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Body Composition Changes and Predictors of Lipodystrophy in a Cohort of Pre-pubertal HIV- infected Children

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Authors' contributions

This work was carried out in collaboration among all authors. Author CZP designed the study, contributed to the generation, collection, analysis and/or interpretation of data, and wrote the first draft of the manuscript. Author RCMS designed the study, contributed to the analysis and/or interpretation of data. Author VLS designed the sudy, contributed to the analysis and/or interpretation of data. Author PFT contributed to the collection and analysis and/or interpretation of data. Author RVP contributed to the analysis and/or interpretation of data. Author AFTB contributed to the collection and analysis and/or interpretation of data. Author FLCO designed the study, contributed to the analysis and/or interpretation of data and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To evaluate body composition changes in HIV-infected patients and to identify the predictors of lipodystrophy over time.
Methods: A cohort study, evaluated over two and a half years (Time 1: T1; Time 2: T2), including prepubertal HIV-infected children of both genders, between 7-12 years of age. Patient's data such as transmission, use of prophylaxis for vertical HIV transmission, clinical and immunological classification of disease and current antiretroviral therapy were derived from the medical records. At T1, only subjects with pubertal stage 1 were included. Clinical, anthropometric, body composition and biochemical data were assessed. Patients were divided into two groups: with (LD+) and without lipodystrophy (LD-).
Results: A total of 40 patients were enrolled, and 35 patients completed the study. Mean (SD) age was 9.6 (1.1) and 11.6 (1.2) years at T1 and T2, respectively. At T2, 16 (45.7%) children remained prepubertal. LD+ group (n = 8) showed a higher prevalence of short stature (p = 0.008) in T1; higher insulin (p = 0.010) and HOMA-IR (p = 0.013) and reduction of triceps skinfold thickness (p = 0.026) at T2. In both times, we observed lower concentrations of HDLc (p = 0.027), higher values of trunk to arm ratio (p = 0.002, p = 0.001) and lower values of limb to trunk ratio (p = 0.001) and gynoid fat (p= 0.001) in LD+ group. At T1, predictors of lipodystrophy were short stature (OR = 46.198, p = 0.019) and limb to trunk ratio (OR = 0.00009, p = 0.011); in T2, waist circumference (OR = 1.199, p = 0.025) and HDLc (OR = 0.835, p = 0.015). Presence of lipodystrophy was determinant of high insulin levels at T2.
Conclusion: In a short period, LD+ group had significant changes in body fat distribution and also biochemical alterations associated to lipodystrophy syndrome.

Keywords: HIV; child; body composition; lipodystrophy.

CORE TIP

At baseline, prepubertal HIV-infected children with lipodystrophy presented clinical and metabolic changes compared to children without clinical signs of lipodystrophy, including short stature, lower concentrations of HDLc, higher values of trunk to arm ratio and lower values of limb to trunk ratio and also gynoid fat. In a short period of time, children with lipodystrophy continued to have more impairment of subcutaneous fat of the upper limb and greater accumulation of central adiposity, as well as higher levels of insulin and HOMA-IR values.

1. INTRODUCTION

Lipodystrophy, known as the abnormal distribution of fat, was first described in the classic study in HIV-infected adults by Carr et al. [1]. Moreover, it has also been early identified in the pediatric population [2]. Studies indicate that its prevalence increases due to age, time of exposure to antiretroviral drugs (ARV) and puberty [2,3]. The pediatric prevalence of this clinical condition varies from 8.4% in a study conducted in South Africa [4] to 53.3% in a Brazilian study [5]. Considering lipodystrophy's classification, lipohypertrophy seems to be more frequent in patients with higher exposure to antiretrovirals and in more advanced stages of pubertal development, whereas lipoatrophy is most commonly found in young children [3,6].

