Body-composition measurements as predictors of glucose and insulin abnormalities in HIV-positive men[1–3]

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ABSTRACT

Background: Fat redistribution and metabolic abnormalities are seen increasingly in HIV-positive patients. However, the degree to which abnormalities in fat distribution predict glucose and insulin concentrations in these patients remains unknown.

Objective: We determined how well measurements of fat distribution derived from anthropometry, dual-energy X-ray absorptiometry, and computed tomography predicted hyperinsulinemia in HIV-positive men.

Design: Body-composition data were analyzed in 41 HIV-positive men (21 with fat redistribution and 20 without) and 20 HIV-negative control subjects matched for age and body mass index (BMI). Multivariate modeling was performed to determine the effects of body composition on fasting insulin and insulin area under the curve (AUC) during standard glucose tolerance testing.

Results: WHR was superior to other body-composition measures in predicting fasting hyperinsulinemia and was a strong predictor of insulin AUC in HIV-positive men. Fasting insulin increased by 77.4 pmol/L for each 0.1-unit change in WHR (95% CI: 18.6, 136.1; $P = 0.011$), overall $r^2 = 0.415$ in a model also including age, BMI, and protease inhibitor use. Measures of intraabdominal and subcutaneous fat did not predict fasting hyperinsulinemia but were independent predictors of insulin AUC in multivariate modeling. The ratio of visceral to subcutaneous abdominal fat predicted the largest degree of variance in insulin AUC.

Conclusions: Fat redistribution contributes to hyperinsulinemia in HIV-positive men, independent of BMI and protease inhibitor use. WHR is an integrated index of body-composition changes and strongly predicts both fasting hyperinsulinemia and insulin AUC in HIV-positive men. *Am J Clin Nutr* 2002;76:460–5.

KEY WORDS HIV, insulin, lipodystrophy, visceral fat, waist-to-hip ratio, WHR, body composition, men

INTRODUCTION

Since the early description of HIV lipodystrophy in the early 1990s (1–3), fat redistribution has been increasingly recognized among HIV-positive patients treated with combination antiretroviral therapy. Fat redistribution is characterized by both excess abdominal visceral fat and reduced abdominal and peripheral subcutaneous fat in most patients (4). It remains unknown whether lipodystrophy encompasses a single syndrome of fat redistribution with phenotypic heterogeneity or multiple distinct subsyndromes.

Several different techniques are available to assess fat distribution and body composition in HIV-positive patients (5). Waist-to-hip ratio (WHR) can be determined by anthropometric measurement, relative trunk and extremity fat by dual-energy X-ray absorptiometry (DXA), and abdominal visceral and subcutaneous fat areas by computed tomography (CT) and magnetic resonance imaging (MRI). These techniques can be used to quantify fat distribution in different ways, ie, to determine segmental circumferences and relative fat redistribution (anthropometry), total body fat and relative body fat distribution (DXA), absolute fat areas and relative visceral and subcutaneous fat distribution (single-slice CT), and visceral and subcutaneous fat volumes (whole-body MRI). In HIV-negative patients, measures of abdominal visceral adiposity predict hyperinsulinemia (6, 7).

Hyperinsulinemia and insulin resistance have been well established among HIV-positive patients (4, 8–10). In a previous study, Mynarcik et al (11) showed decreasing insulin sensitivity, measured with a hyperinsulinemic clamp, in association with decreased extremity fat among HIV-positive patients with fat redistribution. Furthermore, we previously showed that fasting hyperinsulinemia is greatest in HIV-positive patients with combined abdominal hypertrophy and peripheral lipoatrophy on physical examination (4). However, the relative ability of various measures of fat redistribution to predict hyperinsulinemia has not been evaluated in this population.

SUBJECTS AND METHODS

Subjects

Body-composition data were analyzed from 41 previously studied HIV-positive men with ($n = 21$) and without ($n = 20$) evidence of fat redistribution. Twenty healthy, HIV-negative males matched for age and body mass index (BMI; in kg/m^2) served as an additional control group. The subjects were recruited between October 1999 and June 2000 through community-based advertisements.

