Human Immunodeficiency Virus/Highly Active Antiretroviral Therapy-Associated Metabolic Syndrome: Clinical Presentation, Pathophysiology, and Therapeutic Strategies

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Definition and assessment of IR

IR has been defined as “a state (of a cell, tissue, or organ) in which a greater than normal amount of insulin is required to elicit a quantitatively normal response” (6), or as a state in which a subnormal glucose-lowering response is observed in the setting of a known concentration of insulin (7, 7a).

Currently, several methods are available to clinically assess IR (7, 8). Perhaps the simplest and most practical method is to determine fasting insulin and glucose levels (9, 9a). The homeostasis model assessment (HOMA) of IR (HOMA-IR), i.e. fasting insulin \times\text{fasting glucose}/22.5, has been used by many to assess IR (10). This method is closely associated (R = 0.88; P < 0.0001) with what is currently considered to be the gold standard in the assessment of IR, the euglycemic hyperinsulinemic clamp, discussed below. Fasting and/or peak insulin and glucose levels after an oral glucose tolerance test (OGTT) have also been used to calculate the degree of IR through a variety of methods (9a, 11). Severe IR is typically characterized by fasting insulin levels greater than 50–70 \mu U/ml or post-OGTT insulin levels above 350 \mu U/ml. In contrast, fasting insulin levels of 5–20 \mu U/ml and post-OGTT insulin levels of less than 150 \mu U/ml are seen in normal individuals (8). Although there are currently no clearly defined normal ranges for fasting insulin, some would argue that IR should be suspected when fasting insulin levels are greater than 15–20 \mu U/ml.

Other methods for the in vivo assessment of IR are more complex and are typically used only in the research setting. The insulin tolerance test involves obtaining sequential plasma glucose levels after the iv administration of insulin (9, 9b, 9c). The rate at which plasma glucose declines gives an indication of insulin sensitivity. Because this test is associated with the secretion of counterregulatory hormones such as epinephrine, glucagon, cortisol, and GH, its utility in assess-
ing insulin sensitivity has been questioned. The frequently sampled iv glucose tolerance test allows the calculation of the insulin sensitivity index (Si) by using minimal model kinetic analysis (8, 9d). In this test, a fixed amount of glucose is administered iv, followed by frequent blood sampling for plasma glucose and insulin. Analysis of the data then results in indices of insulin sensitivity (Si) and glucose effectiveness. Individuals with severe IR typically have Si values less than $2 \times 10^4 \mu U/ml-min$, whereas normal individuals have values typically greater than $5 \times 10^4 \mu U/ml-min$ (8). The frequently sampled iv glucose tolerance test has been shown to correlate very well with insulin-mediated glucose disposal in the euglycemic hyperinsulinemic clamp technique.

The euglycemic hyperinsulinemic clamp technique is the gold standard for the assessment of IR. This technique involves the iv infusion of insulin at a fixed rate and the concurrent iv administration of glucose at a variable rate to achieve steady state normoglycemia (12, 12a). Glucose disposal rate at steady state is directly proportional to the exogenous glucose infusion rate such that insulin-resistant individuals require the infusion of less glucose, and insulin-sensitive individuals require the infusion of more glucose to maintain normoglycemia. Although currently considered to be the gold standard in assessing IR, the clamp technique is typically used only for research purposes.

Congenital lipodystrophies are associated with IR

There are several hypothesized mechanisms for the development of IR. Some of these mechanisms include the role of lipids, specifically triglycerides, counterregulatory hormone excess (GH and cortisol), and autoantibodies to insulin or the insulin receptor itself as well as postreceptor defects. Because IR is associated with both obesity and fat wasting, the contribution of adipocyte-secreted proteins to its pathogenesis is a current area of active research and is discussed below.

Although it is adipose tissue excess that is classically associated with IR, this metabolic abnormality is also seen in diseases of fat wasting and fat redistribution (3, 4). Lipodystrophies are a heterogeneous group of disorders characterized by abnormal body fat distribution, which may be focal, partial, or generalized. These disorders classically involve complete or partial lack of adipose tissue. Moreover, they are typically associated with significant metabolic abnormalities, which include severe IR, hypertriglyceridemia, and fatty infiltration of the liver (8, 12b).

Generalized lipodystrophies include the congenital Seip-Berardinelli syndrome (13, 14) and the acquired Lawrence syndrome (15). Examples of partial lipodystrophies include the familial Dunnigan’s (16, 17) and Koberling’s syndromes (18), and the acquired Barraquer-Simons’ syndrome (19). These extremely rare conditions share the common feature of being associated with severe IR. Interestingly, the severity of the associated metabolic abnormalities, such as IR, is proportional to adipose tissue depletion.

Although the etiologies of these disorders include genetic abnormalities and autoimmune processes, the underlying pathophysiology of the individual disease phenotypes has yet to be defined. For example, the phenotypic changes observed in the monogenic familial partial lipodystrophy of the Dunnigan variant may be related to a mutation (R482Q) of the LMNA gene on chromosome 1q21-q22 that encodes the nuclear envelope proteins, lamins A and C (20–22). Such lamins form a fibrous structural network around the nucleus and interact with numerous molecules, including transcription factors. However, it remains unknown exactly how this leads to lipodystrophy and IR.

It has also been hypothesized that IR in these syndromes may be due to genetic defects in the insulin receptor or important downstream intracellular signaling proteins such as insulin-receptor substrate (IRS)-1 and IRS-2. However, linkage analysis in 10 families with congenital lipodystrophy failed to show an association with candidate genes (23). Indeed, further elucidation of the pathogenic pathways of lipodystrophic models of IR may be instructive in better defining the pathogenesis of other IR syndromes and may provide new targets for drug therapies aimed at treating these conditions.

HIV/HAART-associated lipodystrophy syndrome

It was not until the late 1990s that clinicians began to observe metabolic and anthropometric changes in HIV-infected patients treated with HAART (5, 24–28). The development of morphologic changes, including lipoatrophy and lipohypertrophy, or a combination of the two, were accompanied by profound metabolic abnormalities such as hyperglycemia, hyperinsulinemia, hyperlipidemia, and hypertension, which are now commonly referred to as the metabolic syndrome.

Epidemiology. The determination of the prevalence and incidence of HIV/HAART-associated lipodystrophy is somewhat complicated because there are currently no universally agreed on criteria for its diagnosis. Nevertheless, epidemiological studies have identified several morphologic and metabolic features, which will undoubtedly provide guidance for the diagnosis of this syndrome in the future. Additionally, these studies have begun to provide important information that addresses the relative importance of various risk factors for the development of a syndrome whose pathogenesis will likely prove to be multifactorial.