Recent studies concerning HIV-infected patients have described that several mechanisms may contribute to the complex genesis of lipodystrophy. Some classes of, such as nucleoside analogue reverse transcriptase (NRTI) and protease inhibitors (PI) are associated with the etiology of lipodystrophy. NRTIs inhibit mitochondrial DNA polymerase gamma (mtDNA), resulting in respiratory chain dysfunction and apoptosis of adipose tissue cells [7]. Moreover, mechanism of mtDNA dysfunction was also observed in the absence of ARV use, suggesting that this change may also be related to genetic susceptibility [8].

PI decreases the differentiation and increases the apoptosis of peripheral adipocytes [1]. Furthermore, PI acts directly on other lipogenic transcription factors and enzymes involved in lipid biosynthesis. As a result, the onset of dyslipidemia and insulin resistance is observed. Depletion of peripheral fat allied to metabolic alterations promotes fat accumulation in central and dorsal regions [1,9]. Metabolic abnormalities such as dyslipidemia and insulin resistance, combined with body fat redistribution (especially

visceral fat accumulation), characterizes the HIV lipodystrophy syndrome.

It is hypothesized that body changes are also related to alterations in endocrine function of adipose tissue, with increased levels of leptin and decreased adiponectin [10]. Due to infection, adipocytes stimulates proinflammatory cytokines secretion such as tumor necrosis factor (TNF-α), interleukin-6 (IL-6) and monocyte chemotactic protein-1 (MCP-1). In the presence of lipodystrophy, there are elevated inflammatory markers and endothelial dysfunction [11]. This association between clinical and metabolic complications, arising from cumulative exposure to ARVs and also to the virus infection itself, may lead to the premature development of risk factors for cardiovascular disease observed in adulthood [7,12,13].

Some studies have reported precocious body composition changes in HIV-infected children, even without typical clinical signs of lipodystrophy [14,15]. Periodic assessment of anthropometric and body composition measurements can be useful to aid in the early detection of clinical and metabolic abnormalities in these patients. This study aims to prospectively evaluate body composition changes and identify the clinical and metabolic variables determinants of lipodystrophy over time.

2. METHODS

2.1 Study Design and Sample

A prospective cohort study was conducted, including prepubertal HIV-infected children, of both sexes, between 7 and 12 years 11 months, attended at the Care Center of Pediatric Infectious Diseases (CEADIPe), Department of Pediatrics, Universidade Federal de São Paulo - UNIFESP. The research project was approved by the Ethics Committee/UNIFESP.

2.2 Methods

Patient's data, such as transmission, use of prophylaxis for vertical HIV transmission, clinical and immunological classification of disease [16], and current antiretroviral therapy was derived from medical records. Socioeconomic class were also assessed by a questionnaire [17]. These informations were used to characterize the sample.

At T1, after evaluation by pediatricians, only subjects with pubertal stage 1 were included [18]. At T2, pubertal outcome was reassessed.

The diagnosis of lipodystrophy was clinically performed by trained pediatricians that followed the patient routinely. In the presence of this clinical alteration, fat redistribution was classified as lipohypertrophy, lipoatrophy, or mixed type [2].

Measurements of weight and height were used to calculate z-score and classification of body mass index (BMI) and height / age (HA), following the reference standard of World Health Organization, 2007 [19]. Skinfolds were measured by using an adipometer under the brand Lange® (Beta Technology Inc., Santa Cruz, CA, USA) with precision of 1 mm, and circumferences were measured with a flexible, non-extendable tape graduated in 0.1-cm. Trunk to arm ratio was calculated through the sum of the subscapular and suprailiac skinfold divided by the value resulting from the sum of the biceps and triceps skinfolds [2].

Body composition assessment was determined by dual-energy X-ray absorptiometry (DXA), performed by a trained technician in both timepoints (LUNAR DPX-L, pediatric software version 1.5; LUNAR Radiation Corporation, Madison, WI, USA). DXA provided bone mineral density, and total and regional estimates of body composition. Limb to trunk ratio was obtained by the sum of fat (g) of the arms and legs divided by the amount of fat (g) of the trunk.

