



## Cardiovascular Disease Risk Factors Among HIV Patients

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### Abstract

Metabolic disturbances and fat redistribution have been characterized in HIV-infected patients receiving combination antiretroviral therapy according to drug exposure and patterns of fat redistribution. In contrast, we investigated metabolic abnormalities in a well-characterized cohort of HIV-infected patients with clinical lipodystrophy in comparison with an established population of healthy control subjects with known cardiovascular disease (CVD) risk parameters. In order to establish the extent of lipid abnormalities, glucose intolerance, and increased CVD risk in HIV-infected men and women experiencing lipodystrophy, we evaluated metabolic and clinical parameters in comparison with healthy control subjects. We investigated sex-specific differences in CVD risk parameters and the extent to which fat redistribution contributes to the metabolic abnormalities in HIV infected men and women with lipodystrophy syndrome. This study demonstrates a constellation of metabolic abnormalities, including hyperinsulinemia and dyslipidemia, suggestive of a significant insulin resistance syndrome among HIV-infected patients with fat redistribution. In comparison, cardiovascular risk parameters are not substantially increased in HIV-infected patients without clinical evidence of fat redistribution. Although affected patients have a significant increase in waist-to-hip ratio, the observed metabolic abnormalities persist after adjustment for increased waist-to-hip ratio in male patients, and to a lesser degree in female patients, and may result from loss of peripheral or subcutaneous fat.

**Keywords:** Cardiovascular Disease, HIV, Hyperinsulinemia and Metabolic disturbances

### INTRODUCTION

**M**etabolic complications, including dyslipidemia, insulin resistance and altered fat distribution (loss of subcutaneous fat and a relative increase in central fat), are common in adults infected with the human immunodeficiency virus (HIV) who are receiving highly active antiretroviral therapy (HAART). These complications may increase these patients risk of cardiovascular disease.

People with the metabolic syndrome are at increased risk for developing diabetes mellitus (Haffner et al, 1992) and cardiovascular disease (Isomaa et al, 2001 and Trevisan et al, 1998). The recently released Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (ATP III) draws attention to the importance of the metabolic syndrome and provides a working definition of this syndrome for the first time (National Institute of Health, 2001). The prevalence of the metabolic syndrome as defined by ATP III in the India is unknown. Because the implications of the metabolic syndrome for health care are substantial, we sought to establish the prevalence of this condition.

Recently published observations (Duong et al, 2001) suggest that among HIV-positive patients treated with highly active antiretroviral therapy (HAART), the incidence of cardiovascular diseases is increased. Until now, no specific risk factors have been identified except for those related to behavior or metabolic abnormalities.

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So far, a sum of metabolic abnormalities have frequently been reported among these patients, including increased lipid levels, abnormal fat distribution, elevated blood pressure, and disturbance in glucose metabolism (Hadigan et al, 2001).

Studies designed to identify subclinical atherosclerosis in HIV-infected patients on HAART have been inconclusive. Numerous modalities, including carotid intimal thickness measurement, brachial reactivity, and electron beam computed tomography, have shown varying results; at this time, it is unclear what the results mean. The metabolic syndrome is a cluster of risk factors (disturbance in glucose metabolism, central obesity, hypertension, and dyslipidemia) caused by insulin resistance (NCEP, 2001 and Isomaa et al, 2001). Metabolic syndrome is considered a powerful independent risk factor for cardiovascular morbidity and mortality (Isomaa et al, 2001).

Insulin resistance is frequent among HIV patients on HAART (Grinspoon, 2001), but there are no data about the prevalence of the metabolic syndrome in these patients. HIV lipodystrophy syndrome is a recently recognized syndrome characterized by body composition changes, including the development of an enlarged posterior cervical fat pad (i.e., a buffalo hump), increased truncal adiposity, breast enlargement, peripheral fat loss, and facial fat atrophy (Dong et al, 1999). The mechanism of the HIV lipodystrophy syndrome remains unknown.

Recent studies suggest that up to 83% of patients treated with protease inhibitor (PI) therapy develop fat redistribution (Carr et al, 1999), but fat redistribution has also been reported among non-PI-treated patients (Roth et al, 1998). Previous studies of the lipodystrophy syndrome often selected patients on the basis of medication status—for example, PI use, combination antiretroviral therapy, or specific medications (Saint-Merc et al, 1999 and Carr et al, 1998) and were not always limited to patients with fat redistribution. Metabolic disturbances and fat redistribution have been characterized in HIV-infected patients receiving combination antiretroviral therapy according to drug exposure and patterns of fat redistribution (Saint-Merc et al, 2000).

