Serum Adiponectin and Leptin Concentrations in HIV-Infected Children with Fat Redistribution Syndrome

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ABSTRACT: Human immunodeficiency virus (HIV)-related lipodystrophy is characterized by adipose tissue redistribution, dyslipidemia, and insulin resistance. We hypothesized that fat redistribution and metabolic abnormalities in HIV-infected children are related to alterations in endocrine function of adipose tissue. A multicenter study was conducted in 130 HIV-infected children. Lipodystrophy definition was based on the central to peripheral skinfold ratio. Fasting adiponectin, leptin, insulin concentrations, glycemia, and lipid profile were measured in all children. Fat redistribution syndrome was apparent in 32 children: 14 with atrophic (LPDA) and 18 with hypertrophic lipodystrophy (LPDH). Mean serum adiponectin levels were significantly decreased in LPDA and LPDH groups compared with the group with no lipodystrophy (LPD-). Fasting insulin concentration was significantly higher in LPDA and LPDH groups *versus* LPD-. Mean serum leptin concentration was significantly increased only in LPDH compared with LPDA and LPD- groups. Triglyceride levels were significantly increased and high-density lipoprotein (HDL)-cholesterol concentration decreased in the LPDA *versus* LPD- group. Controlling for puberty stage, gender, percentage of total fat mass, serum lipids, HIV treatment, and disease severity, adiponectin was significantly and inversely associated with central obesity and insulin/glucose ratio. Fat redistribution had no significant effect on leptin concentration, which was directly related to the percentage of body fat, female gender, and insulin/glucose ratio. In conclusion, HIV-infected children with symptoms of fat redistribution have decreased levels of adiponectin, associated with insulin resistance and dyslipidemia. (*Pediatr Res* 60: 225–230, 2006)

HIV-infected individuals, and especially those receiving a highly active antiretroviral therapy (HAART), frequently develop a fat redistribution syndrome, also called lipodystrophy, characterized by central fat accumulation or peripheral fat wasting or a combination of both. Lipodystrophy has been first described in adults but has also been reported in children (1–5). The frequency of children presenting with lipodystrophy is variable (10–33%) in the series of patients under study. Similar to other congenital forms of

lipodystrophies, HIV lipodystrophy has been shown to be associated with dyslipidemia and insulin resistance (1,3,6). These metabolic alterations are probably, at least in part, secondary to fat redistribution but could also result from drug toxicity (4,7) and can be influenced by individual susceptibility; the role of the virus itself has also been suggested (8). Protease inhibitors (PIs) have been reported to favor insulin resistance and hypertriglyceridemia (9), but the prevalence and severity of altered fat distribution are increased in patients treated with both PIs and nucleoside reverse-transcriptase inhibitor (NRTI) (10).

Adipose tissue, in addition to its lipid storage function, is an active endocrine tissue and a major determinant of insulin sensitivity, modulating glucose and lipid metabolism through the secretion of adipocytokines (11). Two of these, adiponectin and leptin, have been shown to be involved in the regulation of insulin sensitivity. In non-HIV linked human generalized lipodystrophies, leptin levels are markedly reduced and are thought to contribute to altered insulin action, which is corrected by exogenous leptin administration (12,13). Accordingly, low circulating levels of adiponectin have been linked to several components of the metabolic syndrome, including intraabdominal fat distribution, hyperlipidemia, low HDL-cholesterol levels, and insulin resistance in congenital and HIV-associated forms of lipodystrophies in adults (14–18). In obese adolescents, a direct correlation of body mass index (BMI) with serum leptin and a negative one with serum adiponectin is reported (19–22). However, the associations of lipodystrophy with hormonal disturbances are still poorly known in the HIV-infected pediatric population. We previously reported a prevalence of lipodystrophies in 25% of HIV-infected children, and 43% of these children had at least one of the components of metabolic disturbances (insulin resistance, high total cholesterol, low HDL-cholesterol levels, or hypertriglyceridemia) (23). Therefore, we hypothesized that the alterations of adipocytokine secretion by adipose

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Abbreviations: HAART, highly active antiretroviral therapy; LPD-, no lipodystrophy; LPDA, atrophic lipodystrophy; LPDH, hypertrophic lipodystrophy; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PIs, protease inhibitors

tissue could be detectable already in childhood in HIV-infected patients receiving HAART and could be related to lipodystrophy and metabolic abnormalities. For that purpose, serum adipocytokines secretion was assessed in relation to fat redistribution syndrome and metabolic parameters in 130 HIV-infected children in a multicenter study.

