Management of Dyslipidemia in Patients with Complicated Metabolic Syndrome

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As the prevalence of the metabolic syndrome increases, 2 comorbid conditions—hepatic steatosis and human immunodeficiency virus (HIV) lipodystrophy—have become difficult clinical challenges. Dyslipidemia in patients with nonalcoholic fatty liver disease or nonalcoholic steatohepatitis may improve with use of statins, fibrates, niacin, and thiazolidinediones, but the data are presently very limited. HIV lipodystrophy is associated with a marked risk of coronary artery disease (CAD), and more aggressive management of the dyslipidemia is likely necessary to improve the prognosis. **(Am J Cardiol 2005;96[suppl]:22E–25E)**

Treatment of dyslipidemia in the patient with the metabolic syndrome is frequently complicated by comorbid conditions. The majority of patients with the metabolic syndrome have hypertension and/or diabetes mellitus, requiring medications to treat these important coronary artery disease (CAD) risk factors. Therefore, in managing dyslipidemia in patients with the metabolic syndrome, the efficacy and safety of combining lipid-altering drugs with antihypertensive and hypoglycemic agents must be considered. In particular, 2 comorbid conditions associated with the metabolic syndrome—hepatic steatosis and human immunodeficiency virus (HIV) lipodystrophy—provide unique challenges for the clinician in the management of dyslipidemia. These conditions are rapidly increasing in prevalence as the epidemic of obesity continues to expand and as drug therapy for HIV infection is markedly prolonging the life expectancy of affected individuals. Management of dyslipidemia in these patient populations is therefore becoming increasingly more important.

Nonalcoholic Fatty Liver Disease

The prevalence of nonalcoholic fatty liver disease (NAFLD), according to the Third National Health and Nutrition Examination Survey, ranges from 16% to 23%.[1] NAFLD is a spectrum of disorders that range from simple steatosis (fat accumulation within liver cells) to steatohepatitis (fat accumulation and liver cell injury) or nonalcoholic steatohepatitis (NASH). NASH can progress to cirrhosis (fibrosis, scarring, and nodule formation), especially if other insults to the liver occur, such as excessive alcohol intake, hepatitis C infection, or a toxic insult to the liver.[2] The prevalence of NASH is between 2% and 6%, depending on the diagnostic method. NAFLD is commonly associated with the metabolic syndrome and obesity, with 21% to 55% of patients with NAFLD having diabetes. In patients with morbid obesity, the prevalence of NAFLD is >95%.[3]

Fat accumulation in the liver is associated with several features of insulin resistance even in individuals whose weight is normal or who are moderately overweight. At present, it is unclear whether the extent of hepatic steatosis is a cause rather than a consequence of the metabolic syndrome.

Hepatic triglyceride content is balanced by the activities of cellular molecules that facilitate hepatic triglyceride uptake, fatty acid synthesis and esterification (input),[4] fatty acid oxidation, and the export of triglycerides by the secretion of low-density lipoprotein (LDL) (output). Hepatic steatosis appears when input exceeds output. In the presence of insulin resistance, free fatty acid (FFA) levels are increased, causing an increase in input to the liver. Other factors such as high-fat diets and leptin or adiponectin deficiencies may result in excessive amounts of fatty acid delivery to the liver. There are also examples of intrahepatic causes of steatosis such as high sucrose feeding, which induces fat accumulation by increased de novo lipogenesis. Factors that impair hepatic triglyceride output include a decrease in β-oxidation of hepatic free fatty acids or drugs that inhibit microsomal transfer protein, which is involved in very-low-density lipoprotein (VLDL) assembly. Therefore, as input exceeds output of free fatty acids, hepatic steatosis occurs.

Clinically, hepatic steatosis may result in elevation of the liver enzymes aspartate aminotransferase and alanine aminotransferase. Active liver disease is a contraindication for the use of most lipid-lowering drugs and, consequently, many patients with hepatic steatosis may not receive the appropriate therapy to treat dyslipidemia because of safety concerns. There are little data regarding the safety of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) and other lipid-lowering drugs in patients with

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Table 1
Possible signs and symptoms of the HIV-associated lipodystrophy syndrome*

A	≥1 symptom (patient report, physical examination) occurring since the initiation of HAART
	1. Peripheral subcutaneous fat loss (face, arms, legs)
	2. Central adiposity (abdomen, dorsocervical fat pads, increased breast size in women)
B	≥1 metabolic change since starting HAART
	1. Fasting triglycerides 5.3 mmol/L (>200 mg/dL)
	2. Fasting cholesterol 2.2 mmol/L (>200 mg/dL)
	3. Fasting C-peptide 2.5 nmol/L (>7.5 ng/mL)
	4. Impaired glucose metabolism
	—Impaired fasting glucose 6.1–7.0 mmol/L (110–126 mg/dL)
	—Impaired glucose tolerance 7.8–11.1 mmol/L (140–200 mg/dL)
	—Diabetes mellitus: fasting glucose 11.1 mol/L (≥200 mg/dL)
	5. Hyperlactatemia >2.1 mmol/L (18.9 mg/dL)
C	No active AIDS-defining or other severe illness during last 3 mo
D	No current steroid therapy or treatment with immunomodulators

AIDS = acquired immunodeficiency syndrome; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus.

