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Management of Hypertriglyceridemia in the Diabetic Patient

Ishwarlal Jialal · William Amess · Manpreet Kaur

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Abstract The hypertriglyceridemia of diabetes can be classified into mild to moderate (triglycerides between 150–499 mg/dL) and severe hypertriglyceridemia (triglycerides ≥500 mg/dL). As in any other individuals with hypertriglyceridemia, secondary causes need to be excluded. The management of severe hypertriglyceridemia (chylomicronemia syndrome) includes aggressive reduction of triglycerides with intravenous insulin, fibrates, omega-3 fatty acids, and/or niacin therapy to avert the risk of pancreatitis. In patients with mild to moderate hypertriglyceridemia, the treatment of choice is statin therapy to achieve the low-density lipoprotein (LDL) and non-high-density lipoprotein (HDL) target goals. The evidence base would favor niacin therapy in combination with statin therapy to achieve the goals pertaining to LDL cholesterol and non-HDL cholesterol. The data about the combination of fibrate therapy with statin therapy are disappointing.

Keywords Hypertriglyceridemia · Diabetes · Dyslipidemia · Statins · Niacin · Fibrates

Clinical Trial Acronyms

ACCORD	Action to Control Cardiovascular Risk in Diabetes
AIM HIGH	Niacin Plus Statin to Prevent Vascular Events
ARBITER 3	Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 3
ARBITER 6-HALTS	Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis
CDP	Coronary Drug Project
CTT	Cholesterol Treatment Trialists'
DAIS	Diabetes Atherosclerosis Intervention Study
FIELD	Fenofibrate Intervention and Event Lowering in Diabetes
HATS	HDL-Atherosclerosis Treatment Study
HPS2-THRIVE	Treatment of HDL-C to Reduce the Incidence of Vascular Events
UKPDS	United Kingdom Prospective Diabetes Study
VA-HIT	Veterans Affairs High-Density Lipoprotein Intervention Trial.

I. Jialal (✉) · W. Amess · M. Kaur
VA Medical Center and Laboratory for Atherosclerosis and Metabolic Research, Department of Pathology and Internal Medicine, UC Davis Medical Center,
4635 Second Avenue, Research 1 Building, Room 3000, Sacramento, CA 95817, USA
e-mail: ishwarlal.jialal@ucdmc.ucdavis.edu

Introduction

The major cause of morbidity and mortality in type 2 diabetes is cardiovascular disease (CVD). Regarding the lipid profile in patients with type 2 diabetes mellitus (T2DM), the usual abnormalities include hypertriglyceridemia (HTG) and low levels of high-density lipoprotein-cholesterol (HDL-C). However, in the UKPDS [1], low-density lipoprotein-cholesterol (LDL-C) levels were significantly increased in women, but not in men. Thus, the major abnormalities with the respect to the dyslipidemia in T2DM include increased number of triglyceride-rich particles, increased postprandial concentrations of triglyceride-rich particles, increased number of LDL particles, small dense LDL particles, decreased HDL particle numbers, and several changes in particle composition of HDL [2]. Also, we have shown that remnant-like particle cholesterol levels are elevated in

diabetic patients [3]. When risk factors are ranked in patients with T2DM for CVD, LDL-C and HDL-C are most important [4]. Following diet and exercise, the cornerstone of treatment for the dyslipidemia of diabetic patients is 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) therapy. In the CTT Collaborators study [5••], a meta-analysis of 14 randomized statin trials, it was shown that each millimole reduction in LDL-C (38.6 mg/dL of LDL-C) was associated with a 21% reduction in major vascular events and a 21% reduction in stroke. The benefits of statin therapy were evident in diabetic patients both with and without a prior history of vascular disease [5••].

The major focus of this review is the management of HTG in diabetes. Table 1 demonstrates a practical classification of HTG in diabetes. HTG will be discussed under two broad categories: "mild to moderate," in which the triglycerides are between 150 to 499 mg/dL, and "severe HTG," when the triglyceride levels are ≥500 mg/dL. As in any other patient with HTG, it is important to take into account the other causes, which include obesity, alcoholism, renal disease, drugs (eg, steroids, β blockers, retinoids, oral estrogens, tamoxifen, protease inhibitors, and bile acid sequestrants), lipodystrophy, and pregnancy (Table 1).

