

# Hypertriglyceridemia

*Bret R. Haymore, MD, CPT*

*Jonathan R. Parks, MD, CPT*

*Thomas G. Oliver, MD, MAJ*

*Babette C. Glister, MD, CPT*

**H**ypertriglyceridemia is a commonly encountered but often overlooked component in the evaluation of dyslipidemias. Although the importance of elevated triglycerides as a risk factor for atherogenesis has not been clarified, recent evidence suggests it may be more important than previously recognized. An appreciation of lipoprotein metabolism provides the foundation for understanding the mechanisms by which triglycerides become elevated in the serum. Hypertriglyceridemia may occur as a primary disorder due to a variety of enzymatic and/or genetic defects or as a secondary disorder associated with a number of medical conditions. A comprehensive treatment plan includes nonpharmacologic measures as first-line therapy, effective management of secondary causes, and, when indicated, drug therapy with fibric acid or nicotinic acid derivatives. A working knowledge of the therapeutic options, their expected impact, and possible side effects are essential. This article will review the etiologies, complications, and management of hypertriglyceridemia.

## SIGNIFICANCE OF ELEVATED TRIGLYCERIDES

The importance of triglycerides as an independent risk factor for coronary artery disease has not been completely delineated.<sup>1-2</sup> Data from population-based studies have suggested that an elevated triglyceride level is an independent risk factor for cardiovascular events.<sup>3</sup> In 2 prospective trials, the Physician's Health Study<sup>4</sup> and the Copenhagen Male Study,<sup>5</sup> triglyceride levels were also found to be independent predictors of coronary heart disease (CHD). The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial found that a 31% decrease in triglyceride levels and 6% increase in high-density lipoprotein (HDL) levels after treatment with gemfibrozil resulted in a 22% relative risk reduction for a primary coronary event.<sup>6</sup> However, other prospective trials have failed to yield similar findings, and the issue of whether triglyceride levels are an independent predictor of CHD remains unsettled.<sup>1,2,7</sup> Even though a

consensus has not been reached, the recent National Cholesterol Education Program (Adult Treatment Panel [ATP] III) concluded in its latest report that the link between serum triglycerides and CHD is stronger than previously recognized and published guidelines reflecting an association of triglyceride levels greater than 200 mg/dL with an increased risk for CHD (**Table 1**).<sup>8</sup>

The particles that are most likely responsible for the atherogenicity of triglycerides are remnant lipoproteins, including very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL). These are cholesterol-enriched particles with many of the properties of low-density lipoprotein (LDL). The most readily available means of measuring these remnant lipoprotein particles in practice is as serum VLDL.

In addition to having this direct role in atherogenesis, hypertriglyceridemia tends to be associated with other conditions, which, in and of themselves, predispose to atherosclerosis. These conditions include low levels of HDL, increased levels of small dense LDL, elevated levels of apolipoprotein (apo) B, and insulin resistance.<sup>8-10</sup> LDL cholesterol can be classified according to its size and density. Small, dense LDL has the strongest association with CHD.

## LIPOPROTEIN METABOLISM

An understanding of lipoprotein metabolism is essential to understanding the etiologies of hypertriglyceridemia (**Figure**). Lipoproteins (**Table 2**) are particles that have a hydrophobic core (made of triglycerides and/or cholesterol) and a hydrophilic outer layer that

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*Drs. Haymore and Parks are residents, Internal Medicine Section, Department of Medicine, William Beaumont Army Medical Center, El Paso, TX. Dr. Oliver is chief and Dr. Glister is assistant chief, Endocrinology Section, Department of Medicine, William Beaumont Army Medical Center.*

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**Table I.** Classification of Serum Triglyceride Levels

Category	Serum Concentration*
Normal	< 150 mg/dL (1.7 mmol/L)
Borderline high	150–199 mg/dL (1.7–2.2 mmol/L)
High	200–499 mg/dL (2.2–5.6 mmol/L)
Very high	≥ 500 mg/dL (≥ 5.6 mmol/L)

\*To convert from mg/dL to mmol/L, divide by 88.5.

