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

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Highly active antiretroviral therapy (HAART) has contributed considerably towards decreasing morbidity and mortality from human immunodeficiency virus (HIV)-related diseases over the past two 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 (LDL)-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 10-30%, 20-40%, and 20-30% 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 (not infrequently starting even before birth) exposure to both HIV and antiretroviral therapies [7-9]. Similar to adults, the prevalence of

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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], 15-30% of young patients without major evidence of body fat redistribution have impaired glucose tolerance and/or insulin resistance and 20-50% have dyslipidemia. These estimates varied somewhat with the type of treatment used but remained relatively stable over ~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 effect of different types of drugs and treatment duration may level off with very prolonged HAART exposure.

Prospective observations in treatment-naïve 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 ~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. Central role in the development of morphologic changes and the altered metabolic profile (dyslipidemia and insulin resistance) in HIV-related lipodystrophy may play the dysregulation of peripheral adipose tissue metabolism [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 (adipose tissue has a small proportion of cells with adequate mitochondrial capacity) or, most probably, that intracellular fatty acid reesterification in adipose tissue is also 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 higher 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 FFA rate of appearance in plasma is also increased, giving rise to greater plasma FFA concentrations [21]. The oxidation rate of plasma FFA remains unaltered and non-oxidative fatty acid disposal may be increased via reesterification in the liver [21]. Augmented intrahepatic fatty acid availability, in turn, contributes to increased very low-density lipoprotein (VLDL)-triglyceride secretion rate [20,23], thereby resulting in greater plasma triglyceride concentration, i.e., the most common plasma lipid abnormality in HIV-infected lipodystrophic patients [16]. Hypertriglyceridemia is accentuated by the impaired removal of triglycerides from both endogenous (i.e., VLDL) and exogenous (i.e., 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 triglycerides 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, since 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 due to 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 that 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 (e.g., in the liver, skeletal muscle) and, subsequently, to multi-organ insulin resistance [29].

A better understanding of pathophysiology may provide valuable insights into the effects of pharmacological agents on adipose tissue lipid metabolism and may open new avenues for the treatment of this multifactorial disorder. Various novel treatment strategies have been employed 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 (IGFBP)-3 or other factors, such as Growth Hormone Release Factor analogues, that increase circulating levels of IGF-1, also decrease total body, but 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/IGFBP-3 (which increase skeletal muscle insulin sensitivity) have additive effects and together alleviate multi-organ 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 may not affect significantly 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 LDL-cholesterol concentrations); neither drug affects significantly either body fat mass or fat distribution in this population. Selective PPARgamma modulators, such as INT-131, that may have a much better metabolic profile and apparently a better safety profile than pioglitazone and rosiglitazone, have not yet been tested in HIV positive subjects with lipodystrophy and the metabolic syndrome.

In this issue of *Metabolism*, Sekhar and colleagues 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 [36]. 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 [37]. 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 [36]. 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 due to the simultaneous increase in lipolytic rate. The mechanisms responsible for thiazolidinedione-mediated acceleration of lipolysis are not entirely clear; both direct effects (e.g., upregulation of adipose triglyceride lipase [38]) and indirect effects (e.g., reduction in circulating insulin) may be involved and this should be the focus of future investigation(s). 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 pharmacological modulators of adipose tissue lipolysis.

Administration of lipolysis inhibitors (nicotinic acid analogues such as niacin and acipimox) in HIV-infected lipodystrophic patients acutely reduces plasma FFA availability and increases insulin sensitivity [39,40]. Short-term (3 months) treatment with acipimox preserves these metabolic benefits, attenuates hypertriglyceridemia and tends to reduce intramyocellular triglyceride deposition (i.e., ectopic fat), although it does not affect body fat redistribution [41]. Also, treatment for 3 months with extended-release niacin downregulates hormone-sensitive lipase (responsible for hydrolysis of intracellular triglycerides) and upregulates lipoprotein lipase (responsible for hydrolysis of circulating triglycerides and subsequent fatty acid tissue uptake) in subcutaneous adipose tissue [42]. Furthermore, leptin treatment [43], which typically results in reduction of visceral fat in HIV-infected patients [30,31], has resulted in reduced glycerol rate of appearance in plasma (i.e., whole-body lipolysis), decreased triglycerides and free fatty acids and augmented insulin-mediated suppression of lipolysis [31]. It is therefore tempting to speculate that co-administration of lipolysis inhibitors with thiazolidinediones, which act in part through increasing levels of adiponectin (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. Studies focusing on the use of leptin alone or in combination with pioglitazone are ongoing (F.M. and C.S.M. unpublished observations).

In summary, HIV-related lipodystrophy and the associated metabolic syndrome is a prevalent disease state 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 which, if proven by future clinical trials, could result in tangible benefits for the patients suffering from this syndrome.

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List of abbreviations

FFA	free fatty acid
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
IGF	insulin-like growth factor
IGFBP	insulin-like growth factor binding protein
HDL	high-density lipoprotein
LDL	low-density lipoprotein
VLDL	very low-density lipoprotein