In contrast, we investigated metabolic abnormalities in a well-characterized cohort of HIV-infected patients with clinical lipodystrophy in comparison with an established population of healthy control subjects with known cardiovascular disease (CVD) risk parameters. In order to establish the extent of lipid abnormalities, glucose intolerance, and increased CVD risk in HIV-infected men and women experiencing lipodystrophy, we evaluated metabolic and clinical parameters in comparison with healthy control subjects. In this paper we investigated sex-specific differences in CVD risk

parameters and the extent to which fat redistribution contributes to the metabolic abnormalities in HIV infected men and women with lipodystrophy syndrome.

## MATERIALS AND METHODS

### Case patients.

Seventy-one patients (49 men and 22 women) with HIV infection who reported recent changes in body fat distribution (case patients) were prospectively evaluated from December 2009 through July 2011 at Medical camps conducted at Adilabad district, Telangana State, India.

Patients were recruited from respondents to community-based advertisements seeking HIV-infected patients with fat redistribution, or they were referred by their physicians for evaluation of fat redistribution. Patients were screened by personnel interview and asked if they had experienced any of the following: (1) loss of fat in the face, (2) increased fat under the chin or back of the neck, (3) increased abdominal girth, (4) increased chest or breast fat, or (5) loss of fat in the arms or legs. Patients who identified a change in fat distribution in >1 body areas were invited to participate, and fat redistribution was confirmed by physical examination for all patients.

Patients were excluded if they had changed antiviral medications within 6 weeks of the study; had a history of diabetes mellitus or previous treatment with anti-diabetic agents; reported use of testosterone, estrogen, growth hormone, or other steroids in the past 6 months; were active alcohol or substance abusers; or were not 18–60 years of age. A subsample of the patients who participated in this evaluation was subsequently enrolled in a treatment study of metformin for HIV lipodystrophy.

### Case patient examination protocol

Each case patient underwent a complete medical history and physical examination to confirm fat redistribution. Fat redistribution was scored as absent (0), present (1), or severe (2) by a single investigator with regard to facial fat loss, increased neck fat (anterior or posterior), and increased trunk or chest fat, and decreased leg and arm fat. Patients were categorized as having primary lipoatrophy (with no evidence of increased abdominal fat), primary lipohypertrophy (increased abdominal fat with or without increased neck fat and no evidence of peripheral fat atrophy), or mixed lipodystrophy (presenting with both increased abdominal fat and peripheral fat atrophy).

Blood pressure, weight, height, BMI (expressed as weight in kilograms divided by height in meters squared), and waist (at the umbilicus), hip, mid-arm, and mid-thigh circumference were determined (Lohman et al, 1988). After a 12-h fast, a standard 75-g oral glucose tolerance test (OGTT) was performed according to World Health Organization (WHO) standards (WHO, 1980) with

determination of blood glucose and insulin level, at 0 and at 1–2 h. In addition, fasting cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride levels were obtained.

Antiretroviral therapy was characterized as to current or past use and duration of therapy with PIs, nucleoside reverse transcriptase inhibitors (NRTIs), and/or non-nucleoside reverse transcriptase inhibitors (NNRTIs). Insulin resistance and pancreatic beta cell function were calculated with use of the homeostatic model, a mathematical estimate of insulin sensitivity and resistance derived from values for fasting glucose and insulin concentration.

#### HIV-infected control patients without Lipodystrophy

Thirty HIV-infected patients (18 men and 12 women) without clinical evidence of fat redistribution were also evaluated. None of these patients had experienced fat redistribution of the face, neck, arms, legs, or trunk, and this was confirmed by physical examination in all cases. The remaining exclusion criteria were identical to the criteria used for HIV-infected patients with lipodystrophy. Measurement of height, weight, blood pressure, and waist (at the umbilicus), hip, mid-thigh, and mid-arm circumference. After measurement of levels of fasting glucose, insulin, and lipids, control subjects underwent a 75-g OGTT administered according to WHO standards, and 2-h post challenge glucose and insulin levels were measured.