Adapted with permission from Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Circulation* 2002; 106:3169.

facilitates transport in the serum. They also have specific proteins, termed apolipoproteins, that regulate or bind enzymes or receptors. Dietary triglycerides are hydrolyzed by pancreatic lipase, absorbed by intestinal mucosal cells, and secreted into mesenteric lymphatics as chylomicrons. Chylomicrons contain 3 populations of surface apolipoproteins: B48, which is unique to chylomicrons; apo CII; and apo E. After entering the circulation, chylomicrons attach to binding sites in the capillary endothelium of muscle and adipose tissue where the CII apolipoproteins activate lipoprotein lipase (LPL). This activation results in triglycerides from chylomicrons being transferred to cells where they either are used in metabolism or stored. The triglyceride-depleted chylomicron remnant is then internalized by hepatocytes that express apo E receptors. VLDL serve a function analogous to chylomicrons but are synthesized by the liver from plasma free fatty acids when there is an excess of calories in the diet. They contain apolipoproteins B100, CII, and E and are also hydrolyzed by LPL via apo CII in muscle and adipose tissue.

A degraded or triglyceride-reduced VLDL particle is referred to as an IDL, reflecting the fact that decreasing triglyceride content increases particle density while decreasing particle size. About half of the IDLs are further triglyceride-reduced and become LDL, while the other half are taken up by the liver. LDL contains largely cholesterol and its major apolipoprotein is B100. LDL receptors are present on all cells but are found in higher concentration on hepatocytes. Tissue uptake (via apo B100) accounts for about two thirds of LDL particle removal, while monocytes or smooth muscle cells scavenge the other third. In addition, lipoprotein (a), also called apo (a), is a modified LDL particle in which the apo B protein of LDL is covalent-

ly bonded to apo (a). Apo (a) is a protein of unknown function that shares high sequence homology with plasminogen. Due to this structural similarity, apo (a) interferes with fibrinolysis by competing with plasminogen binding and thus attenuates clot lysis. This may result in an increased risk of CHD.<sup>11</sup>

HDL is composed mainly of protein and phospholipids, with very little cholesterol or triglycerides. It scavenges unesterified cholesterol in plasma, aided by apo AI. The cholesterol is transferred from HDL to IDL or LDL and then removed from the circulation via the liver. HDL also acts as a reservoir for apo CII. Therefore, when HDL levels are low, the associated reduction in available apo CII compromises chylomicron and VLDL metabolism in muscle and adipose tissue, which can lead to higher triglyceride levels.<sup>12</sup>

