HIV-ASSOCIATED LIPODYSTROPHY: Pathogenesis, Prognosis, Treatment, and Controversies

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Abstract Potent antiretroviral agents markedly suppress HIV and have dramatically improved the clinical course, prognosis, and survival of HIV-infected patients. Unfortunately, highly active antiretroviral therapy is often compromised by metabolic complications, including insulin resistance, dyslipidemia, and fat redistribution. Together these changes have been termed the HIV-lipodystrophy syndrome, which is estimated to affect a majority of patients treated with potent combination antiretroviral therapy. Routine testing of fasting glucose is recommended for all HIV-infected patients, particularly those who are obese, have a family history of diabetes mellitus, or are receiving protease inhibitor therapy. Preliminary investigations have demonstrated the potential utility of insulin-sensitizing agents and lipid-lowering therapies to ameliorate these metabolic disturbances. Patients with HIV infection who demonstrate fat redistribution and develop hyperinsulinemia and dyslipidemia may be at increased risk of cardiovascular disease. However, the long-term effects on cardiovascular disease have not yet been determined.

INTRODUCTION

Human immunodeficiency virus (HIV) is a major global health problem. However, significant progress has been made in the treatment of HIV infection with highly active antiretroviral therapies (HAART). Potent antiretroviral agents markedly suppress HIV and have dramatically improved the clinical course, prognosis, and survival of HIV-infected patients. Unfortunately, HAART is often compromised by metabolic complications, including insulin resistance, dyslipidemia, and fat redistribution. Together these changes have been termed the HIV-lipodystrophy syndrome. Fat redistribution is characterized by selective loss of subcutaneous fat from the face and extremities, and in some patients, accumulation of fat around the neck, dorsocervical region, abdomen, and trunk (1, 2). Discrete subcutaneous fat deposits, particularly in the dorsocervical area, have also been described (3). A
minority of patients exhibit pure fat atrophy, a second group demonstrates increased abdominal visceral adiposity alone, and a third, larger group demonstrates both abnormalities (4). Breast enlargement has been observed in both women and men but whether it is due to excess subcutaneous fat, glandular hypertrophy, or both is not clear.

Lipodystrophy in HIV-infected patients is associated with a cluster of metabolic abnormalities, including insulin resistance, impaired glucose tolerance, hypertriglyceridemia, and low serum levels of high-density lipoprotein (HDL) cholesterol (5, 6). Diabetes is a less common finding (4). Patients affected by severe lipodystrophy are often troubled by the disfiguring facial fat atrophy and changes in body habitus, including discomfort from dorsocervical fat accumulation in some cases. The disturbing changes in body composition may contribute to noncompliance or discontinuation of HAART despite adequate HIV suppression (7).

In the United States, the prevalence of lipodystrophy is estimated at 25%–50% of HIV-infected patients receiving combined antiretroviral therapy. Although increased truncal fat has been described in patients investigated prior to the current era of HAART (5), most studies suggest that the changes in body composition are associated with use of the two major classes of antiretroviral drugs, nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) (8). Use of both agents simultaneously may result in the most severe changes in body composition.

Much of the initial search for the cause of fat redistribution among HIV-infected patients focused on PI therapy, and studies compared patients who were PI-exposed to PI-naïve patients. Exposure to NRTI therapy has also been implicated in the development of fat redistribution, particularly fat atrophy (9). Mallal and colleagues (9) evaluated 277 patients participating in the Western Australian HIV Cohort Study and found that fat atrophy was associated with increased age and longer duration of NRTI treatment in addition to PI treatment. Stavudine exposure, in this study and others (10), significantly increased the risk of developing fat atrophy.

