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# IGF-1, IGFBP-3, IGF-1/IGFBP-3 ratio and insulin resistance in HIV fat redistribution syndrome/ IGF-1, IGFBP-3, rácio IGF-1/IGFBP-3 e insulinorresistência na síndrome de lipodistrofia por infeção VIH

**março, 2018**

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**Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO**

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IGF-1, IGFBP3, IGF-1/IGFBP-3 ratio and insulin resistance in HIV fat redistribution syndrome.

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# IGF-1, IGFBP-3, IGF-1/IGFBP-3 ratio and insulin resistance in HIV fat redistribution syndrome

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## ABSTRACT

**Background:**

Alterations in GH–IGF-1 axis were shown to play an important role in body composition and pathogenesis of HIV-associated lipodystrophy. The aim of our study was to evaluate the levels of IGF-1, IGFBP-3, IGF-1/IGFBP-3 ratio and insulin resistance (IR) and determine their relationship with metabolic syndrome (MS), fat redistribution, lipodystrophy and body max index (BMI) categories, in HIV-infected patients treated with combined antiretroviral therapy (cART).

**Methods:**

Anthropometric and metabolic parameters, HOMA-IR, body composition by DXA and CT, IGF-1 and IGFBP-3 were evaluated in 236 HIV-infected patients. We defined lipodystrophy by fat mass ratio (L-FMR) as the ratio of the percentage of the trunk fat mass to the percentage of the lower limb fat mass by dual-energy X-ray absorptiometry (DXA). Patient's fat redistribution was classified into 4 different groups according the presence or absence of either clinical lipoatrophy or abdominal prominence: no lipodystrophy, isolated central fat accumulation, isolated lipoatrophy and mixed forms. Concerning to BMI, patients were categorized in three categories: BMI ≥ 18,5 and <25; ≥ 25 and <30; and ≥30 kg/m². MS was defined according to the consensus IDF/AHA/NHLBI of 2009.

**Results:**

IGF-1 was significantly lower (p=0.001) in patients with MS. No other meaningfully differences were found in IGF-1, IGFBP-3 and IGF-1/IGFBP-3 ratio in relation to fat redistribution syndrome, presence of lipodystrophy and BMI categories.

HOMA-IR was positively correlated with the presence of lipodystrophy (p=0.034), isolated central fat accumulation and mixed forms of lipodystrophy (p=0.005). HOMA-IR was higher in obese patients (BMI ≥30 Kg/$m^2$) (p=0.033) and in patients with MS (p=0.004).

**Conclusion:**

In HIV-infected patients on cART, alterations in body composition were verified and were associated with IR. However, no associations were found between fat redistribution and IGF-1, IGFBP-3 and IGF-1/IGFBP-3 ratio. A negative association between IGF-1 levels and the presence of MS was observed. Further studies are needed to fully understand the relationship between the IGF system and HIV fat redistribution syndrome as well as their clinical implications.

**Keywords:** Body composition, Lipodystrophy, Metabolic Syndrome, Combined Antiretroviral Therapy, HIV infection, Insulin-like Growth Factors, Insulin-like growth factor binding protein, Insulin Resistance.

## BACKGROUND

The use of combined antiretroviral therapy in order to treat human immunodeficiency virus (HIV)-1 infection led to an increase in the life expectancy as well as to a significant decline in mortality and morbidity related to acquired immunodeficiency syndrome (AIDS) [1,2,3]. Nonetheless, cART in HIV infection is associated with lipodystrophy with or without increased visceral fat mass as well as metabolic complications such as dyslipidemia, insulin resistance, glucose intolerance and type 2 diabetes mellitus that hike the risk to develop cardiovascular diseases (CVD) [4-9].

HIV-infected patients with lipodystrophy share several components of the Metabolic Syndrome (MS) [4]. MS has been playing a major role as a marker for metabolic disorders even though the actual prevalence of MS in HIV populations is still questionable since it depends on the definition used and the population being studied. Reported prevalence for MS in HIV population ranges from 11.2% up to 45.4% [4,10-13]. MS incorporates a group of risk factors such as obesity, higher blood pressure, raised triglyceride (TG), lower high-density lipoprotein cholesterol levels (HDL-c) and defective glucose metabolism [10,14]. MS is also associated with abnormalities in the growth hormone (GH)/ insulin-like growth factor 1 (IGF-1) axis [15,16].

The serum levels of IGF-I are inversely related to the percentage of body fat (BF) and its low serum concentration in obese people is assumed to be mainly related not to the amount of subcutaneous fat but to the amount of visceral adipose tissue [15]. It was also demonstrated an association between IGF-1 deficit and deregulated lipid metabolism, diabetes, CVD and metabolic changes [13].

Therefore, alterations in GH-IGF-1 axis were shown to play an important role in pathogenesis of HIV-associated lipodystrophy and in the past were also related with

AIDS wasting syndrome [17,18].

The aim of our study was to determine the levels of IGF-1, IGFBP-3, ratio IGF-1/IGFBP-3 and insulin resistance and to evaluate their relationship with metabolic syndrome, fat redistribution, lipodystrophy objectively defined by FMR and BMI categories, in HIV-infected patients treated with cART, possibly allowing a better understanding of its clinical implications and the development of new therapeutic approaches in order to reduce the problems associated with HIV infection particularly metabolic changes.

## METHODS

### Study participants

We evaluated 236 HIV-infected Caucasian patients on cART (154 males and 82 females), as part of a cross-sectional study, referred from the Infectious Diseases to the Endocrinology Out-patient Clinic of Hospital São João due to lipodystrophy or any metabolic disorders.

### Clinical Assessment

For each patient the following information was compiled using a standardized protocol: age, gender, HIV infection risk factors, and duration of HIV infection and cART exposure. We used the "Centers for Disease Control and Prevention" (CDC) criteria for classifying the degree the infection [19].

We measured weight, height, circumferences of neck, arm, waist, hip and thigh as formerly described [20]. Body weight was measured using a TANITA scale (Tanita, model TBF 300, Chicago, IL), and height was measured to the nearest centimeter in the standing position, using a wall stadiometer (Holtain Limited, Crymych, Dyfed, UK).

Body mass index (BMI) was calculated as weight divided by height squared ($kg/m^2$). Waist/hip circumference ratio was calculated as waist circumference divided by hip circumference. Clinical lipodystrophy was defined as a peripheral lipoatrophy with or without a central fat accumulation evaluated by patient and practitioner, as earlier described [3,20,21]. The occurrence of central fat accumulation or abdominal prominence was outlined by the measurement of waist circumference using the International Diabetes Federation (IDF) criteria for metabolic syndrome [22]. Patients were organized into four different categories according the presence or absence of either clinical lipoatrophy or abdominal prominence: no lipodystrophy - patients without clinical lipoatrophy and without abdominal prominence; isolated central fat accumulation - patients without clinical lipoatrophy and with abdominal prominence; isolated lipoatrophy - patients with clinical lipoatrophy and without abdominal prominence; mixed forms of lipodystrophy - patients with clinical lipoatrophy and with abdominal prominence.

Metabolic Syndrome was defined using 2009 consensus that combined International Diabetes Federation (IDF) and American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI), considering that the presence of any 3 of 5 following risk factors constitutes a diagnosis of metabolic syndrome: elevated waist circumference, elevated triglycerides, reduced HDL-C, elevated blood pressure and elevated fasting glucose; drug treatment of any of these risk factors is an alternate indicator [22]. All measurements were completed using standard techniques and executed by the same observer (PF) [23].