#### Biochemical and Immunologic Assays

Levels of glucose, insulin, cholesterol, triglyceride, and LDL were determined in both case patients and control patients by use of methods reported elsewhere (Melgs et al, 1998) the same methods were used in this study for both case patients and control subjects. Insulin

levels were measured by radioimmunoassay in the same laboratory with the same kit (Diagnostic Product) to maximize comparability between the groups (Robbins et al, 1996).

#### Statistical analysis

We made crude bivariate comparisons of clinical end points for HIV and for control subjects by use of a Student's t test. Insulin and triglyceride levels were log transformed before statistical comparison. We used a series of linear regression models, including covariates for waist-to-hip ratio and waist, hip, mid-thigh, or mid-arm circumference to control for the effects of regional fat distribution on differences between the groups. We also determined the effects of regional fat distribution on fasting insulin with a single model that included all covariates (waist, hip, mid-thigh, and mid-arm) stratified by group (HIV and control subjects).

Analyses were stratified by sex and repeated. Logistic regression models with and without adjustment for waist-to-hip ratio were used to assess the risk of 2-h glucose levels of >140 mg/dL and >200 mg/dL, a fasting insulin level >18 mU/mL, systolic blood pressure >140 mm Hg, diastolic blood pressure >90 mm Hg (JNCV, 1993), a cholesterol level 1200 mg/dL, a triglyceride level >200 mg/dL, and an HDL level <35 mg/dL (NCEP, 1994) between HIV-infected patients with lipodystrophy and PI exposure was categorized as current use, past use, or PI naive. The effects of PI exposure on hyperinsulinemia were also analyzed by use a multivariate regression model predicting fasting insulin level, with age, BMI, waist-to-hip ratio, current use of PI therapy (yes/no), total duration of PI exposure, and total duration of NRTI therapy included in the model as predictors.

**Table-1. Clinical characteristics of patients infected with human immunodeficiency virus (HIV) with and without Lipodystrophy and for control subjects**

Variable	HIV-infected patients with lipodystrophy	Control subjects	<i>p</i>	HIV-infected patients without lipodystrophy	Control subjects	<i>p</i>
n	71	213	-	30	90	-
Sex (Male/Female)	49/22	147/66	-	18/12	53/36	-
Age, y	41.7 ± 1.0	42.6 ± 0.5	0.40	39.4 ± 0.9	39.6 ± 0.5	0.83
Body Mass Index, kg/m <sup>2</sup>	26.5 ± 0.5	26.8 ± 0.3	0.71	24.0 ± 0.4	24.1 ± 0.3	0.81
Duration of HIV infection, y	6.8 ± 0.5	-	-	7.7 ± 0.7	-	-
Duration of antiviral therapy, y	4.2 ± 0.3	-	-	3.0 ± 0.6	-	-
Current protease Inhibitor therapy, % of patients	70	-	-	43	-	-
Current NTRI therapy, % of patients	100	-	-	73	-	-

NOTE: Data are mean + SEM, except as indicated *p* values were calculated by use of Student's test results, NTRI=nucleoside reverse transcriptase inhibitor.

### Statistical analyses

Statistical analyses were performed by use of SAS software. Statistical significance was determined by use of 2-tailed tests;  $P < .05$  was considered significant). Results are presented as mean + SEM unless otherwise indicated.

## RESULTS

### Clinical characteristics

Clinical characteristics of the HIV infected patients with lipodystrophy, HIV-infected patients without lipodystrophy, and their respective control subjects are shown in table 1. Seventy-seven percent of the case patients were white and 11% were black. Level of education was similar for case patients and for the control subjects (mean education, 15 years for each group). Of the female case patients, 86% were eumenorrheic. Seventy percent of case patients were receiving PI therapy at the time of the study, 100% were receiving a NRTI, and 30% were receiving a NNRTI. Eighty percent of the case patients were receiving highly active antiretroviral therapy (HAART), defined as the use of 2 NRTIs and either a PI or a NNRTI. Virus load was undetectable in 65% of the case patients.