Several cohort studies have helped to establish prevalence estimates of HIV-associated lipodystrophy. The prevalence of this syndrome is estimated to range between 2% and 84% of patients on protease inhibitor (PI)-containing HAART regimen (5, 29–31). The large difference in prevalence is undoubtedly due to a lack of consensus for a formal definition of the syndrome and the subjective nature of patients’ perception of lipodystrophy as opposed to an objective evaluation of fat redistribution. Additionally, prevalence may differ according to the nature of the study (e.g. cohort/prospective study vs. cross-sectional study) and may vary due to inherent differences in study populations. One retrospective cohort study showed that 13% of 221 patients treated with PI therapy for 5 yr developed lipodystrophy, suggesting that the effect of antiretroviral medication may be an important contributor to the development of the syndrome (32).

Based on what is currently known about HIV/HAART-
associated lipodystrophy from epidemiological studies, the syndrome typically presents with fat redistribution and anthropometric changes after 10–18 months of antiretroviral drug therapy. The median time of onset may vary according to the specific antiretroviral therapy used, the time being shorter for those taking the PIs ritonavir and saquinavir, compared with indinavir or nelfinavir (5).

Observational studies have identified several potential risk factors for the development of HIV-associated lipodystrophy. These risk factors include: exposure to PIs, the duration of PI and nucleoside reverse transcriptase inhibitor (NRTI) use, increasing age, gender, duration and severity of HIV disease, viral load, time since reversal of clinical progression of HIV infection, and extreme changes in body mass index (BMI; Ref. 33). Multivariate analyses have revealed that fat accumulation is correlated with female gender, low viral load, and high BMI, whereas fat depletion is associated with low BMI and the use of the NRTI stavudine (34). Additionally, these analyses showed that males were at greater risk of developing metabolic abnormalities, including hypertriglyceridemia, hypercholesterolemia, and hyperglycemia. Another study has suggested that mixed fat redistribution (concurrent fat wasting and fat accumulation) may be related to effective HIV suppression by HAART (35).

Perhaps the most compelling risk factor identified thus far has been PI use. Carr et al. (5) showed that 64% (74 of 116) of patients receiving PI therapy suffered from lipodystrophy, as opposed to only 3% (1 of 32) of PI-naive patients. That PI exposure is an important risk factor was reinforced when Veny et al. (36) showed that the cumulative risk for the development of lipodystrophy after 6, 12, 18, 24, and 30 months of PI use was 3.2%, 10.7%, 29.1%, 62.5%, and 75%, respectively. In that study, 47% of the patients receiving PI therapy developed impaired glucose tolerance (IGT), whereas 60% of patients receiving PI therapy had dyslipidemia. Although PI use has consistently been associated with the development of lipodystrophy in many studies, some studies have not shown such a striking association. For example, Martinez et al. (31) prospectively followed 494 HIV-infected patients for 7 yr after the initiation of antiretroviral drug therapy, and only 17% of these subjects developed lipodystrophic changes after a median follow-up of 18 months. Moreover, although subject age and duration of antiretroviral therapy appeared to confer risk, specific classes of antiretroviral medications did not appear to be risk factors.

Clinical features and diagnosis. The clinical features of HIV/HAART-associated lipodystrophy include both lipoatrophy and lipohypertrophy (36a, 36b). Lipoatrophic changes are characterized by sc fat depletion in the face, arms, legs, and gluteal region. Muscles of the extremities may appear more pronounced, and veins may appear more prominent in fat-depleted regions. The fat wasting observed in this syndrome should be distinguished from other wasting conditions associated with HIV infection, including the AIDS-wasting syndrome, malnutrition, cachexia, adrenal insufficiency due to HIV-related factors, and severe chronic infections. Lipohypertrophy is characterized by truncal obesity, dorso cervical fat accumulation (buffalo hump), and breast enlargement (Ref. 37; Fig. 1). Changes in fat distribution may be associated with a gradual net weight loss of up to 0.5 kg per month, and fat may be depleted peripherally while simultaneously accumulating centrally (Fig. 2).

Perhaps the most cost-effective method to assess central fat accumulation in a clinical setting is to measure the waist circumference. More accurate assessment of body fat distribution includes the use of skin-fold calipers, bioelectrical impedance, regional dual energy x-ray absorptiometry (DEXA), ultrasonography, and whole-body/single-slice magnetic resonance imaging (MRI), or computed tomography (CT), although these techniques are typically used only in the setting of research (38–41). Single-slice CT or MRI at the L4–5 interspace is well correlated with whole-body CT or MRI measurement of body fat and is a less costly alternative (42).

Metabolic abnormalities are commonly observed in HIV/HAART-associated lipodystrophy and include hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and hypercholesterolemia. A retrospective cohort evaluation of patients followed at our medical center reported the cumulative incidence of hyperglycemia, hypercholesterolemia, and hypertriglyceridemia as 5%, 24%, and 19%, respectively, in 221 patients followed for 5 yr after the initiation of PI therapy (32). Although a diagnosis of IGT and frank type 2 DM is possible, particularly for those patients with other risk factors, IR most commonly manifests as hyperinsulinemia in the setting of normoglycemia. Thus, the comparison of a cohort of patients with HIV-lipodystrophy to age- and BMI-matched controls may show no difference in fasting glucose levels (28), whereas fasting insulin levels and insulin levels 2 h after a glucose challenge can be increased in the lipo-
dystrophic group, compared with the control group. These increases are usually correlated with increased waist circumference and loss of peripheral sc fat (28, 43). IR in these patients may rarely be so severe as to manifest with acanthosis nigricans, hypertrichosis, and hirsutism. Although overt DM is uncommon in HIV-infected patients, patients receiving HAART should be closely monitored for the development of IR and/or DM because its diagnosis would necessitate therapy with lifestyle modifications, antihyperglycemic agents, and/or insulin (44, 45).

Similar to other syndromes of IR, lipid abnormalities are commonly observed in patients with HIV/HAART-induced lipodystrophy. Hyperlipidemia is commonly observed in this population and has been reported in as many as 66% of HIV-infected patients taking PIs (46–48). Hypertriglyceridemia is perhaps the most common lipid abnormality seen in these patients, and triglycerides have been reported to increase as much as 6-fold in less than 1 yr of PI therapy (5, 49). Moreover, serum triglyceride levels may exceed 500–1000 mg/dl and may therefore contribute to the development of acute pancreatitis (50). Hepatomegaly due to fatty liver may be present due to chronic hypertriglyceridemia and increased lipid biosynthesis in the liver (Ref. 51; Fig. 3).

Hypercholesterolemia in this syndrome can potentially predispose individuals to accelerated atherosclerosis and premature coronary artery disease (CAD; Refs. 52 and 53). One retrospective study of over 1,300 patients demonstrated an increased frequency of myocardial infarction in HIV-infected patients receiving PI therapy (54). Many HIV-infected patients may exhibit more than one risk factor for the development of CAD: hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, increased low-density lipoprotein (LDL) cholesterol, elevated diastolic blood pressure, decreased tissue plasminogen activator levels, and increased plasminogen activator inhibitor-1 (PAI-1) levels (55, 56). The median time to the development of hypercholesterolemia may precede that of lipodystrophy by 3–6 months (57, 58). Thus, it is important that clinicians be quickly alerted to the potential diagnosis of HIV/HAART-associated metabolic syndrome in HIV-infected patients with any manifestation of IR, particularly if fat redistribution, dyslipidemia, and/or hyperglycemia are present.