Abnormalities of glucose homeostasis, including insulin resistance and related metabolic abnormalities (hypertriglyceridemia, low HDL, atherogenic lipid profile) frequently accompany changes in body composition among HIV-infected patients receiving HAART (4, 11). Fasting hyperinsulinemia, inappropriate insulin responses to standard glucose challenge, and decreased glucose disposal rates have now been shown both in association with changes in body composition, e.g., loss of subcutaneous abdominal and extremity fat and increased abdominal visceral fat (12), and in response to specific antiviral therapies (13). An effect of PIs on GLUT-4-mediated glucose transport in vitro (14) and on insulin sensitivity in vivo has been demonstrated (13). Insulin resistance is associated with an atherogenic lipid profile and impaired fibrinolysis in HIV-infected patients with fat redistribution (15) and may contribute independently to an increased risk of cardiovascular disease in this population.
PATHOGENESIS

Fat Redistribution

The mechanisms responsible for fat atrophy and visceral adiposity in HIV-infected patients are not known. However, specific medications and drug classes may affect adipocyte differentiation and promote apoptosis (16). Domingo et al. (17) performed subcutaneous fat cell biopsies on HIV-infected patients treated with a PI who were experiencing subcutaneous fat atrophy and truncal adiposity. Ten of eleven samples demonstrated apoptosis, suggesting increased adipocyte cell death in the subcutaneous fat compartment (17). The disturbances in fat redistribution and metabolism among HIV-infected patients cannot currently be explained by a single agent or class of agents, but there is mounting evidence that antiretroviral therapies play a role in the development of lipodystrophy (18).

Similarities in body fat distribution between patients with HIV lipodystrophy and Cushing’s syndrome have prompted investigation of the hypothalamic-pituitary-adrenal axis as a possible mechanism by which PIs or NRTIs cause fat redistribution (19, 20). However, serum and urine cortisol concentrations are usually normal and dexamethasone suppression appropriate, ruling out true Cushing’s syndrome. Furthermore, subjects with HIV lipodystrophy demonstrate facial fat atrophy rather than plethora and lack many of the specific signs and symptoms of Cushing’s syndrome. Cortisol may be locally produced in adipose tissue from conversion of biologically inactive cortisone by the enzyme 11β-hydroxysteroid dehydrogenase type 1. The expression of this enzyme and of glucocorticoid receptors is significantly higher in omental fat than in subcutaneous fat (21, 22). Therefore, locally increased glucocorticoid concentrations or action without systemic hypercortisolism may induce regional adiposity, but whether this mechanism contributes to the development of HIV lipodystrophy is unknown.

Carr et al. (23) identified a homology between a 12–amino acid sequence of the catalytic domain of HIV-1 protease and the retinoic acid–binding domain of cytoplasmic retinoic acid–binding protein-1 (CRABP-1) and the lipid-binding domain of low-density lipoprotein receptor–like protein (LRP). CRABP-1 carries retinoic acid (24), which, when isomerized to cis-9-retinoic acid, activates a nuclear retinoid X receptor-α peroxisome proliferator-activated receptor-γ (PPARγ) complex known to regulate adipocyte proliferation and differentiation (25). Thus, PIs, by inhibiting CRABP-1, may inhibit adipocyte differentiation. However, preliminary results of in vitro studies do not support this hypothesis. Three-dimensional crystal analyses of CRABP-1 and HIV-1 protease showed no structural similarity (26). Furthermore, none of the PIs directly binds to retinoid X receptor-α or PPARγ (16, 27). Inhibition of LRP by PIs may not account for hyperlipidemia, since inactivation of LRP in the liver of wild-type mice does not result in hyperlipidemia (28). Other investigators propose that nonspecific inhibition of human proteins, such as insulin-degrading enzymes or cathepsins (aspartyl proteases), by PIs can cause primary hyperinsulinemia (29, 30). However, this mechanism cannot explain the loss of body fat.

Limited information on the histopathology of fine-needle biopsy or surgical specimens of the adipose deposition reveals nonencapsulated mature adipose tissue (31), some with fibrotic changes, ruling out dysplastic or neoplastic pathology. Subcutaneous adipocyte apoptosis has also been reported in patients with HIV lipodystrophy (32). Furthermore, apoptosis has not been reversed by switching from indinavir to nevirapine despite improvement in the metabolic parameters (32). In vitro studies with C3H10T1/2 murine mesenchymal stem cells, 3T3-L1 preadipocytes, and human preadipocytes demonstrated that several PIs inhibit adipocyte differentiation. Recently, Bastard et al. (33) showed reduced mRNA expression of many transcription factors, including sterol regulatory element–binding protein-1 (SREBP-1) in adipocytes from patients with HIV lipodystrophy receiving PIs compared with healthy subjects; however, SREBP-1 protein levels were increased. As SREBP-1c overexpression in adipose tissue causes lipodystrophy in mice, PI-induced alterations of SREBP-1 expression may contribute to changes in body composition and fat distribution in HIV-infected patients.

