

Triglycerides and HDL Cholesterol

Stars or second leads in diabetes?

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Diabetes carries a high risk of atherosclerosis, and cardiovascular disease, especially coronary heart disease (CHD) and stroke, is by far the leading cause of death among patients with type 2 diabetes. Although statins reduce the risk of major vascular events by about one-fifth per millimole per liter reduction in LDL cholesterol, with similar proportional reductions in major coronary events, stroke, and the need for coronary revascularization, the residual risk remains high. In the Scandinavian Simvastatin Survival Study (4S) (1), although the relative risk reduction in diabetic patients was larger than in nondiabetic patients, simvastatin-treated diabetic patients were still at higher risk of death than the placebo-treated nondiabetic patients. Multifactorial intervention reduces the risk even further, but significant danger remains. Current guidelines call for an aggressive treatment strategy to reduce LDL cholesterol, blood pressure, and glucose levels in diabetic patients, but data concerning the management of high triglyceride (TG) levels and low HDL cholesterol levels remains inconclusive. This article reviews the data concerning diabetic dyslipidemia and its management.

DIABETIC DYSLIPIDEMIA— The cluster of lipid abnormalities associated with type 2 diabetes is defined by a high concentration of TG and small dense LDL and a low concentration of HDL cholesterol. Plasma LDL cholesterol levels are generally normal. Insulin resistance is believed to contribute to this atherogenic dyslipidemia by increasing the hepatic secretion of VLDL and other apolipoprotein (apo)B-containing lipoprotein particles,

as a result of increased free fatty acid flux to the liver (2,3). This may also be the result of a diminished suppressive effect of insulin on apoB secretion, either at the level of the regulation of apoB degradation, or inhibition of microsomal TG transfer protein activity (4). Through the action of cholesterol ester transfer protein, TGs are transferred from VLDL to HDL, creating TG-rich HDL particles, which are hydrolyzed by hepatic lipase and rapidly cleared from plasma (5). A similar cholesterol ester protein-mediated transfer of TGs from VLDL to LDL contributes to the formation of small dense LDL particles (6). Other mechanisms, including impaired clearance of lipid and lipoproteins may also be involved.

TRIGLYCERIDES, HDL CHOLESTEROL, AND CARDIOVASCULAR RISK— The question whether hypertriglyceridemia causes coronary artery disease (CAD) or is simply a marker for the accompanying lipoprotein abnormalities (especially low HDL cholesterol levels and small dense LDL particles) is still controversial. In a meta-analysis of 17 population-based prospective studies, increased plasma TG levels were associated with increased coronary disease risk in both men and women, after adjustment for HDL cholesterol and other risk factors (7). A direct atherogenic effect of TG-rich particles, particularly intermediate-density lipoprotein, and remnant particles has been presumed. In a more recent meta-analysis, adjustment for established coronary risk factors, especially HDL cholesterol, substantially attenuated the magnitude of risk associated with high

TG levels, leaving an odds ratio of about 1.7 in individuals with TG levels in the top third of the population, compared with those in the bottom third (8).

Two recent studies shed light on the role of nonfasting TG levels as a risk factor for cardiovascular disease. In the Women's Health Study (9), adjustment for levels of total and HDL cholesterol, and measures of insulin resistance (diabetes, BMI, and C-reactive protein), weakened the association between TG levels and the risk of cardiovascular events, leaving little independent relationship with cardiovascular events. In contrast, nonfasting TG levels were associated with incident cardiovascular events, independent of traditional risk factors, levels of other lipids, and markers of insulin resistance (9). In the Copenhagen City Heart Study (10), nonfasting TG levels were associated with increased risk of myocardial infarction, ischemic heart disease, and death after adjustment for age, total cholesterol, BMI, hypertension, diabetes, smoking, alcohol consumption, physical inactivity, lipid-lowering therapy, postmenopausal status, and hormone therapy in women (10). The levels of nonfasting TG were highly correlated with those of remnant lipoprotein cholesterol (10). These results may also reflect the effect of postprandial hypertriglyceridemia (independent of and cumulative to the effect of hyperglycemia) on endothelial function.

The association between reduced HDL cholesterol levels and increased risk of heart disease is, on the other hand, well established, independently of TG levels and other risk factors (11). In fact, the "low HDL cholesterol" or "hypoalpha" syndrome is the most frequent lipoprotein abnormality in coronary patients (12). Intravascular ultrasound studies demonstrate that patients with low HDL cholesterol and high TG levels have more extensive coronary atheromas than those with an isolated elevation of LDL cholesterol (13). Patients with reduced HDL cholesterol levels show intima-media thickness results similar to those with familial hypercholesterolemia (14), while a high level of HDL cholesterol reduced plaque growth in subjects with preexisting carotid atherosclerosis (15).