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HIV status was confirmed by enzyme-linked immunosorbent assay and Western blots in all subjects. Subjects were characterized as having fat redistribution on the basis of a WHR ≥ 0.95 and confirmation by physical examination. Degree of fat deposition in the trunk and neck or fat atrophy in the extremities and face was objectively rated by a single investigator using a 0- to 2-point scale with 0.5-point increments. A score of 0 indicated that no discernible change in fat was present, and a score of 2 signified the presence of severe fat deposition, atrophy, or both. Subjects with an abnormal iliac WHR (for men, ≥0.95) and physical evidence of significant fat deposition in one or more areas were determined to have lipodystrophy (12). In contrast, HIV-positive subjects without fat redistribution were defined on the basis of a WHR < 0.95 and were without evidence of significant fat redistribution in any area on physical examination. The HIV-negative control subjects were in good health, were consuming no medications known to affect insulin resistance, and had a WHR < 0.95. All subjects receiving testosterone, growth hormone, anabolic hormones, glucocorticoid, antidiabetic agents, or megestrol acetate were excluded.

Subjects with known diabetes mellitus, with a hemoglobin concentration < 90 g/L, age > 60 or < 18 y, or with BMI < 20 were also excluded. HIV-positive subjects were excluded if they had changed their antiretroviral medications within the 6 wk before the study. Four persons of 95 screened for the study were excluded on the basis of a BMI < 20, none of whom had a WHR > 0.95. Metabolic data, including growth hormone and insulin concentrations, body composition, and bone density were previously reported on these subjects (12, 13). Written, informed consent was obtained from each subject before testing in accordance with the guidelines of the Committee on the Use of Humans as Experimental Subjects of the Massachusetts Institute of Technology and the Subcommittee on Human Studies at the Massachusetts General Hospital.

Study design

We retrospectively analyzed data from a previous study on growth hormone pulsatility in HIV-positive patients (12). Although the body-composition and metabolic data on the study subjects were published, the relative contribution of fat distribution to abnormalities in glucose and insulin were not previously analyzed in these patients. We chose this data set to analyze because the subjects were well characterized with the use of 3 different body-composition techniques that are increasingly used to determine fat distribution in HIV-positive patients and measures of glucose homeostasis were performed. To our knowledge, a similar analysis on a well-characterized cohort of HIV-positive patients has not been performed.

In our previous study we showed that waist circumference, WHR, trunk fat, and visceral fat were increased in the subjects with fat redistribution compared with the HIV-positive subjects without fat redistribution and the control subjects. Extremity fat and subcutaneous abdominal fat were decreased in the subjects with fat redistribution compared with the HIV-positive subjects without fat redistribution and the healthy control subjects. In contrast, total body fat was not different between the groups. Fasting hyperinsulinemia and insulin area under the curve (AUC) were also elevated in the HIV-positive subjects with fat redistribution compared with the other groups (12). In the comparison of all HIV-positive patients with control subjects, the WHR, fasting insulin concentration, and glucose AUC were increased and extremity fat and subcutaneous fat were decreased (**Table 1**).

Hormonal, biochemical, and immunologic assessment

After a 12-h overnight fast, the subjects underwent a standard 75-g oral glucose tolerance test at 0800, with insulin and glucose

TABLE 1
Group comparison of HIV-positive and control subjects[1]

