METABOLIC COMPLICATIONS OF ANTIRETROVIRAL THERAPY

The body fat abnormalities and metabolic derangements that constitute the so-called "HIV lipodystrophy syndrome" were initially reported in patients receiving protease inhibitor-containing antiretroviral regimens. However, the metabolic abnormalities associated with HIV-1 disease have also been reported in protease inhibitor-naive patients, suggesting a complex pathophysiologic mechanism related only in part to protease inhibitor therapy. The syndrome is characterized by (1) changes in body composition ("fat redistribution"), including dorsocervical fat deposits (buffalo hump) and truncal obesity, facial and peripheral fat atrophy, and breast enlargement in women; (2) insulin resistance and hyperglycemia; and (3) lipid abnormalities ("dyslipidemia") including hypertriglyceridemia and reduced high-density lipoprotein (HDL) levels. However, there is significant heterogeneity in the presentation of HIV lipodystrophy syndrome, with variable prevalence estimates depending on the definition of the syndrome. One group has reported a prevalence of 83% among patients receiving protease inhibitors based on self-reporting and clinical examination, whereas others have reported prevalence rates of 12% based on dual-energy x-ray absorptiometry (DEXA) scans. A prevalence rate of 16% was shown in women based on self-assessment in a preliminary study. At the current time, no consensus exists for the most appropriate terminology to describe and define the metabolic changes and body fat abnormalities that have been observed.

Figure 1. Insulin sensitivity among HIV-seronegative controls (n=180) and patients with HIV infection receiving antiretroviral regimens containing a protease inhibitor (+PI; n=13) or not containing a protease inhibitor (-PI; n=61). Adapted from Walli R, et al. AIDS. 1998.

POTENTIAL PATHOPHysiologic MECHANISMS

A number of mechanisms have been proposed to account for HIV lipodystrophy syndrome. Carr and Cooper have posited that abnormalities in fat redistribution result from protease inhibitor suppression of chylomicron and triglyceride uptake by the endothelial lipoprotein-related peptide (LRP)-lipoprotein lipase complex and inhibition of CRABP-1 (cis-retinoic acid binding protein-1)-mediated adipocyte differentiation and apoptosis, resulting in increased peripheral fat deposition and redistribution. However, a number of other groups have observed the syndrome in protease inhibitor-naive patients. It has thus been suggested that pathophysiologic mechanisms may include interaction of underlying metabolic abnormalities due to HIV disease itself and weight gain resulting from potent antiretroviral therapy. For example, hypertriglyceridemia has long been associated with HIV disease, and may worsen in association with weight gain and use of potent therapy.

Other potential mechanisms contributing to the observed metabolic abnormalities in HIV lipodystrophy syndrome include the effects of cytokines and/or hormonal factors. The buffalo hump and centripetal fat deposition observed in the syndrome are similar to the clinical picture of Cushing's syndrome, which is associated with hypercortisolism. The association of the syndrome with elevated cortisol levels, however, remains unclear, with some studies indicating elevated serum and urine cortisol levels and other studies indicating primarily normal levels and appropriate
suppression testing in patients with borderline elevated cortisol levels. It is currently unknown whether, in the absence of systemic cortisol elevations, there are abnormalities in regional cortisol metabolism in affected patients.

**INSULIN RESISTANCE AND HYPERGLYCEMIA**

Hyperglycemia was previously observed in patients with HIV disease primarily in association with pentamidine or megestrol acetate use. The recent increase in prevalence of hyperglycemia is associated with use of potent antiretroviral therapy, with one study documenting fasting blood glucose levels above 120 mg/dL in 14% of patients receiving protease inhibitor-containing regimens. Further, impaired glucose tolerance was detected by oral glucose tolerance testing in 41% of patients on protease inhibitor-containing regimens. Insulin sensitivity in those taking protease inhibitor-containing regimens was significantly lower than in patients not receiving protease inhibitors or in HIV-seronegative controls (Figure 1).