**Evaluation of Body Composition**

Body composition was evaluated with whole-body dual- energy X-ray absorptiometry (DXA – Lunar Expert XL). DXA measurement was accomplished while the patient

was in a supine position, with standard positioning of the arms and feet. Markers for the trunk and lower limbs that defined regions of interest were described according manufacturer's directives. Regional fat mass values were grouped and assessed for the following anatomical regions: neck, arms, legs, trunk and total body. The fat mass ratio (FMR) was estimated as the ratio of the percentage of the trunk fat mass to the percentage of the lower limb fat mass (FMR = % of the trunk fat mass/% of the lower limb fat mass) [24]. The cut-off values for lipodystrophy by FMR were 1.961 for men and 1.329 for women [25]. We performed the quantification of total, visceral, and peripheral abdominal fat with a 64-slice CT scanner (Siemens Sensation 64 Cardiac) using the same technique as previously described [26,27].

All values were expressed in $cm^2$ rounded to the closest centesimal.

**Laboratory Analysis**

A venous blood sample was drawn after a 12-hour overnight fast. All the samples were analysed at the central laboratory of Hospital São João. Patients without a previous diagnosis of diabetes were proposed to perform a glucose tolerance test (OGTT).

The CD4+ cell count ($\times 10^6$ cell/L) was determined by flow cytometry and plasma HIV-1 RNA loads were measured by a quantitative reverse transcriptase polymerase chain reaction (Roche Diagnostic Systems, Inc., Branchburg, NJ, USA), which has a lower limit of detection of 50 copies/mL [28].

IGF-1 and IGFBP-3 were measured using solid-phase enzyme-labelled chemiluminescent immunometric assay (*immulite 2000*, Siemens, Germany).

IGF-1 was expressed in ng/mL and IGFBP-3 in ug/mL. These samples were analysed at Chemistry Clinical Laboratory of our hospital.

**Insulin resistance evaluation**

Insulin resistance was described by the homeostasis model assessment of insulin resistance (HOMA-IR) and insulin sensitivity by the quantitative insulin sensitivity check index (QUICKI). These indexes were calculated by the following formulas:

HOMA-IR index = (insulin 0 × glucose 0)/22.5 [27]

QUICKI = 1/[log (fasting insulin in mU/l) + lo5 (fasting plasma glucose in mg/dL)] [29]

We expressed glucose in mmol/L and insulin in μUI/mL.

**Statistical Analysis**

Statistical analysis was performed using SPSS version 24.0 software (SPSS Inc., Chicago, Illinois, USA). Categorical variables are presented as absolute frequencies and proportions, and were analysed using Chi-square or Fisher's exact test. Continuous variables are presented as means and standard deviations and compared using the Student's t-test and ANOVA or using Mann-Whitney or Kruskal-Wallis tests as appropriate.

Generalized linear models were used to estimate the adjusted means for selected variables according to different body fat mass distribution categories (lipodystrophy by FMR, classes of body composition; BMI and MS), and adjusted for sex.

All probabilities were two-tailed and p values $<0.05$ were considered to be statistically significant.

**Ethics statement**

Ethics Committee for Health of Hospital São João approved the study protocol and each patient agreed to provide written informed consent.

## RESULTS

### Sample characteristics according to gender

In table 1, we briefly compared some variables according to the gender of HIV infected patients. We observed that males had a significantly higher weight, neck and waist/hip ratio circumferences as well as visceral adipose tissue (VAT) ($p=0.02$) and VAT/subcutaneous adipose tissue (SAT) ratio values ($p<0.001$). Females had a higher hip circumference, SAT ($p<0.001$) and fat mass (both in % and kg) ($p<0.001$). No gender-related differences were observed in BMI, HOMA-IR, QUICKI, waist, thigh and arm circumferences (Table 1).

With regard to viral suppression rate, all the patients analysed had RNA<50 and 31 patients we had no information for that parameter (data not shown).

### Sample characteristics, body composition, metabolic parameters and insulin-like growth factors according to the presence of lipodystrophy defined by FMR

Table 2 shows the characteristics of the study sample with continuous variables adjusted for sex while table 3 presents categorical variables not adjusted, according to the presence of lipodystrophy defined by FMR (FMR-L). We observed that patients with FMR-L were older, had longer duration of HIV infection and length of cART, along with higher waist/hip ratio ($p<0.001$), mean CD4+ cell count, total cholesterol levels and insulin at 2 hours. HOMA-IR was also substantially higher ($p=0.034$). Patients without FMR-L, in addition to a superior QUICKI value, had a significantly higher waist circumference ($p=0.015$), total ($p=0.018$) and arm ($p=0.020$) fat mass (%) together with higher leg fat mass (% and kg) ($p=0.001$), on DXA evaluation (Table 2). Use of injecting drugs and heterosexual contact were also significantly more prevalent in this group of patients (Table 3). On CT evaluation at abdominal level, patients with FMR-L had higher VAT ($p<0.001$) and VAT/SAT ratio ($p<0.001$)

and lower SAT (p=0.009), with no major differences in total fat mass (Table 2). No significant differences were found in trunk fat mass (in %) or total, trunk and arm fat mass (in kg). Also, no significant differences were found in weight, BMI, neck, arm, hip and thigh circumferences (Table 2) nor in ART regimens and CDC classification among patients with or without FMR-L (Table 3). Additionally, no differences were detected regarding TG, LDL and HDL cholesterol levels. In what concerns to IGF-1, IGFBP-3 and IGF-1/IGFBP- 3 ratio levels no significant differences were detected among patients with or without FMR-L, and this was independent of sex (Table 2).

**Sample characteristics, body composition, metabolic parameters and insulin-like growth factors according to the four categories of body composition**

Tables 4 and 5 demonstrate the characteristics of the study sample with adjusted and not adjusted results for sex, respectively, according to the four categories of body composition. Patients with isolated central fat accumulation and mixed forms of lipodystrophy were older, had higher BMI, waist, hip, thigh, arm, neck circumferences, waist/hip ratio (p<0.001), insulin at 0 h and HOMA-IR (p=0.005) compared to patients with no lipodystrophy or patients with isolated lipoatrophy. Additionally, we observed that patients with isolated lipoatrophy and mixed forms of lipodystrophy had longer duration of HIV infection and length of cART. On DXA evaluation, patients with isolated central fat accumulation and mixed forms of lipodystrophy had higher total (p<0.001), trunk (p<0.001) and arm fat mass (p<0.001) (either in % and Kg). Moreover, patients with isolated central fat accumulation and no lipodystrophy had higher leg fat mass (in % and Kg) (p<0.001). On CT evaluation at abdominal level, patients with isolated central fat accumulation and mixed forms of lipodystrophy had a positive correlation with VAT (p<0.001), SAT (p<0.001) and total fat mass (p<0.001) while those with isolated lipoatrophy and mixed forms of

lipodystrophy had higher VAT/SAT ratio (p=0.003) (Table 4). All these results are independent of sex. No significant differences were observed in mean CD4+ cell count (Table 4), HIV infection risk factors, cART regimens and CDC classification between the four groups of body composition (Table 5). Also, no significant differences were detected in insulin at 2 h, QUICKI, triglycerides, total cholesterol, LDL and HDL cholesterol levels between the four groups of body composition (Table 4).