	All HIV-positive subjects (n = 41)	Healthy control subjects (n = 20)
Age and disease status		
Age (y)	43 (38, 48)	43 (37, 49)
$CD4^+$ T cells (no./mm^3)	341 (154, 506)	NA
Viral load (copies/mL)	280 (50, 20800)	NA
Duration of HIV (y)	8 (5, 9)	NA
Number of patients currently using protease inhibitors	29	NA
Duration of protease inhibitor use (mo)	28.5 (2.3, 36)	NA
Duration of combination antiretroviral therapy (mo)	31 (5, 36)	NA
Body composition		
BMI (kg/m^2)	24.4 (22.6, 26.6)	24.8 (22.7, 26.1)
Waist circumference (cm)	92.1 (86.4, 94.7)	91.5 (84.8, 97.1)
Waist-to-hip ratio	0.95 (0.91, 0.99)[2]	0.92 (0.86, 0.95)
Total body fat by DXA (kg)	14.1 (11.5, 18.8)	16.7 (13.4, 19.4)
Trunk fat (kg)	7.5 (5.2, 10.0)	7.8 (6.1, 9.9)
Extremity fat (kg)	5.9 (3.9, 7.5)[3]	7.2 (6.0, 8.6)
Subcutaneous fat measured by CT (mm^2)	11764 (8882, 18277)[3]	15936 (12395, 23523)
Intraabdominal fat measured by CT (mm^2)	11476 (6988, 17324)	8803 (6165, 11623)
Measures of glucose homeostasis		
HbA_{1c} (%)	5.5 (5.2, 5.7)	5.3 (5.1, 5.5)
Fasting glucose (mmol/L)	5.22 (4.77, 5.38)	5.05 (4.77, 5.27)
OGTT glucose response, AUC (mmol/L)	959.87 (833.55, 1077.87)[3]	798.81 (729.27, 918.47)
Fasting insulin (pmol/L)	66 (55, 110)[2]	54 (46, 59)
OGTT insulin response, AUC (pmol/L)	38135 (26481, 59394)	32975 (24363, 42990)

[1] Values are medians; interquartile range in parentheses. NA, not applicable; DXA, dual-energy X-ray absorptiometry; CT, computed tomography; HbA_{1c}, glycated hemoglobin; OGTT, oral-glucose-tolerance test; AUC, area under the curve.
[2,3] Significantly different from healthy control subjects (Wilcoxon's rank-sum test): [2] $P < 0.01$, [3] $P < 0.05$.

concentrations measured at 0, 30, 60, 90, and 120 min. Fasting glycated hemoglobin (Hb A_{1c}) concentrations, $CD4^+$ count, and viral load were also determined. Current use and duration of antiretroviral therapy were determined.

Body-composition analysis

Weight was determined after the subjects fasted 12 h overnight. Anthropometric measurements were obtained by the Bionutrition Staff of the Massachusetts General Hospital General Clinical Research Center while the subjects were undressed. All measurements were obtained in triplicate and then averaged. WHR was calculated from the waist circumference measured at the iliac crest divided by the hip circumference measured at the horizontal level of maximum extension of the buttocks (14). Total body fat, fat-free mass, and trunk and extremity fat were determined by DXA with a Hologic-4000 densitometer (Hologic, Inc, Waltham, MA). Regions of interest were standardized (1995 Users Guide, Hologic, Inc). Extremity fat represented the arithmetic sum of the fat found in each arm and leg. The technique has a precision error of 3% for fat and 1.5% for fat-free mass (15). Cross-sectional abdominal CT scanning was performed as previously described to assess subcutaneous and visceral abdominal fat areas. A lateral scout image was obtained to identify the level of the L4 pedicle, which served as a landmark for the single-slice image (16).

Laboratory methods

Insulin was assessed by radioimmunoassay (Diagnostics Products Corporation, Los Angeles) with an intraassay CV of 4.7–7.7%. $CD4^+$ cell counts, viral load, glucose, and Hb A_{1c} concentrations were determined by previously published methods (17).

Statistical analysis

Variables were compared between the groups with the use of Wilcoxon's rank-sum test. Results are given as medians and interquartile ranges (Table 1). The independent contributions of WHR, DXA-derived trunk and extremity fat, and CT-derived abdominal visceral and subcutaneous fat were determined in separate multivariate regression models including all HIV-positive subjects, controlling for age, BMI, and current protease inhibitor (PI) use, in which the dependent *Y* variables were fasting insulin, insulin AUC, fasting glucose, and glucose AUC. This design was chosen because there were strong interrelations between WHR and intraabdominal fat as well as between WHR and trunk fat and between WHR and the ratio of trunk to extremity fat in univariate regression analyses among the HIV-positive men (*see* Results). Nonnormally distributed data were log transformed. The log-transformed ratios were also tested in the multivariate models. We also tested for interactions between lipodystrophy categorization and WHR, visceral fat, and trunk fat in the multivariate modeling. Repeat multivariate regression analyses were performed in the subgroup of patients with fat redistribution and among the healthy control subjects. The statistical analyses used JMP STATISTICAL DATABASE SOFTWARE (SAS Institute, Cary, NC). Statistical significance was defined as $P < 0.05$.