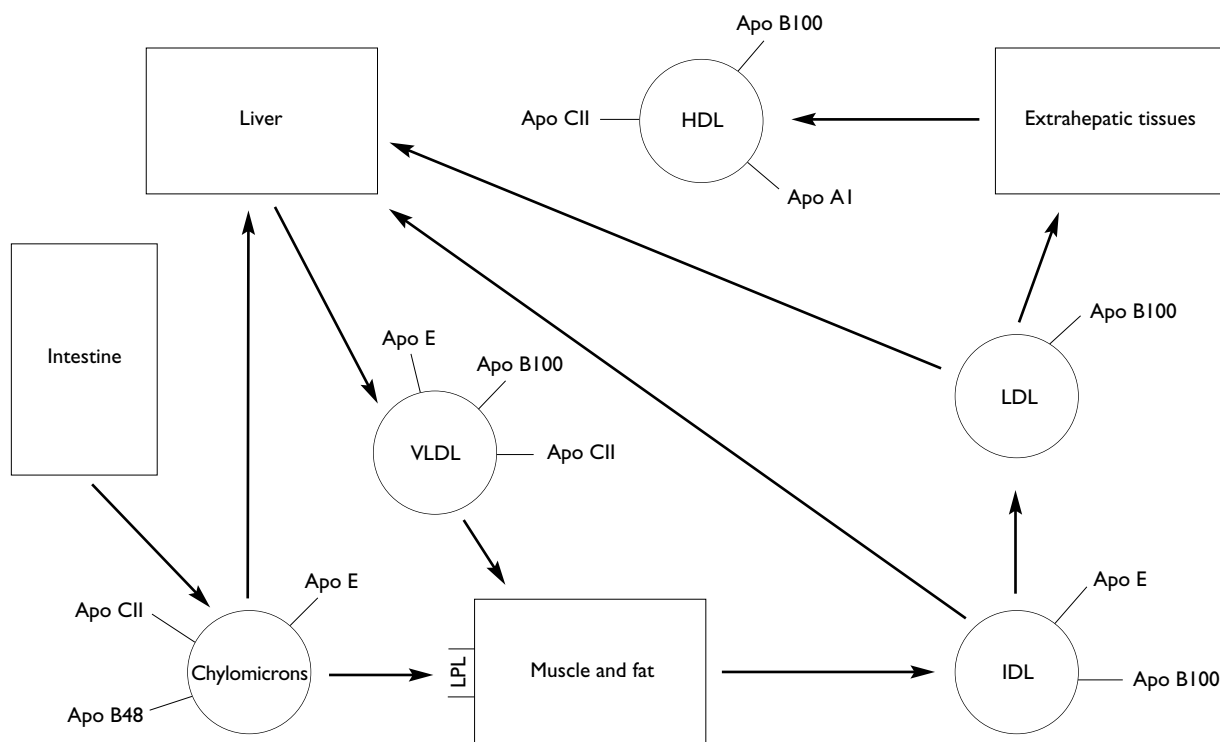
### FAMILIAL HYPERLIPIDEMIA SYNDROMES

The nomenclature of familial hyperlipidemia syndromes is somewhat confusing given the considerable overlap of phenotypic and genotypic expression. The same genetic defect can contribute to a number of phenotypic syndromes. Thus, classification of these syndromes is somewhat arbitrary. A common classification, first described by Fredrickson,<sup>13</sup> divides patients into 5 phenotypic groups, and elevations in triglycerides are seen in 4 of these (**Table 3**). Type IIa is the familial hypercholesterolemia syndrome, which is caused by a defect in the LDL receptor. As triglycerides are uninvolved, this syndrome will not be discussed.

Type I familial dyslipidemia results from a complete deficiency of LPL or apo CII, leading to elevated chylomicrons and serum triglycerides due to the inability to transport these particles to tissues. This is in contrast to type V (discussed below), in which there may be a partial defect in one of these enzymes.

Type IIB, also known as familial combined hyperlipidemia (FCHL), is an autosomal disorder caused by overproduction of hepatocyte-derived apo B100 associated with VLDL. FCHL is associated with a clear increase in coronary risk and accounts for one third to one half of familial causes of CHD.<sup>14</sup> The primary defect in FCHL is not known, but a locus has been identified on chromosome 1q21.<sup>15</sup> Affected patients typically present with moderate hypercholesterolemia and hypertriglyceridemia, both in the 300 to 400 mg/dL ranges. Either abnormality may also be seen alone. LPL may be responsible for part of this phenotypic variability as hypertriglyceridemia is more prominent in patients with LPL deficiency.<sup>16</sup>

Type III, or familial dysbetalipoproteinemia, is a multifactorial disorder that is inherited as an autosomal



**Figure.** General scheme summarizing the major pathways involved in the metabolism of lipids, including chylomicrons synthesized by the intestine and VLDL synthesized by the liver. Apo = apolipoprotein; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; LPL = lipoprotein lipase; VLDL = very low-density lipoprotein.