**Sample characteristics, body composition, metabolic parameters and insulin-like growth factors according to the BMI categories**

Overweight patients (BMI ≥25 and < 30 kg/m2) and obese patients (BMI≥30 kg/m2) had a meaningfully lower duration of HIV infection (Table 6), use of injecting drugs and homosexual contact (Table 7). In normoponderal patients (≥18.5 and <25 kg/m2), heterosexual contact was less common (Table 7). Obese patients were significantly older and had a higher waist, hip, thigh, arm, neck, waist/hip ratio circumferences and HOMA-IR (p=0.033). On DXA evaluation, the higher levels of total, trunk, leg and arm fat mass (either in % and Kg) were directly proportional to the BMI, with higher values in patients with BMI ≥30 $Kg/m^2$ (p<0.001). On CT evaluation at abdominal level, values of total fat mass (p<0.001), VAT (p<0.001) and SAT (p<0.001) were also directly proportional to the BMI (Table 6). No differences were found in CD4+ cell count, length of cART, viral suppression, cART regimens (Table 6) and CDC classification (table 7) between the three classes of BMI. Also no differences were observed in insulin (0h and 2h), QUICKI, LDL, HDL, total cholesterol, triglycerides levels and VAT/SAT ratio. Moreover, no differences were found in IGF-1, IGFBP-3 and IGF-1/IGFBP-3 ratio between the three categories of BMI (Table 6).

**Sample characteristics, body composition, metabolic parameters and insulin-like growth factors according to the presence of metabolic syndrome**

Patients with MS were significantly older and had higher BMI, waist, hip, arm, neck, waist/hip ratio circumferences, total cholesterol and TG levels. Additionally, they had a positive correlation with HOMA-IR ($p=0.004$) (Table 8). Homosexual and heterosexual contacts were also more common in these patients (Table 9). Inversely, QUICKI and HDL were statistically lower. On DXA evaluation, patients with MS had a positive correlation with total ($p<0.001$), trunk ($p<0.001$) and arm ($p<0.001$) fat mass (either in % and Kg). No differences were observed in leg fat in these groups as well as in insulin (0h and 2h) and LDL levels. On CT evaluation at abdominal level, all the values: total ($p<0.001$), VAT ($p<0.001$), SAT ($p<0.001$) and VAT/SAT ($p<0.002$) ratio were meaningfully higher in patients with MS. IFG-1 levels were significantly lower in patients with MS ($p=0.001$). No differences were found in IFGBP-3 and IGF-1/IGFBP-3 ratio levels (Table 8). No differences were found in cART regimens (Table 9), duration of HIV infection, length of cART, mean CD4+ cell count, CDC classification and in thigh circumferences between the two groups (Table 8).

## DISCUSSION

To our knowledge, there are not many studies focused on the role of IGF-1, IGFBP-3, IGF-1/IGFBP-3 ratio and insulin resistance in HIV-infected patients treated with cART addressing lipodystrophy, fat redistribution groups, classes of BMI and MS. However, some reports have analysed the influence of the IGF system on the metabolic syndrome as well as insulin resistance in patients with and without HIV infection [17,30,32] nevertheless there are still a lot of controversial data in the

literature [31].

The HIV infection itself together with the use of cART is associated with metabolic alterations such as lipodystrophy, insulin resistance, metabolic syndrome as well as with disturbances in the IGF-system [33-39]. IGF-1 levels essentially depend on the level of immunodeficiency in HIV-infection and may provide a connection between immune dysfunction and development of HIV-associated lipodystrophy, diabetes and cardiovascular diseases in HIV-infected patients [13,30].

The IGF biding protein (IGFBP) gene family involves six members that encode a family of homologous multifunctional proteins that can guide IGF-1 to specific tissues, potentiate or inhibit IGF-1 actions [13]. IGFBP-3 is the most abundant IGFBP in serum; it is regulated positively by GH and has IGF-independent effects that are largely the opposite of those of IGF-1 [40-42]. The IGF-1/IGFBP-3 ratio may represent a balance between cardiac and metabolic risk and was also used to help to distinguish patients that are prone to be insulin-resistant [31] and it has been suggested to be a reasonable approximation of free IGF-1 levels under normal physiological conditions since its modifications will mirror the course of the change of IFG-1 levels [43].

Our aim was to compare the levels of IGF-1, IGFBP-3 and IGF-1/IGFBP-3 ratio and the existence of IR in HIV-infected patients on cART, according to the presence of lipodystrophy, to the four different patterns of body fat redistribution previously described, BMI and MS.

In our study, we used an objective technique to evaluate lipodystrophy to overcome the diverse and heterogeneous approaches for the diagnosis of lipodystrophy of previous studies [25]. We used simple methods for estimation of IR (HOMA-IR and QUICKI) that have shown a good association with the euglycaemichyperinsulinaemic

clamp, which is considered the gold standard method [44-46].

Lipodystrophy in HIV-1 infected patients was considered to be multifactorial in their pathophysiology and an adverse effect of cART, not restricted to a particular drug or a class of drugs [39], and we have patients that did multiple different regimes in the past, over the years. No differences were detected between the class of drugs used in patients with or without CL defined either by FMR, MS, categories of BMI or body composition.

When HIV-infected patients were compared according to gender, differences were observed (Table 1). Males had a significantly higher weight, VAT and VAT/SAT ratio, and consequently a lower SAT. On the other hand, females, as expected, had a higher SAT and total fat mass (both % and Kg). This is coherent with the observation that males are more prone to abdominal fat deposition mainly in the abdominal cavity and women have a ginoid obesity pattern, accumulating more fat mass in buttocks and thighs [47-49]. In relation to corporal circumferences, we only observed significant differences in hip circumferences (higher in females), neck and waist/hip circumferences (higher in males), and no differences in relation to arm, thigh and waist circumferences. Although a higher waist/hip ratio in males may be justified by the fact that higher waist circumference seems to be a good predictor of VAT [6,50]. Since, the sample size was small, we could not investigate IGF-1, IGFBP-3 and IGF-1/IGFBP- 3 ratio stratified by gender, and so adjusted models were computed.

Regarding the presence or absence of lipodystrophy, according to the FMR (Table 2 and Table 3), we observed a not surprising linkage between lipodystrophy and abnormalities in glucose homeostasis with a significantly higher number of patients with IR, corroborated by a great body of evidence in the literature [1,51,52]. Total cholesterol, VAT and VAT/SAT ratio were also higher in those patients, with higher

SAT in patients with no lipodystrophy, which is probably the effect of the increased intra-abdominal fat in lipodystrophic patients [20]. In relation to IGF-1 and IGFBP-3, no differences were found in our data between patients with and without lipodystrophy. The existing results in the literature may differ from each other. For example, Anderson et al., found out that HIV lipodystrophic patients counterbalance impairments in GH secretion by increasing GH sensitivity of GH target tissues, concluding that the IGF-1 and IGFBP-3 levels were increased in those patients compared with patients without lipodystrophy [51]. On the other hand, Koutkia and Rietschel et al., demonstrated decreased GH levels but similar IGF-1 levels in males with HIV lipodystrophy when compared to BMI-matched HIV-infected males without lipodystrophy, which they considered to be a result of increased sensitivity to GH or increased free insulin levels associated with lipodystrophy [53,54]. In relation to IGF-1/IGFBP-3 ratio we also did not find any significant association and, as we know, there are no current studies focused particularly in the relationship between lipodystrophy and this ratio, however, we expected a similar variation to that of IGF-1.

When we classified patients into four categories of body fat redistribution (Table 4 and Table 5), besides the expected outcomes in terms of metabolic modifications such as significantly higher weight, VAT, SAT and body circumferences in patients with isolated central fat accumulation and mixed forms of lipodystrophy, we found out that patients with isolated lipoatrophy had a higher VAT/SAT ratio which is the product of a decrease in subcutaneous fat [21]. IR was also more predominant in those two groups, as we previously demonstrated [1]. In relation to IGF-1, IGFBP-3 and IGF-1/IGFBP-3 ratio, no significant findings were found when we compared patients with different body compositions, adjusted for sex, and, as far as we know, there are no

studies focused specifically in those patterns of body fat redistribution and IGF-system proteins, therefore we cannot assure that the different categories of body fat will have a translation in the body concentration of IGF-1, IGFBP-3 and the corresponding ratio.