RESULTS

Interrelation of body-composition indexes in univariate regression analyses

Among all HIV-positive men ($n = 41$), WHR was significantly associated with intraabdominal fat measured by CT ($r = 0.7289$, $P < 0.0001$), trunk fat measured by DXA ($r = 0.387$, $P = 0.012$), and ratio of trunk fat to extremity fat measured by DXA ($r = 0.6844$, $P < 0.0001$).

Relation of body-composition indexes to fasting hyperinsulinemia

Multivariate regression analyses were performed to predict fasting insulin concentrations among all HIV-positive male subjects (**Table 2**). Independent models were constructed; all included age, BMI, and PI use but differed from one another by substituting WHR, trunk and extremity fat determined by DXA, or intraabdominal and subcutaneous fat determined by CT as measures of body fat distribution. WHR was the only body-composition measurement from these models other than BMI to independently predict fasting insulin concentrations. Substitution of extremity fat determined by skinfold thicknesses for extremity fat measured by DXA or subcutaneous fat measured by CT did not alter the results. WHR and BMI were not significantly correlated ($r = 0.157$, $P = 0.32$), and consideration of WHR in addition to BMI significantly improved the overall predictiveness of our modeling for the determination of fasting hyperinsulinemia (overall $r^2 = 0.288$ for the model including age, BMI, and PI use compared with $r^2 = 0.415$ for the model including age, BMI, PI use, and WHR). In the multivariate model including age, BMI, PI use, and WHR, fasting insulin increased 18.8 pmol/L for each 1.0-unit increase in BMI (95% CI: 7.6, 29.9; $P = 0.002$) and 77.4 pmol/L for each 0.1-unit change in WHR (95% CI: 18.6, 136.1; $P = 0.011$), $r^2 = 0.415$ for the model. Fasting insulin therefore increased ≈46.5 pmol/L for each 10% increase in BMI and 73.6 pmol/L for each 10% increase in WHR among the HIV-positive patients we studied, in a model controlling simultaneously for the effects of age, BMI, PI use, and WHR. The ratio of intraabdominal fat to subcutaneous fat and the ratio of trunk fat to extremity fat were not statistically significant as predictors of fasting insulin in the multivariate models (**Table 3**). Substitution of extremity fat determined by skinfold thicknesses for extremity fat measured by DXA or subcutaneous fat measured by CT into the above ratios did not alter the results. Furthermore, substituting months of PI use for current PI use in the analysis did not alter the results in any of the 3 multivariate models shown in Table 2 (data not shown). The relation of lipodystrophy status to insulin or insulin AUC was not significant in the multivariate regression models (data not shown). There was an interaction between lipodystrophy status and WHR because lipodystrophy status was in part defined on the basis of WHR. Substitution of the log-transformed ratios of trunk to extremity fat and visceral to subcutaneous fat did not alter the results of the multivariate models (data not shown).

Identical multivariate regression models to predict fasting glucose concentrations and glucose AUC did not show any significant independent associations with WHR, trunk and extremity fat measured by DXA, or intraabdominal and subcutaneous fat measured by CT.

In a subanalysis limited to the subset of HIV-positive men with fat redistribution, WHR (estimate: 965.0 pmol/L; 95% CI: 436.7, 1493.3; $P = 0.002$) remained a highly significant independent predictor of fasting hyperinsulinemia in a model controlling for age (estimate: 0.5 pmol/L; 95% CI: −3.9, 4.9; $P = 0.797$), BMI (estimate: 24.9 pmol/L; 95% CI: 17.8, 32.0; $P < 0.0001$), and PI use (estimate: 35.9 pmol/L; 95% CI: 37.0, 108.8; $P = 0.307$), with the model accounting for 89% of the variability in fasting insulin. In contrast, determinations of fat by DXA or CT scan were not significantly predictive of fasting hyperinsulinemia in this subanalysis (data not shown).