Autosomal dominant familial partial lipodystrophies have been attributed to defects in lamin A/C (34), and autosomal recessive congenital generalized lipodystrophy has been traced to mutations in 1-acylglycerol-3-phosphate O-acyltransferase-2. There are phenotypic similarities between HIV lipodystrophy and familial partial lipodystrophies. Whether lipodystrophy in HIV-infected patients is due to PI-induced changes in the expression of these genes or other homologous genes, particularly those involved in the triglyceride or phospholipid biosynthetic pathways, or with adipocyte differentiation remains to be determined.

The mechanism for fat loss and gain in HIV-infected patients remains unknown. In vitro studies to date suggest that PIs may decrease adipogenesis, but no unifying hypothesis has thus far emerged. Furthermore, sequence homology of the PIs to lipoprotein receptor-like protein (LRP) suggests a potential effect of the PI’s on lipid clearance, but the clinical importance of this observation remains unknown (23). Alternatively, NRTIs may inhibit DNA polymerase-γ, decreasing oxidative phosphorylation. However, no specific link between any effects of NRTI therapy on DNA polymerase-γ and clinical fat loss has thus far been demonstrated. Some studies suggest that drug exposure alone is not sufficient to cause changes in fat distribution (35, 36). Potential interactions with immune function, cytokines, and other mediators have been postulated. For example, one study of HIV-infected men related an increase in soluble type 2 TNF-α receptor levels to the severity of extremity fat loss (37).

**Lipid Abnormalities**

Lipid disorders are seen frequently among HIV-infected patients. Prior to the era of HAART, hypertriglyceridemia was common among HIV-infected patients (38). Increased hepatic very-low-density lipoprotein (VLDL) synthesis and decreased triglyceride clearance were demonstrated among HIV-infected patients (39). More recently, severe hypertriglyceridemia has been found, particularly among patients
receiving PIs. Recent studies have investigated the effects of various PIs on lipids in HIV-negative patients and people with occupational exposure to HIV infection. For example, Purnell et al. demonstrated hypertriglyceridemia in response to ritonavir in non-HIV-infected patients (40). Several mechanisms have been proposed for PI-induced hypertriglyceridemia, including reduction of lipoprotein lipase activity (41) and protection of apolipoprotein B from degradation by proteasomes (42). These mechanisms may contribute to the development of dyslipidemia in patients receiving antiretroviral therapy, and individual PIs may have varying effects on triglyceride synthesis.

Abnormalities of Insulin and Glucose

Insulin resistance and impaired glucose tolerance are commonly seen among HIV-infected patients with fat redistribution who are on HAART. HIV-infected patients with fat redistribution demonstrate fasting hyperinsulinemia and decreased insulin sensitivity. Among patients with fat redistribution in the era of HAART, fasting glucose levels do not differ from those of control subjects of comparable age and body mass index (BMI) (4). In contrast, levels of fasting insulin, two-hour insulin, and two-hour glucose on standard glucose challenge are markedly increased. In a recent study, 35% of the HIV-infected patients with fat redistribution demonstrated glucose intolerance compared with only 5% of age- and BMI-matched healthy control subjects. In contrast, 7% of HIV-infected patients with fat redistribution compared with 0.5% of control subjects demonstrated markedly increased two-hour glucose responses, diagnostic of diabetes (two-hour glucose > 200 mg/dl) (4). Increased diastolic blood pressure, hypertriglyceridemia, low HDL, increased LDL, and markedly increased levels of tissue type plasminogen activator (tPA) and plasminogen activator inhibitor-I (PAI-1) are also associated with hyperinsulinemia in this population (4, 43, 44). The percentage of HIV-infected patients with fasting hyperinsulinemia that will develop type II diabetes is not known.