As we expected, HIV-infected obese patients (BMI≥30 kg/m$^2$) were side by side with significantly elevated body circumferences as well as higher levels of fat mass (both in % and kg). HOMA-IR was also significantly higher in those patients since adipose tissue deposition is shown to exacerbate IR [55]. Once again, we could not find any significant association between BMI and IGF-1, IGFBP-3 or IGF-1/IGFBP-3 ratio (Table 6). Faupel-Badger et al., settled that BMI was inversely associated with IGF-1 levels; that IGFBP-3 was slightly increased as BMI rises; and that IGF-1/IGFBP-3 ratio was inversely associated with all anthropometric measures, except height, although this was not in a HIV-infected population [56].

When we compared HIV-infected patients with and without MS (Table 8 and Table 9), we found out that IR was higher in patients with MS as well as VAT, SAT and VAT/SAT ratio. This is consistent with the majority of reports about MS in HIV-infected and non-infected populations [57]. We also noticed that patients with MS had significantly lower levels of IGF-1 which is coherent with several other studies that presented that lower IGF-1 levels were related to higher prevalence of MS [58] and that metabolic syndrome is related with activation of the renin–angiotensin–aldosterone system that leads to a vast setting of metabolic transformations that may contribute to altered insulin/IGF-1 signalling [59]. In our data, no differences were found in relation to IGFBP-3 and IGF-1/IGFBP-3 ratio and this juxtaposes with J. Sierra-Johnson et al., that concluded that the low ratio IGF-1/IGFBP-3 had a stronger association with all the metabolic syndrome components than either IGF-1 or IGFBP-

3 alone, although this was also a study in a non- HIV infected population [31].

In conclusion, apart from the positive correlation between decreased IGF-1 levels and patients with MS, we did not find any significant association between the levels of IGF-1, IGFBP-3 and IGF-1/IGFBP-3 ratio and the other variables of body fat or body redistribution. In a way, we could justify this lack of positive statistical findings with the fact that there are many factors that can affect the physiological concentrations of these proteins such as age, dietary habits, circadian rhythm, cardiometabolic status and individual features.

**Limitations**

Several limitations of this study should be noted. The sample size available enable us to stratified our results by gender, but we feel that this did not impaired our conclusions as the results were modelled considering this adjustment. Since our study has a cross-sectional design it hampered the possibility to determine causality. Also, we did not eliminate patients with diabetes or hypertension diagnosed previous to HIV infection. In addiction, we cannot reject the influence of the pre-HIV body composition; and the cumulative exposure time of each drug as well as the nadir value of $CD4^+$ factors were not evaluated. It is challenging to compare results on the prevalence of MS because of the heterogeneity in populations regarding past and actual cART regimens and treatment adherence in addition to the several definitions in literature [22]. Finally, bias in the referral cannot be excluded even though all patients referred from Infectious Diseases to our department were included. Some patients were referred from to Endocrinology Clinics specifically for lipodystrophy or metabolic disorders related to cART, and so we might have selected from a population with augmented metabolic complications.

**Some aspects of this study should be highlighted**

The study was performed in a unit that is extremely experienced in the assessment of metabolic and body fat abnormalities in HIV-infected patients; the clinical measurements were carried out by the same investigator (PF); and an objective definition of lipodystrophy (Fat Mass Ratio by DXA), visceral and subcutaneous fat mass by CT were used.

## CONCLUSION

In conclusion, we found out that modifications in body composition were observed and were associated with IR in HIV-infected patients on cART. However, we did not find any significant correlation between fat redistribution and IGF-1, IGFBP-3 and IGF-1/IGFBP-3 ratio. Contrastingly, an inverse association between IGF-1 levels and MS was observed.

The present study adds a growing body of evidence linking the IGF system to the HIV- related adipose redistribution syndrome and may provide an insight into distinct pathways that lead to immune dysfunction, lipodystrophy, IR and metabolic syndrome in HIV infected patients treated with cART. Moreover, this could motivate new clinical studies and the search for therapeutic methods related to IGF system that might avoid the beginning or the progress of those metabolic changes in HIV infected patients.

Nevertheless, more studies, particularly longitudinal ones, are needed in order to fully understand the exact mechanism by which IGF-system impacts and its consequences.

**Abbreviations**

IR: insulin resistance; MS: metabolic syndrome; BMI: body mass index; HIV: human immunodeficiency virus; cART: combined antiretroviral therapy; DXA: dual-energy X-ray absorptiometry; CT: computed tomography, L-FMR: lipodystrophy by fat mass ratio; IDF:

International Diabetes Federation; AHA/NHLBI: American Heart Association/National Heart, Lung, and Blood Institute; IGF: insulin-like growth factor; AIDS: acquired immunodeficiency syndrome; CVD: cardiovascular diseases; TG: triacylglyceride, HDL-c: lower high-density lipoprotein cholesterol; GH: growths hormone; IGFBP: IGF-binding protein; BF: body fat; FMR: fat mass ratio; OGTT: glucose tolerance test; HOMA-IR: homeostasis model assessment of insulin resistance; QUICKI: quantitative insulin sensitivity check index; VAT: visceral adipose tissues; SAT: subcutaneous adipose tissue

**Ethics approval and consent to participate**

Ethics Committee for Health of Hospital São João approved the study protocol and each patient agreed to provide written informed consent.

**Availability of data and materials**

The datasets created during the present study are available from the corresponding author on reasonable request.

**Competing interests**

All the authors declare that they have no competing interests.

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**Authors' contributions**

PL participated in the study design, in the acquisition of data, and drafted the manuscript; ACS performed the statistical analysis and critically revised the manuscript; AJM performed the CT scans and reviewed the data; JP performed DXA scans and reviewed the data; RS participated in the acquisition of data; AS and DC critically revised the manuscript and PF conceived the study, participated in the acquisition of data and revised the manuscript. All authors read and approved the final manuscript.

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**Table 1: Basal sample characteristics according to gender**

| | Male | Female | p |
|---|---|---|---|
| n | 154 | 82 | |
| Age [years, mean (SD)] | 46.3(11.2) | 46.2(12.1) | 0.932 |
| BMI [(kg/m$^2$), mean (SD)] | 24.5(3.8) | 25.8(5.6) | 0.058 |
| Duration of HIV infection [years, mean (sd)] | 7.7(3.7) | 8.4(4.0) | 0.119 |
| cART [years, mean (sd)] | 6.8(3.8) | 6.5(3.9) | 0.677 |
| CD4 cell count [cells/mm$^3$, mean (sd)] | 553.6(317.4) | 568.4(359.4) | 0.744 |
| Weight [Kg, mean (sd)] | 69.4(11.5) | 63.4(12.4) | <0.001 |
| Waist circumference [cm, mean (sd)] | 90.8(10.5) | 91.0(13.2) | 0.936 |
| Hip circumference [cm, mean (sd)] | 93.0(6.7) | 96.8(10.4) | 0.003 |
| Thigh circumference [cm, mean (sd)] | 47.2(4.2) | 48.5(6.7) | 0.115 |
| Arm circumference [cm, mean (sd)] | 27.0(2.5) | 26.5(3.7) | 0.326 |
| Neck circumference [cm, mean (sd)] | 38.5(3.3) | 34.3(3.2) | <0.001 |
| Waist/hip circumference ratio | 1.0(0.1) | 0.9(0.1) | 0.002 |
| HOMA [mean (sd)] | 3.3(3.3) | 2.6(2.7) | 0.140 |
| QUICKI [mean (sd)] | 0.4(0.1) | 0.4(0.1) | 0.340 |
| Body Fat Mass by Quantitative CT | | | |
| VAT [cm$^2$, mean (sd)] | 137.9(86.6) | 112.7(70.2) | 0.025 |
| SAT [cm$^2$, mean (sd)] | 101.2(75.9) | 231.7(126.5) | <0.001 |
| VAT/SAT ratio [mean (sd)] | 2.1(2.4) | 0.6(0.4) | <0.001 |

| | | | |
|---|---|---|---|
| Fat mass [%, mean (sd)] DXA | | | |
| Total | 16.9(8.1) | 33.5(10.0) | <0.001 |
| Fat mass [Kg, mean (sd)] DXA | | | |
| Total | 12.3(7.8) | 22.0(10.4) | <0.001 |

Note: BMI- body mass index; HIV: human immunodeficiency virus; cART: combined antiretroviral therapy; HOMA: homeostasis model assessment; QUICKI: quantitative insulin sensitivity check index; CT: computed tomography; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; DXA: dual-energy X-ray absorptiometry.