Pathogenesis of HIV/HAART-associated lipodystrophy. The etiology and pathogenic mechanisms of HIV-HAART-associated lipodystrophy remain to be fully elucidated. There is conflicting evidence as to which class of antiretroviral therapy, if any, may be causative. PIs have emerged as the most strongly implicated drug class, however NRTI use has been increasingly targeted as a potential risk factor. Furthermore, PIs and NRTIs may act synergistically, or it may simply be that effective treatment of HIV infection may independently contribute to the development of the syndrome. Moreover, current evidence points toward a multifactorial etiology, which includes the interaction of HIV with HAART.
One of the molecular pathophysiological mechanisms proposed to explain the role of PIs in the development of the lipodystrophic syndrome is based on the high affinity of PIs for the catalytic site of HIV-1 aspartyl protease. The catalytic region of this protease shares about 60% homology with the sequence of the lipid binding domain of the LDL receptor (LPR) and the C-terminal region of the cellular retinoic acid (RA) binding protein type I (CRABP-I; Ref. 59). CRABP-I facilitates the binding of RA to nuclear RA receptors, and RA bound to CRABP-I is a better substrate for metabolizing enzymes than free RA (60, 60a). Thus, CRABP-I binds intra-cellular RA and facilitates its conversion to 9-cis-RA, a major ligand of the retinoic X receptor (RXR). RXRs are ligand-dependent transcription factors of which three isoforms (RXRα, RXRβ, and RXRγ) exist (60b). Interestingly, the heterodimerization of RXRs with peroxisome proliferator-activated receptor (PPAR)-γ significantly enhances the binding affinity of 9-cis-RA to RXR. The complex then serves as a transcriptional switch by binding to hormone responsive elements important in coordinating the regulation of target gene expression, such as adipocyte differentiation (61). The resultant 9-cis-RA-RXRα-PPARγ molecular complex thus enhances the transcription of genes that rescue adipocytes from apoptosis and increase adipocyte differentiation (Fig. 4; Ref. 62, 62a). Because PPAR-γ is preferentially expressed in peripheral adipocyte tissue, it is conceivable that inhibition of CRABP-I by PIs could result in apoptosis and impaired differentiation of peripheral adipocytes, with relative sparing of intra-abdominal and visceral adipocytes thereby contributing to the development of the previously described changes in fat distribution.

PIs may also contribute to IR by inhibiting the LPR, an important receptor responsible for clearance of triglycerides in the circulation. The increased levels of free fatty acids (FFA) in the splanchnic circulation, which are associated with increased triglyceride synthesis, in turn contribute to IR via competitive metabolism of substrates (Randle’s cycle).

The exacerbation of hyperlipidemia may cause glucose intolerance and even frank DM in susceptible individuals (63–65). One study in which HIV-infected patients had a PI replaced with a non-NRTI (NNRTI) demonstrated increased insulin sensitivity but no improvement in sc adipocyte apoptosis (66). This observation suggests that NNRTIs can influence IR independently of changes in fat mass and supports the likelihood that the pathogenesis of this syndrome is multifactorial, but it does not negate the potential importance of PI therapy in the development of IR.

Another potential mechanism whereby PI therapy may contribute to IR has been suggested by recent in vitro studies demonstrating that PIs directly inhibit the translocation and intrinsic activity of glucose transporter 4 (GLUT4), the insulin-sensitive glucose transporter (67, 68). GLUT4 is predominantly expressed in tissues responsible for whole-body glucose disposal, such as skeletal muscle and adipose tissue, and represents the principal glucose transporter isoform mediating insulin-stimulated glucose uptake at these sites. PIs may therefore directly induce IR through GLUT4 inhibition, especially given that glucose transport is the rate-limiting step for whole-body glucose disposal (68a). Further support of this theory comes from the observation that IR in this syndrome often precedes the manifestation of lipodystrophy, suggesting that IR due to PI use may be directly mediated by GLUT4 inhibition rather than occurring secondary to lipodystrophy.

NRTIs, another important class of medications used in HAART, have also been implicated in the development of HIV/HAART-lipodystrophy. Use of this medication class has been associated with mitochondrial toxicity, which may be accentuated by concurrent PI use. Mitochondrial DNA (mtDNA) polymerase, an enzyme essential for mtDNA replication, is acutely sensitive to NRTIs (69, 70). mtDNA encodes genes for several integral enzymes of the respiratory oxidative phosphorylation electron transport chain. Hence, it is postulated that the crippling of mitochondrial function due to NRTI use results in the accumulation of pyruvate and the subsequent development of lactic acidosis, a potent trigger of adipocyte death (70a). This process may ultimately contribute to the characteristic lipodystrophic changes observed in this syndrome.

Vironally mediated mechanisms pose yet additional hypotheses for the development of HIV/HAART-associated lipodystrophy. The HIV-1 accessory proteins (Tat, Vpr, Vif, Vpu, Rev, Nef) play important roles in mediating viral replication and host cell functions. One such protein, Tat, appears to heighten tissue sensitivity to glucocorticoids by acting as a coactivator of the positive transcription elongation factor-β complex on glucocorticoid-responsive promoters (71). Another accessory protein, Vpr, increases tissue sensitivity to glucocorticoids by functioning as a coactivator of promoters of the glucocorticoid receptor together with host cell coactivators p300/CREB-binding proteins (72). In vitro evidence has also demonstrated that Vpr inhibits PPAR-γ activity, which could contribute to IR and adipocyte apoptosis (73). Furthermore, Vpr antagonizes the insulin-induced translocation of the forkhead transcription factor (FKHR) from the nucleus to the cytoplasm. Because FKHR binds to the promoter region of insulin-responsive genes, this action of Vpr...
impedes the transcriptional activity of insulin, thereby conferring a state of IR (74).

HIV/HAA RT-associated lipodystrophy may therefore be the result of complex interactions of viral factors and antiretroviral agents (Fig. 5). The elaboration of various cytokines due to the combined interaction of HIV viral proteins and HAART may mediate or in part explain this interaction. Before the initiation of antiretroviral therapy, CD4 cells are predominantly of the T-helper (Th)2 profile and primarily secrete antiinflammatory cytokines such as IL-4 and IL-10. After the initiation of HAART, the profile of the CD4 cell changes to the Th1 subtype. Th1-differentiated CD4 cells secrete primarily inflammatory cytokines such as IL-2, interferon-γ, and TNF-α (75). Th1 cells produce significantly more TNF-α than Th2 or Th3 cells, which express cytokines such as TGFβ. Additionally, HIV proteins such as Tat may activate nuclear factor-κB with subsequent induction of TNFα. Data from Ledru et al. (76) suggest that the progressive increase in TNF-α during HAART may mediate some of the metabolic changes observed in the HIV-lipodystrophy syndrome. TNF-α inhibits the uptake of FFA by adipocytes through suppression of lipoprotein lipase activity and leads to fat wasting. Furthermore, TNF-α increases lipogenesis via the stimulation of hepatic triglyceride synthetase, resulting in hyperlipidemia (77), which is positively correlated with the absolute number of TNF-α-producing CD8 T-cells in lipodystrophic HIV-1 infected patients. TNF-α also causes IR directly, by inhibition of insulin signaling transduction at the insulin receptor, by phosphorylating IRS-1 and decreasing GLUT4 translocation, and indirectly by increasing FFA levels (78–80). Because adipocytes are also known to secrete TNF-α, and because of the fat redistribution observed in this syndrome, the possibility exists that other adipocyte secreted proteins may also contribute to worsening IR in HIV-HAART-associated lipodystrophy.

