduce TG up to 17.7%.[14] Pioglitazone, a thiazolidinedione oral diabetes agent, is a selective peroxisome proliferator-activated receptor-gamma agonist. It reduces plasma TG levels (10% to 25%) and raises HDL-C (10% to 20%), but has a limited use in lipid management secondary to adverse reactions, including weight gain, edema, and increased risk of long bone fractures and bladder cancer.[14] Dipeptidyl peptidase 4 inhibitors are oral diabetes agents that are generally well tolerated and have been shown to lower serum TG levels by about 15%.[14]

In development. Volanesorsen is an antisense oligonucleotide that inhibits hepatic ApoC-III messenger RNA, which lowers serum TG by up to 80% through LPL inhibition.[17] Pemafibrate is a selective PPAR-alpha inhibitor that promotes macrophage cholesterol efflux to HDL, reduces inflammatory markers, and has been shown to decrease TG by 43% and increase HDL-C by 21%.[17] There are also several other TG-lowering therapies, including gene therapy in phase I or II trials that require additional exploration before becoming a viable option to be commercially available.[17]

Moving forward

Hypertriglyceridemia is an increasingly common disorder that requires vigilant efforts by both the patient and the provider. Being proactive at addressing not only the condition itself but also the associated risks of cardiovascular disease and pancreatitis will increase survival. It is important to explain treatment and any changes while avoiding medical jargon as well as validating the patient's understanding of the disorder and its treatment.

Patients should be encouraged during each visit to adapt and maintain lifestyle changes to not only lower TG levels but to also increase overall health. Understanding cultural diversity in diet, exercise, and views about medications will lead the NP to effectively communicate management options and address any concerns patients may have.

New guidelines and patient-centered recommendations have been published over the past 2 years that help guide the NP's approach to better management of this disorder. It is important for NPs to keep current on advances in knowledge about hypertriglyceridemia in the form of continuing education to provide optimal evidence-based practice. Clinical reasoning, along with treatment guidelines, is essential in managing patients with hypertriglyceridemia. NP

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