**Table 2 Sample characteristics, body composition, metabolic parameters and insulin-like growth factors according to the presence of lipodystrophy defined by FMR, adjusted for sex**

| | Without lipodystrophy | With lipodystrophy | p |
|---|---|---|---|
| n | 86 | 150 | |
| Age [years, adjusted mean (95%CI)] | 44.5(42.6-46.5) | 49.6(47.2-52.0) | 0.002 |
| Duration of HIV infection [years, adjusted mean (95%CI)] | 7.4(6.8-8.1) | 8.8(8.0-9.6) | 0.009 |
| cART [years, adjusted mean (95%CI)] | 5.8(5.1-6.4) | 8.1(7.4-8.9) | <0.001 |
| CD4 cell count [cells/$mm^3$, adjusted mean (95%CI)] | 495.3(441.2-549.4) | 648.0(581.7-714.3) | 0.001 |
| Weight [Kg, adjusted mean (95%CI)] | 67.8(65.7-69.8) | 67.7(65.2-70.3) | 0.982 |
| BMI [($kg/m^2$), adjusted mean (95%CI)] | 24.9(24.1-25.7) | 25.5(24.5-26.4) | 0.374 |
| Waist circumference [cm, adjusted mean (95%CI)] | 95.6(94.2-96.8) | 92.8(91.1-94.5) | 0.015 |
| Hip circumference [cm, adjusted mean (95%CI)] | 90.0(88.0-92.0) | 92.8(90.3-95.2) | 0.085 |
| Thigh circumference [cm, adjusted mean (95%CI)] | 48.1(47.2-49.0) | 47.1(46.0-48.2) | 0.148 |
| Arm circumference [cm, adjusted mean (95%CI)] | 26.7(26.2-27.3) | 27.2(26.5-27.9) | 0.278 |
| Neck circumference [cm, adjusted mean (95%CI)] | 36.7(36.0-37.3) | 37.6(36.8-38.3) | 0.078 |
| Waist/hip circumference ratio [adjusted mean (95%CI)] | 0.9(0.9-1.0) | 1.00(0.98-1.01) | <0.001 |
| Insulin 0 [µU/mL, adjusted mean (95%CI)] | 10.1(8.2-11.9) | 12.9(10.6-15.2) | 0.063 |

| | | | |
|---|---|---|---|
| Insulin 2 h at OGTT [μU/mL, adjusted mean (95%CI)] | 51.8(32.6-71.0) | 88.9(65.4-112.4) | 0.017 |
| HOMA [adjusted mean (95%CI)] | 2.7(2.1-3.3) | 3.7(3.0-4.3) | 0.034 |
| QUICKI [adjusted mean (95%CI)] | 0.37(0.36-0.39) | 0.34(0.32-0.35) | <0.001 |
| Total Cholesterol [mg/dL, adjusted mean (95%CI)] | 217.3(207.7-227.0) | 235.3(223.5-247.2) | 0.022 |
| LDL-cholesterol [mg/dL, adjusted mean (95%CI)] | 124.7(116.5-132.9) | 135.8(125.7-145.8) | 0.097 |
| HDL- cholesterol [mg/dL, adjusted mean (95%CI)] | 46.5(44.3-48.7) | 45.2(42.5-48.0) | 0.483 |
| Triglycerides [mg/dL, adjusted mean (95%CI)] | 248.4(217.9-279.0) | 293.6(256.2-331.1) | 0.069 |
| IGFBP-3 [ug/mL, adjusted mean (95%CI)] | 3.9(3.0-4.8) | 5.0(3.9-6.0) | 0.135 |
| IGF-1 [ng/mL, adjusted mean (95%CI)] | 133.5(124.4-142.7) | 132.7(121.6-143.8) | 0.916 |
| IGF-1/IGFBP-3 ratio [adjusted mean (95%CI)] | 0.04(0.03-0.04) | 0.03(0.03-0.04) | 0.116 |
| Body Fat Mass by Quantitative CT | | | |
| Total [$cm^2$, adjusted mean (95%CI)] | 274.1(247.0-301.1) | 284.8(253.1-316.4) | 0.615 |
| VAT [$cm^2$, adjusted mean (95%CI)] | 111.9(97.4-126.4) | 158.0(141.1-175.0) | <0.001 |
| SAT [$cm^2$, adjusted mean (95%CI)] | 162.2(144.9-179.4) | 126.7(106.5-147.0) | 0.009 |
| VAT/SAT ratio [adjusted mean (95%CI)] | 1.2(0.8-1.5) | 2.3(1.9-2.7) | <0.001 |
| Fat mass [%, adjusted mean (95%CI)] DXA | | | |
| Total | 23.6(22.1-25.1) | 20.7(18.9-22.5) | 0.018 |
| Trunk | 24.5(22.8-26.2) | 25.5(23.4-27.6) | 0.485 |

| | | | |
|---|---|---|---|
| Leg | 23.3(21.7-24.8) | 12.7(10.8-14.6) | <0.001 |
| Arm | 25.5(23.9-27.2) | 22.4(20.4-24.4) | 0.020 |
| Fat mass [Kg, adjusted mean (95%CI)] DXA | | | |
| Total | 16.4(14.9-17.9) | 14.2(12.3-16.0) | 0.066 |
| Trunk | 8.8(7.9-9.7) | 9.4(8.3-10.5) | 0.399 |
| Leg | 4.9(4.5-5.4) | 2.5(2.0-3.0) | <0.001 |
| Arm | 2.00(1.8-2.2) | 1.7(1.4-2.0) | 0.128 |

Note: HIV: human immunodeficiency virus; cART: combined antiretroviral therapy; BMI- body mass index; OGTT: glucose tolerance test; HOMA: homeostasis model assessment; QUICKI: quantitative insulin sensitivity check index; LDL- low density cholesterol; HDL: high density cholesterol; IGFBP-3: insulin-like growth factor-binding protein-3; IGF-1: insulin-like growth factor-1; CT: computed tomography; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; DXA: dual-energy X-ray absorptiometry

**Table 3: HIV risk factor, CDC classification and ART regime, according to the presence of lipodystrophy defined by FMR**

| | Without lipodystrophy | With lipodystrophy | p |
|---|---|---|---|
| n | 86 | 150 | |
| HIV risk factor [n (%)] | | | |
| Injecting drug user | 39(29.8) | 17(19.1) | |
| Homosexual contact | 8(6.1) | 16(18.0) | |
| Heterosexual contact | 82(62.6) | 54(60.7) | |
| Others | 2(1.5) | 2(2.2) | 0.019 |
| CDC [n (%)] | | | |
| A | 69 (54.8) | 57 (45.2) | 0.132 |
| B | 2(100) | 0(0) | |
| C | 61(65.6) | 32(34.4) | |
| ART [n (%)] | | | |
| IP | 69(59) | 48(41) | 0.999 |
| NNRTI | 63(58.3) | 45(41.7) | 0.867 |
| NRTI | 126(59.4) | 86(40.6) | 0.999 |