Increased truncal fat may account for the insulin resistance observed in HIV-infected patients on potent antiretroviral therapy. In a recent study by Hadigan and colleagues of 75 HIV-infected women, fasting morning insulin levels were significantly higher in the HIV-infected patients compared with body mass index (BMI)-matched noninfected controls. No difference in insulin levels was observed between patients who had received a protease inhibitor and those who had not, or between patients who were less than 90% or more than 90% of ideal body weight, both of whom exhibited elevated insulin levels compared with controls. However, insulin levels were most significantly elevated in those patients with truncal adiposity (>2 standard deviations from controls in the relative ratio of trunk fat to extremity fat) (Figure 2). These findings suggest (1) the presence of underlying metabolic abnormalities in HIV-infected patients, and (2) that the degree of truncal obesity may be a primary determinant of fasting hyperinsulinemia in HIV-infected women. The available data thus indicate that relative truncal adiposity occurs even in patients not receiving protease inhibitors and may make patients prone to the metabolic effects of these drugs.

**TRIGLYCERIDE AND LIPID ABNORMALITIES**

Prior to the era of potent antiretroviral therapy, hypertriglyceridemia was commonly observed among HIV-infected patients and was shown to result from increased production of very low density lipoprotein and decreased triglyceride clearance. Correlation of hypertriglyceridemia and interferon levels suggests a potential cytokine-mediated mechanism for hypertriglyceridemia in HIV disease. In the setting of potent antiretroviral therapy, however, the frequency of lipid abnormalities has greatly increased. Hypertriglyceridemia is more common than hypercholesterolemia in this setting and is often associated with decreased HDL levels, with data indicating a sequential increase in triglyceride levels over 12 months of protease inhibitor-containing treatment. Other data indicate that of the currently available protease inhibitors, ritonavir is associated with greater severity of hypertriglyceridemia, with decreasing comparative effects observed for ritonavir/saquinavir, nelfinavir, indinavir, and

![Figure 2. Fasting morning insulin levels in HIV-seronegative controls (C; n=20) and HIV-infected patients (HIV; n=70) and according to whether HIV-infected patients had <90% (n=21) or >90% (n=49) ideal body weight, had truncal obesity (+TR; n=13) or not (-TR; n=57), and were receiving (+PI; n=16) or not receiving (-PI; n=54) a protease inhibitor. Adapted from Hadigan C, et al. Fasting hyperinsulinemia and changes in regional body composition in human immunodeficiency virus-infected women. J Clin Endocrinol Metab. 1999;84:1932-1937. Copyright The Endocrine Society.

NS indicates not significant.

**P<0.01; ***P<0.001, patients versus controls; +++P<0.001, patients with versus patients without truncal adiposity.**
saquinavir, in that order (Figure 3). One study has documented changes in lipid levels within 3 months of initiating protease inhibitor treatment, with less severe changes in patients receiving non-protease inhibitor-based regimens. It has also been shown that lipid abnormalities in patients receiving potent antiretroviral regimens correlate with central adiposity. Taken together, these data suggest exacerbation of hyperglycemia due to protease inhibitor therapy in HIV-infected patients, which may result from increased truncal adiposity or direct effects of protease inhibitor therapy on lipid metabolism.

CLINICAL MANAGEMENT

Hyperglycemia/Insulin Resistance

Management of the metabolic abnormalities must be individualized for each patient and consideration must be made of the virologic as well as immunologic status of the patient. An option in the case of hyperglycemia is switching antiretroviral drugs. Preliminary data indicate that nefinavir is less frequently associated with hyperglycemia than other protease inhibitors. However, the glycemic effects of protease inhibitor therapies may relate to their relative antiretroviral potencies. At the current time, insufficient data are available to recommend switching antiretroviral therapy based on metabolic abnormalities. Dietary measures such as restriction of total calorie and carbohydrate intake may also be effective. For patients with severe hyperglycemia, use of oral antidiabetic drugs or insulin may be necessary. Preliminary data indicate the potential utility of insulin-sensitizing drugs to reduce insulin levels and truncal fat in HIV lipodystrophy syndrome. The efficacy of insulin-sensitizing drugs in the syndrome is now being assessed in clinical trials.