The role of adipocyte-secreted proteins in HIV-associated lipodystrophy. Adipose tissue is now viewed as a relatively complex endocrine organ, given its wide array of secreted proteins and adipocytokines, many of which appear to play a critical role in metabolism (81). Adipocyte-secreted proteins such as leptin, adiponectin, adipin, perilipin, angiotsinogen, retinol-binding protein, TNF-α, PAI-1, IL-6, and metallothionein have all been associated with either IR or features of the metabolic syndrome (78, 82–88). Additionally, the role of regulators of adipocyte differentiation such as PPAR-γ has been closely examined, given the improvement in insulin sensitivity after the administration of PPAR-γ-agonists to insulin-resistant individuals.

Like TNF-α, other adipocyte-secreted proteins may also play an important role in the pathogenesis of the metabolic abnormalities associated with HIV-associated lipodystrophy. Animal models of complete or partial lipodystrophy have provided insights into the role of adipose tissue in IR. Transgenic (A-ZIP/F-1) mice with absent white adipose tissue have a phenotype resembling that of syndrome X and are metabolically similar to humans with generalized lipodystrophy (89). Expression of molecules such as PPAR-γ, insulin receptors, IRS-1 and IRS-2, and leptin are down-regulated, whereas TNF-α is increased (90–91). Transplantation of adipose tissue in diabetic, insulin-resistant mice with lipodystrophy and low serum leptin concentrations resulted in improved glycemia and a decrease in serum insulin concentrations (92). On the basis of these observations, it appears that adipose-secreted proteins may increase or decrease insulin sensitivity such that an excess or deficiency of adipocytes could determine whether the metabolic state is one of insulin sensitivity or one of IR.

Leptin is perhaps the best known adipocyte-secreted protein. Although primarily recognized as a central regulator of neuroendocrine function, energy balance, and reproductive function (86, 93), leptin deficiency in rodents and humans is associated with profound IR and hyperlipidemia. This observation lends support to the hypothesis that adipocyte-secreted factors are necessary to maintain metabolic normalcy. Indeed, leptin replacement has been observed to dramatically improve the metabolic profile in both rodents and humans with leptin deficiency (94–98). Leptin replacement in congenitally lipodystrophic mice with DM was shown to dramatically improve, but not fully normalize, the metabolic abnormalities (97). Oral et al. (98) made similar observations after humans with congenital lipodystrophy were treated with leptin. Furthermore, recent studies have shown that in vivo leptin administration in rodents leads to activation of signaling molecules and protein expression that

overlap, but are distinct from, signaling and protein expression induced by insulin (99), which may in part explain the mechanism by which leptin improves insulin sensitivity. These observations in lipodystrophic rodents and congenitally lipodystrophic humans, together with the observation of decreased leptin levels in patients with HIV/HAART-associated lipoatrophy (100), further highlight the potential role of leptin deficiency in the pathogenesis of IR in these syndromes. It is important to note, however, that leptin administration to lipodystrophic animals and humans has resulted in only partial improvement in the metabolic abnormalities. This observation suggests that leptin, acting in concert with other adipocyte-secreted proteins, may be necessary to maintain metabolic normalcy.

Adiponectin (adipocyte complement-related protein-30 kDa, Acrp-30, AdipoQ, apM1, GBP28) is a newly discovered protein that is secreted exclusively by adipocytes (101–104). Genomewide scans recently mapped a susceptibility locus for type 2 DM and the metabolic syndrome to chromosome 3q27 (105, 106). The fact that this locus is the location of the gene encoding adiponectin emphasizes the potential role of adiponectin deficiency in the development of IR syndromes. The concentration of adiponectin in plasma is inversely correlated to fasting insulin levels and IR (88). Interestingly, although secreted exclusively by adipose tissue, levels of adiponectin are decreased in the setting of obesity, IR, type 2 DM, congenital lipodystrophy, and CAD (87, 88, 107). Similar to other syndromes of IR, HIV/HAART-associated lipodystrophy is also associated with decreased levels of adiponectin (43, 107a). We have shown in a cross-sectional study of 112 HIV-infected subjects that adiponectin levels were decreased in those with fat redistribution, characterized by central fat accumulation and peripheral fat wasting. Adiponectin levels were inversely correlated with fasting insulin levels, HOMA-IR, and serum triglycerides, and positively correlated with HDL cholesterol (43).

Mechanistically, adiponectin increases insulin sensitivity by inhibiting target hepatic gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase and glucose-6-phosphatase (108). Adiponectin also reduces IR by up-regulating the expression of molecules involved in fatty acid combustion and muscle energy expenditure with overall reduction of triglycerides in muscle and liver as demonstrated in obese mice (109). Interestingly, one in vitro study demonstrated that TNF-α decreased the expression of the apM1 gene and its gene product, adiponectin, from 3T3-L1 adipocytes (110). That HAART has been associated with increased TNF-α levels in some studies may explain the decreased adiponectin levels in this patient population. Additionally, PPAR-γ agonists, a class of medications associated with improved insulin sensitivity and increased adipocyte differentiation, have been shown in in vitro, animal, and human models to increase adiponectin secretion (111–113). The inhibition of the RXR-PPAR-γ heterodimer by PIs may therefore further implicate the importance of adiponectin deficiency in the pathogenesis of HIV/HAART-associated lipodystrophy. Bastard et al. (114) recently showed that sterol-regulatory-element-binding-protein-1c was decreased in a cohort of patients with HAART-induced lipoatrophy and that this was associated with decreased expression of PPAR-γ and leptin, decreased adipocyte differentiation, and increased levels of TNF-α. Most recently, Yamashita et al. (111) reported decreased serum adiponectin and leptin levels in a murine model of lipoatrophy. Partial restoration of insulin sensitivity and lipid abnormalities was observed after either adiponectin or leptin was administered. However, the coadministration of adiponectin and leptin was able to fully correct the metabolic abnormalities. These observations all suggest that the combined effects of adipocyte-secreted proteins are necessary to maintain a normal metabolic state and that it is the relative proportions of adipocyte-secreted proteins that determine insulin sensitivity or resistance.