TABLE 2
Multivariate models to predict fasting insulin concentration and insulin area under the curve (AUC) in HIV-positive men[1]

Variable	Fasting insulin model			Insulin AUC model		
	Estimate	95% CI	*P*	Estimate	95% CI	*P*
	pmol/L			*pmol/L*		
Model 1[2]						
Age (y)	−4.9	(−10.4, 0.7)	0.097	1020.2	(−1698.7, 3739.2)	0.451
BMI (kg/m^2)	18.8	(7.6, 29.9)	0.002	8974.3	(3694.7, 14253.2)	0.002
WHR[3]	773.7	(186.1, 1361.2)	0.011	409145.9	(130622.3, 687671.0)	0.005
PI use[4]	−73.6	(−143.1, −4.9)	0.037	−4739.3	(−37546.1, 28068.2)	0.771
Model 2[5]						
Age (y)	−1.4	(−6.9, 4.2)	0.563	2153.6	(−261.1, 4568.4)	0.079
BMI (kg/m^2)	22.2	(5.6, 39.6)	0.012	14920.0	(7633.2, 22206.6)	0.0002
Trunk fat measured by DXA (g)	0.007	(−0.007, 0.02)	0.468	2.1	(−3.5, 8.3)	0.436
Extremity fat measured by DXA (g)	−0.007	(−0.03, 0.01)	0.325	−13.9	(−22.9, −4.9)	0.003
PI use[4]	−61.1	(−144.5, 22.2)	0.146	−16388.1	(−52127.1, 19350.9)	0.357
Model 3[6]						
Age (y)	−2.8	(−8.3, 3.5)	0.385	1297.3	(−1284.1, 3878.8)	0.314
BMI (kg/m^2)	16.0	(−0.1, 32.6)	0.052	12437.8	(5340.0, 19535.6)	0.001
Intraabdominal fat measured by CT (mm^2)	0.007	(−0.001, 0.01)	0.139	3.5	(0.7, 6.9)	0.015
Subcutaneous fat measured by CT (mm^2)	0.001	(−0.007, 0.007)	0.902	−4.2	(−7.6, −0.7)	0.019
PI use[4]	−49.3	(−125.0, 25.7)	0.190	−7479.8	(−40106.7, 25147.2)	0.644

[1] All HIV-positive men (n = 41), with and without fat redistribution, were included in the models. WHR, waist-to-hip ratio; PI, protease inhibitor; DXA, dual-energy X-ray absorptiometry; CT, computed tomography.
[2] r^2 = 0.415 for the fasting insulin model and 0.524 for the insulin AUC model.
[3] Estimate refers to a change of 773.7 pmol/L in insulin concentration for a 1.0-unit change in WHR. The equivalent change in insulin concentration for a 0.1-unit change in WHR would be 77.4 pmol/L.
[4] Treated as a dichotomous variable (0 = no PI use, 1 = PI use).
[5] r^2 = 0.314 for the fasting insulin model and 0.542 for the insulin AUC model.
[6] r^2 = 0.338 for the fasting insulin model and 0.552 for the insulin AUC model.

Among the healthy control subjects, BMI (estimate: 5.5 pmol/L; 95% CI: 0.06, 11.0; P = 0.048) but not WHR (estimate: −39.1 pmol/L; 95% CI: −337.9, 259.7; P = 0.785) was a significant predictor of fasting insulin value in a multivariate regression model. Neither fat distribution measured by DXA nor intraabdominal fat area measured by CT scan was an independent predictor of fasting insulin concentrations (data not shown).

Relation of body-composition indexes to insulin AUC responses to an oral glucose tolerance test

Multivariate regression analyses were performed to predict insulin AUC in all HIV-positive male subjects (Table 2). Independent models were constructed; all included age, BMI, and PI use but differed from one another by substituting WHR, trunk and extremity fat determined by DXA, or intraabdominal and subcutaneous fat determined by CT as measures of body fat distribution. WHR, extremity fat measured by DXA, and intraabdominal and subcutaneous fat measured by CT were all significant independent predictors of insulin AUC in their respective models (Table 2). Insulin AUC increased 4368 pmol/L (≈7.3%) for every 10% increase in visceral fat area and increased 5202 pmol/L (≈8.7%) for every 10% decrease in subcutaneous abdominal fat area. The ratios of intraabdominal to subcutaneous fat and trunk to extremity fat were highly significant predictors of insulin AUC in multivariate modeling (Table 3). Sixty-two percent of the variability in insulin AUC was explained in a model controlling for the ratio of abdominal to subcutaneous fat, age, BMI, and PI use. In a subanalysis limited to the HIV-positive patients with fat redistribution, a similar strong predictive effect of increased abdominal visceral fat and decreased subcutaneous fat on insulin AUC was seen (data not shown).

