Hypertriglyceridemia: Identifying Secondary Causes

Carrie Bowling, PA-C, Joyce Ross, MSN, CRNP, CLS, FPCNA, FNLA

Screening for cardiovascular (CV) risk often includes a routine serum fasting lipid profile. However, with the focus on LDL cholesterol, triglyceride measurement is frequently overlooked. Yet this element of the lipid profile is particularly important, given its strong association with not only atherosclerotic coronary heart disease but also pancreatitis.

Hypertriglyceridemia is defined as a serum triglyceride level that exceeds 150 mg/dL. In the US, an estimated 25% of patients have hypertriglyceridemia.[1] Of these, 33.1% have "borderline high" triglyceride levels (150 to 199 mg/dL), 17.8% have "high" levels (200 to 499 mg/dL), and 1.7% have "very high" levels (> 500 mg/dL).[1,2]

Most of the time, hypertriglyceridemia is caused (or at least exacerbated) by underlying etiology. The best way to identify and manage these secondary causes is through a systematic approach.

CONSIDER THE EVIDENCE

For mild to moderately elevated (borderline high) triglyceride levels, our reflex reaction may be to recommend a triglyceride-lowering medication, such as fenofibrate. But this may not be the best answer. Although there is increasing evidence of an independent association between elevated triglyceride levels and CV risk, it remains unclear whether targeting them specifically can reduce that risk.[3]

In well-designed, peer-reviewed clinical trials, statins have been shown to reduce CV risk in patients with known cardiovascular disease (CVD) and those at high risk for CVD, as well as in primary prevention. However, these trials also suggest that significant residual CV risk remains after statin therapy.[4]

Several trials have attempted to prove residual risk reduction following combination therapy including statins—with inconclusive results:

ACCORD: Fenofibrate showed no overall macrovascular benefit when added to a statin in patients with type 2 diabetes and a triglyceride level < 204 mg/dL.[3,5]

AIM-HIGH: There was a 25% reduction in triglyceride levels when niacin was added to a regimen of a statin +/- ezetimibe, with an aggressive LDL treatment target (40 to 80 mg/dL). But the study was stopped early due to the lack of expected reduction in CVD events.[4,6]

JELIS: A reduction in major CV events was seen with 1,800 mg/d of eicosapentaenoic acid (EPA) supplementation plus a low-dose statin, compared to statin monotherapy. However, there was minimal change in triglyceride levels, leading the researchers to hypothesize that multiple mechanisms—such as decreasing oxidative stress, platelet aggregation, plaque formation and stabilization—contributed to the outcome.[4,7]

Informed by the JELIS results, the much-anticipated REDUCE-IT trial is currently in progress to address the lingering question of whether combination therapy can reduce residual CV risk. In this trial, EPA omega-3 fatty acid is being added to the regimen of statin-treated patients with persistently elevated triglycerides. Results are expected in 2017 to 2018.[8]

Remember that a triglyceride level of 150 mg/dL is a parameter—it does not represent a therapeutic target. There is insufficient evidence that treating to this level improves CV risk beyond LDL target recommendations.[7]

The National Lipid Association Expert Panel's consensus view is that non-HDL is a better primary target than triglycerides

Carrie Bowling practices at the South Georgia Medical Center Diabetes Management Center and Valdosta Specialty Clinic, Endocrinology, in Valdosta, Georgia. **Joyce Ross** is President of the National Lipid Association and Past President of the Preventive Cardiovascular Nurses Association.

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alone or LDL. Using non-HDL as a target for intervention also simplifies the management of patients with high triglycerides (200 to 499 mg/dL). The non-HDL goal is considered to be 30 mg/dL greater than the LDL target. For patients with diabetes and those with CVD, the individualized non-HDL targets are 130 mg/dL and 100 mg/dL, respectively.[9]

REVIEW THE MEDICATION LIST

Several commonly used medications, including ß-blockers and thiazide diuretics, can increase triglyceride levels.[10] Other medications with exacerbating effects on triglycerides include corticosteroids, retrovirals, immunosuppressants, retinoids, and some antipsychotics.[10] Bile acid sequestrants (eg, colesevelam) should be avoided in patients with elevated triglycerides (> 200 mg/dL).[7]

In women, oral estrogen (ie, menopausal hormone replacement and oral birth control) can greatly exacerbate triglyceride levels, making transdermal delivery a better option. Tamoxifen, the hormonal medication used for breast cancer prophylaxis, can also increase triglyceride levels.[11]

LOOK FOR UNDERLYING CONDITIONS

Among those to consider: Hypothyroidism is common and easily ruled out by a simple blood test. Nephrotic syndrome should be ruled out, particularly in patients with concomitant renal dysfunction and peripheral edema, by checking a random urine protein-to-creatinine ratio or 24-hour urine for protein. Other factors that should be explored because of their potential effect on lipid metabolism include obesity and excessive intake of sugary beverages (ie, soda, fruit juice) and alcohol.[11]