The fact that lipodystrophic syndromes are associated with fat wasting and/or fat redistribution leads to the hypothesis that an excess or deficiency of important adipocyte-secreted proteins may explain the IR seen in these patients. Hypoadiponectinemia and hypoleptinemia have been noted in patients with congenital and acquired lipodystrophies (43, 100, 107), and leptin replacement in a similar cohort of patients resulted in significant improvement in insulin sensitivity and serum triglycerides (98).

Other adipocytokines such as IL-6 may also be mediators of IR (85). These cytokines, including TNF-α, may activate the IκB kinase complex (IKK), resulting in serine phosphorylation of IRS-1 and inhibition of insulin signaling. Blocking the effects of the IKK cascade is predicted to increase insulin sensitivity, thereby implying that IKK may be an excellent new target for the development of novel drugs to treat IR in obesity (115). Resistin, yet another newly discovered adipocyte-secreted protein, also appears to be positively correlated with IR in rodent models. However, its pathogenic role in humans is currently debated (116). Lastly, PAI-1, although not related specifically to IR, is closely linked to the metabolic syndrome, given its association with defective fibrinolysis and cardiovascular morbidity and mortality (82, 83), as are other defects in the hemostatic system including hyperuricemia, microalbuminuria, increased factor VIII, and fibrinogen (117, 118).

Adrenal and gonadal hormones may also play a role in the IR observed in HIV/HAART lipodystrophy. Excess of counterregulatory hormones such as cortisol is one proposed mechanism of IR (119), especially given that the phenotype of this syndrome is reminiscent of Cushing’s syndrome. The association of Cushing’s syndrome with IR is well known. Although the plasma level of cortisol is typically normal in the setting of most cases of HIV/HAART-associated lipodystrophy and these individuals have normal overnight suppression of cortisol secretion after an evening dose of dexamethasone, subtle abnormalities on the hypothalamic-pituitary-adrenal axis have been detected (120). In a cross-sectional study of HIV-infected subjects using HAART, Christeff et al. (121) showed that subjects with and without lipodystrophy had higher cortisol levels than non-HIV-infected controls. Moreover, subjects with lipodystrophy had significantly lower dehydroepiandrosterone levels and an increased cortisol/dehydroepiandrosterone ratio compared with nonlipodystrophic HIV-infected controls. Christeff et al. (121) suggest that these findings may be explained by alterations in steroid metabolism due to changes in P450 enzymes secondary to HAART and that the fat redistribution, which
is associated with IR, may be due to a subsequent imbalance between lipogenesis and lipolysis. Consideration has also been given to the possibility that local glucocorticoid excess may lead to IR (121a, 121b). The overexpression of 11-β hydroxysteroid dehydrogenase type 1, an oxidoreductase that catalyzes the conversion of inactive keto-precursors of steroids to active glucocorticoids in the adipose tissue of transgenic mice, resulted in the development of visceral obesity, insulin-resistant DM, and hyperlipidemia (122). Thus, it is possible that fat redistribution and the metabolic syndrome could involve amplification of glucocorticoid effects selectively confined to adipose tissue via the local action of 11-β hydroxysteroid dehydrogenase type 1 without plasma hypercortisolemia. This proposed mechanism lends credence to the IR and hyperlipidemia, which are commonly associated with visceral fat accumulation (123–125).

Gonadal androgens have also been associated with IR in HIV/HAART lipodystrophy. Hadigan et al. (126) observed that insulin concentrations and IR, as measured by HOMA-IR, were inversely associated with serum free testosterone levels (P < 0.05) in 50 HIV-infected men with AIDS-wasting syndrome. Hypogonadal men were randomized to either testosterone replacement (300 mg im every 3 wk) or placebo for 6 months. Subjects that received testosterone showed a reduction in HOMA-IR (−0.6 ± 0.7 vs. +1.41 ± 0.8; P = 0.05, compared with placebo), which may be due to a significant increase in lean body mass compared with placebo-treated men (P < 0.02). Interestingly, Hadigan et al. (127) also showed that women with HIV-lipodystrophy characterized by central fat accumulation had increased insulin and androgen levels as well as an increased LH/FSH ratio compared with nonlipodystrophic HIV-infected women and non-HIV-infected women, similar to what has been observed in women with polycystic ovarian syndrome. The fact that insulin levels and androgen levels were positively correlated with truncal adiposity, but not with each other, emphasizes the importance of truncal adiposity in both IR and hyperandrogenemia. Nishizawa et al. (128) recently demonstrated that androgens decrease adiponectin secretion in 3T3-L1 adipocytes, which may in part explain these associations.

**Current management strategies and the future**

Given the increasing prevalence of HIV/HAART-associated lipodystrophy coupled with the decline in mortality in this patient population, it has become increasingly important to diagnose and treat the metabolic and anthropometric abnormalities associated with this syndrome.

**Fat redistribution.** Currently, there is no single effective Food and Drug Administration (FDA)-approved measure for the treatment of fat redistribution in HIV/HAART-associated lipodystrophy. Although few studies have investigated the impact of formal exercise programs on anthropometric changes and metabolic abnormalities, some have suggested potential benefits as has been shown in non-HIV-infected populations. One study of 18 HIV-infected men showed that 16 wk of resistance training resulted in no change in total body fat mass as measured by DEXA (129); however, resistance training in this cohort did result in a significant reduction in serum triglycerides. In addition, 12 wk of aerobic exercise did result in decreased BMI, sc fat, and abdominal girth in a small cohort of patients (130). Sixteen weeks of combined resistance training and aerobic training in 10 HIV-infected subjects resulted in an overall decrease in total body fat by 2.1% (P < 0.01). Most of this change occurred due to loss of truncal fat, which was decreased by 1.1 kg (P < 0.03; Ref. 131). Lastly, one recent case report has suggested that an exercise program combined with a moderate fat, low glycemic index, and high-fiber diet can reverse many of the lipodystrophic changes observed in HIV-infected patients (132).

It remains to be determined whether dietary factors contribute to changes in body composition or whether dietary manipulation alone can help to reverse fat redistribution. Two cross-sectional studies of HIV-infected patients showed no association between total fat or saturated fat intake and fat redistribution. However, total energy intake was increased in the fat redistribution compared with the nonfat redistribution group (133, 133a). Although interventional studies examining the potential benefits of exercise and dietary interventions in improving changes in body composition and fat distribution have not yet been performed, it is recommended that diet and exercise plans be included in the treatment regimens for patients with HIV-lipodystrophy.

Ongoing studies are under way to determine whether changes in various antiretroviral regimens might improve lipodystrophy while maintaining HIV infection treatment goals. There is some suggestion that substituting a NNRTI for a PI may lead to some improvement in lipodystrophic changes (134–135a). Because there are no definitive therapies for fat redistribution to date, it is important to recognize that the central fat accumulation seen in many of these patients has been long associated with an increased risk for cardiovascular disease (136). This point further emphasizes the need for future interventional studies that target fat redistribution and the associated metabolic changes. Lastly, one needs to consider that lipodystrophic changes may be perceived as disfiguring by some patients and may ultimately affect their compliance with antiretroviral therapy.