Management of Severe HTG

With respect to severe HTG, also referred to as chylomicronemia syndrome, triglyceride levels are generally greater than 1,000 mg/dL and usually greater than 2,000 mg/dL. In children this can result from a deficiency of lipoprotein lipase (LPL) or its cofactor, apolipoprotein (apo) C-II. However, the focus of this review is in the more common type V hyperlipidemia seen in adults. These patients have both elevated levels of very low density lipoproteins (VLDLs) and chylomicrons. The major risk for these patients is pancreatitis. Other clinical features in patients with chylomicronemia syndrome include eruptive xanthoma, hepatosplenomegaly, lipemia retinalis, abdominal pain with or without pancreatitis, peripheral neuropathy, dyspnea, memory loss, and dementia. There is an excellent review on this topic by Chait and Brunzell [6]. The management of severe HTG is important to achieve a triglyceride level less than 500 mg/dL to prevent pancreatitis. Thus, in these patients the fat intake should be reduced to less than 10–15% of total calories.

In a patient who is admitted to a hospital, it would be reasonable to start them on intravenous insulin and allow no calories by mouth if there is poor diabetes control, newly diagnosed diabetes, or they present with pancreatitis. In addition, they can be started on fibrate therapy and also omega-3 fatty acids. After the patient is discharged and diabetes control is reasonable with hemoglobin A_{1c} as close to 7%, one can institute niacin therapy in addition, to target triglyceride levels less than 500 mg/dL. In clinical practice, triple therapy with a fibrate, niacin, and omega-3 fatty acids is sometimes required to target the HTG. The dose of omega-3 fatty acid that has been found to be efficacious ranges from 4 to 10 g/d. In this regard, the prescription Lovaza (Pronova BioPharma, Lysaker, Norway) of omega-3 ethyl ester concentrate, a rich source of omega-3 fatty acid (840 mg/1-g capsules), can prove very efficacious in lowering triglycerides [7].

There is some debate within the literature regarding the role of continuous intravenous heparin in the treatment of severe HTG. It has been established that unfractionated heparin infusion can lead to an increase in the release of LPL [8]. This results in a temporary increase in lipolysis and, therefore, lower triglyceride levels. However, the circulating heparin-apoenzyme complex undergoes hepatic metabolism and degradation, which ultimately leads to a significant decrease in lipolysis activity [9, 10]. If the rate of hepatic metabolism/degradation of LPL exceeds the release of LPL from peripheral tissues, the net result would be worsening of HTG [9, 10]. Thus, we do not recommend heparin therapy.

Hospitalized patients may also benefit greatly from inpatient education to emphasize the importance of maintaining an improved lipid profile and potential dangers associated with poor lipid control. Nutritionist and/or endocrine consultation to discuss dietary, lifestyle, and exercise modifications would be appropriate for such individuals.

Table 1 Diabetic hypertriglyceridemia

Mild to moderate: 150–499 mg/dL
Severe hypertriglyceridemia: ≥ 500 mg/dL
Exclude other causes:
Obesity
Alcoholism
Renal disease
Drugs (eg, steroids, β blockers, retinoids, oral estrogens, tamoxifen, protease inhibitors, bile acid sequestrants)
Lipodystrophy
Pregnancy

Management of Mild to Moderate HTG

Sarwar et al. [11] reported in a recent meta-analysis that triglyceride levels are an independent cardiovascular risk factor even when adjusted for HDL-C. For mild to moderate HTG, consideration should be given to familial dyslipidemias that include familial combined hyperlipidemia, familial HTG, and familial dysbetalipoproteinemia

(type III dyslipidemia). Familiar HTG is an autosomal-dominant disorder with elevated levels of VLDL-cholesterol (VLDL-C) mainly due to large VLDL particles [12, 13••]. These patients generally have normal levels of LDL-C and apo B levels and can have low levels of HDL-C [12, 13••]. They do not appear to have an increased risk for CVD unless they also have enough features to define them as having the metabolic syndrome. Familial combined hyperlipidemia is also an autosomal-dominant disorder with an overproduction of apo B-100 particles [13••]. In this disorder, there is a family history of premature heart disease; and family members can have elevated levels of cholesterol, triglycerides, or combined hyperlipidemia. These patients are at increased risk for premature coronary artery disease (CAD) and have elevated apo B levels [13••]. Invariably these patients have a preponderance of small dense LDL particles. The third familial disorder that can result in mild to moderate HTG is type III dyslipidemia or dysbetalipoproteinemia. These patients usually are homozygous for apo E2; its frequency in the population is approximately 1% and can be easily determined by genotyping for apoprotein E. However, to manifest type III hyperlipoproteinemia, a second hit is required; this usually is a secondary factor such as diabetes, obesity, hypothyroidism, or renal disease. They classically present with cholesterol and triglyceride levels in the same order of magnitude between 200 to 600 mg/dL. Clinically, these patients present with tuberoeruptive xanthomas and xanthomas in palm creases (xanthoma palmaris striata), and can manifest features of CAD and peripheral arterial disease. They have elevated levels of VLDL-C and intermediate-density lipoprotein cholesterol and low levels of HDL-C and LDL-C by β quantification. On electrophoresis, they have a broad β band spanning the pre-β/β area. The diagnostic test for type III hyperlipoproteinemia is ultracentrifugation and reporting the VLDL-C/total triglycerides ratio. In patients with type III hyperlipoproteinemia, a ratio of greater than 0.3 is diagnostic and usually means that there is β-VLDL present. Table 2 depicts laboratory tests that can be useful in the workup of patients with HTG.