Changes in body composition may also contribute to insulin resistance. Using an insulin clamp technique, Mynarcik et al. demonstrated decreased glucose disposal (insulin resistance) among HIV-infected patients, in association with reduced peripheral fat on dual energy–X-ray absorptiometry (DEXA) determination (37). Fasting insulin levels are most elevated among patients with significant peripheral fat loss and increased abdominal visceral adiposity, whereas patients with either fat loss or increased visceral adiposity demonstrate lesser degrees of hyperinsulinemia (4).

Severity of body composition abnormalities, use of specific antiretroviral therapies, and family history may all contribute to the development of diabetes in this population. In multivariate modeling, Meininger et al. demonstrated a 1% increase in fasting insulin for each 1% increase in visceral fat and an independent 1% increase in fasting insulin for each 1% reduction in abdominal subcutaneous fat (12). Eighty-nine percent of the variability in fasting insulin was explained in
multivariate modeling, which included age, BMI, PI use, and waist-to-hip ratio (12).

Direct effects of protease inhibitors on glucose regulation have recently been shown. Murata et al. demonstrated a specific effect of PI therapy on insulin-stimulated glucose transport and GLUT-4 in 3T3-L1 adipocytes (14). The protease inhibitor indinavir did not affect early insulin signaling events (insulin receptor autophosphorylation and subsequent tyrosine phosphorylation or phosphatidylinositol-3 kinase activation) or the translocation of intracellular GLUT-4. At physiological concentrations, indinavir was associated with a 26% reduction in glucose uptake. Similar inhibition of insulin-mediated glucose uptake was seen with ritonavir and amprenavir.

Noor et al. investigated the use of indinavir over four weeks in HIV-negative patients. A significant decrease in glucose disposal occurred with no clinically significant change in body composition (13). These data suggest more direct effects of antiretroviral agents, particularly PIs, on glucose uptake. However, changes in body composition resulting from PIs and other antiretrovirals may also simultaneously contribute to changes in glucose metabolism among HIV-infected patients receiving chronic antiretroviral therapy. Increased lipolysis resulting from direct effects of antiretroviral drugs and changes in body composition may also contribute to insulin resistance in this population. Increased free fatty acid levels and lipolytic rates have been shown among HIV-infected patients receiving HAART and predict insulin responses to standard glucose-tolerance testing (45, 46). Furthermore, acute dosing studies have shown that reduction in free fatty acids by inhibition of lipolysis increases insulin sensitivity (47).

Clinical Consequences of Metabolic Abnormalities in HIV-Infected Patients

Whether the anthropometric (increased waist-to-hip ratio, increased visceral fat, reduced subcutaneous fat) and metabolic (hypertriglyceridemia, low HDL, modest increases in LDL and diastolic blood pressure) abnormalities seen among HIV-infected patients receiving HAART contribute to an actual increase in cardiovascular disease remains unknown. Recent studies using Framingham risk equations suggest increased risk for myocardial infarction among HIV-infected patients with fat redistribution (48). In addition, recent case reports suggest premature coronary artery disease in this population (49). Two recent cross-sectional studies suggest increased risk of myocardial infarction and cardiovascular events in HIV-infected patients. Mary-Krause et al. demonstrated a substantially increased risk of myocardial infarction among French HIV-infected patients receiving a PI for >30 months compared to <18 months (50). In contrast, Klein et al. investigated coronary heart disease (CHD) event rates among 4541 persons followed from 1996 to 2000 in the Kaiser Permanente system (51). CHD event rates were not significantly different among PI users versus non–PI users (5.8 versus 5.2 events/1000 PY), but overall CHD event rates were higher in the HIV-infected patients than in control subjects.
(2.8 events/1000 PY of follow-up). In contrast, use of antiretroviral medication was not associated with increased coronary artery disease events in a recently published Veteran’s Affairs cohort (52). Further longitudinal studies with larger numbers of patients are needed to determine whether HIV-infected patients in the era of HAART are at increased risk for myocardial infarction or CHD.