HIV viral load in plasma was determined by the methodology bDNA (branched DNA) (Versant ® - bDNA HIV-1 RNA 3.0 assay, Bayer Health Care LLC, Bayer Corporation Tarrytown, NY) with a minimum detection limit of 50 copies / mL and up to 500,000 copies / mL. The CD4 and CD8 T lymphocytes in plasma were evaluated by flow cytometry (BD FACSCalibur ™ System, Franklin Lakes, USA).

Triglycerides and total cholesterol were measured by the enzymatic colorimetric test, while HDLc was measured by the homogeneous enzymatic colorimetric test (System Roche / Hitachi COBAS® c501chemistry analyzer, Roche Diagnostics Ltd, Brazil, IN). LDLc fraction was obtained using the equation of Friedewald et al. 1972 Fasting plasma glucose was measured by the enzymatic hexokinase method and insulin was determined in serum by electrochemilumine-scence immunoassay method (Roche System /

Hitachi COBAS® c501chemistry analyzer, Roche Diagnostics Ltd, Brazil, IN).

2.3 Statistical Analysis

Statistical analysis was performed by Statistical Package for Social Sciences (SPSS) version 17.0. Categorical variables were presented as absolute frequencies (n) and relative (%), using the McNemar test. For quantitative variables, mean and standard deviation (SD) were evaluated by paired Student t test or median (minimum and maximum) assessed by the Wilcoxon test. ANOVA for repeated measures was used to compare the changes between groups with (LD+) and without (LD-) lipodystrophy over time.

Considering the insulin control variable, linear regression was applied. First, the important variables (lipodystrophy, antiretroviral use time, puberty, and sex) were included in the univariate model. Subsequently, variables with significant results were included in the multivariate model to determine the independent predictor of increased serum insulin concentrations.

For the categorical variable lipodystrophy, binomial logistic regression was applied at both times to identify the predictors of this clinical condition. Initially, all variables described in Tables 2 and 3 were included in the univariate model and those with significant result ($p \leq 0.05$) participated in the multivariate model. For all tests, a level of significance of 5% ($p \leq 0.05$) was adopted.

3. RESULTS

Initially, 52 prepubertal regularly attended were recruited. Of all the individuals screened for the study, five children with cerebral palsy or other genetic syndromes were excluded from the study, six other children were not given permission to participate, and one hospitalized patient died during the study period, leaving 40 eligible patients to complete the study at time 1 (T1) in 2008. At the second time (T2), performed after an interval of 24±6 months, 35 patients were included (there were two deaths and three moved out of the area).

The population consisted of 35 patients and 18 (51.4%) were girls. At T2, 16 (45.7%) patients remained prepubertal and nine (56.3%) were girls. Among the 19 (54.3%) patients who became pubescent, 10 (52.6%) were boys. Considering pubertal development, 11 (58%) patients had Tanner 2, four (21%) Tanner 3 and four (21%) Tanner 4.

Most children (n = 34, 97.1%) acquired HIV through vertical transmission, and in 19 (55.8%) cases there was no transmission prophylaxis (pregnancy, childbirth, or neonatal period). The only patient infected by a blood transfusion was diagnosed with AIDS before the age of two. We included him in the study due to the patient having all the same clinical and metabolical disorders as the other children, based off the statistical program we use that evaluates the different variables of the population studied. Concerning socioeconomic status, results showed that patients and their families belonged to low social classes.

Regarding patients'nutritional status at T1, 82.9% (n = 29) were eutrophic and 17.1% (n=6) overweight / obesity (n = 6). At T2, 74.3% (n = 26) remained eutrophic, 17.1% (n = 6) overweight / obesity and 8.6% (n = 3) were classified as underweight (p = 0.223). Short stature was present in 11.4% (n = 4) in T1 and in 22.9% (n = 8) in T2 (p = 0.125).