Lipid Abnormalities

In the case of lipid abnormalities, discontinuation or switching of protease inhibitors is a potential management option, although the time course to return to normal lipid levels has not been well de-
The safety and effectiveness of testosterone treatment of body composition changes in eugonadal patients have not been established and are currently being investigated.

Occasionally been used in patients with facial wasting, but results have tended to be poor, with the reemergence of fat atrophy. Use of anabolic steroids to reduce fat is currently being investigated. Testosterone reduces fat and builds muscle mass in hypogonadal HIV-infected men. However, the safety and effectiveness of testosterone treatment in eugonadal patients, who would likely constitute the majority of men with the syndrome, have not been established; the effects of testosterone treatment in this setting currently are being investigated in clinical trials. The oral anabolic steroid oxandrolone was associated with significant hepatotoxicity at doses greater than 20 mg/d in one study, and thus far no clinical trial data on its efficacy in reducing fat are available; testosterone and other anabolic steroids may also lower HDL levels. Growth hormone has also been used to reduce overall fat mass in a small number of months, high doses of recombinant human growth hormone (4 to 6 mg) resulted in a 25% to 75% reduction in buffalo hump and abdominal girth with no change in total body fat; no effects on peripheral lipodystrophy or lipid levels were observed, and no data on effect on glucose levels were reported. Use of such high doses of growth hormone may have been motivated by findings of growth hormone resistance in patients with HIV-associated wasting; however, growth hormone resistance has not been shown in patients with HIV lipodystrophy. Study of lower growth hormone doses that may reduce fat without adversely affecting insulin resistance is necessary.

Changing Antiretroviral Regimens

A number of small preliminary studies have assessed the effects of changing the antiretroviral regimen in patients with the syndrome. In one study, discontinuation of protease inhibitors in 20 patients, 16 of whom substituted the NNRTI nevirapine, was associated with improvements in triglyceride and cholesterol levels and insulin resistance (but not HDL levels) after 3 months. Plasma viral load remained below the limits of detection in 11 of 15 patients for whom measurements were available. In an additional 12 patients switching to nelfinavir from indinavir or ritonavir/saquinavir, no improvement in these measures was observed. In another study, 23 patients with CD4+ cell counts less than 200/μL receiving 2 nRTIs plus a protease inhibitor replaced the latter with nevirapine. After 7 months, cholesterol level had decreased by 21%, triglyceride level by 56%, glucose level by 16%, and insulin level by 46%, and suppression of viral load was maintained during nevirapine therapy. However, only minor changes in fat distribution were observed. In a study in 13 indinavir-treated patients with plasma HIV RNA levels below 500 copies/mL, substitution of efavirenz for a protease inhibitor resulted in increased weight, decreased abdominal girth, and decreased glucose levels, but increased triglyceride and cholesterol levels, with continued suppression of viral load. Although available data thus suggest that there may be some benefit in switching from protease inhibitor-containing regimens, determination of the virologic consequences and effects on metabolic and body composition abnormalities of switching antiretroviral therapy requires longer-term study in additional trials.
CONCLUSIONS

The metabolic abnormalities being observed are related in part to the effects of protease inhibitors, and also to metabolic derangements from HIV disease itself. In addition to the distress caused by body composition changes and other short-term morbidity, there is concern that many of the abnormalities may be associated with long-term morbidity. Studies of the long-term consequences of HIV lipodystrophy syndrome have not yet been performed. However, in non HIV-infected populations, hyperlipidemia, truncal obesity, and insulin resistance are known to be associated with increased cardiovascular morbidity and mortality. Early cardiovascular morbidity has been reported anecdotally among patients with HIV disease. There is thus an important need for continued research on the syndrome to clarify the pathophysiologic mechanisms involved and to develop effective therapeutic strategies.

Dr Grinspoon is Assistant Professor of Medicine at Harvard Medical School and Assistant Program Director, General Clinical Research Center, MIT.

SUGGESTED READING


(CONTINUED)
SUGGESTED READING (continued)