One mechanism by which hyperinsulinemia and insulin resistance may contribute to increased cardiovascular disease is through an effect on fibrinolysis. Recent data indicate that patients with HIV infection and fat redistribution have markedly elevated PAI-1 and tPA antigen levels in association with significant hyperinsulinemia (15). Data from the Framingham Offspring Study suggest a direct, independent effect of hyperinsulinemia to impair fibrinolysis in glucose-intolerant and diabetic subjects (53). Furthermore, increased tPA antigen, a marker of impaired fibrinolysis, predicts increased risk of (a) coronary artery disease mortality among patients with a history of angina pectoris and CHD and (b) cerebral vascular events among individuals without a prior history of CHD (54). PIs may also directly affect plaque formation by upregulation of CD36 and subsequent sterol accumulation in macrophages (55).

In addition, studies using surrogate markers suggest an effect of PIs on carotid intimal and endothelial function. Maggi and colleagues (56) evaluated carotid arteries for premature lesions in PI-treated and PI-naive HIV-infected patients and compared them to HIV-negative control subjects. Premature carotid lesions were identified in 52.7% of PI-treated patients, 14.9% of PI-naive patients, and only 6.4% of healthy control subjects. In this study, PI exposure, smoking, and CD4 cell count predicted the occurrence of carotid lesions. At concentrations near clinical plasma levels, the PI ritonavir significantly decreased cell viability and increased cytotoxicity in human endothelial cell cultures (57). A clinical study demonstrated reduced flow-mediated vascular dilation in PI-treated versus non-PI treated patients (58).

TREATMENT

Dietary and Lifestyle Modification

Although data from large-scale treatment studies are not yet available, diet and increased physical activity, particularly aerobic exercise, should be encouraged to improve dyslipidemia and insulin resistance among HIV-infected patients. A 16-week pilot study found resistance exercise beneficial in reducing truncal fat as well as total body fat (59). Exercise training can reduce serum triglycerides by as much as 25% and, along with dietary restriction, can reduce total abdominal and visceral fat as well (60, 61). Severely hypertriglycemic patients should be advised to consume low-fat diets and avoid ethanol consumption to prevent chylomicronemia and acute pancreatitis. Low-fat, high-carbohydrate diets, however, may exacerbate hyperinsulinemia in nondiabetic subjects and in patients with type 2 diabetes, and therefore dietary changes should always be individualized. Increased doses of
\(\zeta-3\) polyunsaturated fatty acids (5–10 g/d) from concentrated fish-oil preparations may effectively lower plasma triglyceride concentrations. A cross-sectional study demonstrated that a diet high in polyunsaturated to saturated fats and low in fiber was associated with hyperinsulinemia in HIV-infected patients with fat redistribution (62). There are currently no published interventional studies of the use of diet and exercise to treat or prevent the metabolic disturbances associated with fat redistribution in HIV-infected patients, but dietary and lifestyle counseling should be considered for all patients who present with such disturbances, as potential therapies to reduce the consequences of insulin resistance.

**Treatment for Dyslipidemia**

Given the evidence that PI treatment may directly affect lipid metabolism, interruption or replacement of the PI component of antiretroviral therapy has been investigated as a potential strategy to reverse hyperlipidemia. Martinez and colleagues (63) prospectively evaluated 23 patients who discontinued PI therapy, despite sustained virologic suppression (<200 HIV-1 RNA copies/ml), because of lipodystrophy symptoms. Nevirapine was substituted for the PI, and after approximately 8 months, patients experienced a 22% reduction in total cholesterol and a 57% reduction in triglycerides. These changes were associated with improved indices of insulin resistance and decreased waist-to-hip ratio. However, subsequent reports, including a randomized trial comparing a switch to nevirapine versus continuation of PI (64), failed to demonstrate a significant improvement in hyperlipidemia with the discontinuation of PI treatment. Similarly, switching to efavirenz after discontinuing a PI has not been as effective for the reversal of hypertriglyceridemia and hypercholesterolemia (65). As previously described, Hatano et al. (66) showed significant reductions in cholesterol, LDL cholesterol, and triglycerides following interruption of HAART for a median of 7 weeks. Discontinuing PIs may indeed improve triglyceride and cholesterol levels in HIV-infected patients, but such a course of action is controversial in the well-controlled patient with improved immunologic function, and it remains experimental.