### Comparison of clinical variables between case patients and control subjects.

HIV-infected patients with lipodystrophy demonstrated an increased waist-to-hip ratio, increased waist circumference, reduced hip circumference, and

reduced mid-thigh circumference compared with the age- and BMI-matched in control subjects (table 2). Among case patients, levels of fasting insulin, 2-h insulin, 2-h glucose, cholesterol, triglyceride, the cholesterol-to-HDL ratio, and diastolic blood pressure were higher and HDL lower than they were among the control subjects (table 2). Fasting glucose levels, systolic blood pressure, and LDL levels were not significantly different between the groups.

Adjusting for waist-to-hip ratio did not substantially attenuate most differences between case patients and control subjects (table 2). Differences in the levels of fasting insulin, 2-h insulin, 2-h glucose, cholesterol, and HDL remained significant between the groups (table 2). The difference in diastolic blood pressure between the groups was no longer significant after adjusting for waist-to-hip ratio. Adjustment for waist, hip, mid-arm, or mid-thigh circumference instead of waist-to-hip ratio yielded similar results.

### Risks among HIV-infected patients with lipodystrophy

HIV-infected patients with lipodystrophy were more likely than age- and BMI-matched in control subjects to have impaired glucose tolerance (2-h glucose levels 1140 mg/dL), 2-h glucose levels A greater number 1200 mg/dL, triglyceride levels 1200 mg/dL and HDL levels 135 mg/dL (Table 3). of case patients demonstrated diastolic blood pressure 190 mm Hg (11.3% vs. 5.6%)

**Table-2. Anthropometrics, blood pressure, oral glucose tolerance test results and lipid levels of patients infected with human immunodeficiency virus with lipodystrophy and control subjects**

Variable	Case patients	Control Subjects
n	71	213
Waist-to-hip ratio	0.97 + 0.01	0.90 + 0.01
Circumference, cm		
Waist	95.5 + 1.3	91.5 + 0.9
Hip	98.2 + 1.1	101.3 + 0.6
Midarm	31.5 + 0.5	32.0 + 0.3
Midthigh	51.2 + 0.6	60.3 + 0.4
Systolic blood pressure, mm Hg	120 + 2	118 + 1
Diastolic blood pressure, mm Hg	77 + 1	74 + 1
Fasting glucose level, mg/dL	92 + 1	93 + 1
2-h glucose level, mg/dL	134 + 5	96 + 2
Fasting insulin level, uU/mL	2.7 + 0.0.7	1.7 + 0.06
2-h insulin level, uU/mL	4.2 + 0.1	3.4 + 0.06
Cholesterol level, mg/dL	229 + 7	195 + 2
Triglyceride level, mg/dL	5.5 + 0.07	4.7+ 0.03
LDL level, mg/dL	132 + 6	123 + 2
HDL level, mg/dL	37 + 1	48 + 1
Cholesterol-to-HDL ratio	6.6 + 0.3	4.4 + 0.1

NOTE: Data are mean + SEM, except as indicated. HDL and LDL. *p* value for *t* test (patients infected with HIV vs control subjects).

and LDL levels 1160 mg/dL (21.8% vs. 14.1%), but these differences were not significant. In contrast to the significant increase in 2-h glucose level after glucose tolerance testing, the fasting blood glucose level was normal (1126 mg/dL) in all case patients.

Differences in the risk of impaired glucose tolerance and 2-h glucose levels 1200 mg/dL, triglyceride levels 1200 mg/dL, and HDL levels <35 mg/dL remained highly significant after controlling for waist-to-hip ratio (table 3). A greater proportion of case patients than Framingham control subjects had cholesterol levels 1200 mg/dL, but the difference was not significant after adjusting for waist-to-hip ratio (table 3).

### Risks among HIV-infected patients without lipodystrophy

The proportions of subjects with insulin levels 118 mU/mL, 2-h glucose levels >140 mg/dL, cholesterol levels >200 mg/dL, triglyceride levels >200 mg/dL, and LDL levels >160 mg/dL were not different for the group of HIV-infected patients without lipodystrophy and the matched Framingham control subjects (table 3). None of the HIV-infected patients without lipodystrophy or matched in control subjects had a 2-h glucose level >200 mg/dL. The risk of impaired glucose tolerance an insulin level >18 mU/mL, a cholesterol level >200 mg/dL and a triglyceride level >200 mg/dL was considerably lower among the HIV-infected patients without lipodystrophy compared with the patients with lipodystrophy. The risk of an LDL level >160 mg/dL was also lower among patients without lipodystrophy than among patients with lipodystrophy. The proportions of subjects with HDL levels <35 mg/dL, systolic blood pressure >140 mm Hg, and diastolic blood pressure >90 mm Hg were not different between HIV-infected patients with and those without lipodystrophy.