*At least 1 condition in each section (A through D) must be present.

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NAFLD, but based on the pathogenesis of the hepatic steatosis, there is a rationale suggesting that lipid therapies may not exacerbate hepatic damage in patients with NAFLD while they may provide significant clinical benefits.

On the basis of their potential mechanism of action, drugs that decrease circulating free fatty acid should improve hepatic steatosis. Niacin decreases free fatty acid movement from the peripheral cells, and fibrates as well as peroxisome proliferator-activated receptor (PPAR)–γ agonists increase lipoprotein lipase activity to enhance clearance of free fatty acid. Fibrates also increase hepatic β-oxidation of free fatty acid. Niacin trials for the treatment of NAFLD are ongoing, and a randomized controlled trial of gemfibrozil in 46 patients with NASH demonstrated a significant decrease in serum ALT, but histologic data were unavailable.[5] Statins also may be useful. In a small pilot study, 7 patients with NASH treated with atorvastatin for 1 year had significant improvement in ballooning degeneration and inflammatory scores on liver biopsy.[6]

Because the majority of patients with NAFLD have the metabolic syndrome, drugs that improve insulin resistance and therefore decrease free fatty acid flux to the liver may prove clinically helpful. In a small study with the thiazolidinedione troglitazone, 7 of 10 patients with NASH exhibited normalized serum alanine aminotransferase levels, but follow-up liver biopsies did not show significant improvement after 6 to 10 months of therapy.[7] Both rosiglitazone and pioglitazone have been shown to induce biochemical and histologic improvement in patients with hepatic steatosis. Larger trials are under way, but because thiazolidinedione use has a history of hepatotoxicity, further data are warranted to justify more widespread recommendations. Metformin also improved biochemical markers in 14 patients with NAFLD.[8]

Nonpharmacologic therapy may also be clinically useful. Small trials have demonstrated benefits with vitamin E, which as an antioxidant protects cellular damage from oxygen free radicals and reactive products of lipid peroxidation.[9] Other dietary supplements such as betaine and N-acetyl cysteine have shown biochemical improvement in small studies.[10]

Weight loss is probably the best therapeutic approach for hepatic steatosis. Because low-carbohydrate diets[11] appear to lower levels of circulating triglycerides and improve insulin resistance markers to a greater degree than do low-fat diets, at least in the short term, this dietary approach may prove to be more clinically useful in alleviating the biochemical and histologic effects of hepatic steatosis. Further research is needed to verify this dietary approach.

Dyslipidemia in Patients with HIV

The management of dyslipidemia in patients infected with HIV has become an increasingly more important issue owing to the markedly improved survival associated with the advent of highly active antiretroviral therapy (HAART). On the basis of recent statistics, there is a 25% increase in CAD risk in the first 4 to 6 years of HAART, and 76% of patients with HIV who have acute myocardial infarction are aged <55 years.[12] Of the patients with HIV and premature CAD, 58% have no other risk factors. In patients infected with HIV, there is marked progression of carotid intimal-medial thickness compared with age-matched control subjects.[13] The metabolic syndrome induced by HAART, therefore, represents a significant clinical challenge for clinicians involved in the treatment of patients with HIV (Table 1).[14]

The etiology of the metabolic syndrome and lipodystrophy associated with HAART is uncertain. Before the use of HAART, patients with HIV developed the metabolic syndrome more frequently than did age-matched controls. However, once the protease inhibitors became available, the incidence of the metabolic syndrome sig-