Drug therapy for hypertriglyceridemia in HIV-infected patients may be initiated with a fibric acid inhibitor, e.g., gemfibrozil and/or fenofibrate, which can lower serum triglycerides by \(\sim40\%\). Hydroxymethylglutaryl enzyme coenzyme A (HMG CoA) reductase inhibitors (statins) have also been used effectively but are most effective in lowering LDL and total cholesterol (67). Simultaneous use of PIs and statins can therefore elevate plasma levels of statins and increase the risk of myopathy. Fichtenbaum et al. (68) demonstrated a significant 32-fold increase in simvastatin area-under-the-curve (AUC) concentrations in the presence of ritonavir and saquinavir. In contrast, the AUC concentration of atorvastatin increased 4.5-fold in ritonavir/saquinavir-treated patients, whereas little effect was seen on pravastatin AUC concentrations. Potential interactions between PIs and HMG CoA reductase inhibitors are important to consider in HIV-infected patients requiring lipid therapy. Pravastatin is not metabolized by cytochrome P4503A4.
and can be used to treat dyslipidemia in HIV-infected patients. Similarly, atorvastatin is only moderately affected by PI use and can also be used at low dose with careful monitoring. The interaction of specific PIs other than ritonavir/saquinavir with HMG-CoA reductase inhibitors remains unknown.

Fibrates are also metabolized through cytochrome P450, but the predominant pathway is CYP4A and thus fibrate metabolism is less likely to be affected by PI use. Hyperlipidemia, especially hypertriglyceridemia and low HDL, are common in HIV-infected patients. Dyslipidemia may be further exacerbated by direct effects of PIs and indirect effects mediated through fat redistribution in HAART-treated patients. Patients with severe dyslipidemia should be treated first with diet changes and then medications if necessary. Until further data become available, it is reasonable to use the National Cholesterol Education Program (NCEP) treatment guidelines. However, special care should be taken to avoid interactions with PIs when using HMG CoA reductase inhibitors.

Treatment of Glucose Abnormalities

Recent studies have emphasized the potential utility of insulin-sensitizing agents in treating abnormalities of glucose metabolism in the HIV-lipodystrophy syndrome. A randomized, placebo-controlled, 12-week pilot study investigated the effects of low-dose metformin (500 mg PO BID) (69). Metformin treatment was associated with reductions in insulin, weight, waist circumference, diastolic blood pressure, and concentrations of tPA and PAI-I and was not associated with any significant adverse events (4, 45). Development of lactic acidosis is a rare but potentially serious side effect of metformin. It should be used with caution in HIV-infected patients, especially those recently on NRTI therapy. Modest 10%–20% reduction in plasma triglyceride levels may also be seen with metformin and related to decreased hepatic VLDL production. Taken together, the preliminary studies on metformin suggest a beneficial effect on cardiovascular risk parameters, but additional studies are needed to determine the long-term safety and efficacy of metformin and the optimal target population for this intervention. Furthermore, metformin should not be used in patients with azotemia and significant liver dysfunction.

Insulin resistance may also occur in HIV-infected patients from the loss of subcutaneous fat. Hadigan et al. demonstrated that reduced thigh circumference, a marker of peripheral fat atrophy, was an independent predictor of hyperinsulinemia in HIV-positive patients with fat redistribution (4). Mynarcik et al. demonstrated decreased insulin sensitivity in association with reduced subcutaneous fat (37). A novel class of therapeutic agents, the thiazolidinediones, has been shown to promote adipogenesis, primarily through an action on PPARγ. Although the thiazolidinediones have effects on both hepatic and peripheral insulin resistance, the dominant effect is to improve peripheral glucose uptake.

In a recent study among non-HIV-infected patients with lipodystrophy, troglitazone significantly increased subcutaneous fat and decreased visceral fat in association with improved levels of triglyceride, free fatty acids, and insulin resistance
A small pilot study of HIV-infected patients with subcutaneous fat atrophy demonstrated increased peripheral subcutaneous fat in response to rosiglitazone (71). In a randomized, placebo-controlled study, rosiglitazone affected insulin but not subcutaneous fat (72). Further clinical trials are needed to determine the safety and efficacy of thiazolidinediones in HIV-infected patients.