Note: CDC: Centers for Disease Control and Prevention criteria for staging; IP: protease inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor

**Table 4 Sample characteristics, body composition, metabolic parameters and insulin-like growth factors according to the four categories of body composition, adjusted for sex**

| | No lipodystrophy | Isolated central fat accumulation | Isolated lipoatrophy | Mixed forms of lipodystrophy | p |
|---|---|---|---|---|---|
| n | 27 | 59 | 84 | 66 | |
| Age [years, adjusted mean (95%CI)] | 39.6(35.4-43.7) | 46.6(43.8-49.5) | 43.0(40.6-45.4) | 52.8(50.2-55.4) | <0.001 |
| Duration of HIV infection [years, adjusted mean (95%CI)] | 7.4(6.0-8.8) | 6.1(5.1-7.1) | 9.2(8.4-10.0) | 8.2(7.3-9.1) | <0.001 |
| cART [years, adjusted mean (95%CI)] | 5.3(3.9-6.7) | 4.3(3.4-5.3) | 8.0(7.2-8.7) | 7.7(6.8-8.5) | <0.001 |
| CD4 cell count [cells/$mm^3$, adjusted mean (95%CI)] | 602.4(476.5-728.4) | 463.0(375.6-550.3) | 566.8(493.2-640.3) | 616.4(535.6-697.1) | 0.066 |
| Weight [Kg, adjusted mean (95%CI)] | 61.8(58.6-65.1) | 79.5(77.2-81.8) | 57.5(55.6-59.5) | 71.0(68.9-73.1) | <0.001 |
| BMI [($kg/m^2$), adjusted mean (95%CI)] | 22.6(21.306-23.9) | 29.3(28.4-30.1) | 21.4(20.6-22.1) | 26.7(25.8-27.5) | <0.001 |
| Waist circumference [cm, adjusted mean (95%CI)] | 92.9(90.6-95.2) | 103.4(101.8-105.0) | 88.0(86.7-89.4) | 94.6(93.1-96.1) | <0.001 |
| Hip circumference [cm, adjusted mean (95%CI)] | 82.2(79.3-85.0) | 102.0(100.1-104.0) | 80.5(78.8-82.2) | 97.7(95.8-99.5) | <0.001 |
| Thigh circumference | 46.4(44.7-48.2) | 52.0(50.8-53.2) | 44.5(43.5-45.5) | 48.0(46.9-49.1) | <0.001 |

| | | | | | |
|---|---|---|---|---|---|
| [cm, adjusted mean (95%CI)] | | | | | |
| Arm circumference [cm, adjusted mean (95%CI)] | 25.0(23.8-26.3) | 28.9(28.2-29.6) | 25.0(24.3-25.7) | 27.2(26.6-27.9) | <0.001 |
| Neck circumference [cm, adjusted mean (95%CI)] | 35.1(33.7-36.5) | 38.5(37.7-39.3) | 34.8(34.1-35.5) | 38.4(37.6-39.1) | <0.001 |
| Waist/hip circumference ratio [adjusted mean (95%CI)] | 0.89(0.86-0.91) | 0.99(0.97-1.01) | 0.92(0.90-0.93) | 1.03(1.02-1.05) | <0.001 |
| Insulin 0 [µU/mL, adjusted mean (95%CI)] | 6.8(2.5-11.1) | 13.0(10.3-15.7) | 8.7(6.3-11.2) | 13.8(11.2-16.3) | 0.006 |
| Insulin 2 h at OGTT [µU/mL, mean (sd)] | 53.6(4.8-102.3) | 51.8(21.3-82.3) | 75.5847.3-103.7) | 85.5(57.1-114.0) | 0.360 |
| HOMA [adjusted mean (95%CI)] | 1.5(0.2-2.8) | 3.5(2.7-4.3) | 2.5(1.8-3.2) | 3.9(3.1-4.6) | 0.005 |
| QUICKI [adjusted mean (95%CI)] | 0.38(0.35-0.42) | 0.35(0.33-0.37) | 0.35(0.36-0.39) | 0.34(0.32-0.36) | 0.079 |
| Total Cholesterol [mg/dL, adjusted mean (95%CI)] | 211.6(190.0-233.2) | 236.3(221.3-251.3) | 214.4(201.8-227.0) | 229.5(215.7-243.4) | 0.111 |
| LDL-cholesterol [mg/dL, adjusted mean (95%CI)] | 125.2(106.5-143.8) | 135.0(122.0-147.8) | 122.3(111.4-133.2) | 132.2(120.2-144.1) | 0.490 |
| HDL-cholesterol [mg/dL, adjusted mean | 44.5(39.6-49.4) | 47.9(44.4-51.3) | 46.0(43.2-48.9) | 44.6(41.4-47.7) | 0.502 |

| | | | | | |
|---|---|---|---|---|---|
| (95%CI)] | | | | | |
| Triglycerides [mg/dL, adjusted mean (95%CI)] | 216.4(148.0-284.7) | 265.9(218.5-313.3) | 266.7(226.8-306.6) | 297.3(253.5-341.2) | 0.275 |
| IGFBP-3 [ug/mL, adjusted mean (95%CI)] | 4.1(1.8-6.3) | 4.3(3.1-5.6) | 3.6(2.4-4.7) | 5.3(4.1-6.6) | 0.220 |
| IGF-1 [ng/mL, adjusted mean (95%CI)] | 142.3(122.1-162.4) | 137.1(123.7-150.5) | 126.2(114.3-138.0) | 134.7(122.0-147.4) | 0.474 |
| IGF-1/IGFBP-3 ratio [adjusted mean (95%CI)] | 0.033(0.025-0.041) | 0.037(0.033-0.042) | 0.038(0.034-0.042) | 0.034(0.029-0.038) | 0.476 |
| Body Fat Mass by Quantitative CT | | | | | |
| Total [$cm^2$, adjusted mean (95%CI)] | 194.9(152.1-237.7) | 417.8(388.0-447.5) | 152.4(127.1-177.7) | 330.1(302.9-357.3) | <0.001 |
| VAT [$cm^2$, adjusted mean (95%CI)] | 75.0(48.9-101.1) | 168.7(150.6-186.8) | 71.7(56.3-87.1) | 187.5(171.0-204.1) | <0.001 |
| SAT [$cm^2$, adjusted mean (95%CI)] | 119.9(90.0-149.7) | 249.1(228.4-269.8) | 80.8(63.1-98.4) | 142.6(123.6-161.5) | <0.001 |
| VAT/SAT ratio [adjusted mean (95%CI)] | 0.8(0.1-1.6) | 1.0(0.5-1.6) | 2.1(1.7-2.6) | 1.9(1.4-2.3) | 0.003 |
| Fat mass [%, adjusted mean (95%CI)] DXA | | | | | |
| Total | 20.0(17.4-22.5) | 32.3(30.6-34.0) | 15.4(14.0-16.8) | 23.4(21.8-25.0) | <0.001 |
| Trunk | 19.7(16.8-22.7) | 34.8(32.8-36.8) | 16.7(15.0-18.3) | 28.4(26.6-30.2) | <0.001 |

| | | | | | |
|---|---|---|---|---|---|
| Leg | 21.0(17.6-24.4) | 29.6(27.3-31.8) | 13.2(11.3-15.1) | 16.0(13.9-18.2) | <0.001 |
| Arm | 21.1(17.9-24.3) | 33.7(31.6-35.8) | 17.7(15.9-19.5) | 25.4(23.8-27.4) | <0.001 |
| Fat mass [Kg, adjusted mean (95%CI)] DXA | | | | | |
| Total | 11.9(9.4-14.5) | 25.3(23.6-27.0) | 8.7(7.3-10.1) | 16.6(15.1-18.2) | <0.001 |
| Trunk | 6.0(4.4-7.5) | 14.1(13.1-15.1) | 4.8(4.0-5-7) | 11.0(10.0-11.9) | <0.001 |
| Leg | 4.1(3.3-4.9) | 7.2(6.7-7.7) | 2.3(1.9-2.8) | 3.0(2.5-3.5) | <0.001 |
| Arm | 1.3(0.9-1.8) | 3.1(2.8-3.4) | 1.1(0.9-1.4) | 1.9(1.7-2.2) | <0.001 |