At the time of collecting, six (17.1%) patients in T1 and four (11.4%) in T2 were not using antiretroviral therapy. In table 1, the variables characterizing the population are described for both times. At T1, eight children presented lipodystrophy. None of the children with lipodystrophy at T1 had regression of the syndrome by the end of the study. Indeed, over two years and a half, two children developed new lipodystrophy syndrome.

In Table 2, demographic data, antiretroviral use, virological, immunological and biochemical parameters, and also bone mineral density results were compared by ANOVA.

Insulin levels were higher in children with lipodystrophy at T2 compared to T1 and also compared to children without lipodistrophy at T2. Considering that insulin concentrations may be influenced by factors such as puberty, lipodystrophy, sex, and time of antiretroviral use, we decided to perform linear regression analysis. Using a univariate linear regression model, we obtained the following results for puberty ($\beta = 7.8 \pm 3.4$, $p = 0.030$), lipodystrophy ($\beta = 8.6 \pm 3.7$, $p = 0.028$), sex ($\beta = -0.31 \pm 3.7$, $p = 0.934$) and time of antiretroviral use ($\beta = 1.07 \pm 0.71$, $p = 0.143$). In multivariate linear regression, using only the variables that were significant in univariate

models (puberty and lipodystrophy), lipodystrophy was the independent variable and predictor of increased serum concentrations of insulin (β = 8.6±3.7, p = 0.028).

Table 3 illustrates the longitudinal data of nutritional status and body composition. At the endpoint of the study, both groups expressed worsening BMI Z- score. At T1, patients with lipodystrophy had significant short stature compared to those without lipodystrophy. Interestingly, at T2, we noticed that there was no difference between both groups anymore.

Triceps skinfold thickness showed a significant decrease in patients with lipodystrophy. It also had a positive correlation with the other skinfolds, circumferences, and percentage of fat and lean body mass (p <0.005); negative correlation with absolute serum triglycerides (r = - 0.369, p = 0.029). There was an increase in trunk to arm ratio obtained by skinfold ratio and a decrease in DXA limb to trunk ratio in the LD+ group, indicating accumulation of fat in the central region and thinning of members. Such relationships described above are inversely correlated (r = - 0.638, p = 0.000).

For a better understanding of the predictors of lipodystrophy in two different times in the study, logistic regression univariate and multivariate are expressed in Tables 4 and 5. The presented model was adjusted for sex, age, puberty, and clinical and immunological classification disease.

4. DISCUSSION

In this cohort of HIV-infected patients, we observed that changes in body composition in the presence or absence of lipodystrophy occurred in a period of two and half years. Patients with lipodystrophy had more impairment of subcutaneous fat of the upper limb and greater accumulation of central adiposity, showing that body composition changes must be identified due to its early and progressive clinical and metabolic manifestation.

The patients maintained their clinical and immunological classification throughout the study. The number of patients with undetectable viral load, remained the same at both times. Regarding anthropometric parameters, weight and height evolution has not kept growth patterns.

BMI and HA z-scores of all patients at both times were lower when compared to 369 HIV-infected patients (age 12.2 + 2.6 years) of the Pediatric HIV / AIDS Cohort Study [20]. Undoubtedly, the use of ARVs has contributed to the improvement of the immune system and nutritional status in pediatric patients. However, it is known that adolescents are likely to reduce adherence to drug therapy, especially when patients associate medications to body composition changes [7,12]. Furthermore, this population is also at risk of ARV resistance and virologic failure [21].

There was a reduction of serum HDLc in the LD+ group in both times of the study and a concomitant increasing trend of TG concentrations. A study with 30 patients followed for two years also showed lower HDLc and higher TG and total cholesterol values over time [22]. Rosso et al. [23] related that patients with lipodystrophy presented higher concentrations of triglycerides, insulin and glucose. Lower values of HDLc appear to be a predictive factor in the development of lipodystrophy.