Preliminary studies suggest improvement in insulin levels with substitution of a non-nucleoside reverse transcriptase inhibitor (NNRTI) for a PI, but further studies of the efficacy of switching strategies are needed (63). As with insulin resistance and lipid abnormalities, treatment strategies to minimize or reverse fat redistribution are under investigation. In a pilot study of resistance training and aerobic exercise for HIV-infected patients with increased abdominal fat \((n = 10)\), Roubenoff and colleagues (59) showed significant decreases in trunk fat after 16 weeks of exercise. Exercise may have additional benefits in reducing insulin resistance and improving lipid profiles and should be considered in all patients, particularly those with increased central adiposity.

Routine performance of fasting glucose is recommended for all HIV-infected patients, particularly those who are obese, have a family history of diabetes, or are receiving PI therapy. Because recent data demonstrate a high prevalence of impaired glucose tolerance among HIV-infected patients with fat redistribution, performance of a standard 75-g glucose tolerance test may also be useful, particularly in patients receiving HAART. Measurement of fasting insulin may be helpful but is not generally recommended outside the research setting.

### Treatment of Fat Redistribution

Cosmetic surgery has been used to improve lipodystrophic changes and reduce excess dorsocervical fat. To date, there have been only small case series published with few or no follow-up data on the use of plastic surgery to correct fat redistribution. Wolfert and colleagues (73) report on two patients who underwent liposuction of the dorsocervical fat pad and one patient who had liposuction of the abdomen and flanks. Patients reported satisfaction with the outcome, but no long-term follow-up information was presented. Carefully designed studies that control for antiretroviral exposure and evaluate the safety and efficacy of plastic surgery for lipodystrophy, including liposuction and fat transplantation, are imperative.

Rietschel and colleagues (74) found reduced mean concentrations of growth hormone (GH) as well as reduced basal and pulse-amplitude GH concentrations among HIV-infected men with lipodystrophy compared to HIV-infected controls without lipodystrophy and compared to healthy men. Recombinant human GH (rhGH) has been used successfully in HIV-negative GH-deficient adults to reduce abdominal adiposity (75). Wanke and colleagues (76) conducted a 12-week open-label trial of rhGH (6 mg/d s.c.) in 10 patients with HIV infection and fat redistribution. Waist-to-hip ratio, a measure of central adiposity, was significantly reduced with rhGH therapy. However, the use of rhGH may induce or exacerbate insulin resistance and glucose intolerance, and one patient in this trial developed...
hyperglycemia. Therefore, the utility of rhGH for the treatment of lipodystrophy may be limited in this population with increased risk of insulin resistance and diabetes. Treatment with lower doses of rhGH may be useful, particularly for patients with central adiposity, but additional information from controlled trials is necessary to determine the long-term efficacy and safety of rhGH to treat HIV-infected patients with fat redistribution.

Antiretroviral switching and structured therapy interruptions have also been used to attempt reversal of fat redistribution. Martinez and colleagues (63) found significant reductions in waist-to-hip ratio after 8 months in patients who switched from a PI-containing regimen to nevirapine. In addition, after 6 months of nevirapine, 91% of patients reported subjective improvement of body fat changes. In another study, 50% of patients who switched from a PI to nevirapine reported improvements in body shape abnormalities after 6 months, whereas no patient who remained on a PI reported such improvement (64). Short-term interruption of HAART, however, has not been found to improve anthropometric measurements in patients with HIV infection and fat redistribution (66).

CONCLUSIONS

HIV-associated lipodystrophy is estimated to affect the majority of patients treated with potent combination antiretroviral therapy. Significant metabolic disturbances have been identified in association with fat redistribution in these patients, including insulin resistance and hyperlipidemia. Preliminary investigations have demonstrated potential utility in the use of insulin-sensitizing agents and lipid-lowering therapies to ameliorate these metabolic disturbances. Patients with HIV infection who demonstrate fat redistribution and who develop hyperinsulinemia and dyslipidemia may be at increased risk of cardiovascular disease. However, the long-term effects on cardiovascular disease have not yet been determined.

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