Note: HIV: human immunodeficiency virus; cART: combined antiretroviral therapy; BMI- body mass index; OGTT: glucose tolerance test; HOMA: homeostasis model assessment; QUICKI: quantitative insulin sensitivity check index; LDL- low density cholesterol; HDL: high density cholesterol; IGFBP-3: insulin-like growth factor-binding protein-3; IGF-1: insulin-like growth factor-1; CT: computed tomography; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; DXA: dual-energy X-ray absorptiometry

**Table 5: HIV risk factor, CDC classification and ART regime, according to the four categories of body composition**

| | No lipodystrophy | Isolated central fat accumulation | Isolated lipoatrophy | Mixed forms of lipodystrophy | p |
|---|---|---|---|---|---|
| n | 27 | 59 | 84 | 66 | |
| HIV risk factor [n (%)] | | | | | |
| Injecting drug user | 9(33.3) | 9(15.5) | 37(44.6) | 7(10.6) | |
| Homosexual contact | 4(14.8) | 4(6.9) | 10(12.0) | 7(10.6) | |
| Heterosexual contact | 14(51.9) | 45(77.6) | 33(39.8) | 50(75.8) | |
| Others | 0(0) | 0(0) | 3(3.6) | 2(3.0) | 0.063 |
| CDC [n (%)] | | | | | |
| A | 14(51.9) | 34(57.6) | 48(57.8) | 35(53.0) | |
| B | 2(7.4) | 0(0) | 0(0) | 0(0) | |
| C | 11(40.7) | 25(42.4) | 35(42.2) | 31(47.0) | 0.201 |
| ART [n (%)] | | | | | |
| IP | 14(11.3) | 35(28.2) | 43(34.7) | 32(25.8) | 0.533 |
| NNRTI | 12(10.5) | 24(21.1) | 44(38.6) | 34(29.8) | 0.600 |
| NRTI | 25(11.1) | 53(23.6) | 82(36.4) | 65(28.9) | 0.197 |

Note: CDC: Centers for Disease Control and Prevention criteria for staging; IP: protease inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor

**Table 6 Sample characteristics, body composition, metabolic parameters and insulin-like growth factors according to the BMI categories, adjusted for sex**

| BMI [kg/m$^2$] | ≥18.5 and < 25 | ≥25 and < 30 | ≥30 | P |
|---|---|---|---|---|
| n | 114 | 78 | 29 | |
| Age [years, adjusted mean (95%CI)] | 44.2(42.2-46.2) | 48.1(45.6-50.7) | 50.3(46.1-54.5) | 0.009 |
| Duration of HIV infection [years, adjusted mean (95%CI)] | 8.5(7.8-9.1) | 6.9(6.1-7.8) | 8.3(6.9-9.7) | 0.014 |
| cART [years, adjusted mean (95%CI)] | 7.2(6.5-7.8) | 5.8(5.0-6.7) | 6.8(5.3-8.2) | 0.052 |
| CD4 cell count [cells/mm$^3$, adjusted mean (95%CI)] | 546.5(488.4-604.7) | 570.2(495.8-644.7) | 582.4(459.0-705.9) | 0.819 |
| Waist circumference [cm, adjusted mean (95%CI)] | 89.6(88.6-90.6) | 97.6(96.3-98.9) | 106.2(104.0-108.3) | <0.001 |
| Hip circumference [cm, adjusted mean (95%CI)] | 83.3(82.1-84.5) | 96.4(94.9-98.0) | 109.7(107.1-112.3) | <0.001 |
| Thigh circumference [cm, adjusted mean (95%CI)] | 45.3(44.5-46.1) | 49.3(48.3-50.3) | 53.1(51.5-54.8) | <0.001 |
| Arm circumference [cm, adjusted mean (95%CI)] | 25.1(24.6-25.5) | 27.9(27.3-28.4) | 30.4(29.5-31.3) | <0.001 |
| Neck circumference [cm, adjusted mean (95%CI)] | 35.1(34.6-35.7) | 38.0(37.4-38.6) | 40.9(39.9-42.0) | <0.001 |
| Waist/hip circumference ratio [adjusted mean | 0.93(0.92-0.94) | 0.99(0.97-1.01) | 1.04(1.01-1.07) | <0.001 |

| | | | | |
|---|---|---|---|---|
| (95%CI) | | | | |
| Insulin 0 [µU/mL, adjusted mean (95%CI)] | 9.7(7.8-11.6) | 12.3(10.0-14.7) | 13.9(10.1-17.7) | 0.074 |
| Insulin 2 h at OGTT [µU/mL, adjusted mean (95%CI)] | 75.3(54.3-96.3) | 58.1(30.3-86.0) | 74.5(32.3-116.7) | 0.608 |
| HOMA [adjusted mean (95%CI)] | 2.5(2.0-3.1) | 3.5(2.8-4.2) | 3.9(2.8-5.0) | 0.033 |
| QUICKI [mean (sd)] | 0.37(0.35-0.38) | 0.35(0.33-0.37) | 0.35(0.32-0.38) | 0.311 |
| Total Cholesterol [mg/dL, adjusted mean (95%CI)] | 218.5(208.6-228.4) | 232.2(219.5-244.8) | 224.7(203.7-245.8) | 0.249 |
| LDL-cholesterol [mg/dL, adjusted mean (95%CI)] | 124.9(116.4-133.3) | 138.3(127.5-149.1) | 118.6(100.7-136.5) | 0.079 |
| HDL- cholesterol [mg/dL, adjusted mean (95%CI)] | 46.3(44.1-48.6) | 46.1(43.2-49.0) | 43.6(38.8-48.4) | 0.590 |
| Triglycerides [mg/dL, adjusted mean (95%CI)] | 266.3(235.1-297.6) | 259.3(219.2-299.3) | 309.6(243.2-376.0) | 0.427 |
| IGFBP-3 [ug/mL, adjusted mean (95%CI)] | 4.6(3.7-5.5) | 4.2(3.1-5.3) | 3.8(2.0-5.6) | 0.692 |
| IGF-1 [ng/mL, adjusted mean (95%CI)] | 137.6(128.5-146.8) | 131.5(120.0-143.1) | 119.7(100.9-138.4) | 0.227 |
| IGF-1/IGFBP-3 ratio [adjusted mean (95%CI)] | 0.036(0.033-0.040) | 0.035(0.031.0.039) | 0.037(0.030-0.043) | 0.927 |
| Body Fat Mass by Quantitative CT | | | | |
| Total [$cm^2$, adjusted mean (95%CI)] | 184.2(166.2-202.3) | 333.6(310.05) | 499.3(357.1) | <0.001 |
| VAT [$cm^2$, adjusted | 90.8(78.1-103.5) | 162.5(146.0-179.1) | 207.7(181.6-233.7) | <0.001 |