## DISCUSSION

In this study, we characterized metabolic abnormalities and CVD risk parameters in men and women with HIV lipodystrophy by contrasting their clinical characteristics with those of healthy participants from the Framingham Offspring Study cohort (Kannel et al, 1979 and Melgs et al, 1998). We were thus able to determine increased CVD risk for patients with lipodystrophy compared with the expected risk for healthy individuals of similar age and weight. We also compared CVD risk parameters in HIV-infected patients without lipodystrophy to matched control subjects to further distinguish the syndrome versus HIV infection alone.

Our data demonstrate a clustering of metabolic abnormalities among HIV-infected patients with fat redistribution, characterized by hyperinsulinemia, hypercholesterolemia, hypertriglyceridemia, low levels of HDL, and truncal adiposity. These metabolic abnormalities indicate a significant insulin resistance syndrome (Melgs et al, 1997) in HIV-infected patients with fat redistribution. Insulin resistance, dyslipidemia, truncal adiposity, and increased diastolic blood pressure are known to increase cardiovascular risk in patients who are not infected with HIV (Strokes et al, 1989, Stamler et al, 1986 and Howard et al, 1998) and may similarly predispose HIV-infected patients with fat redistribution to accelerated CVD (Henry et al, 1998). A number of previous studies have investigated metabolic and body composition parameters in patients with the HIV lipodystrophy syndrome. Carr et al. (1998) demonstrated moderate hyperinsulinemia in patients selected for PI use in comparison with non-PI-treated patients and age- and BMI-matched control subjects.

**Table: 3. Assessment of risk of hypertension, impaired glucose tolerance, diabetes, and dyslipidemia of patients infected with human immunodeficiency virus with and without lipodystrophy (case patients) and control subjects**

Variable	Lipodystrophy patients		Without lipodystrophy patients	
	HIV-infected patients, %	Control subjects, %	HIV-infected patients, %	Control subjects, %
Systolic BP >140 mm Hg	4.2	5.2	6.7	3.3
Diastolic BP >90 mm Hg	11.3	5.6	6.7	1.1
Fasting insulin level >18 mU/mL	26.5	6.1	3.5	2.2
2-h glucose level >200 mg/dL	7.0	0.5	5.6	0.4
IGT (2-h glucose level >140 mg/dL)	35.2	5.2	5.6	3.3
Cholesterol level >200 mg/dL	57.1	41.8	16.7	30.0
Triglyceride level >200 mg/dL	57.1	8.9	13.3	5.6
LDL level >160 mg/dL	21.8	14.1	6.9	4.4
HDL level <35 mg/dL	45.7	16.9	43.3	5.6

**NOTE:** BP, blood pressure; HDL, high-density lipoprotein; IGT, impaired glucose tolerance; LDL, low-density lipoprotein.

Our data suggest that fasting and post glucose-challenge hyperinsulinemia is much more marked in patients who present with clinical lipodystrophy. Walli et al. (1998) demonstrated reduced insulin sensitivity in PI-treated patients but did not exclude patients with known diabetes or receiving diabetes therapy and did not select patients on the basis of clinical symptoms. More recently, Saint-Marc et al. (1999) investigated 43 HIV-infected patients who were receiving dual NRTI therapy and did not show increased insulin levels. Abnormal lipid levels were shown in these studies, as well as in others (Vigourouz et al, 1999), which have all selected patients on the basis of therapy, rather than by clinical manifestations.

Several studies have investigated body composition and metabolic abnormalities in HIV-infected women. Gervasoni et al. (1999) evaluated a large number of HIV-infected women who were receiving dual NRTI therapy, only 10.5% of whom demonstrated fat redistribution. Dong et al. (1999) investigated 21 women receiving HAART who were concerned about changes in body habitus, compared with patients receiving HAART who did not experience changes. No difference in fasting insulin levels was reported between groups; however, 29% of the patients without lipodystrophy had reported increased abdominal size. In these previous reports, antiretroviral therapy was a selection criteria for the investigation, and many patients did not exhibit symptoms of lipodystrophy.