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The HDL particles induce the removal of cholesterol from cells, including those in atherosclerotic plaques, and carry them to the liver, but the mechanisms by which HDL confer protection from atherosclerosis include more than just reverse cholesterol transport. HDL particles seem to have anti-inflammatory and antioxidant properties, inhibiting the oxidation of LDL cholesterol and the expression of cellular adhesion molecules and monocyte recruitment. The HDL may also reduce the risk of thrombosis by inhibiting platelet activation and aggregation.

Recent studies, however, demonstrated that it may be the level of apoA-I, rather than the level of HDL cholesterol, that is important in reducing the risk of atherosclerosis (16). In fact, high plasma HDL cholesterol and large HDL particles may be associated with increased CAD risk when levels of apoA-I and apoB remain constant. In contrast, apoA-I remains negatively associated with CAD risk, even in high concentrations.

DO WE NEED DRUGS TO REDUCE TG AND/OR INCREASE HDL CHOLESTEROL LEVELS?

— Statins are potent in reducing LDL cholesterol levels and CAD risk, and statin therapy in patients with lower HDL cholesterol levels reduces coronary risk to approximately that of patients with higher HDL cholesterol levels on placebo. But even statins fail to eliminate most of the risk, especially in subjects at high risk, such as diabetic patients. In the Collaborative Atorvastatin Diabetes Study (CARDS), treatment of diabetic patients with atorvastatin (10 mg/day for 3.9 years) reduced the risk for major cardiovascular events by approximately one-third (17), leaving two-thirds of the risk unaffected. In the Treating-to-New-Targets (TNT) study, significantly more patients with metabolic syndrome than those without had a major cardiovascular event, irrespective of statin treatment (18).

A post hoc analysis of the TNT study demonstrated that the HDL cholesterol level was predictive of major cardiovascular events also in patients receiving statins (19). Even among statin-treated subjects who achieved LDL cholesterol levels below 70 mg/dl, the subjects in the highest quintile of HDL cholesterol levels were at less risk for major cardiovascular events than those in the lowest quintile.

In a post hoc analysis of four prospective randomized intravascular ultrasound trials, a decrease in LDL cholesterol levels and an increase in HDL cholesterol levels were independent predictors of atheroma regression (20). Statin therapy was associated with regression of coronary atherosclerosis when LDL cholesterol was substantially reduced, and HDL cholesterol was increased by >7.5% (20).

Similar results were found regarding TG levels in statin-treated patients. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study, low on-treatment TG (<150 mg/dl) was associated with reduced CHD risk, compared with higher TG, independent of the level of LDL cholesterol (21). For each 10 mg/dl decrement in on-treatment TG, the incidence of major coronary events was lower by 1.4% after adjustment for LDL cholesterol or non-HDL cholesterol and other covariates (19). The combination of low LDL cholesterol (<70 mg/dl), low C-reactive protein (<2 mg/l), and low TG (<150 mg/dl) was associated with the lowest event rates.

However, although statins can reduce LDL cholesterol levels by as much as 50% or more, their effect on HDL cholesterol levels is modest, at best. These data demonstrate the need for TG-reducing and/or HDL cholesterol-elevating therapy with a proven efficacy in terms of reducing morbidity and mortality.

CURRENT THERAPIES AIMED AT REDUCING TG AND INCREASING HDL CHOLESTEROL LEVELS

Peroxisome proliferator-activated receptor- α agonists

Fibrates are among the oldest agents used to treat patients with lipid disorders, but even after more than 5 decades of use, their role in preventing CAD is still disputed.

Activation of peroxisome proliferator-activated receptor (PPAR)- α has numerous effects that lead to an improvement in dyslipidemia. These include the induction of enzymes mediating fatty acid oxidation, stimulation of lipid import into the cell in part by induction of lipoprotein lipase, and suppression of apoC-III, which interferes with the clearance of TG-containing lipoproteins. The result is a reduction of TG levels, increase in HDL cholesterol levels, and reduction of small dense LDL levels. These changes have a favorable effect on endothelial function

and hemorrheologic parameters. Fibrates also increase adiponectin levels and may reduce the incidence, or delay the onset, of diabetes in patients with impaired fasting glucose.

However, data on the effect of fibrates on markers of inflammation, cell adhesion, and oxidation are controversial: in one study, fenofibrate did not reduce plasma levels of C-reactive protein, soluble intercellular adhesion molecule-1 (sICAM)-1, vascular cell adhesion molecule-1 (sVCAM-1), matrix metalloproteinase-9 (MMP-9), secretory phospholipase A₂ (sPLA₂), and oxidized LDL (22), whereas in other studies, PPAR- α activation decreased levels of endothelin-1, tissue factor, and VCAM-1 (23) and cytokine release (24).