DISCUSSION

Our data show that fat redistribution contributes significantly to abnormal insulin dynamics in HIV-positive men in the era of combination antiretroviral therapy. WHR, but not the ratios of more specific measures of trunk to extremity fat or visceral to abdominal subcutaneous fat, significantly predicted fasting hyperinsulinemia independent of BMI and PI use. In contrast, WHR and the ratios of trunk to extremity fat and visceral to subcutaneous fat were strong predictors of insulin AUC response to glucose tolerance testing. Our study therefore suggests that basic information on age, BMI, WHR, and antiretroviral use predict a great degree of the variability in fasting insulin among HIV-positive men, suggesting a useful schema for the assessment and prediction of metabolic abnormalities in such patients.

Numerous studies show significant insulin resistance in HIV-positive patients with fat redistribution (11, 18, 19). Similarly, the subjects in the present study with clinical evidence of fat redistribution had significant fasting hyperinsulinemia despite normal fasting glucose and a normal Hb A_{1c} concentration, consistent with insulin resistance. Fasting hyperinsulinemia is a reasonable surrogate index for insulin resistance in epidemiologic studies and was shown to contribute independently to cardiovascular disease in HIV-negative patients (20, 21).

The specific mechanisms for hyperinsulinemia in HIV-positive patients are not known and may relate to both drug and nondrug

TABLE 3
Multivariate models using ratios of fat redistribution to predict fasting insulin concentration and insulin area under the curve (AUC) in HIV-positive men[1]

Variable	Fasting insulin model			Insulin AUC model		
	Estimate	95% CI	*P*	Estimate	95% CI	*P*
	pmol/L			*pmol/L*		
Model 1[2]						
Age (y)	−2.8	(−8.3, 2.8)	0.318	1659.9	(−967.4, 4287.1)	0.208
BMI (kg/m^2)	22.2	(10.4, 33.3)	0.0005	10660.6	(5310.8, 16010.3)	0.0003
Trunk fat:extremity fat measured by DXA	58.3	(−10.4, 126.4)	0.093	40231.7	(8679.2, 71784.2)	0.014
PI use[3]	−70.8	(−148.6, 6.3)	0.071	−8555.5	(−44245.2, 27134.1)	0.629
Model 2[4]						
Age (y)	−2.1	(−7.6, 3.5)	0.425	1380.0	(−777.8, 3537.8)	0.202
BMI (kg/m^2)	22.9	(11.1, 34.7)	0.0004	11688.4	(7015.1, 16361.0)	<0.0001
Intraabdominal fat:subcutaneous fat measured by CT	24.3	(−6.9, 55.6)	0.120	27154.3	(14767.8, 39540.7)	<0.0001
PI use[3]	−53.5	(−124.3, 16.7)	0.131	−2538.4	(−30532.3, 25454.8)	0.855

[1] All HIV-positive men (n = 41), with and without fat redistribution, were included in the models. DXA, dual-energy X-ray absorptiometry; PI, protease inhibitor; CT, computed tomography.
[2] r^2 = 0.347 for the fasting insulin model and 0.497 for the insulin AUC model.
[3] Treated as a dichotomous variable (0 = no PI use, 1 = PI use).
[4] r^2 = 0.339 for the fasting insulin model and 0.622 for the insulin AUC model.

factors; they may include use of PIs, increases in fatty acids, cytokine abnormalities associated with HIV disease, and immune recovery and refeeding (9, 22, 23). PIs have been associated with disturbances in glucose (24, 25) and have been shown to have direct effects on insulin resistance in vivo (25). Importantly, as shown in HIV-negative patients, fat redistribution itself may contribute to the metabolic abnormalities, including hyperinsulinemia, in HIV-positive patients.