High triglyceride levels occurring with low HDL are characteristic of insulin resistance and concerning for metabolic syndrome and/or polycystic ovarian syndrome.[3,12] Often, patients will have underlying prediabetes (fasting glucose ≥ 100 mg/dL or random glucose ≥ 140 mg/dL with an A1C > 5.7%[13]) or covert type 2 diabetes. Another underdiagnosed but very common condition, obstructive sleep apnea, can greatly affect insulin sensitivity and has been associated with lipid abnormalities and metabolic syndrome.[14]

EXAMINE YOUR PATIENT

The physical exam is an essential component of assessment for patients with high triglycerides. As discussed, elevated triglycerides and low HDL are hallmarks for insulin resistance. As triglyceride levels are affected by obesity and body fat distribution, measuring BMI and assessing for visceral adiposity are an important part of the physical exam.[4]

The physical exam may also yield dermatologic clues, such as skin tags or acanthosis nigricans, a dark, velvety lesion usually found on the posterior and lateral neck creases, axillae, groin, and elbows.[13] In rare cases—usually those with genetic involvement from a familial lipid metabolism disorder—patients may exhibit xanthomas. These cutaneous, lipid-rich lesions can appear as flat, yellowish plaques on various parts of the body, such as the eyelids (xanthelasma) or tendons of the hands, feet, and heels. Widespread, eruptive xanthomas, which manifest as pruritic pink papules with creamy centers, are associated with severe emergent triglyceride elevation and pancreatitis.[10]

CONSIDER NONPHARMACOLOGIC MANAGEMENT

In mild to moderate hypertriglyceridemia, intensive lifestyle changes are considered firstline therapy. Weight loss is recommended in obese patients; a 5% to 10% reduction in body weight can lower triglycerides by 20%.[15]

A quick 24-hour diet recall, including beverages, is helpful for identifying key issues. The goal should be to reduce carbohydrates—in particular, simple, high glycemic index, processed foods—as well as total and saturated fats. A substantial problem in our population is the consumption of high-fructose beverages and fruit juices. Referral to a dietitian can be very helpful, not only

for initial meal planning but also for continuing counseling on successful long-term weight loss and maintenance.

Exercise is also very helpful for improving lipid parameters. A daily minimum of 30 to 60 minutes of intermittent aerobic exercise or mild resistance exercise has been shown to reduce triglyceride levels.[10]

PRESCRIBE APPROPRIATELY

The most important indication for treatment of hypertriglyceridemia is reduction of CVD risk. However, in patients with very high triglyceride levels (> 500 mg/dL), the goal is to decrease risk for life-threatening pancreatitis.[15] Lipid-lowering medications and dietary restrictions should be promptly employed.

There are medications, as discussed earlier, that specifically lower triglycerides. Fibrates offer the most robust decrease, with a 20% to 50% reduction in triglyceride levels. Fenofibrate is considered a safer option when used in combination with a statin, due to the risk for significant muscle toxicity with gemfibrozil. There is some evidence that adding a fibrate may actually increase risk for pancreatitis; since this risk is otherwise low in patients with mild to moderate triglyceride elevation, the addition of a fibrate to their regimen should be avoided.[3]

Statins are the drug of choice when CV risk reduction is the goal (for patients with hypertriglyceridemia < 500 mg/dL). In addition to lowering LDL, statins can reduce triglycerides by 7% to 30%, depending on the dose.[15]

Other triglyceride-lowering medications include omega-3 fatty acids and niacin preparations. Prescription-strength omega-3 fatty acids have been found to lower serum triglyceride levels by 50% or more; the newest preparation, icosapent ethyl, demonstrated up to 45% reduction without significant effect on LDL levels.[3] (Other preparations have been shown to substantially increase LDL in many cases.) Niacin (1,500 to 2,000 mg/d) can decrease triglycerides by 15% to 25%. However, it is no longer recommended for CV risk reduction; recent data indicate it may increase stroke risk when used in combination with statins.[3,10] In April 2016, the FDA revoked its approval of the co-administration of niacin and fenofibrate with statin therapy, due to a lack of CV benefit.[16]

Other secondline options to consider for patients with insulin resistance or diabetes are metformin and pioglitazone. These medications have been shown to improve insulin sensitivity and decrease LDL and triglycerides in patients with prediabetes. Pioglitazone has proven beneficial in the treatment of steatohepatitis.[17] Insulin is an excellent rapid triglyceride-lowering agent for patients with diabetes. It is important to reinforce that reduction of glucose is a key component in reduction of triglyceride levels.[3]

CONCLUSION

Hypertriglyceridemia is a complex condition that requires individualized and comprehensive management strategies. Clinicians must be able to identify and address secondary causes. Treatment options should be tailored to decrease CV and pancreatitis risk, and medication recommendations should be evidenced based and carefully selected to mitigate potential adverse effects. Patients should receive education and lifestyle management support to help motivate and equip them to employ strategies to improve their health. **CR**

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