PATIENTS AND METHODS

Patients. Patients were included from December 2000 to April 2002 in the Clinical Immunology Departments of three university children's hospitals in Paris. Eligibility criteria were proven HIV infection, age 2–18 y, and not receiving treatment for any other chronic disease. Exclusion criteria were severe clinical illness in the weeks before the observation and administration of steroids.

A total of 130 children were included after informed parental consent. The study protocol was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale (CCPPRB) Paris/St.-Louis (Paris, France). Consents from the children were also obtained whenever possible.

Protocol. The children were evaluated at the time of an outpatient medical visit. All patients were seen by the same investigator in each center.

Puberty was rated using Tanner stages (24). To describe adiposity and fat distribution, three parameters were used: BMI, fat mass percentage and skinfold thickness. BMI was expressed as a Z score according to reference values established in French children (25).

The percentage of body fat mass was measured using bioelectrical impedance technique at 50 kHz and standard electrode positions (RJL Systems, Clinton Township, NJ), and calculated using the equation by Schwenk *et al.* (26) in children. An independent investigator blinded to the children's treatment performed the evaluation of fat distribution. Skinfold thicknesses (biceps, triceps, suprailiac, and subscapular) were measured twice by a Harpenden skinfold caliper (Chambly-Medical, Chambly, France) at 5-min intervals in each site. Subsequently, two individual values for each site were averaged, and the results were expressed as a Z score of the normal distribution for gender and age according to the French growth standard curve (27). Central-to-peripheral skinfold ratio was calculated as the ratio of (subscapular skinfold + suprailiac skinfold) to (biceps skinfold + triceps skinfold) and expressed as a Z score.

Serum samples were collected after a 10-h fast for the measurements of total cholesterol, HDL-cholesterol, triglycerides, adiponectin, leptin, insulin concentrations, and glycemia.

Antiretroviral treatment (medication and dose) was recorded from the medical charts of the children from 4 y before inclusion onward. This time lag covers the whole period of prescription of PIs widely used since 1996, but not the period of prescription for all antiretroviral drugs in the study population; indeed, in the majority of children, treatment had been initiated for much longer than 4 y.

Nadir values of the CD4 T lymphocyte percentage and highest plasma HIV RNA were recorded from the medical chart and current values were measured at the time of observations.

Severity of the disease was classified according to the Centers for Disease Control and Prevention revised pediatric classification identifying classes of severity (N: less severe; A, B, C: more severe) (28).

Definition of lipodystrophy. The definition of lipodystrophy was based on skinfold thickness measurements. Values of each skinfold were transformed into Z scores for gender and age.

Hypertrophic lipodystrophy was defined as accumulation of fat in the truncal region: at least one abnormal central skinfold measurement (>3 SD for age and gender) together with an increased ratio of central/peripheral skinfolds (>3 SD) with no major evidence of obesity (BMI <3 SD).

Atrophic lipodystrophy was defined as loss of subcutaneous adipose tissue in extremities and periphery; it was defined as sunken cheeks and/or any thin peripheral skinfold (<-3 SD) with BMI in the normal range (between -2 SD and $+2$ SD) to exclude "wasting syndrome."

Analytical methods. Glucose, cholesterol, HDL-cholesterol, and triglycerides were measured by automated enzymatic methods.

