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Editorial

Body fat redistribution and metabolic abnormalities in HIV-infected patients on highly active antiretroviral therapy: novel insights into pathophysiology and emerging opportunities for treatment

Highly active antiretroviral therapy (HAART) has contributed considerably toward decreasing morbidity and mortality from human immunodeficiency virus (HIV)–related diseases over the past 2 decades. At the same time, however, use of HAART has also been associated with metabolic complications including hyperinsulinemia and insulin resistance, dyslipidemia (hypertriglyceridemia, reduced high-density lipoprotein [HDL] cholesterol, and increased total and low-density lipoprotein cholesterol concentrations), as well as body fat redistribution (lipodystrophy) [1,2]. All these metabolic abnormalities may in turn increase risk for cardiovascular disease [3].

The prevalence of these abnormalities in adult patients depends on the type of HAART treatment and increases with use of HAART over time [1,3,4]. Hypercholesterolemia, hypertriglyceridemia and low HDL cholesterol concentrations are present in approximately 10% to 30%, 20% to 40%, and 20% to 30% of HIV-infected patients, respectively; and prevalence rates are much greater (45%-60%) among those with clinical evidence of lipodystrophy [3]. Lipodystrophy typically manifests as subcutaneous adipose tissue wasting in the face, gluteal region, and extremities with retention of visceral fat (lipoatrophy). Generalized fat accumulation or central fat accumulation may also occur (lipohypertrophy) [5], but most patients tend to have a combination of lipoatrophy and lipohypertrophy called *mixed lipodystrophy*. Lipodystrophy is strongly associated with the use of nucleoside reverse transcriptase inhibitors and protease inhibitors, and may affect as few as 10% to as many as 85% of patients; its prevalence rate increases with prolonged exposure to HAART [1,3,6]. Approximately 35% of lipodystrophic patients have impaired glucose tolerance [3]. These morphologic and metabolic abnormalities are also evident among HIV-infected children and adolescents, who experience long-term (frequently starting even before birth) exposure to both HIV and antiretroviral therapies [7-9]. Similar to adults, the prevalence of lipodystrophy in young patients has been reported to range from 5% [7] to 85% [8]. However, even in the absence of clinically evident lipodystrophy, metabolic abnormalities are still highly prevalent [7]. As reported in this issue of *Metabolism* by Dimock et al [10], 15% to 30% of young patients without major evidence of body fat redistribution have impaired glucose tolerance and/or insulin resistance; and 20% to 50% have dyslipidemia. These estimates varied somewhat with the type of treatment used but remained relatively stable over about 2 years of observation [10], contrary to the robust adverse changes occurring during the first year after beginning or changing antiretroviral therapy [11]. These observations imply that the effects of different types of drugs and of treatment duration may level off with very prolonged HAART exposure.

Prospective observations in treatment-naive HIV-infected adults demonstrate that peripheral fat mass (limb fat) initially increases during the first few months or even years of antiretroviral therapy but then decreases in an almost linear fashion, whereas central fat deposition (trunk fat) increases modestly by about 6 months of therapy [12-14]. Hypercholesterolemia usually develops early into treatment (~4 months), whereas hypertriglyceridemia and hyperinsulinemia usually develop later on (~2 years) [12]. The cumulative incidence of new-onset hyperglycemia, hypercholesterolemia, hypertriglyceridemia, and lipodystrophy is approximately 5%, 25%, 20%, and 15%, respectively, within 5 years from initiation of HAART [15].

The etiology and pathophysiology of lipodystrophy and metabolic dysfunction associated with HAART remain to be fully elucidated. Dysregulation of peripheral adipose tissue metabolism may be central in the development of morphologic changes and the altered metabolic profile (dyslipidemia and insulin resistance) in HIV-related lipodystrophy [16].

Even before any evidence of major body fat redistribution, HIV-infected patients have significantly greater glycerol rates of appearance in plasma (an index of whole-body peripheral adipose tissue lipolysis) compared with healthy control subjects [17]. In contrast, plasma free fatty acid (FFA) concentration and appearance rates are not different at this stage [17,18]. This implies either that FFA oxidation is increased (which is unlikely because adipose tissue has a small proportion of cells with adequate

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mitochondrial capacity) or, most probably, that intracellular fatty acid reesterification in adipose tissue is increased [19].