recessive trait and is characterized by the presence of 2 apo E2 alleles.<sup>17,18</sup> Premature CHD and peripheral vascular disease are commonly associated with this disorder. Physical findings include xanthomas of the palmar creases (xanthomata palmare striatum) and tuberoeruptive xanthomas. An additional genetic or acquired disorder is generally needed for full expression.<sup>17</sup> The apo E ligand is required for receptor-mediated clearance of chylomicron and VLDL remnants from the circulation, with the most common isoform being apo E3. The apo E2 ligand has a lower affinity for the apo B/E (LDL) receptor than apo E3.<sup>19</sup> Thus, VLDL and chylomicron remnants that contain apo E2 on their surface are cleared less efficiently from the plasma, leading to accumulation in the serum and resulting in moderately increased concentrations of triglycerides and cholesterol (300–400 mg/dL).<sup>12</sup>

Type IV (familial hypertriglyceridemia) is an autosomal dominant disorder associated with moderate elevations in the serum triglyceride concentration (200–500 mg/dL).<sup>8,20</sup> It is often accompanied by insulin resistance, obesity, hyperglycemia, hypertension, and hyperuricemia. These patients are heterozygous for

inactivating mutations of the LPL gene and typically have low serum HDL. Familial hypertriglyceridemia is associated with increased coronary risk and is also seen in patients with premature CHD.

Type V (mixed hypertriglyceridemia) is characterized by triglyceride levels above the 99th percentile due to elevations in both VLDL and chylomicrons.<sup>21,22</sup> Clinical manifestations include hepatosplenomegaly and occasional eruptive xanthomas. Patients with marked hypertriglyceridemia (> 1000 mg/dL) may develop the chylomicronemia syndrome. Manifestations of this disorder include recent memory loss, abdominal pain and/or pancreatitis, dyspnea, eruptive xanthomas, flushing with alcohol ingestion, and lipemia retinalis.<sup>23</sup> Most patients, however, have a secondary form in which partial apo CII or LPL deficiency is exacerbated by 1 or more of the acquired disorders noted below.

A classic method of diagnosing mixed hypertriglyceridemia is by confirming the presence of chylomicrons and excess VLDL in plasma supernatant. Plasma is refrigerated overnight, after which chylomicrons will form a creamy supernatant and VLDL forms a turbid infranant. In contrast, only chylomicrons accumulate

**Table 2.** Common Types of Lipoproteins

Type	Site of Origin	Composition	Major Apolipoproteins
Chylomicrons	Intestine	85% triglyceride (15% protein)	B48, E, CII
VLDL	Liver	55% triglyceride, 20% cholesterol (25% protein)	B100, E, CI, CII, CIII
IDL	Derived from VLDL	35% cholesterol, 25% triglyceride (40% protein)	B100, E
LDL	Derived from IDL	60% cholesterol, 5% triglyceride (35% protein)	B100
HDL	Liver, intestine, plasma	25% phospholipid, 20% cholesterol, 5% triglyceride (50% protein)	AI, AII, CI, CII, CIII, E

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

Adapted from Mahley RW, Weisgraber KH, Farese RV. Disorders of lipid metabolism. In: Larsen PR, Kronenberg HM, Melmed S, Polonsky KS, editors. *Williams' textbook of endocrinology*. 10th ed. Philadelphia: W.B. Saunders; 2003:1648. Copyright © 2003, with permission from Elsevier.

and the infranant is clear (due to the absence of VLDL) in type I hyperlipoproteinemia.

### SECONDARY CONDITIONS ASSOCIATED WITH HYPERTRIGLYCERIDEMIA

Conditions associated with hypertriglyceridemia are listed in **Table 4**. A common cause of hyperlipidemia occurs in association with insulin resistance as a harbinger of type 2 diabetes mellitus.<sup>24</sup> Hyperinsulinemia is associated with hypertriglyceridemia and low serum HDL concentrations, which can often be identified prior to hyperglycemia or the actual diagnosis of diabetes mellitus. The hypertriglyceridemia results both from increased substrate availability (glucose and free fatty acids) and from decreased lipolysis of VLDL.