Serum insulin concentrations were measured using an immunoradiometric method Bi-Insulin IRMA (Cisbio International, Gif sur Yvette, France). Cross-reactivity with intact proinsulin and 31–32 proinsulin was $<1\%$. The detection limit was 0.5 mIU/L and the interassay coefficient of variation (CV) was $<8\%$. Serum adiponectin and leptin concentrations were determined using radioimmunoassay kits (Linco Research, St. Charles, MO). The detection limit of the leptin assay was 0.5 ng/mL and the interassay CV was $<9\%$. The detection limit of the adiponectin assay was 1 ng/mL and the interassay CV was $<11\%$.

Statistical analyses. Data were analyzed with SAS 8.2 statistical package (SAS-Abacus, Meylan, France). The association between lipodystrophy status and quantitative variables were tested using a χ^2 test. Plasma insulin, adiponectin, and leptin values were log transformed before statistical analyses to normalize distribution.

Because most anthropometric variables and metabolic parameters vary with age, gender, and puberty, crude values have been translated into Z scores to allow statistical comparisons (29).

General linear model (GLM) analysis was used to perform statistical comparisons of anthropometric, disease severity, and metabolic and hormonal parameters between different groups of lipodystrophies with adjustment for age and gender where appropriate.

The relative influence of clinical and biologic parameters to the serum hormonal concentrations was assessed using multiple regression models on the whole cohort. A further GLM was performed to investigate the independent effect of lipodystrophy on serum insulin, adiponectin, and leptin concentrations.

A p value ≤ 0.05 was considered as statistically significant.

RESULTS

A total of 130 children (64 boys and 66 girls) with a median age of 10 y (range, 2–18 y) were included. Most children had acquired HIV infection through mother-to-child transmission. At the time of observation, 14 children did not receive any treatment, of whom five had never been previously treated. The remaining children were receiving various HAART regimens.

As estimated by clinical evaluation described above, 98 (75%) children were considered to have no lipodystrophy (LPD– group), and fat redistribution syndrome was apparent in 32 (25%) children: 14 with atrophic lipodystrophy (LPDA group) and 18 with hypertrophic lipodystrophy (LPDH group). There was no significant difference in HAART regimens between children with or without symptoms of fat redistribution (Table 1).

Patient's characteristics according to the status of fat redistribution. The characteristics of the study group by status of body fat redistribution are given in Table 2. Age at inclusion was similar between the three groups as was the gender ratio. Patients in LPDH group had significantly higher mean BMI and the percentage of body fat mass compared with the LPD– group. Mean skinfold ratio was considerably increased in both groups of lipodystrophies compared with the LPD– group. On the contrary, the percentage of body fat was comparable between the LPD– and LPDA groups. Mean

Table 1. HAART among children with (LPD+) and without (LPD–) lipodystrophy

	No treatment	PI only	NRTI only	PI+NRTI	PI+NRTI+NNRTI	NRTI+NNRTI
LPD– ($n = 98$)	11 (11.2)	0	13 (13.3)	41 (41.8)	15 (15.3)	18 (18.4)
LPD+ ($n = 32$)	3 (9.4)	1 (3.1)	8 (25)	11 (34.4)	4 (12.5)	5 (15.6)

Values are numbers (%) of patients per LPD group; $p = 0.13$ for distribution of treatment regimens between the two groups. NNRTI, nonnucleoside reverse-transcriptase inhibitor.

Table 2. Characteristics of anthropometric parameters and disease severity of the subjects by status of lipodystrophy