A European study of 426 HIV-infected patients aged 12.2 (9-15) years old determined by multivariate analysis that white ethnicity, BMI, use of ritonavir / lopinavir, and NRTI were associated with increased risk lipodystrophy syndrome, defined as lipodystrophy and dyslipidemia [24]. The constant presence of metabolic changes characteristic of dyslipidemia in lipodystrophic patients can trigger the early onset of arteriosclerotic process [12].

In this study, we note an increase in insulin only at T2, where the majority of patients were no longer prepubertal. Despite prior knowledge of physiology increased levels of insulin in the years preceding puberty and higher levels at pubertal growth spurt [25,26] it was found that the presence of lipodystrophy was determinant of this pathological outcome. Viganò et al. [27] results showed significantly higher fasting insulin and HOMA-IR in children with lipohypertrophy and mixed type of lipodystrophy.

The literature proposes some mechanisms for insulin resistance. The accumulation of visceral fat present in lipodystrophic patients can result in increased circulating fatty acids [22], increased production of resistin [28] and reduced adiponectin concentration [27]. Another proposed mechanism is the direct inhibition of glucose transporter-4 responsive to glucose (GLUT4) by IP and NRTI, decreasing glucose uptake [29].

By comparing body composition between groups, no difference between the percentage of lean

and fat mass was found, suggesting that lipodystrophy is characterized by a redistribution of fat, not a higher percentage of total body fat. Regarding the regional distribution of body fat, it was found that the gynoid fat, characterized by lower body fat accumulation was significantly higher in the LD- group. This result was expected since lipodystrophic patients tend to have central obesity. Although the values of waist circumference and android fat did not differ among the groups, it was found in the multivariate regression that increased waist circumference is an independent predictor of lipodystrophy.

In the LD+ group, triceps skinfold thickness was initially lower; maintaining this decreased during the study. This parameter may be useful to investigate subcutaneous fat loss. A study in African prepubertal demonstrated that biceptal skinfold <5 mm can aid in the early detection of lipoatrophy [30]. Supporting the theory of thinning of upper and lower limbs in the presence of body fat redistribution, it appears that the percentage of fat legs tended to be lower in the LD+ group (p = 0.06).

The relationships obtained by the sum of skinfolds and by DXA showed parameters consistent with body composition changes characteristic of lipodystrophy. Cut-off points have not been established yet, but can be useful for identifying body composition changes of these patients over time. DXA methodology requires technology and higher costs; on the other hand, the application of skinfold measurement can be more easily obtained in clinical practice [31].

Table 1. Characterization of HIV-infected patients at Time 1 (T1) and Time 2 (T2) (n = 35)

Variables	T1 Mean (SD)	T2 Mean (SD)	p
Age (years)*	9.6(1.1)	11.6 (1.2)	**0.001**
Virological and immunological parameters			
HIV viral load (copies) **	182 (50 -73.423)	53 (50-97.685)	**0.011**
CD4+ (cells/mm³) *	756(393)	701.5 (430.5)	0.222
CD8+ (cells/mm³) *	1099 (595)	1120 (515)	0.768
Nutritional status			
Weight (kg) **	26.8 (18.2-53.0)	34.3 (21.1-65.5)	**0.001**
BMI (kg/m^2) **	15.7 (13.6-24.2)	16.8 (13.1-25.9)	**0.001**
BMI Z-score**	- 0.23(-1.9 – 4.5)	- 0.51(-3 – 2.2)	**0.011**
Height (cm) *	131.7 (8.9)	142.3 (10.3)	**0.001**
HA Z-score*	- 0.68 (1.1)	- 0.81 (1.2)	0.086
	n (%)	**n (%)**	
Undetectable viral load ǂ	18 (51.4)	17 (48.6)	1.000
HIV clinical classification‡			
N and A	7 (20)	7 (20)	1.000
B and C	28 (80)	28 (80)	
HIV immunological classification‡			
1	9 (25.7)	6 (17.1)	0.083
2	14 (40.0)	17 (48.6)	
3	12 (34.3)	12 (34.3)	
Lipodystrophy ǂ	8 (22.8)	10 (28.5)	0.500
Lipodystrophy classification‡			
Lipoatrophy	4 (50)	3 (30)	0.368
Lipohipertrophy	2 (25)	3 (30)	
Mixed	2 (25)	4 (40)	
Time of ARV use (years)**	8.4 (0 – 10.7)	10.1 (0 – 13.1)	**0.001**
Use of ARV class‡			
PI	19 (54.3)	22 (62.9)	0.508
NRTI	29 (82.9)	31 (88.6)	0.625
NNRTI	10 (28.6)	8 (22.9)	0.727