Insulin resistance was demonstrated in the HIV-infected patients with lipodystrophy by significant fasting hyperinsulinemia in the setting of a normal fasting blood glucose level. Fasting insulin levels were not different between male and female case patients and were higher in each group than in control subjects. In 25% of case patients the fasting insulin level was above the 90th percentile expected for the matched control subjects. The fasting insulin level and homeostatic model are good single-sample epidemiologic markers for insulin resistance in patients without diabetes (Howard et al, 1998) that have been shown to predict elevated CVD risk and the development of diabetes mellitus (Haffner et al, 1996 and M. Estari, 2006) and strongly correlate with results of euglycemic hyperinsulinemic clamp testing (Anderson et al, 1995).

Analysis of our data suggests at least adequate pancreatic  $\beta$  cell function by use of the homeostatic model (Hermans et al, 1999). Further studies are necessary to better define the pathophysiologic mechanism of insulin resistance in HIV lipodystrophy, using direct methods to determine relative hepatic and peripheral insulin resistance. Seven percent of the previously undiagnosed population we studied who had clinical evidence of fat redistribution had diabetes mellitus, and 35% demonstrated impaired glucose tolerance on the basis of WHO criteria (WHO, 1980). Therefore, this population of HIV-infected patients is at

high risk of developing clinically significant glucose abnormalities in addition to hyperinsulinemia.

In contrast, rates of diabetes mellitus, impaired glucose tolerance, and significant fasting hyperinsulinemia were not higher among the patients without lipodystrophy than among the matched Framingham control subjects, which suggest that these metabolic disturbances are not simply a function of HIV infection. Glucose intolerance is associated with increased cardiovascular risk in non-HIV-infected populations (Feskens et al, 1992) and may similarly increase cardiovascular risk in HIV-infected patients with fat redistribution. In our study, fasting glucose levels were not increased among the HIV-infected patients with fat redistribution.

Analysis of these data suggests that, in this population, a fasting glucose level is unlikely to be abnormal and is not a good screening test of glucose abnormalities. Glucose response to standard oral glucose challenge is a more sensitive test to detect glucose abnormalities in HIV-infected patients with lipodystrophy. The mechanism of insulin resistance among HIV-infected patients with fat redistribution is not known. Possible mechanisms include the following: direct metabolic effects of antiretroviral therapies (Carr et al, 1998) metabolic dysfunction secondary to HIV disease itself, related cytokine and hormonal abnormalities, or both; an interaction between effects of antiviral therapy; and HIV disease. Fasting and 2-h insulin levels were uniformly increased among PI-naive patients as well as patients who were current and past recipients of PI therapy. Furthermore, duration of NRTI exposure and not PI exposure predicted fasting hyperinsulinemia in a multivariate regression analysis that controlled for age, sex, BMI, and waist-to-hip ratio. Although the differences between patients with and without lipodystrophy may be partially attributable to differences in exposure to antiretroviral therapy, analysis of these data suggests a complex pathophysiologic mechanism for the metabolic abnormalities associated with fat redistribution in HIV-infected patients, which is not due exclusively to the effects of PI therapy.

The present study demonstrates that hypertriglyceridemia, hypercholesterolemia, and low HDL levels are common in this population of patients. The ratio of cholesterol to HDL levels, an index of cardiovascular risk, was also significantly increased among the HIV-infected patients with lipodystrophy. Separate analyses showed significant differences in all parameters within the groups of male and female patients. These data indicate significant dyslipidemia in HIV-infected patients with fat redistribution. Hypertriglyceridemia is the most pronounced lipid abnormality in such patients; in our study, >50% of patients had triglyceride levels >200 mg/dL. Previous studies have identified hypertriglyceridemia in HIV-infected patients. In addition, recent studies have

suggested that PIs have effects that specifically increase triglyceride levels.