	LPD- (n = 98)	LPDA (n = 14)	LPDH (n = 18)
Auxology			
Age at inclusion, y	10.5 ± 4.3	11.3 ± 2.5	10.1 ± 3
Gender, M/F	51/47	7/7	6/12
Height, SDS	0.4 ± 1.6	-0.23 ± 1.4	0.7 ± 1.3
BMI, SDS	0.1 ± 1	-0.3 ± 1	1.8 ± 1.2*
Waist circumference, SDS	0.4 ± 1.1	0.4 ± 0.9	2.4 ± 2*
Skinfold ratio, SDS	1.7 ± 1.9	3.6 ± 3.5**	6.3 ± 3.4*
Percentage of body fat	19.1 ± 7.3	20.7 ± 8.3	23.8 ± 6.3†
Systolic BP, SDS	0.4 ± 1	0.07 ± 1	0.9 ± 1.1
Diastolic BP, SDS	-0.6 ± 0.9	-0.5 ± 0.6	-0.3 ± 1.1
Disease severity			
CD4 min, cells/m ³	454 ± 493	282 ± 318	528 ± 333
HIV RNA max, log copies/mL	5.5 ± 3.9	5.1 ± 0.9	4.7 ± 1
CD4 at examination, cells/m ³	796 ± 571	735 ± 345	922 ± 434
HIV RNA at examination, log copies/mL	2.5 ± 1.4	3.3 ± 1.5	2.6 ± 1.1
CDC symptoms classification			
N + A, no. (%)	81 (83)	14 (100)	15 (83)
B + C, no. (%)	17 (17)	0	3 (17)

Results are expressed as mean ± SD. Comparisons of LPDA and LPDH groups *versus* LPD- group were made after adjustment for age and gender, when appropriate.

* $p < 0.0001$; ** $p < 0.01$; † $p < 0.05$ *versus* LPD- group. M, male; F, female; BP, blood pressure; SDS, standard deviation score; CDC symptoms: evaluation of the severity of HIV infection following the Center for Diseases Control and Prevention guidelines.

skinfold ratio was considerably increased in both groups of lipodystrophies compared to LPD- group. There were no significant differences in the parameters of disease severity neither at presentation nor at the time of investigation between the two groups of lipodystrophies and the LPD- group. Fasting glycemia was within the normal range for the entire study population and very similar in all three patients' groups (4.4 ± 0.5 , 4.5 ± 0.7 , and 4.4 ± 0.5 mM in the LPD-, LPDA, and LPDH groups, respectively). Fasting insulin was significantly higher in the LPDA and LPDH groups compared with the LPD- group (4.6 ± 3.1 , 7.5 ± 6.4 , and 8.4 ± 7.5 mIU/L in the LPD-, LPDA, and LPDH groups, respectively; $p < 0.01$ between the LPDA and LPD- and $p < 0.0001$ between the LPDH and LPD- groups; Fig. 1). HDL-cholesterol was significantly lower and triglycerides higher in the LPDA group *versus* the LPD- group (HDL-cholesterol: 1.4 ± 0.4 , 1.0 ± 0.3 , and 1.4 ± 0.3 mM and triglycerides: 0.9 ± 0.7 , 1.6 ± 1.1 , and 1.1 ± 0.8 mM in the LPD-, LPDA, and LPDH groups, respectively, $p < 0.01$ between the LPDA and LPD-

groups; Fig. 1). In contrast, total cholesterol was similar in all three groups of children (4.4 ± 1.1 , 4.2 ± 1.0 , and 4.5 ± 1.3 mM, $p > 0.5$ in the LPD-, LPDA, and LPDH groups, respectively). Mean serum leptin concentration was significantly increased only in the LPDH compared with the LPD- group (4.0 ± 4.0 , 3.9 ± 3.0 , and 7.2 ± 4.4 ng/L in the LPD-, LPDA, and LPDH groups, respectively; $p < 0.01$ between the LPDH and LPD- groups). Mean serum adiponectin levels were significantly decreased in the LPDA and LPDH groups compared with LPD- group (17.2 ± 10 , 10.1 ± 4.2 , and 12.4 ± 7.1 in the LPD-, LPDA, and LPDH groups, respectively; $p < 0.01$ between the LPDA and LPD- groups and $p < 0.05$ between the LPDH and LPD- groups; Fig. 1).