Table 2 Investigation of hypertriglyceridemia

Creatinine
Thyroid-stimulating hormone
Post-heparin lipolytic activity
Apo C-II
Apo B
Apo E genotyping
β quantification-type III dyslipidemia
Glucose/hemoglobin A_{1c} levels

Apo apolipoprotein

With respect to the management of mild to moderate HTG, therapeutic lifestyle change is a primary treatment, with a focus on reduction of saturated fat, cholesterol, trans fat, refined carbohydrates, and encouragement of a high-fiber diet with at least 30–40 g/d. Cigarette use is another modifiable risk factor that can be part of life-style changes. Smoking cessation results in an improved lipid profile despite the weight gain that often occurs after one stops smoking [13••]. In addition, statin therapy will be the treatment of choice to achieve levels of LDL-C less than 100 mg/dL and non-HDL-C less than 130 mg/dL in patients with diabetes without CVD [14]. In a diabetic patient with CVD, the LDL-C goal is less than 70 mg/dL and the non-HDL-C goal is less than 100 mg/dL. The non-HDL-C goal should also be a secondary target, especially if the triglyceride levels are greater than 150 mg/dL [14]. In achieving these goals, in addition to statin therapy, one has to consider combination therapy with niacin, fibrates, or omega-3 fatty acids.

Regarding therapeutic lifestyle change and HTG, body weight control is critical, regular physical activity should be encouraged, alcohol intake should be restricted, and avoidance of high-carbohydrate diets (especially with refined carbohydrates) should be encouraged. The evidence base for niacin therapy in diabetic patients on statins is scant. However, niacin therapy has been known to reduce LDL-C, non-HDL-C, and triglycerides, and increase HDL-C. In the CDP, niacin therapy resulted in reduction of cardiovascular events (CVEs) and mortality in patients with CAD [15]. Side effects of niacin therapy include flushing, abnormal liver function tests, hyperglycemia, and hyperuricemia. Generally, niacin therapy should be combined with statin therapy in patients with mild to moderate HTG, if the hemoglobin A_{1c} is around 7% (ie, good diabetes control). In the HATS study, there was a clear benefit of the combination of simvastatin/niacin therapy versus placebo on both coronary angiographic progression and CVEs. However, only 16% of the 160 patients with coronary heart disease (CHD) were diabetic [16]. In the ARBITER 3 study, patients were followed up for 24 months and carotid intima-media thickness (IMT) regression was evident with niacin therapy. The subcohort with diabetes or the metabolic syndrome included 62 patients [17]. In the ARBITER 6-HALTS study, which comprised 208 patients with CHD or CHD risk equivalent, all of whom were on statin therapy with LDL levels less than 100 mg/dL and HDL-C levels below 50 and 55 mg/dL in men and women, respectively, 40% of the patients on ezetimibe and 32% on niacin were diabetic [18]. Niacin therapy resulted in significant reduction in mean and maximum carotid IMT over 14 months and decrease in major CVEs. The effect of niacin therapy on mean carotid IMT was consistent across prespecified subgroups including presence and absence of diabetes [18].

Studies that are in progress that include diabetic patients are the AIM HIGH study with a comparison of niacin/simvastatin versus simvastatin therapy on CVD, and also the HPS2-THRIVE study in which niacin combined with laropiprant (D2 antagonist) plus statin therapy is being examined. Because both of these studies include diabetic patients, they will better inform us about niacin therapy in addition to statins in patients with mild to moderate hypertriglyceredemia to reduce the residual risk that is manifest even in statin-treated diabetics. Although the sample sizes of diabetic patients are small in the studies summarized above, the collective results are promising.