In the Diabetes Atherosclerosis Intervention Study (DAIS), fenofibrate therapy was associated with less angiographic progression of atherosclerotic lesions in diabetic patients without known coronary disease. This effect seemed to be mediated, at least in part, by changes in LDL particle size (25).

In the Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT), treatment with gemfibrozil in men with CHD, an HDL cholesterol level of \leq 40 mg/dl (mean 32 mg/dl), and a TG level of \leq 300 mg/dl (mean 160 mg/dl) resulted in a 22% reduction in the relative risk for nonfatal myocardial infarction or death from coronary causes. The risk was reduced by 34% in patients with diabetes or a high fasting plasma insulin level (26).

Post hoc analyses from other studies have demonstrated the efficacy of fibrates in preventing cardiovascular events in patients with diabetes or metabolic dyslipidemia. In the Helsinki Heart Study, treatment with gemfibrozil resulted in a 71% lower incidence of CHD events in the subgroup of patients free of CHD at baseline, with the LDL cholesterol/HDL cholesterol ratio above 5 and TG level >200 mg/dl (27). In the Bezafibrate Infarction Prevention (BIP) study, although bezafibrate had no effect on all-cause and cardiac mortality in the entire study population, it was associated with a 31% relative reduction in the risk of myocardial infarction in patients with the metabolic syndrome (28).

The largest trial designed to test the efficacy of fibrates in preventing morbidity and mortality was the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial (29). In this trial, fenofibrate failed to significantly reduce the risk of the primary outcome of coronary

events. Possible explanations for this finding include a higher than expected rate of patients receiving statins, a lower than expected increase in HDL cholesterol levels, and unfavorable nonlipid effects, including increases in the levels of homocysteine, creatinine, and hemoglobin A1C (29). The effect of fenofibrate on lipoprotein particle subclasses also seemed somewhat unfavorable: while there was an increase in LDL particle size, HDL2 was decreased, and small dense HDL3 increased, with no effect on apoA-I levels.

Efforts of developing more potent and selective PPAR- α agonists have met with safety concerns, including an increase in LDL cholesterol and creatinine levels.

Because virtually all diabetic patients should receive statins, and the effects of statins and fibrates may be complementary, the combination of statins and fibrates is of great interest. Clinical studies with fibrate-statin combinations have shown superior lipid-modifying efficacy compared with statin monotherapy in reducing TG, VLDL cholesterol, non-HDL cholesterol, and LDL cholesterol levels, as well as raising HDL cholesterol levels. A greater effect in reducing small dense LDL levels, as well as markers of inflammation (C-reactive protein and lipoprotein-associated phospholipase A₂) (30), was also found. Although there are safety concerns, no cases of rhabdomyolysis were reported in about 1,000 patients who received fenofibrate plus statin in the FIELD study (29). The lipid-lowering arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, involving about 5,500 patients with type 2 diabetes, is comparing the effect of simvastatin plus fenofibrate to simvastatin alone on cardiovascular morbidity and mortality (30). Data from ACCORD are expected in 2009.

Niacin

Niacin monotherapy or in combination with other agents was in clinical use during the late 1970s and 1980s, but lipid-lowering treatments shifted largely to statins. Recent failures in developing HDL cholesterol-raising drugs have rekindled interest in this drug. High-dose niacin (1–3 g) decreases VLDL, increases HDL, and has a modest effect on LDL. Among lipid-modifying agents, niacin is the most potent agent currently available to increase HDL cholesterol and the only one that reduces lipoprotein(a) concentrations.

Much of VLDL production is controlled by the provision of fatty acids to

the liver. Niacin is thought to decrease circulating fatty acids by inhibiting the release of fatty acids in adipose tissue mediated by hormone-sensitive lipase. The underlying mechanism is unknown, but recent data suggest that an orphan G protein-coupled receptor may be the nicotinic acid receptor and mediate the antilipolytic effects of this vitamin.

In the Coronary Drug Project, niacin reduced mortality among myocardial infarction survivors, although, contrary to the relatively rapid effect of statins, mortality rates were almost identical throughout the first 68 months of follow-up and did not begin to diverge until month 72 (31). In the HDL-Atherosclerosis Treatment Study (HATS), the combination of niacin and simvastatin was associated with regression of atherosclerosis, as assessed by coronary angiography (32). The simvastatin-niacin combination was also associated with a 90% reduction in the composite end point of major cardiovascular events (32). In the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol-2 (ARBITER-2) study, the addition of niacin to statin therapy slowed the progression of atherosclerosis as assessed by intima-media thickness among individuals with known CHD and moderately low HDL cholesterol (33). In addition to the beneficial effects on intima-media thickness progression, a large, although statistically nonsignificant, reduction in recurrent CHD events was also noted (33).