Several methods of measuring body composition are available to assess fat distribution and to determine accurately the amount of visceral and subcutaneous fat in HIV-positive patients (23, 26–30). These techniques differ significantly in cost and complexity. Anthropometric assessment is a noninvasive, easy-to-perform technique. In contrast, DXA and CT require more sophisticated equipment and exposure to radiation, at far greater cost. Although increased WHR is a feature of the lipodystrophy syndrome, previous studies did not quantify the relation of WHR to hyperinsulinemia in HIV-positive patients nor determine the ability of WHR to predict hyperinsulinemia compared with other, more complex techniques of body-composition measurement.

WHR was a strong predictor of fasting hyperinsulinemia and insulin AUC response to glucose tolerance testing in the present study. Our data showed a highly significant relation between WHR and fasting hyperinsulinemia, such that fasting insulin increased by 77.4 pmol/L for each 0.1-unit increase in WHR, controlling for age, BMI, and PI use. The strength of the association between WHR and insulin in this model underscores the relation between fasting hyperinsulinemia and changes in body composition in HIV-positive patients. Among the subjects with fat redistribution, our model, including age, BMI, WHR, and PI use, explained 89% of the variance in fasting insulin. Our data suggest that the degree of body fat redistribution, in addition to weight itself, is a critical determinant of the metabolic abnormalities in such persons.

WHR is an integrated index of body composition that takes into account increased waist circumference (increased visceral fat) and reduced hip circumference (decreased subcutaneous fat). Unlike in other populations with simple obesity, WHR and BMI did not correlate in our study, and subjects with lipodystophy had increased visceral fat and reduced subcutaneous fat, in contradistinction to the increased subcutaneous abdominal fat seen in obesity (12). Increased visceral fat and decreased subcutaneous fat have been shown to be associated with hyperinsulinemia in other populations of healthy control subjects and patients with congenital lipodystrophy and fat atrophy (31). Mynarcik et al (11) previously showed that loss of extremity subcutaneous fat was associated with insulin resistance in HIV-positive patients with fat redistribution. In contrast, we showed that a ratio of increased visceral fat and reduced subcutaneous fat strongly predicted abnormal insulin dynamics in HIV-positive men, with the use of surrogate markers for insulin resistance. Assessment of WHR may be of particular use in HIV-positive patients as a simple integrated index of excess visceral adiposity and reduced subcutaneous fat. Taken together, these data highlight the contribution of fat distribution per se to insulin concentrations in HIV-positive patients, independent of BMI.

Numerous large epidemiologic studies show an association between increased WHR and cardiovascular disease risk in HIV-negative subjects. Terry et al (32) showed that WHR was an independent predictor of premature cardiovascular disease in a longitudinal study controlling for BMI. Saito et al (33) showed that WHR was an independent predictor of coronary artery disease events in diabetic patients. Further studies are required to determine the relation between increased WHR and cardiovascular disease risk in HIV-positive patients.

The design of the present study has several advantages. The multivariate regression analysis we performed was not dependent on the definition of fat redistribution. Rather, we compared the predictive strength of body-composition measures for insulin across a range of fat distribution. Furthermore, we did not limit our analysis to affected men but investigated the relations among all HIV-positive subjects with and without fat redistribution. Therefore, our results can be generalized to the larger population of HIV-positive men, with and without fat redistribution, independent of the definition of fat redistribution. Further studies in a greater number of patients will be necessary to confirm these results.

Data from this study were limited to men, and important sex differences may exist in the metabolic profile of patients with HIV infection. Further studies of the relation between change in body-composition and insulin concentrations in HIV-positive patients

are necessary because it is possible that insulin resistance contributes to changes in body composition as well. In addition, we did not use whole-body MRI, which provides information on overall abdominal visceral and subcutaneous fat volume. Whole-body MRI may be more sensitive in predicting fasting hyperinsulinemia than are the techniques we used.

Our data suggest that fat distribution contributes significantly to hyperinsulinemia in HIV-positive patients. WHR is an easy and cost-effective, office-based measure of fat distribution that strongly predicts both fasting hyperinsulinemia and insulin AUC in HIV-positive men with and without fat redistribution when age, BMI, and PI use are controlled for. Information on BMI and WHR should be considered when HIV-positive men are screened to determine which patients are most likely to have hyperinsulinemia. Future therapies aimed at reversing the abnormal distribution of fat in HIV-positive patients may improve the hyperinsulinemia found in this population.

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