*ARV= antiretroviral; BMI = body mass index; HA= height for age; PI = protease inhibitors NRTI = nucleoside reverse transcriptase; NNRTI = inhibitors of reverse transcriptase nucleoside analogues. * Student's t test; **Median (minimum-maximum values); Wilcoxon test; ǂ n (%), McNemar test*

Table 2. Characterization, antiretroviral medication, immunological, biochemical tests and bone densitometry in HIV-infected patients with (LD+) and without (LD-) lipodystrophy at time 1 (T1) and time 2 (T2)

Variables	T1		T 2					
	LD+1 (n=8)	LD-1 (n=27)	LD+2 (n=8)	LD-2 (n=27)	*P* intragroup	*p* intragroup	*p* intergroup	*p* intergroup
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	LD+ 1 x LD+2	LD- 1 x LD- 2	LD+ 1 x LD- 1	LD+ 2 x LD-2
Age (years)	9.9 (1.1)	9.5(1.1)	12.0 (1.2)	11.52(1.2)	**0.001**	**0.001**	0.308	0.308
ARV								
Use of ARV (years)	8.8 (0.9)	7.6 (2.5)	10.8 (0.9)	9.6(2.7)	**0.001**	**0.001**	0.191	0.191
PI (n;%)	5.0 (62.5)	14.0 (51.9)	3.0 (37.5)	19.0 (70.4)	0.500	**0.049**	0.595	**0.041**
NRTI (n;%)	7.0 (87.5)	22.0 (81.5)	7.0 (87.5)	24.0 (88.9)	0.317	0.317	0.867	0.867
NNRTI (n;%)	3.0 (37.5)	7.0 (25.9)	1.0 (12.5)	7 (25.9)	0.183	0.183	0.951	0.951
Virological and immunological paramenters								
HIV viral load (log)	3.1 (1.2)	2.7 (1.2)	3.5 (1.3)	2.7 (1.3)	0.399	0.399	0.217	0.217
CD4+ (cel/mm^3)	714 (395)	768 (399)	683 (527)	707 (409)	0.385	0.385	0.810	0.810
CD8+ (cel/mm^3)	1175 (255)	1076 (665)	1281 (424)	1072 (536)	0.552	0.552	0.467	0.467
Biochemical assay								
Triglycerides(mg/dL)	143.8 (64.8)	109.2 (45.1)	133.3 (48.7)	105.7 (43.5)	0.523	0.523	*0.056*	*0.056*
Total cholesterol(mg/dL)	151.3 (34.4)	159.5 (33.6)	141.8 (33.7)	162.4 (39.9)	0.490	0.490	0.303	0.303
LDLc (mg/dL)	84.3 (31.8)	89.9 (26.2)	80.3 (30.5)	94.2 (31.8)	0.971	0.971	0.398	0.398
HDLc (mg/dL)	38.1 (6.9)	46.0 (14.8)	34.8 (9)	47.0 (10.7)	0.623	0.623	**0.027**	**0.027**
Glucose (mg/dL)	81.4 (6.9)	84.8 (9.5)	80.7 (7.3)	84.5 (5.9)	0.791	0.791	0.174	0.174
Insulin (uUI/mL)	6.0 (5.8)	3.4 (2.6)	15.4 (10.5)	4.7 (2.5)	**0.048**	0.082	*0.062*	**0.010**
HOMA-IR	1.2 (1.2)	0.7 (0.5)	3.2 (2.2)	1.0 (0.5)	**0.048**	0.072	*0.067*	**0.013**
Bone density								
BMC (g)	1103 (142)	1062 (308)	1389 (221)	1363 (412)	**0.001**	**0.001**	0.794	0.794
TBMD Z-score	-0.26 (0.69)	0.01 (0.85)	- 0.52 (1.01)	- 0.15 (1.02)	*0.052*	*0.052*	0.381	0.381
LSBMD Z-score	-0.70 (0.92)	-0.65 (1.02)	- 0.80 (1.41)	- 0.71 (1.21)	0.529	0.529	0.877	0.877