Adiponectin, leptin concentrations, and the insulin/glucose ratio association with anthropometric, metabolic parameters, and disease severity. The correlation of adiponectin, leptin concentrations, and insulin/glucose ratio with anthropometric and metabolic parameters and disease severity at the time of examination is shown in Table 3. Adiponectin concentration was significantly and inversely associated with puberty stage according to Tanner, SD of skinfold ratio, but not with percentage of total body fat mass. An inverse correlation was observed between adiponectin and fasting insulin concentrations, as well as fasting insulin to glucose ratio (Fig. 2A). Adiponectin was directly related to HDL-cholesterol levels; however, this association was of borderline significance ($p = 0.07$). In contrast to adiponectin, leptin concentration, and insulin/glucose ratio were directly related to age, puberty stage, BMI, and percentage of body fat. Central obesity, reflected by skinfold ratio, was not significantly associated with leptin concentration, and its correlation with insulin/glucose ratio was of borderline significance. Interestingly, leptin concentration was significantly directly related to insulin/glucose ratio (Fig. 2B).

Figure 1. Fasting adiponectin, insulin, triglycerides and HDL-cholesterol concentrations (mean ± SE) in the LPD- (open columns), LPDA (shaded columns), and LPDH (filled columns) groups. ** $p < 0.01$; * $p < 0.05$ *vs* the LPD- group.

Table 3. Spearman correlation coefficients of adiponectin and leptin concentrations and the insulin/glucose ratio with anthropometric and metabolic parameters and disease severity

Variable	Adiponectin	Leptin	Insulin/glucose ratio
Age	-0.16†	0.20**	0.53*
Puberty stage Tanner	-0.19**	0.21**	0.43*
BMI	-0.08	0.68*	0.52*
Waist circumference	-0.03	0.54*	0.62*
Percentage of body fat	-0.13	0.59*	0.44*
Skinfold ratio	-0.34**	0.09	0.18**
Systolic BP	0.11	0.04	0.31**
Diastolic BP	0.07	0.002	0.24**
Fasting insulin/glucose ratio	-0.20**	0.47*	—
Leptin	-0.03	—	0.48*
Total cholesterol	0.009	0.08	0.17†
HDL-cholesterol	0.17†	-0.1	-0.14
Triglycerides	-0.04	0.07	0.42*
CD4	0.03	-0.1	-0.17†
HIV RNA	0.04	0.19**	-0.08

Adiponectin, leptin, and insulin/glucose ratio were log transformed before analysis to normalize distribution.

* $p < 0.0001$; ** $p < 0.05$; † $p < 0.1$.

Figure 2. (A) Relationship of adiponectin concentration with the insulin/glucose ratio by status of LPD. Solid regression line for lipodystrophy group (LPD+; ♦) and dashed regression line for no lipodystrophy group (LPD-; ○). Total group $r = -0.2$, $p = 0.035$; LPD+ group $r = -0.29$, $p = 0.1$; LPD- group $r = -0.1$, $p = 0.4$. (B) Relationship of leptin concentration with the insulin/glucose ratio by status of lipodystrophy. Solid regression line for lipodystrophy group (LPD+; ♦) and dashed regression line for no lipodystrophy group (LPD-; ○). Total group $r = 0.47$, $p < 0.0001$; LPD+ group $r = 0.46$, $p = 0.007$; LPD- group $r = 0.43$, $p < 0.0001$.

Determinants of serum adiponectin, leptin concentrations, and the insulin/glucose ratio. To evaluate whether the association of adiponectin and leptin with insulin resistance differs according to body fat redistribution, we performed a general linear model analysis, adjusting for puberty stage, gender, percentage of total fat mass, serum lipids, HIV treatment (with PI, NRTI, and NNRTI) and disease severity (CD4 and HIV RNA). No significant interaction was found between the status of lipodystrophy and insulin resistance on adiponectin and leptin concentrations. Therefore, the independent influence of anthropometric and metabolic parameters, disease severity and treatment to the concentrations of adiponectin, leptin and the insulin/glucose ratio was tested in a multiple linear regression models on the whole cohort (Table 4). Adiponectin was significantly and inversely associated with skinfold ratio and insulin/glucose ratio; its direct association with gender (females having higher levels of adiponectin) was of borderline significance. Skinfold ratio had no significant effect on leptin