Obesity also is associated with a number of deleterious changes in lipid metabolism, including high serum concentrations of total cholesterol, LDL, VLDL, and triglycerides, and a reduction in serum HDL.<sup>25</sup> Loss of body fat can reduce hypercholesterolemia and hypertriglyceridemia.<sup>26</sup>

Marked hyperlipidemia may occur in the nephrotic syndrome, primarily due to high serum total and LDL cholesterol concentrations. Increased hepatic production of lipoproteins, induced in part by the fall in plasma oncotic pressure, is the major abnormality, but diminished lipid catabolism may play a contributory role.

Hypothyroidism associated with hypercholesterolemia has been studied in some detail. A significant proportion of patients with primary hypothyroidism—up to one third in some studies—have one of the familial dyslipidemia syndromes.<sup>27</sup> The severity of the lipid abnormalities increases in a graded fashion with the severity of the hypothyroidism.<sup>28</sup> A survey of patients in a lipid disorders clinic revealed approximately 5% had hypothyroidism.<sup>29</sup> Thus, serum thyrotropin should be measured in all patients with dyslipidemia, as normalization of

thyroid hormone may lead to an improvement in the lipid profile.

Some medications, including thiazide diuretics,  $\beta$ -blockers, and oral estrogens can cause modest changes in serum lipid concentrations. The elevation in serum triglyceride levels may not be seen with transdermal estrogen delivery and is minimal with oral contraceptives because of the lower estrogen dose in current formulations.<sup>30</sup> Tamoxifen can cause marked hypertriglyceridemia in a minority of women.<sup>31</sup> Immunosuppressive medications, such as glucocorticoids and cyclosporine, can adversely affect triglyceride levels.<sup>32,33</sup> The deleterious effects of antiretroviral agents, most commonly protease inhibitors used in the treatment of HIV, on triglycerides has also been well-described.<sup>34,35</sup> Some of the atypical antipsychotic agents, particularly clozapine and olanzapine, have been associated with weight gain, obesity, hypertriglyceridemia, and development of diabetes mellitus.<sup>36,37</sup> The mechanism(s) by which atypical antipsychotic agents cause these abnormalities have not been defined.

### PANCREATITIS AND HYPERTRIGLYCERIDEMIA

An emergent problem that may be associated with marked hypertriglyceridemia is acute pancreatitis. In one series of 70 such patients, the mean serum triglyceride concentration was 4587 mg/dL.<sup>38</sup> Serum triglyceride values above 1000 mg/dL cause the serum to be opalescent due to an increase in VLDL; at higher levels it may be lactescent (ie, milky) due to hyperchylomicronemia. Most patients with serum levels in this range have one of the primary dyslipidemias described above with an additional secondary cause.<sup>39,40</sup> Affected patients typically present with the acute onset of abdominal pain, nausea, and vomiting, and the serologic features of pancreatitis. This report found 3 characteristic profiles in these patients. The most common was a

**Table 3.** Familial Dyslipidemia Syndromes

Type	Name	Particles Elevated	Genetic Defect
I	Familial LPL deficiency Familial CII deficiency	Triglycerides (chylomicrons)	LPL* deficiency or CII <sup>†</sup> deficiency
IIA	Familial hypercholesterolemia Familial combined hyperlipidemia	Cholesterol (LDL)	Decreased LDL receptors apo B and VLDL overproduction
IIB	Familial combined hyperlipidemia	Triglycerides and cholesterol (VLDL and LDL)	Apo B and VLDL overproduction
III	Familial dysbetalipoproteinemia	Triglycerides and cholesterol (IDL)	Abnormal apo E (E2/E2)
IV	Familial hypertriglyceridemia Familial apo CII deficiency Familial combined hyperlipidemia	Triglycerides (VLDL)	LPL deficiency or CII deficiency or apo B and VLDL overproduction
V	Familial LPL deficiency Familial CII deficiency Familial combined hyperlipidemia	Triglycerides (VLDL and chylomicrons)	LPL deficiency or CII deficiency or apo B and VLDL overproduction

Apo = apolipoprotein; HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; LPL = lipoprotein lipase; VLDL = very low-density lipoprotein.