Importantly, the suppression of plasma FFA flux in response to exogenous insulin infusion is lower in HIV-infected patients than in healthy subjects [18], indicative of greater adipose tissue resistance to the antilipolytic action of insulin; similar results have been obtained in response to oral [17] and intravenous [20] glucose. Aberrations in adipose tissue regulation of lipolysis are more pronounced in HIV-infected patients with *mixed lipodystrophy* (peripheral lipoatrophy and central adiposity) and are accompanied by more unfavorable changes in plasma lipid profile [21] and severely impaired postprandial lipid metabolism [22]. Lipodystrophic HIV-positive patients have markedly greater basal rates of glycerol appearance in plasma than healthy control subjects; despite accelerated intracellular reesterification within the adipose tissue, the rate of appearance of FFA in plasma is also increased, giving rise to greater plasma FFA concentrations [21]. The oxidation rate of plasma FFA remains unaltered, and thus nonoxidative fatty acid disposal is increased, likely via reesterification in the liver [21]. Augmented intrahepatic fatty acid availability, in turn, may contribute to increased very low-density lipoprotein (VLDL)–triglyceride secretion rate [20,23], thereby resulting in greater plasma triglyceride concentration, which is the most common plasma lipid abnormality in HIV-infected lipodystrophic patients [16]. Hypertriglyceridemia is accentuated by the impaired removal of triglycerides from both endogenous (ie, VLDL) and exogenous (ie, chylomicrons) lipoproteins in the fasted and fed states [22-24]. Adipose tissue is responsible for a considerable part of plasma triglyceride clearance [25]; and thus, these observations imply that the capacity of adipose tissue to take up circulating triglycerides may also be impaired. Animal studies have demonstrated that antiretroviral agents inhibit not only lipoprotein lipase-mediated VLDL-triglyceride hydrolysis and uptake of VLDL-triglyceride–bound fatty acids but also the uptake of albumin-bound fatty acids, specifically in adipose tissue but not liver, skeletal, or cardiac muscle [26].

Collectively, increased lipolysis of adipose tissue triglyceride during fasting and decreased adipose tissue triglyceride uptake for storage and replenishment after meal ingestion could progressively deplete adipose tissue mass and induce or worsen peripheral lipoatrophy. Interestingly, this does not appear to hold true for visceral fat depots because central fat remains unaltered or may increase following initiation of HAART [12-14], suggesting that changes in local fatty acid turnover, if any, lead to net fatty acid uptake in this adipose depot. The mechanisms whereby antiretroviral agents differentially affect subcutaneous and visceral fat remain largely unknown. Studies in animals indicate that thymidine nucleoside analogues reduce the oxidative and lipogenic capacity of subcutaneous fat pads, perhaps because of altered phosphorylation of adenosine monophosphate–activated protein kinase, and lead to decreased subcutaneous adipose tissue cellularity, fat cell size, and lipid content; however, no such changes are observed in visceral fat pads [27]. The reasons underlying these differences remain to be fully elucidated, but it has been suggested than an imbalance in the autonomic control of subcutaneous and visceral adipose tissue could be responsible for the observed body fat redistribution in HIV-infected patients on HAART [28]. Whatever the case, excess plasma FFA availability resulting from accelerated lipolysis and reduced fatty acid uptake in subcutaneous adipose tissue could lead to ectopic fat accumulation (eg, in the liver, skeletal muscle) and, subsequently, to multiorgan insulin resistance [29].

A better understanding of the pathophysiology of HIV lipodystrophy may provide valuable insights into the effects of pharmacologic agents on adipose tissue lipid metabolism and may open new avenues for the treatment of this multifactorial disorder. Various novel treatment strategies have been used recently in an attempt to counter HIV-associated lipodystrophy and its dysmetabolic sequelae. It is reasonable to assume that altered adipose tissue size (peripheral lipoatrophy or central lipohypertrophy), and by extension adipose tissue–secreted molecules such as leptin and adiponectin, may be involved in the development of metabolic abnormalities. We [30] and others [31] have demonstrated that administration of recombinant methionyl human leptin reduces total body and trunk fat and improves insulin sensitivity in the liver and adipose tissue, but not skeletal muscle, in hypoleptinemic lipoatrophic patients with HIV infection [30,31]. Furthermore, it was recently reported that treatment with either recombinant insulin-like growth factor (IGF)-1/insulin-like growth factor binding protein–3 or other factors, such as Growth Hormone Release Factor analogues that increase circulating levels of IGF-1, also decreases total body fat and mainly trunk fat. IGF-1 treatment also improves insulin sensitivity in skeletal muscle, does not affect insulin sensitivity in adipose tissue, and may cause a mild reduction in hepatic insulin sensitivity [32]. It might thus be interesting to examine whether leptin (which increases hepatic and adipose tissue insulin sensitivity) and IGF-1/insulin-like growth factor binding protein–3 (which increase skeletal muscle insulin sensitivity) have additive effects and together alleviate multiorgan insulin resistance in HIV-infected patients. Evidently, however, none of these novel therapeutic approaches appears to be able to favorably affect peripheral lipoatrophy. Similarly, thiazolidinediones including pioglitazone and rosiglitazone have been used rather extensively in this syndrome, but results from randomized clinical trials [33-35] reveal that pioglitazone does not significantly affect insulin sensitivity and lipid profile (other than a mild increase in HDL cholesterol concentration), whereas rosiglitazone may improve insulin sensitivity (it reduces insulin and perhaps also glucose concentrations) but has unfavorable effects on blood lipids (reduces HDL cholesterol concentration and increases triglyceride and low-