Increased levels of cholesterol, LDL, and triglyceride were much less common among the HIV-infected patients without lipodystrophy than among the HIV-infected patients with lipodystrophy, but were not different in comparison with control subjects. HDL levels were low among the patients without lipodystrophy, which suggests that low HDL levels are a feature of HIV infection, independent of the lipodystrophy syndrome. These data are consistent with reports of low HDL levels in HIV-infected patients that were written before the recognition of the lipodystrophy syndrome (Crunfeld et al, 1992; (M. Estari, 2004, 2005, 2006; M Radha Krishna et al, 2005). Biochemical assays on case and control subjects were not run simultaneously because of the prior collection of samples in this study. However, the same methods were used, and it is unlikely that technical variability would account for the findings in this study.

An important aim of this study was to investigate the sex specific characteristics of the lipodystrophy syndrome. Stratification by sex demonstrated a similar pattern of fat redistribution, insulin resistance, and dyslipidemia among HIV- infected men and women with lipodystrophy. The significant and expected sex difference in waist-to-hip ratio seen in the control population was not seen in the comparison between male and female case patients. Waist-to-hip ratio and waist circumference were strikingly elevated in HIV-infected women with lipodystrophy. In the study by Rexrode et al. (1998), a waist-to-hip ratio of  $>0.88$  conferred an increased CVD risk ratio of 4.47 in women  $>60$  years old. The mean waist-to-hip ratio of women with HIV and fat redistribution was 0.96. Most of the metabolic abnormalities in female case patients were a function of fat redistribution, because few differences between HIV-infected women and control subjects persisted after adjusting for waist-to-hip ratio. Female patients affected by HIV lipodystrophy thus lose the expected advantage in fat distribution with respect to similarly aged healthy female subjects, and they develop a more android body habitus.

Fat redistribution in patients with lipodystrophy can also be manifested by peripheral fat wasting, as demonstrated by the reduced mid-thigh circumference in the population in this study. This study simultaneously controlled for waist, mid-arm, hip, and mid-thigh circumference in a regression model stratified by subject group in order to assess independent effects of peripheral fat loss on the fasting insulin level in patients with lipodystrophy in comparison with Framingham control subjects. Among the HIV lipodystrophy patients, but not the control subjects, mid-thigh circumference as well as waist circumference were significant predictors of fasting insulin levels. Peripheral fat loss may also be an important predictor of insulin resistance independent of

central fat accumulation in HIV lipodystrophy. In a sub-analysis comparing patients with lipodystrophy to patients with lipohypertrophy and mixed lipodystrophy, there was less evidence of insulin resistance among patients with lipodystrophy alone. However, patients with lipodystrophy did have increased triglyceride concentrations and lower HDL levels, and most of the differences between fat redistribution subgroups was attributable to differences in BMI.

Further studies are necessary to investigate the metabolic affects of lipodystrophy in HIV-infected patients with fat redistribution and to determine whether lipodystrophy is clinically distinct or linked pathogenetically to the accumulation of truncal fat in such patients. This study has significant clinical implications for the management of HIV-infected patients. HIV-infected patients with evidence of fat redistribution, including those who are PI-naive and who have peripheral fat loss, are at high risk for metabolic abnormalities, and their fasting lipid levels and glucose tolerance should be tested. Treatment of significant dyslipidemia and diabetes mellitus are indicated. Therapy for insulin resistance without overt glucose abnormalities may confer a cardiovascular benefit on such patients, but this remains investigational at the current time. Elucidation of the mechanisms by which HIV infection or HIV-related treatment strategies increase insulin resistance in this population may suggest novel therapies to improve insulin sensitivity in patients with HIV infection or in noninfected subjects at risk for complications of insulin resistance. Furthermore, prospective studies of the risk factors for the development of fat redistribution and associated metabolic abnormalities are needed.

This study demonstrates a constellation of metabolic abnormalities, including hyperinsulinemia and dyslipidemia, suggestive of a significant insulin resistance syndrome among HIV-infected patients with fat redistribution. In comparison, cardiovascular risk parameters are not substantially increased in HIV-infected patients without clinical evidence of fat redistribution. Although affected patients have a significant increase in waist-to-hip ratio, the observed metabolic abnormalities persist after adjustment for increased waist-to-hip ratio in male patients, and to a lesser degree in female patients, and may result from loss of peripheral or subcutaneous fat. Diabetes mellitus and accelerated CVD may become important clinical problems for HIV-infected patients with fat redistribution and elevated cardiac risk factors.

#### Ethics statement

Ethics approval was not sought for this article.

#### Competing interests

The authors have declared that no competing interests exist.

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