\*Lipoprotein lipase.

<sup>†</sup>Apo CII.

poorly controlled diabetic with a history of hypertriglyceridemia. The second was an alcoholic found to have hypertriglyceridemia or lactescent serum on hospital admission. The third scenario was a nondiabetic, nonalcoholic, and nonobese patient with a drug- or diet-induced hypertriglyceridemia.

### TREATMENT OF HYPERTRIGLYCERIDEMIA

In 2001, the National Cholesterol Education Program ATP III provided revised recommendations regarding treatment of elevated triglycerides.<sup>8</sup> Since elevated serum triglycerides are often related to lifestyle habits, the foundation of therapy includes weight reduction, regular exercise, smoking cessation, restriction of alcohol use, and avoiding a high carbohydrate diet. Other nonpharmacologic interventions, such as avoiding medications that raise serum triglycerides and strict glycemic control in diabetics, should also be included in first-line therapy. Borderline elevations in triglycerides (150–199 mg/dL) should signal a need for change in lifestyle habits.

Agents used to lower lipid and triglyceride levels are listed in **Table 5**. In the management of mixed hyperlipidemias, LDL cholesterol is the primary target of therapy. For this reason, statins should be the first-line agents when drug therapy is indicated. When triglyceride levels are high (200–499 mg/dL), LDL cholesterol remains the primary and non-HDL (LDL + VLDL) cholesterol is the secondary target, with statins being the most effective drugs for lowering non-HDL

**Table 4.** Conditions Associated with Elevated Triglycerides

#### Common

Diabetes mellitus  
Hypothyroidism  
Medications (β-blockers, diuretics, estrogens, tamoxifen, antipsychotics, protease inhibitors)  
Obesity  
Alcohol use  
Nephrotic syndrome

#### Less common

Acromegaly  
Glycogen storage disease  
Hypopituitarism (ateliotic dwarfism)  
Lipodystrophy (congenital or acquired)  
Monoclonal gammopathy  
Systemic lupus erythematosus

cholesterol. In this setting, statins lower triglyceride levels by 20% to 40% and VLDL to a similar degree.<sup>41</sup>

For isolated hypertriglyceridemia where LDL cholesterol is not significantly elevated, the goal for non-HDL is usually obtainable with a triglyceride-lowering drug. The most effective agents are fibric acid derivatives and nicotinic acid. Fibric acids are generally preferred in such patients due to their greater potency. Triglyceride levels are typically reduced by 40% to 60% and HDL levels increase by 15% to 25%. A disadvantage of the

**Table 5.** Treatment of Hyperlipidemia and Impact on Lipid Profile

Drug Class	Percent Change in Serum Lipid Level		
	LDL	HDL	Triglycerides
Fibric acids	↓ 5–10	↑ 15–25	↓ 40–60
Nicotinic acid	↓ 10–25	↑ 20–30	↓ 30–50
Statins	↓ 25–50	↑ 5–10	↓ 10–30
Bile acid sequestrants	↓ 15–30	No change to slight increase	No change*
Cholesterol absorption inhibitors	↓ 15–20	No change	No change

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

\*May cause increase if there is pre-existing hypertriglyceridemia.