**IR and glucose homeostasis abnormalities.** HIV-infected patients on HAART require regular surveillance to monitor for the development of IGT or DM. This can be accomplished by performing an OGTT or by obtaining a measurement of fasting blood glucose. As in non-HIV-infected patients, diet and exercise are the initial step in the management of IGT and DM. One cross-sectional study of HIV-infected subjects suggested that diets with a high polyunsaturated-to-saturated fat ratio and diets low in fiber are associated with increased IR, as measured by an OGTT (137), but other studies did not confirm these associations (133a). Thus, although specific diet interventional studies are not available, nutritional counseling is important in these patients. Roubenoff et al. (132) studied the combined effects of a low-fat, high-fiber diet and an intense exercise regimen (aerobic plus resistance training) in one HIV-infected subject with fat redistribution. IR, as measured by HOMA-IR, was noted to decrease by 52% (from 29.23 to 14.05). However, Yarasheski et al. (129) found no significant change in fasting insulin levels in 18 HIV-infected subjects treated with a 16-wk program of resistance exercise training. As in treating non-HIV-infected patients
with DM, pharmacological therapy should be initiated if treatment goals are not achieved with diet and exercise alone. Because IGT and DM are diagnoses characterized by IR, use of insulin-sensitizing therapies such as metformin and thiazolidinediones (TZDs) may specifically target the underlying mechanism of disease.

Metformin acts as an insulin-sensitizing agent primarily by inhibiting hepatic glucoseogenesis and, to a much lesser extent, by promoting peripheral glucose uptake. It has been commonly used in the treatment of obese patients with type 2 DM and dyslipidemia. Metformin used in patients with IR results in modest weight reduction, and it has been shown to decrease plasma insulin, triglycerides, LDL cholesterol, and FFA (138). Thus, metformin has been studied in a cohort of HIV-infected subjects with fat redistribution. In one study, 27 subjects received placebo or metformin, 850 mg three times daily for 8 wk (139). Metformin-treated subjects were observed to have significant improvements in fasting insulin (18.4 ± 4.1 vs. 41.7 ± 14.6 mU/ml; P < 0.01) and visceral adipose tissue as measured by DEXA scan (121.8 ± 49 vs. 231.4 ± 52 cm²; P < 0.01) compared with subjects treated with placebo. More recently, Hadigan et al. (140) made similar observations after 26 HIV-infected subjects were randomized to receive metformin, 500 mg two times daily, or placebo for 12 wk. Compared with placebo-treated subjects, metformin-treated subjects had a 20% decrease in insulin levels 120 min after a 75-g OGTT and were also noted to have significant decreases in body weight and diastolic blood pressure. Additionally, metformin was well tolerated, with few side effects. Although these initial studies support the use of metformin in HIV-lipodystrophy, longer term interventional studies are necessary to further evaluate its efficacy and safety.

TZDs are PPAR-γ agonists that improve insulin sensitivity by increasing glucose transport and peripheral glucose disposal as well as by promoting adipocyte differentiation (141, 142). Interestingly, recent studies have shown that TZDs increase the expression and plasma concentrations of adiponectin, which may explain the associated improvement in insulin sensitivity with their use (112, 113). Rosiglitazone and pioglitazone have been approved and are currently used for the treatment of type 2 DM (143, 144). However troglitazone, also a TZD, was taken off the market by the FDA because of rare, but life-threatening, hepatic toxicity, which has not been reported with use of other TZDs (145). Before its removal from the market, troglitazone was administered for 3 months to six HIV-infected patients with DM (146). Four of the six subjects were observed to have significant improvement in insulin sensitivity, and two of these four subjects had normalization of insulin sensitivity after 3 months of therapy. Overall, there was a decrease in total body fat, visceral adipose tissue, serum triglycerides, and serum very LDL, whereas increases in lean body mass, sc adipose tissue, and serum HDL were noted. The results of this study may have been confounded, in part, because troglitazone up-regulates CYP3A, leading to decreased levels of PIs that are also metabolized by CYP3A. Currently available TZDs do not appear to have this effect. Troglitazone was also studied in a cohort of subjects with congenital lipodystrophy with similar improvements (147). Although TZD therapy typically results in modest weight gain in non-HIV infected patients, the noted improvements in body fat distribution, insulin sensitivity, and serum lipids warrant further investigation. Two recent pilot studies looking at the effect of rosiglitazone in the treatment of HIV-infected patients have demonstrated conflicting results. In the first study, eight subjects were treated with 8 mg of rosiglitazone for 6–12 wk (148). After treatment, the glucose disposal rate during a hyperinsulinemic-euglycemic clamp improved from 3.8 ± 0.4 to 5.99 ± 0.9 mg glucose/kg lean body mass/min (P = 0.02), an improvement of 59 ± 22%. The authors found that sc adipose tissue increased by 23 ± 10% (P = 0.05) and that visceral adipose tissue decreased by 21 ± 8% (P = 0.04). Another group performed a similar study, randomizing 30 patients with HAART-associated lipodystrophy to 8 mg of rosiglitazone or placebo for 24 wk (149). Compared with placebo, the rosiglitazone group had a significant decrease in fasting insulin (13 ± 2 to 9 ± 1 mU/liter vs. 10 ± 2 to 16 ± 6 mU/liter; P < 0.05). However, this improvement in insulin sensitivity was accompanied by significant increases in triglycerides compared with the placebo group (P < 0.05), and there were no significant changes in sc fat, visceral fat, or waist-to-hip ratio (WHR) compared with the placebo group. Ongoing studies are currently being performed to determine the long-term safety and efficacy of the use of this class of medications in the treatment of HIV/HAART-associated lipodystrophy and the metabolic syndrome.

Dyslipidemia in HIV-associated lipodystrophy syndrome. Although the National Cholesterol Education Program (NCEP) guidelines are not specifically targeted to the HIV-infected patient population, it is not unreasonable to follow the NCEP guidelines, taking into consideration each patient’s risk factors for the development of CAD or other hyperlipidemic disorders such as pancreatitis.