Table 4. Determinants of adiponectin and leptin concentrations and insulin/glucose ratio in a multivariate stepwise regression model

Variables	Adiponectin		Leptin		Insulin/glucose	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>
Age	—	—	-0.14	0.049	0.53	<0.0001
Gender	0.18	0.069	0.29	0.0002	0.14	0.059
Percentage fat mass	—	—	0.62	<0.0001	—	—
Skinfold ratio	-0.25	0.01	—	—	—	—
Adiponectin	—	—	—	—	-0.15	0.039
Leptin	—	—	—	—	0.40	<0.0001
Insulin/glucose	-0.2	0.05	0.18	0.01	—	—
Total cholesterol	—	—	—	—	0.19	0.01
Triglycerides	—	—	—	—	0.11	0.1
NRTI treatment	—	—	—	—	0.11	0.1
HIV RNA	—	—	0.18	0.019	—	—
Model r^2	0.15		0.57		0.54	

Adiponectin, leptin, and insulin/glucose ratio were log transformed before analysis to normalize distribution. Values are adjusted correlation coefficients (r) with the level of significance (p).

concentration, which was strongly and positively related to percentage of body fat and to a lesser extend to female gender, insulin/glucose ratio, and HIV RNA. Insulin resistance, reflected by the insulin/glucose ratio, was significantly increased by age, female gender, leptin, total cholesterol concentrations, and NRTI treatment and decreased by adiponectin concentration. In all three models, HDL-cholesterol, treatment with PI and NNRTI, and CD4 count had no independent influence on adiponectin, leptin concentrations, and the insulin/glucose ratio.

DISCUSSION

Our study has demonstrated that fat redistribution syndrome in HIV-infected patients is already detectable in childhood. The assessment of lipodystrophy is hampered by a lack of uniform definition even in adult population. In children, it is further complicated by changing adiposity and body fat distribution with growth and puberty, and it may be difficult to distinguish between physiologic changes and signs of lipodystrophy by clinical observation only. Recently, a more objective and sensitive definition of lipodystrophy was reported with imaging measurement of fat mass in HIV-infected adults (30). However, the use of such method is limited in children because of lack of reference values for body fat compartments in the pediatric population. We therefore chose an assessment of fat mass distribution based on the measurement of central and peripheral skinfold thicknesses and their ratio, for which French reference values are available in healthy children, allowing each individual value to be quantified calculating a Z score.

Despite of some limitations of this study, such as a low prevalence of lipodystrophy in this particular patient group, we could demonstrate an obvious association of fat redistribution with hormonal and metabolic disturbances. Several previous studies on genetic or acquired lipodystrophies have shown a strong relationship between fat redistribution and insulin resistance (1,6,31,32). The results of our study confirm

these data, clearly showing that fasting insulin level as well as insulin/glucose ratio is increased in HIV-infected children with lipodystrophy compared with those without signs of fat redistribution. The mechanisms underlying this association are unclear. The implication of adipocytokines have been suggested by several previous studies (14–18). In this study, we have also shown that central fat distribution is associated with lower adiponectin concentration compared with HIV-infected children without lipodystrophy, suggesting that hypoadiponectinemia is associated with abnormal fat distribution rather than with the HIV infection itself. Of note, in both univariate and multivariate analyses, adiponectin concentration was strongly and inversely associated with the skinfold ratio, a marker of central adiposity, but not with total body fat mass. These findings are in line with data from other studies of adult HIV-infected patients, showing that adiponectin concentration was similar between healthy controls and HIV-infected subjects without evidence of fat redistribution, but significantly decreased in HIV-infected patients with signs of lipodystrophy, related to central adiposity but not to the degree of obesity (17).