Data from NCEP,<sup>8</sup> Knopp,<sup>41</sup> and Meyers et al.<sup>45</sup>

fibric acid derivatives is the potential for a mild increase in LDL cholesterol. In comparison, nicotinic acid is somewhat less potent in lowering triglycerides, usually 30% to 50%, but has a slightly greater effect in increasing HDL, often by 20% to 30%. Nicotinic acid should be used with caution in patients with diabetes mellitus, as it can worsen glucose tolerance.<sup>42</sup> Combination therapy can be given in patients with marked hypertriglyceridemia or acute pancreatitis. Care should be taken if fibric acid derivatives and statins are used in combination as either can result in muscle toxicity, and this risk increases when they are used in combination.<sup>41</sup>

In recent years, evidence for the health benefits of omega-3 polyunsaturated fatty acids (commonly known as fish oil), which include reducing triglyceride levels, has grown. A recent meta-analysis indicated that intake of omega-3 fatty acids reduces overall mortality, mortality due to myocardial infarction, and sudden death in patients with CHD.<sup>43</sup> In refractory cases of hypertriglyceridemia, supplements of up to 5 g/d of omega-3 fatty acids can be beneficial and reduce serum triglycerides by 30% or more. These fatty acids are thought to be antithrombogenic and retard atherosclerotic plaque growth.<sup>44</sup> Recently, an omega-3 acid ethyl ester was approved by the US Food and Drug Administration for those with serum triglyceride levels over 500 mg/dL. However, fish oil use is often limited by metabolic and gastrointestinal side effects.

When triglyceride levels are very high (500 mg/dL), the initial goal is to prevent pancreatitis by lowering triglycerides with a combination of nonpharmacologic therapy and triglyceride-lowering agents. Once triglyceride levels are below 500 mg/dL, LDL goals should be addressed. Bile acid sequestrants should be avoided until triglyceride levels have been normalized because they can increase VLDL synthesis and exacerbate the hypertriglyceridemia.

It is important to note that some preparations of nicotinic acid are not effective in the management of hypertriglyceridemia. Free nicotinic acid, the component that has the beneficial effect on dyslipidemia, is not present in some over-the-counter or “no flush” preparations, and they should be avoided for this reason.<sup>45</sup> Additionally, patients often take garlic supplements in hopes of improving cholesterol levels. A recent meta-analysis of randomized trials comparing garlic with placebo demonstrated that garlic decreased total cholesterol by about 5%, with no statistically significant change in the LDL or HDL cholesterol. This magnitude of change is similar to that of dietary interventions after 6 months.<sup>46</sup>

Interestingly, thiazolidinediones (TZDs), most notably pioglitazone, have demonstrated some promise in reducing serum triglycerides. Pioglitazone has been found to act on a nuclear receptor, peroxisome proliferator-activated receptor  $\gamma$  (PPAR- $\gamma$ ), which alters transcription of genes involved in glucose and lipid metabolism. A related receptor, PPAR- $\alpha$ , is the primary mechanism by which fibrates lower triglycerides. Activation of PPAR- $\gamma$  by pioglitazone results in greater activity of the LPL enzyme, whereas activation of PPAR- $\alpha$  results in greater levels of apo CIII.<sup>47</sup> Thus, there may be some synergy in triglyceride lowering by using these medications concomitantly. The net effect of pioglitazone appears to be a decrease in triglycerides by about 15%, and a slight increase in HDL, while overall LDL levels remain essentially unchanged.<sup>47</sup> There is evidence that TZDs modify LDL particle density, causing a shift from the small dense particles to larger ones that tend to be less atherogenic.<sup>48</sup> Thus, TZDs have the potential to favorably modify the characteristic diabetic dyslipidemia of increased triglycerides, reduced HDL, and predominance of small, dense LDL. This may not be a class effect, however, as rosiglitazone does not appear to decrease triglycerides.<sup>47</sup>

## CONCLUSION

Although some debate remains, the evidence suggests that treating hypertriglyceridemia can reduce a patient's risk for cardiovascular events. An understanding of the causes of triglyceride elevation is vital for the primary care clinician in evaluation and management of patients with dyslipidemias. Knowledge of primary and secondary causes of hypertriglyceridemia guides evaluation and therapeutic decisions, which must include treatment of any associated or complicating disorders. Underlying diseases must be identified and controlled, lifestyle changes implemented, and exacerbating medications should be halted when possible. Nicotinic acid and fibric acids have been demonstrated to have the largest impact on triglycerides. **HP**

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