ARV= antiretroviral; BMI = body mass index; HA= height for age; PI = protease inhibitors NRTI = nucleoside reverse transcriptase; NNRTI = inhibitors of reverse transcriptase nucleoside analogues; BMC = bone mineral content. TBMD = total body bone mineral density; LSBMD = lumbar spine bone mineral density (L1-L4). ANOVA for repeated measures

Table 3. Assessment of nutritional status and body composition in HIV- infected patients infected with with (LD+) and without (LD-) lipodystrophy at time 1 (T1) and time 2 (T2)

Variables	T1		T2		*P* intragroup	*P* intragroup	*P* intergroup	*P* intergroup
	LD+1 (n=8)	LD- 1 (n=27)	LD+ 2 (n=8)	LD-2 (n=27)				
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	LD+ 1 x LD+ 2	LD-1 x LD-2	LD+ 1 x LD- 1	LD+ 2 x LD- 2
Nutritional status								
BMI Z-score	0.22 (1.42)	-0.09 (1.70)	-0.48 (1.28)	-0.36(1.35)	**0.012**	**0.012**	0.874	0.874
HA Z-score	-0.86(1.48)	-0.63 (1.05)	-0.94(1.69)	-0.78 (1.15)	0.217	0.217	0.696	0.696
Eutrophic (n;%)	7.0 (87.5)	22.0 (81.5)	6.0 (75.0)	20.0 (74.1)	0.161	0.161	0.852	0.852
Short stature (n;%)	3.0 (37.5)	1.0 (3.7)	3.0 (37.5)	5.0 (18.5)	1.000	**0.025**	**0.008**	0.261
Circumferences(cm)								
Abdominal	64.5 (8.9)	59.4 (6.7)	66.6 (9.0)	64.3 (8.9)	**0.001**	**0.001**	0.247	0.247
Arm	19.2 (2.1)	18.7 (2.8)	19.8 (2.8)	20.7 (3.4)	**0.005**	**0.005**	0.867	0.867
Calf	25.7 (1.8)	26.0 (3.2)	26.4 (3.7)	27.5 (4.5)	0.097	0.097	0.610	0.610
Skinfolds (mm)								
Triceps	7.5 (1.8)	8.8 (3.2)	5.8 (0.3)	9.7 (4.5)	**0.049**	0.159	0.266	**0.026**
Biceps	4.8 (2.7)	6.0 (1.9)	4.5 (3.7)	6.8 (3.9)	0.621	0.621	0.148	0.148
Subscapular	7.6 (4.1)	6.4 (1.9)	7.4 (3.8)	6.6 (2.7)	0.903	0.903	0.373	0.373
Suprailiac	7.9 (6.1)	6.2 (2.9)	9.6 (8.1)	8.1 (5.3)	**0.003**	**0.003**	0.421	0.421
Trunk to arm ratio	1.2 (0.4)	0.8 (1.2)	1.5 (0.6)	0.9 (0.2)	**0.002**	0.072	**0.002**	**0.001**
DXA (%)								
Total body fat	16.3 (9.2)	17.9 (8.4)	15.2 (7.9)	20.0 (9.2)	0.593	0.593	0.355	0.355
Lean body mass	83.7 (9.2)	82.0 (8.4)	84.7 (7.9)	79.9 (9.2)	0.593	0.593	0.355	0.355
Arm fat	10.3 (11.1)	11.5 (7.7)	7.8 (7.9)	11.3 (8)	0.113	0.113	0.476	0.476
Leg fat	15.6 (7.6)	21.2 (9.5)	13.7 (6.2)	22.8 (10.8)	0.874	0.874	*0.060*	*0.060*
Trunk fat	18.8 (11.6)	18.2 (9.4)	18.4 (10.3)	20.9 (10.0)	0.314	0.314	0.814	0.814
Android fat	22.9 (14.9)	17.9 (9.8)	22.6 (13.9)	20.0 (10.1)	0.445	0.445	0.379	0.379
Gynoid fat	23.4 (9.7)	29.6 (8.8)	20.9 (7.8)	30.7 (10.2)	0.522	0.522	**0.037**	**0.037**
Limb to trunk ratio	0.7 (0.2)	1.0 (0.2)	0.6 (0.1)	1.0 (0.3)	0.090	0.090	**0.001**	**0.001**