Nonpharmacological therapies such as dietary intervention are the initial step in treating the lipid abnormalities associated with HIV-lipodystrophy. Diets high in omega-3 essential fatty acids, as found in fish oil, and mono- and polyunsaturated fatty acids, as found in walnuts and olive oil, have been shown to benefit some non-HIV-infected patients with hypertriglyceridemia (150–153), although no specific interventional studies of diet have been conducted in HIV-infected subjects. Two cross-sectional studies of HIV-infected subjects showed no significant difference in the total or saturated dietary fat intake between subjects with and without fat redistribution and lipid abnormalities (133, 133a). However, another observational study of 85 consecutively enrolled HIV-infected patients with fat redistribution demonstrated a strong association of polyunsaturated fats with hyperlipidemia in this patient population (137). Because some patients with hyperlipidemia may have concomitant fat wasting, the advice of a dietician is recommended to avoid unnecessary weight loss that might result from a low-fat diet. Exercise, weight loss, if appropriate, and reduced alcohol consumption may additionally contribute to decreased serum triglyceride levels (154, 155). Although dietary interventions and lifestyle changes may offer some improvement in serum lipid elevations, pharmacological therapy is usually necessary to achieve treatment goals.
The hydroxy-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), although efficacious in lowering total and LDL cholesterol in non-HIV-infected patients, have not been studied in HIV-infected patients whose primary lipid abnormality is hypertriglyceridemia. Atorvastatin and higher doses of simvastatin (40 mg and 80 mg) have both been shown to exhibit some effect in lowering serum triglycerides compared with the other HMG-CoA reductase inhibitors (156–158). It is important to remember that the pharmacokinetics of these medications are variably altered when coadministered with some antiretroviral therapies. The HMG-CoA reductase inhibitors and many antiretroviral medications, specifically PIs, are metabolized by the cytochrome-P450 enzyme system in the liver. Competition for the same enzyme system may therefore contribute to significant drug interactions between medication classes such that the half-life of a given statin may be increased or decreased. The ACTG 5047 trial investigating the interaction of PIs and HMG-CoA-reductase inhibitors found that levels of atorvastatin and simvastatin, two commonly used HMG-CoA-reductase inhibitors, are increased by 343% and 2676%, respectively, in the presence of the PIs ritonavir and saquinavir (159). Conversely, the level of pravastatin was reduced by nearly 50%. However, none of the statins altered the level of ritonavir or saquinavir to any significant degree. One should therefore be cautious in prescribing a statin concurrently with a PI, and serious consideration should be given to use of pravastatin if a statin is deemed necessary. Concomitant statin and PI therapy obligates strict adherence to regular monitoring of liver chemistries. One should also bear in mind that most HIV-infected patients are taking other medications that may alter the pharmacokinetics of statin metabolism. Caution is therefore warranted with the use of this class of lipid-lowering agents.

Fibric acid derivatives, including clofibrate, fenofibrate, and gemfibrozil, do not appear to interact with antiretroviral agents. Although studies to directly compare the available agents in this class have not been performed, this is perhaps the best class of lipid-lowering agents to treat hypertriglyceridemia and low HDL cholesterol, which are the primary lipid abnormalities associated with HIV-lipodystrophy (159a). Although use of these agents can lower serum triglycerides by as much as 55% (160), these medications have not been extensively evaluated in HIV-infected patients. One retrospective study of eight HIV-infected patients taking both a PI and a minimum of 4 wk of gemfibrozil showed a decrease in median triglyceride levels from 1803 mg/dl to 300 mg/dl, but safety data were not provided (49). Another study examined 24 HIV-infected patients treated with diet and exercise, gemfibrozil, atorvastatin, or gemfibrozil plus atorvastatin (161). Although use of a fibric acid derivative in combination with a statin may potentially result in rhabdomyolysis, this was not reported in the study, and there were no reported increases in creatinine phosphokinase or liver transaminases. A reduction in serum cholesterol compared with baseline was noted in all three pharmacologically treated groups: gemfibrozil (−32%; P = 0.002), atorvastatin (−19%; P = 0.004), and combination therapy (−30%; P = 0.004). Triglyceride reduction was similar between the gemfibrozil-treated (57%; P = 0.01) and combination therapy groups (60%; P = 0.01) but was not significantly lowered in the atorvastatin-only group. Although use of fibric acid derivatives may be the safest means of lowering serum triglycerides, use of these agents needs to be balanced with potential gastrointestinal side effects, which may limit their use. The use of any particular statin or fibrate in HIV-infected patients on PI-containing HAART should be guided by established drug interaction data and dictated by individual circumstances after appropriate risk benefit considerations.

Other lipid-lowering therapies used in non-HIV-infected patients may not be suitable for HIV-infected patients. Resins, such as cholestyramine and colestipol, are commonly associated with gastrointestinal side effects, which may limit their use. Additionally, these agents may result in increased triglyceride levels (160) and impairment of the absorption of other medications. Niacin is another lipid-lowering agent that is effective in lowering LDL and total cholesterol in non-HIV-infected patients. However, niacin may not be suitable for use in HIV-infected patients with hyperlipidemia because it may cause significant side effects, including flushing, liver toxicity, hyperglycemia, and worsening of IR. For these reasons, use of resins and niacin is not currently recommended for the treatment of hyperlipidemia in HIV-infected patients.

The effect of changing antiretroviral regimens on the metabolic syndrome. Because specific antiretroviral therapies have been associated with the development of lipodystrophy in HIV-infected patients, some studies have evaluated the role of changing antiretroviral treatment regimens with the therapeutic goal of reversing the metabolic changes observed in this syndrome, while at the same time maintaining adequate HIV suppression. Some studies have assessed the effect of substituting one PI for another in a given antiretroviral regimen. Because ritonavir is reportedly the PI most commonly associated with lipodystrophy, one study retrospectively examined the effect of substituting this PI with another PI, such as nelfinavir or indinavir, on hyperlipidemia (48). Both plasma cholesterol and triglycerides were significantly reduced 29–63 d after the substitution, however these data represent observations from only seven subjects.

Other studies have examined the effect of substituting a NNRTI for a PI. In one prospective open-label pilot trial, 40 patients with an undetectable viral load on a PI-containing regimen were switched to the NNRTI, nevirapine (163). Fast ing triglyceride levels were significantly decreased (31%; P = 0.005) a mean of 24 wk after the change; however, cholesterol levels were not significantly different. The virologic status worsened after the change in antiretroviral therapies in one subject, but this change improved after resumption of the PI. In a similar uncontrolled study, 20 subjects with an undetectable viral load were switched from a PI to the NNRTI, efavirenz (164). Six months after the change, triglycerides had decreased by 31% (P = 0.03), total and HDL cholesterol levels were not significantly different, and the viral load became detectable in one subject. Although these studies demonstrate an encouraging improvement in serum triglycerides after changing from a PI to a NNRTI, other studies have not shown significant changes in lipid profiles (165, 166). However, one study, although not showing any im-
provement in the lipid parameters of 138 subjects followed for 6 months after changing from PI-based therapy to nevirapine, did show modest improvements in lipodystrophic changes (167). Body fat redistribution was present in 70% of subjects at the time of randomization and was partially improved in 50% of these subjects 6 months after the PI was replaced by nevirapine.