The best data about peroxisome proliferator-activated receptor-α agonist fibrate therapy (fibrate therapy in patients with diabetes) is the VA-HIT study. In this study, they showed that in the 627 diabetic patients there was 24% reduction in the expanded end point of death from CHD, nonfatal myocardial infarction (MI), and confirmed stroke (P=0.05) in the diabetic group who received gemfibrozil compared with placebo [19]. In a subsequent report, in which the diagnosis of diabetes was modified to include the new criteria of fasting plasma glucose ≥ 126 mg/dL, the total cohort of diabetic patients was increased to 769 and there was a 32% risk reduction of the composite end point of CHD death, stroke, or MI (P=0.004) [20]. This decrease was largely due to a reduction in CHD death. In the DAIS, 418 T2DM patients were randomized to fenofibrate (200 mg/d) or placebo for 3 years [21]. There were significant reductions in LDL-C, triglycerides, and increases in HDL-C. In the group that received fenofibrate, there was significantly less coronary angiographic progression in minimum lumen diameter and percent diameter stenosis. There was no significant effect on average of mean segment diameter. Also, there was a decrease in the incidence of microalbuminuria. In the FIELD study, 9725 T2DM patients not on statin therapy, 2131 with previous CVD with total cholesterol between 116 to 251 mg/dL, and triglyceride levels between 88.6 to 443 mg/dL were studied. The primary outcome in the study was CHD death and nonfatal MI. During the trial 17% of the placebo and 8% of the fenofibrate group started other lipid therapy, which was mainly statins. At study end, there was a 22% reduction in triglycerides, 6% decrease in LDL-C, and 1% increase in HDL-C [22]. There was a nonsignificant 11% reduction in the primary end point (P=0.16), 24% reduction in nonfatal MI (P=0.01), nonsignificant increase in CHD mortality of 19% (P=0.22), and total CVE (comprising CVD death, MI, stroke, and revascularization) was reduced by 11% (P=0.035). Other significant effects in the study included reduction in albuminuria and retinopathy needing laser therapy. Also, there was significant increased risk of pancreatitis and pulmonary embolism, and increase in both homocysteine and creatinine levels.

With regard to the fibrate therapy, side effects include gastrointestinal symptoms. Although there is an increased excretion of biliary cholesterol, there does not seem to be any increased risk of gallstones with fenofibrate therapy. Both fenofibrate and gemfibrozil displace warfarin from protein binding, so the warfarin dose has to be titrated in these patients to achieve their goal International Normalized Ratio. There also appeared to be an increase in both creatinine and homocysteine levels with fenofibrate therapy. Furthermore, the combination of statin and fibrate, especially gemfibrozil, in patients with renal failure, cholestasis, hypothyroidism, and aging increases the risk of rhabdomyolysis. It appears that gemfibrozil interferes with statin glucuronidation.

The final study is the ACCORD study (lipid arm), which was published recently [23••]. In this study, 5518 patients on fenofibrate and simvastatin were compared to simvastatin therapy and they were followed up for a mean duration of 4.3 years. There was no significant benefit on the primary end point, which was a composite of nonfatal MI, nonfatal stroke, and CVD death or any of the prespecified secondary end points [23••]. Also, in the prespecified subgroup analyses, there was a benefit for men and possible harm for women. A trend to benefit was evident (P=0.057) in patients with both high triglyceride levels (≥204 mg/dL) and low levels of HDL-C (<34 mg/dL). As in the FIELD and DAIS studies, there was a lower incidence of both microalbuminuria and macroalbuminuria in the fenobibrate group despite a significant increase in creatinine and decrease in glomerular filtration rate. Of interest, the group receiving a combination of fenofibrate and simvastatin did not have a statistically significant increase in myositis or rhabdomyolysis in the ACCORD trial [23••]. The investigators stated in their conclusion that their results do not support the routine use of fenofibrate in combination with simvastatin to reduce CVEs in the majority of patients with diabetes.

Conclusions

For diabetic dyslipidemia, statins are the drug of choice. In patients with severe HTG, especially triglyceride levels greater than 1,000 mg/dL, fibrate therapy and/or niacin and fish oil should be used to lower triglyceride levels to less than 500 mg/dL and to avert the risk of pancreatitis. Intravenous insulin may be considered as another therapeutic option for hospitalized individuals. In patients with mild to moderate HTG, consideration should be given to adding niacin to get both the LDL-C and non-HDL-C levels to goal, especially if the hemoglobin A_{1c} is around 7%. The combination of fibrate therapy to statin as evidenced by the ACCORD study has been disappointing. The greatest

benefit for this combination therapy appears to be in patients who have low HDL-C and elevated triglyceride levels, as shown by subgroup analysis and post hoc analyses of the FIELD study [24].

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