Although there are concerns regarding the effect of niacin on the control of diabetes, most studies demonstrated that niacin therapy has only a minor effect on glucose levels in diabetic patients.

All studies examining the effects of niacin on morbidity and mortality were relatively small-scale. Two large clinical outcome studies, the Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) and the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) studies are under way and expected to shed more light on the role of niacin.

ω -3 fatty acids

ω -3 fatty acids have beneficial effects in lowering TG levels, especially in the postprandial state, including in patients with atherogenic dyslipidemia associated with the metabolic syndrome and diabetes.

The mechanism through which ω -3

fatty acids exert their effect is not entirely understood. They are converted into a wide variety of bioactive eicosanoids and act as ligands for several nuclear transcription factors, thereby altering gene expression. Other proposed beneficial effects of ω -3 fatty acids include effects on arrhythmia, platelet aggregation, inflammation, endothelial function, and blood pressure.

A number of small studies have investigated the combination of a statin and ω -3 fatty acids as therapy in patients with mixed dyslipidemia. In one study, the addition of ω -3 fatty acids to simvastatin significantly decreased TG, VLDL, and non-HDL cholesterol levels compared with simvastatin alone (34). In obese insulin-resistant men with dyslipidemia, consistent with the metabolic syndrome, the combination of ω -3 fatty acids and atorvastatin decreased VLDL-apoB secretion and increased the fractional catabolic rate of VLDL-apoB and conversion of VLDL to LDL (35). In another study, the combination of atorvastatin ω -3 fatty acids increased HDL2 levels, thereby correcting the functional defect in HDL characteristic of the metabolic syndrome (36).

The data on clinical efficacy of ω -3 fatty acids in terms of morbidity and mortality is still controversial. Three large trials—Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI-Prevenzione (GISSI-Prevenzione) (37), Japan EPA Lipid Intervention Study (JELIS) (38), and GISSI-heart failure (39)—have shown clinical outcome benefits of dietary supplementation with ω -3 fatty acids, but a recent systematic review did not demonstrate a clear effect on total mortality, or combined cardiovascular events (40). However, it should be noted that patients in these trials were not dyslipidemic, and the dose of ω -3 fatty acids used did not produce any significant change in the level of triglycerides or HDL cholesterol. The ORIGIN study (Outcome Reduction with an Initial Glargine Intervention) is looking to determine whether ω -3 acid ethyl esters reduce cardiovascular death compared with a placebo in >12,000 patients with dysglycemia (41).

FUTURE PROSPECTS—The concept of cholesterol ester transfer protein (CETP) inhibition suffered a serious blow when the results of the ILLUMINATE trial demonstrated an increase in adverse events in patients treated with torcetrapib (42). However, because the increase in

adverse events may be due to the off-target effects of torcetrapib, studies with other CETP inhibitors such as anacetrapib and JTT-705 are under way and will help to shed light on this question (43).

Another therapeutic approach emphasizes the role of apoA-I in the anti-atherogenic function of HDL particles. In one small study, intravenous recombinant apoA-I Milano/phospholipid complexes produced regression of coronary atherosclerosis as measured by intravascular ultrasound (44). ApoA-I mimetic peptides are being investigated and, at least in animal models, were found to increase the formation of pre- β HDL, improve HDL-mediated cholesterol efflux, increase paraoxonase activity, and convert HDL from proinflammatory to anti-inflammatory (45).

Large unilamellar vesicles have been developed to serve as “sink or sponge” binding cholesterol from HDL, thus regenerating HDL particles able to take up cholesterol from peripheral tissues (46).

Finally, liver X receptor agonists are also investigated as a possible measure of increasing reverse cholesterol transport and reversing atherosclerosis (47). However, the first generation of nonselective LXR α and LXR β agonists increased plasma TG levels, and a search for an LXR β -specific agonist, which may be free of that effect, is under way.

All of these therapies are in the preliminary stages of development, and it will be some time before large-scale clinical trials are conducted.

CONCLUSIONS— The risk of cardiovascular morbidity and mortality in diabetic patients remains high, despite modern effective therapies, such as statins. Some of the risk may be attributed to other components of the metabolic dyslipidemia, namely high TG level, low HDL cholesterol level, and small dense LDL. Current attempts at controlling this form of dyslipidemia have ended with either conflicting or entirely disappointing results. We are in dire need of additional therapeutic options for these high-risk patients. Ongoing trials with currently available therapies are expected to provide some much-needed answers, and new therapies are eagerly expected.

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