density lipoprotein cholesterol concentrations); neither drug affects significantly either body fat mass or fat distribution in this population. Selective peroxisome proliferator-activated receptor−γ modulators, such as INT-131, which may have a better metabolic profile and apparently a better safety profile than pioglitazone and rosiglitazone [36], have not yet been tested in HIV-positive subjects with lipodystrophy and the metabolic syndrome.

In this issue of *Metabolism*, Sekhar and colleagues [37] go one step further in elucidating the underlying physiologic and metabolic pathways of rosiglitazone action by describing the effects of rosiglitazone treatment for 3 months on adipose tissue lipid kinetics in lipodystrophic HIV-infected patients with dyslipidemia. They report that rosiglitazone augments basal glycerol rate of appearance but does not affect FFA rate of appearance in plasma, suggesting that all additional fatty acids produced intracellularly may be reesterified back to triglycerides and do not enter the systemic circulation. These results are corroborated by earlier observations in obese rodents [38]. The drug did not alter plasma FFA oxidation rate or extracellular fatty acid reesterification and did not affect total body and regional (peripheral and central) fat [37]. These results provide a novel insight regarding the mechanisms of thiazolidinedione action on adipose tissue lipid metabolism. The increase in intracellular fatty acid reesterification would be expected to promote retention of triglycerides within adipose tissue, but this was not observed because of the simultaneous increase in lipolytic rate. The mechanisms responsible for thiazolidinedione-mediated acceleration of lipolysis are not entirely clear; both direct effects (eg, up-regulation of adipose triglyceride lipase [39]) and indirect effects (eg, reduction in circulating insulin) may be involved, and this should be the focus of future investigation. If the observations above are confirmed, it would be of great interest to proceed to the next step and evaluate the effects of thiazolidinediones in combination with other pharmacologic modulators of adipose tissue lipolysis, such as nicotinic acid analogues (niacin and acipimox) [40-43] and leptin, which has also been shown to reduce the rate of appearance of glycerol in plasma and enhance insulin-mediated suppression of lipolysis in HIV lipodystrophic patients [31].

It is tempting to speculate that coadministration of lipolysis inhibitors with thiazolidinediones, which act in part through increasing adiponectin concentrations [44], could lead to increased intracellular adipose tissue reesterification without the counterbalancing increase in adipose tissue lipolysis, thereby providing a metabolic basis for the retention of fatty acids within peripheral adipose tissue. This could, in turn, be expected to lead to reversal of peripheral lipoatrophy, with or without concomitantly reduced central fat deposition. In a pilot study published in this issue of *Metabolism*, we report that leptin replacement, in addition to pioglitazone treatment for 3 months, improves fasting insulin sensitivity and postprandial glycemia in HIV-infected patients with lipodystrophy, compared to pioglitazone treatment alone; however it does not favorably affect total body fat mass and body fat distribution [45]. Although the short duration of this study may be responsible for the absence of favorable effects on body fat, it may well be that the combination of thiazolidinediones with leptin, which has fat-reducing effects in these hypoleptinemic patients [30,31], retains the insulin-sensitizing and hypoglycemic effects of leptin while at the same time prevents the decrease in fat mass induced by leptin alone. It is still not clear whether coadministration of thiazolidinediones with mainstream lipolysis inhibitors, which have no fat-reducing properties (such as nicotinic acid analogues) [42], would yield different outcomes in terms of peripheral lipoatrophy.

In summary, HIV-related lipodystrophy and the associated metabolic syndrome are prevalent disease states with important adverse health consequences. Although several traditional as well as novel drugs can independently improve some of the metabolic and morphologic abnormalities of HIV-related lipodystrophy, none is universally effective. Combination treatments hold great promise as a potentially more effective means for reversing the lipodystrophic phenotype and alleviating metabolic dysfunction. Research published in this issue of *Metabolism* sheds new light into the pathophysiology of the syndrome and raises novel hypotheses that, if proven by future clinical trials, could result in tangible benefits for the patients with this syndrome.

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