Although these studies have demonstrated no significant reduction in antiretroviral efficacy, the change in medication classes did not significantly reverse all lipodystrophic changes, and only modest improvement in morphologic changes was observed. However, one study did show favorable improvements in dyslipidemia and IR. Martinez et al. (168) followed 23 subjects whose PI was replaced by nevirapine. Six months after PI withdrawal, total cholesterol decreased by 22% (P = 0.0005), triglycerides decreased by 57% (P = 0.0001), glucose decreased by 15% (P = 0.008), fasting IR index decreased by 45% (P = 0.0001), and WHR decreased from 0.91 to 0.85 (P = 0.048). A total of 91% of the subjects self-reported improvement in body fat redistribution, particularly peripheral fat wasting, and only one patient had significant worsening in the viral load. Although changing PI-based therapy to NNRTI-based therapy may present a viable option for the treatment of HAART-associated lipodystrophy, long-term follow-up data are not currently available. Although there are seemingly few adverse outcomes associated with changes in HAART, it is not known whether these changes may induce the development of drug resistance in HIV infection. This further highlights the need for larger, controlled trials with long-term follow-up. Changes in HAART should therefore be made only under the guidance of HIV-infection specialists.

**Novel approaches.** The challenge of understanding medical disorders such as HIV/HAART-associated lipodystrophy at the molecular level has become increasingly important for the development of new and efficacious therapies. The development of novel therapeutic approaches for the treatment of this syndrome will undoubtedly rely on the use of genetics and molecular biology to better define therapeutic targets for the treatment of IR and fat redistribution, as perhaps evidenced by the use of recombinant therapies such as human GH.

Recombinant human GH (rhGH) was approved for the treatment of HIV-associated wasting in 1996 (169). Although GH deficiency has not been observed in patients with HIV/HAART-associated lipodystrophy, the reduction in total body and visceral fat mass after the administration of rhGH (9.5 μg/kg/d) to non-HIV-infected men with abdominal obesity (170) has prompted the investigation of rhGH therapy in HIV-infected patients with lipodystrophy. Early studies using pharmacological doses of rhGH (4–6 mg/d) demonstrated improvement in body fat redistribution as evidenced by decreased mean change in trunk fat mass or decrease in WHR, however worsening glucose tolerance was also noted in rhGH-treated subjects (171–173). In follow-up to these initial studies, an open-label study was conducted to evaluate the effects of a lower pharmacological dose of rhGH (3 mg/d) in eight HIV-infected men with fat redistribution (174). Significant decreases in total body fat (17.9 ± 10.9 vs. 13.5 ± 8.4 kg; P = 0.05), primarily in the trunk region, and increases in lean body mass (62.9 ± 6.4 vs. 68.3 ± 9.1 kg; P = 0.03) were observed after 6 months of therapy. However, insulin-mediated glucose disposal, as measured by the hyperinsulinemic-euglycemic clamp, decreased significantly after 1 month of therapy before returning to baseline after 6 months of therapy. Importantly, rhGH therapy in this study resulted in IGF-I levels that were up to three times the upper limit of normal range. A companion study of five HIV-infected subjects showed that the same dose of GH (3 mg/d) resulted in significant improvement in serum lipids after 6 months of therapy (175). Total cholesterol decreased by 25% (P < 0.01), LDL cholesterol decreased by 30% (P < 0.01), HDL increased by 15% (P < 0.01), and triglycerides decreased (data not given; P < 0.01). These improvements in serum lipids were accompanied by significant increases in fasting endogenous glucose production (12.0 ± 7.7 vs. 14.9 ± 9 μmol/kg/min; P < 0.03) after 1 month of therapy, however this was not significantly different from baseline after 6 months of therapy. Most recently, 30 HIV-infected subjects were studied in a 24-wk prospective open-label trial of GH 6 mg/d vs. rhGH 4 mg on alternate days (176). Visceral fat, as measured by MRI, decreased by an average of 42% (P < 0.001) in the 6 mg/d group (n = 24) and by an average of 15% (P < 0.01) in the alternate day therapy group (n = 10). Of note, four subjects in the study developed DM, and side effects included myalgias and joint pain. Because of the variable improvement in features of the metabolic syndrome and because of the significant increases in IGF-I, which may potentially lead to long-term adverse effects in these immuno-compromised patients (177), rhGH cannot currently be recommended for treatment of HIV/HAART-associated lipodystrophy. Use of this therapy clearly warrants close monitoring for the development of glucose intolerance and/or DM. Future studies are necessary to investigate the metabolic effects of lower rhGH doses in an attempt to keep IGF-I in the normal range.

One promising therapy for the treatment of HIV/HAART-associated lipodystrophy is leptin, the product of the Ob gene. The levels of this adipocyte-secreted protein are markedly decreased in both lipodystrophic humans and animal models of lipodystrophy (92, 100, 107). Leptin deficiency in mice causes increased hepatic lipogenesis through the action of the sterol regulatory element binding protein-1c and accentuates hepatic gluconeogenesis through down-regulation of IRS-2 (178). The hyperglycemia, in turn, stimulates insulin secretion and initiates a vicious cycle of IR. Predictably, leptin has been shown to dramatically improve IR and diabetes in mice with lipodystrophy (97). Recently, nine patients with congenital and acquired (non-HIV) lipodystrophy received twice daily recombinant leptin via sc injection for 4 months to achieve physiological leptin concentrations (98). Subjects were observed to have significant improvements in hyperglycemia, hyperinsulinemia, hypertriglycerideremia, as well as a significant decrease in fatty infiltration of the liver. In light of a recent study demonstrating leptin deficiency in patients with HIV/HAART-associated lipodystrophy (100), leptin replacement in this patient population theoretically could reverse many of the metabolic abnormalities observed in this syndrome. Although recombinant leptin is not yet commercially available, trials of leptin administration to
HIV-infected patients with the lipodystrophy syndrome are currently under way.

Given that recent data have shown complete normalization of IR after the coadministration of leptin and adiponectin in a murine model of lipopathic diabetes (111) and that patients with HIV/HAA RT lipodystrophy have both leptin and adiponectin deficiencies (43, 100), attention is now additionally focused on future trials of adiponectin, either alone or with leptin, as another treatment option for this syndrome. Undoubtedly, other newly discovered adipocyte-secreted proteins, such as resistin, will also be investigated to explore the potential pathogenic role they may play in the development of IR. As our knowledge of the complex endocrine functions of the fat cell expands in tandem with our ability to manipulate gene expression, we may ultimately have viable options for the treatment of HIV/HAA RT-associated lipodystrophy and other IR syndromes.

Conclusions

In summary, HIV/HAA RT-associated lipodystrophy is most likely a multifactorial disorder due to the interplay of viral, host, and drug-related factors. Among the many drugs used to treat HIV infection, PIs and NRTIs have emerged as two classes of medications that may play a pathogenic role. The synergy between medication classes such as these and viral factors results in a characteristic phenotype typified by lipodystrophic changes, lipid abnormalities, and IR. It is hoped that ongoing research into the molecular mechanisms of IR in the context of HIV infection and antiretroviral therapy will ultimately provide viable treatment options for patients with this syndrome. Given the heightened risk for the development of cardiovascular disease and DM in this growing patient population and the decreased mortality now associated with HIV infection, these therapies will prove to be crucial.

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