Decreased adiponectin levels in our study were significantly associated with increased fasting insulin/glucose ratio, a marker of insulin resistance. This inverse association remained significant even after controlling for age and pubertal stages, known to considerably affect insulin sensitivity in children, as well as other confounding factors such as percentage of body fat, leptin, serum lipids, HIV treatment, and disease severity. It has been shown in previous studies that loss of limb fat in patients with and without HIV disease is associated with decreased sensitivity to insulin (32). However, in our study, in a multiple regression model, there was no independent association of the insulin/glucose ratio and skinfold ratio, suggesting that the association of the body fat distribution with insulin resistance is mediated through adiponectin action. As suggested by animal studies, adiponectin may act directly on the liver by lowering hepatic glucose production in mice (33) and enhancing the effect of insulin to decrease glucose production by isolated hepatocytes (34). Adiponectin administration reduces insulin resistance and improves glucose tolerance in mice with low adiponectin levels resulting from lipoatrophy or obesity-induced insulin resistance (34). Furthermore, low adiponectin concentrations in obese adolescents were associated with increased intramyocellular lipid deposition and impaired insulin action (19). Therefore, it appears that adiponectin can increase insulin action *via* direct effects on hepatic glucose production and by reducing ectopic fat deposition in liver and muscle *via* increased fat oxidation (31,35).

In addition to the regulation of insulin action, increasing arguments are in favor of an important physiologic role of adiponectin in lipid metabolism. Several previous studies have reported an inverse correlation of adiponectin concentration with triglycerides levels and other cardiovascular risk markers in both healthy and HIV-infected subjects (15,16,36,37). In our study, we could also show evidence of increased triglycerides and decreased HDL-cholesterol levels in children with atrophic lipodystrophy together with the lowest mean adi-

ponectin concentration, as compared with HIV-infected children without fat redistribution. However, in a multivariate model on the whole cohort, the association of adiponectin concentration with serum lipids was not significant, possibly indicating that frank metabolic abnormalities are still not present in this age group of HIV-infected patients or maybe because of the relatively small proportion of subjects with atrophic lipodystrophy in our cohort. On the other hand, as we have previously shown, dyslipidemia is found with a similar order of prevalence in both lipodystrophic and in nonlipodystrophic HIV-infected children (1), which could possibly influence the results of our multivariate analysis in the present study.

It was previously reported that leptin levels are reduced in HIV-infected patients even before the initiation of HAART and especially in subjects with signs of lipodystrophy (38,39). We could not confirm these data because in our study population, leptin levels were not decreased in children with fat redistribution syndrome, and in the hypertrophic lipodystrophy group, they were even significantly increased compared with children without lipodystrophy, as was the percentage of body fat mass. Our results are in accordance with data published by Vigouroux *et al.* (15), reporting comparable leptin levels in adult HIV-infected patients with and without lipodystrophy. In contrast to adiponectin, leptin concentration in our study was strongly associated with total body fat mass, but not with central adiposity, assessed by skinfold ratio, and directly related to the insulin/glucose ratio. The role of leptin in the modulation of insulin sensitivity is complex. Recent studies have shown that replacing leptin in lipoatrophic patients reduced insulin resistance and hyperlipidemia, but did not fully restore normal insulin sensitivity (34) and did not affect cardiovascular and metabolic parameters in lean volunteers (40). As in children and adolescents, leptin and insulin concentrations increase with age, and especially during puberty with increasing total body fat, it is more likely that leptin levels correlate directly with insulin resistance through its strong correlation with the amount of adipose tissue in this population.

In summary, in the present study, we have shown that HIV-infected children with symptoms of fat redistribution have decreased levels of adiponectin, associated with insulin resistance and dyslipidemia. Although our data do not establish a cause-and-effect relationship, they nevertheless suggest a potential therapeutic possibility of targeting the metabolic abnormalities associated with the syndrome of lipodystrophy in HIV-infected patients with agents capable of increasing serum adiponectin concentration, such as thiazolidinediones (41).

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