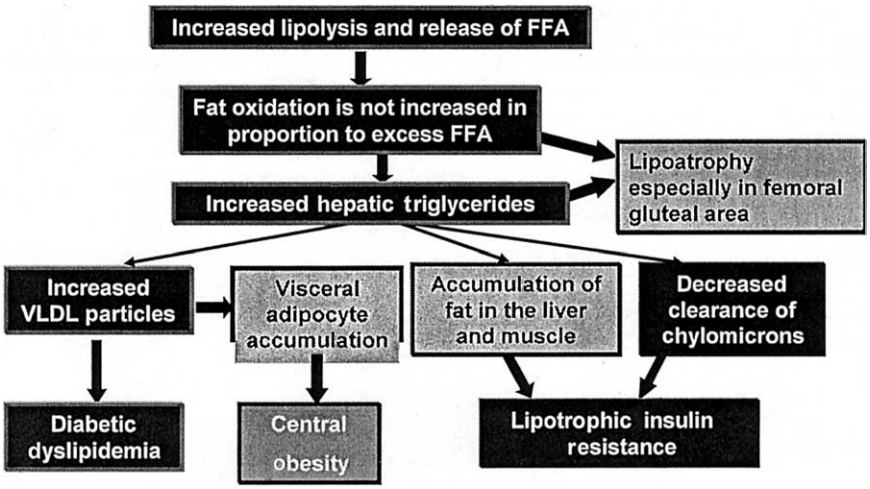

Figure 1. Human immunodeficiency virus infection and the insulin resistance syndrome. FFA = free fatty acids; VLDL = very-low-density lipoprotein.

Table 2
Therapeutic options for HIV-associated lipodystrophy and related metabolic complications

Lifestyle changes (reduce saturated fat and cholesterol intake, increase physical activity, stop smoking)
Change antiretroviral therapy (replacement of protease inhibitor, replacement of stavudine)
Statins (eg, atorvastatin, pravastatin)
Fibrates (eg, gemfibrozil or bezafibrate)
Metformin
Recombinant human growth hormone
Surgical intervention

Adapted with permission from *HIV Medicine 2003.*[18]

nificantly increased. As opposed to the "traditional" metabolic syndrome, which involves high free fatty acid levels due to the inability for appropriate storage into fat cells in the presence of insulin resistance, patients receiving HAART develop a lipotoxicity due to mitochondrial dysfunction resulting in the excess release of free fatty acid.[15] Protease inhibitors may also induce the lipoatrophy by inhibiting sterol regulatory enhancer–binding protein 1 and PPAR-γ, which are both involved in lipogenesis. Free fatty acid levels are increased, resulting in increased production of VLDL and small, dense LDL as well as low plasma levels of high-density lipoprotein (HDL) (Figure 1). This increase in lipolysis appears to cause the characteristic subcutaneous lipoatrophy in the face, legs, and buttocks with accumulation of fat in the visceral area and the back of the neck (buffalo hump).

The risk factors for HAART-induced metabolic syndrome and lipodystrophy include length of therapy, more severe disease, and the specific drugs used.[16] The nucleoside analog most strongly associated with lipoatrophy is stavudine, especially when used in combination with didanosine.[17] Ritonavir, nelfinavir, and indinavir appear to carry different risks of dyslipidemia. Replacement of a protease inhibitor with nevirapine, efavirenz, or abacavir can improve the dyslipidemia.[18]

The management of dyslipidemia in patients taking HAART is complicated by the risk of combining a statin with protease inhibitors that are potent cytochrome P450 3A4 (CYP 3A4) inhibitors (Table 2).[18,19] Therefore, statin doses should not exceed 10 mg/day in combination with a protease inhibitor unless a statin that is not metabolized by CYP 3A4 (eg, pravastatin, fluvastatin, or rosuvastatin) is used. Because these patients usually have moderate to severe hypertriglyceridemia, a fibrate is frequently necessary to achieve the appropriate National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) non-HDL targets. Gemfibrozil should be avoided in combination with a statin (except for fluvastatin) because of the inhibition of glucuronidation metabolism resulting in markedly higher statin levels and, therefore, increasing the risk of myopathy.[20] Fenofibrate, which does not impair statin glucuronidation and does not adversely affect statin levels, is the preferable fibrate option to maximize the safety of combination therapy. Niacin, which reduces the release of peripheral free fatty acid, may also be useful in improving the dyslipidemia but may exacerbate insulin resistance if the doses exceed 1,000 to 1,500 mg/day.[21] The thiazolidinediones, as PPAR-γ agonists, do not appear to improve the lipodystrophy significantly and have not been shown to modify the dyslipidemia beneficially.[21]

Because HIV infection frequently occurs in young individuals, long-term HAART is necessary and, therefore, risk-factor modification is increasingly important to prevent the development of CAD. On the basis of the markedly increased risk of CAD associated with relatively short HAART therapy, lifestyle changes and lipid-lowering therapy will likely be necessary to prevent CAD. Low-carbohydrate diets have been shown to improve the dyslipidemia associated with the metabolic syndrome and, therefore, may also be useful. Use of the nucleoside analog abacavir and lamivudine with the non-nucleoside analog efavirenz appears to result in less lipoatrophy. Tenofovir combined with lamivudine and efavirenz improves the lipid profile compared to stavudine therapy. However, these modifications of HAART should not be used at the expense of successful treatment of the underlying HIV disease. Because the risk of CAD is markedly elevated, patients with HIV receiving HAART should most likely be considered at high risk according to the NCEP ATP III guidelines even though their age may give them an adapted Framingham score for 10-year risk of –20%.

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