BMI = body mass index; HA = height for age; DXA = dual-energy X-ray absorptiometry. ANOVA for repeated measures

Table 4. Predictors of lipodystrophy at time 1 (T1)

	Logistic regression		
Variables	**OR**	**CI 95%**	**p**
Univariate			
Short stature	15.600	1.336 – 182.090	0.028
Trunk to arm ratio	69.932	1.854 – 2638.124	0.022
DXA limb to trunk ratio	0.001	0.000 -0.189	0.009
Multivariate			
Short stature	46.198	1.900 -1123.070	0.019
DXA limb to trunk ratio	0.00009	0.000 – 0.121	0.011

OR = odds ratio; CI = confidence interval; DXA = dual-energy X-ray absorptiometry

Table 5. Predictors of lipodystrophy at time 2 (T2)

	Logistic regression		
Variables	**OR**	**CI 95%**	**p**
Univariate			
Abdominal circumference	1.109	1.005 – 1.223	0.039
HDL c	0.896	0.812 -0.987	0.027
Trunk to arm ratio	2331.641	3.589 - 1514879.404	0.019
DXA limb to trunk ratio	0.006	0.000 – 0.440	0.020
Multivariate			
Abdominal circumference	1.199	1.024 – 1.405	0.025
HDL c	0.835	0.722 – 0.966	0.015

OR = odds ratio; CI = confidence interval; DXA = dual-energy X-ray absorptiometry

Regarding the results of logistic regression, we found that short stature and the relationship DXA limb to trunk ratio were predictors of lipodystrophy in T1. In infected children, resistance to growth hormone (GH) and changes in cortisol production directly influence body composition and growth failure [32]. At T2, significant results covered waist circumference and lower concentrations of HDLc. Although the confidence interval was wide, it is known that these variables are factors associated with lipodystrophy. If the sample were larger, the interval would be narrower, but with the same predictor variables.

5. CONCLUSION

In a short period of time, patients have presented significant changes in body composition, growth and biochemical parameters, regardless of pubertal development. Body fat redistribution with central adiposity and biochemical changes are consistent with lipodystrophy syndrome, which may predispose these children to cardiovascular risk early in life.

Changes in body composition that may start in childhood and continue or even increase body fat redistribution at the puberty are worrisome for health professionals. Since these patients are living longer, monitoring and early intervention should be performed to minimize the risk of developing lipodystrophy syndrome and probable cardiovascular risk in adulthood.

INFORMED CONSENT

All involved patients (subjects or legally authorized representatives) received information concerning the study before enrolling. They have received and signed a two-way written informed consent including all the details of the study.

ETHICAL APPROVAL

The research proposal has been reviewed and approved by a human research ethics committee from Universidade Federal de São Paulo – UNIFESP in May 9, 2008 (project number CEP 0505/08).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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