| | | | | |
|---|---|---|---|---|
| mean (95%CI)] | | | | |
| SAT [$cm^2$, adjusted mean (95%CI)] | 93.5(80.7-106.3) | 171.0(154.4-187.7) | 291.6(265.5-317.8) | <0.001 |
| VAT/SAT ratio [adjusted mean (95%CI)] | 1.8(1.4-2.2) | 1.5(1.0-1.9) | 1.2(0.5-2.0) | 0.295 |
| Fat mass [%, adjusted mean (95%CI)] DXA | | | | |
| Total | 17.3(16.2-18.5) | 25.9(24.4-27.4) | 34.5(32.1-36.9) | <0.001 |
| Trunk | 18.8(17.5-20.0) | 29.2(27.6-30.8) | 39.0(36.4-41.6) | <0.001 |
| Leg | 15.0(13.3-16.7) | 22.1(19.9-24.2) | 28.0(24.5-31.5) | <0.001 |
| Arm | 19.6(18.2-21.1) | 27.3(25.4-29.1) | 35.8(32.8-38.8) | <0.001 |
| Fat mass [Kg, adjusted mean (95%CI)] DXA | | | | |
| Total | 10.2(9.3-11.3) | 18.3(17.0-19.6) | 30.0(27.8-32.1) | <0.001 |
| Trunk | 5.8(5.2-6.4) | 10.9(10.1-11.6) | 17.7(16.4-18.9) | <0.001 |
| Leg | 2.7(2.3-3.2) | 4.6(4.1-5.1) | 7.2(6.4-8.1) | <0.001 |
| Arm | 1.2(1.1-1.4) | 2.1(1.9-2.3) | 4.1(3.7-4.4) | <0.001 |

Note: HIV: human immunodeficiency virus; cART: combined antiretroviral therapy; OGTT: glucose tolerance test; HOMA: homeostasis model assessment; QUICKI: quantitative insulin sensitivity check index; LDL- low density cholesterol; HDL: high density cholesterol; IGFBP-3: insulin-like growth factor-binding protein-3; IGF-1: insulin-like growth factor-1; CT: computed tomography; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; DXA: dual-energy X-ray absorptiometry

**Table 7: HIV risk factor, CDC classification and ART regime, according to the BMI categories**

| BMI [kg/m$^2$, (n (%)] | ≥18.5 and < 25 | ≥25 and < 30 | ≥30 | P |
|---|---|---|---|---|
| n | 114 | 78 | 29 | |
| HIV risk factor [n (%)] | | | | |
| Injecting drug user | 50(39.1) | 8(10.3) | 4(14.3) | |
| Homosexual contact | 14(10.9) | 7(9.0) | 4(14.3) | |
| Heterosexual contact | 60(46.9) | 62(79.5) | 20(71.4) | |
| Others | 4(3.1) | 1(1.3) | 0(0) | <0.001 |
| CDC [n (%)] | | | | |
| A | 72(55) | 42(32.1) | 17(13) | |
| B | 2(100) | 0(0) | 0(0) | |
| C | 54(52.9) | 36(35.3) | 12(11.8) | 0.858 |
| ART [n (%)] | | | | |
| IP | 70(56.5) | 39(31.5) | 15(12.1) | 0.831 |
| NNRTI | 61(53.5) | 41(36.0) | 12(10.5) | 0.647 |
| NRTI | 124(55.1) | 76(33.8) | 25(11.1) | 0.241 |

Note: CDC: Centers for Disease Control and Prevention criteria for staging; IP: protease inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor

**Table 8: Sample characteristics, body composition, metabolic parameters and insulin-like growth factors according to the presence of metabolic syndrome, adjusted for sex**

| MS | Without MS | With MS | p |
|---|---|---|---|
| n | 125 | 108 | |
| Age [years, adjusted mean (95%CI)] | 42.1(40.2-43.9) | 50.8(48.8-52.8) | <0.001 |
| Duration of HIV infection [years, adjusted mean (95%CI)] | 7.8(7.1-8.5) | 8.0(7.3-8.8) | 0.640 |
| cART [years, adjusted mean (95%CI)] | 6.4(5.7-7.0) | 7.0(6.2-7.7) | 0.232 |
| CD4 cell count [cells/$mm^3$, adjusted mean (95%CI)] | 548.8(490.8-606.8) | 568.0(505.6-630.4) | 0.658 |
| Weight [Kg, adjusted mean (95%CI)] | 63.6(61.6-65.6) | 71.6(69.5-73.8) | <0.001 |
| BMI [($kg/m^2$), adjusted mean (95%CI)] | 23.4(22.6-24.1) | 26.9(26.1-27.7) | <0.001 |
| Waist circumference [cm, adjusted mean (95%CI)] | 92.3(90.8-93.7) | 96.8(95.2-98.3) | <0.001 |
| Hip circumference [cm, adjusted mean (95%CI)] | 85.7(83.9-87.5) | 96.9(95.0-98.8) | <0.001 |
| Thigh circumference [cm, adjusted mean (95%CI)] | 47.2(46.3-48.1) | 48.2(47.2-49.2) | 0.155 |
| Arm circumference [cm, adjusted mean (95%CI)] | 26.1(25.5-26.7) | 27.5(26.9-28.1) | 0.001 |
| Neck circumference [cm, adjusted mean (95%CI)] | 35.8(35.2-36.4) | 38.0(37.4-38.6) | <0.001 |
| Waist/hip circumference ratio [adjusted mean (95%CI)] | 0.93(0.92-0.94) | 1.00(0.99-1.02) | <0.001 |
| Insulin 0 [µU/mL, adjusted mean (95%CI)] | 10.1(8.2-12.0) | 12.4(10.3-14.4) | 0.118 |

| | | | |
|---|---|---|---|
| Insulin 2 h at OGTT [μU/mL, adjusted mean (95%CI)] | 67.8(47.7-88.0) | 71.9(47.2-96.5) | 0.803 |
| HOMA [adjusted mean (95%CI)] | 2.5(1.9-3.0) | 3.7(3.1-4.3) | 0.004 |
| QUICKI [ adjusted mean (95%CI)] | 0.37(0.36-0.39) | 0.35(0.33-0.36) | 0.031 |
| Total Cholesterol [mg/dL, adjusted mean (95%CI)] | 215.1(205.2-225.0) | 234.6(224.0-245.3) | 0.009 |
| LDL-cholesterol [mg/dL, adjusted mean (95%CI)] | 127.6(119.0-136.2) | 130.6(121.3-139.8) | 0.646 |
| HDL- cholesterol [mg/dL, adjusted mean (95%CI)] | 47.9(45.7-50..2) | 43.7(41.3-46.2) | 0.014 |
| Triglycerides [mg/dL, adjusted mean (95%CI)] | 226.5(195.8-257.1) | 318.3(285.3-351.3) | <0.001 |
| IGFBP-3 [ug/mL, adjusted mean (95%CI)] | 4.2(3.9-4.4) | 3.9(3.6-4.1) | 0.118 |
| IGF-1 [ng/mL, adjusted mean (95%CI)] | 143.7(134.7-152.7) | 120.8(111.3-130.3) | 0.001 |
| IGF-1/IGFBP-3 ratio [adjusted mean (95%CI)] Body Fat Mass by Quantitative CT | 0.04(0.03-0.04) | 0.04(0.03-0.04) | 0.726 |
| Total [$cm^2$, adjusted mean (95%CI)])] | 214.8(190.2-239.4) | 344.9(318.4-371.4) | <0.001 |
| VAT [$cm^2$, adjusted mean (95%CI)] | 94.3(80.8-107.9) | 170.3(155.7-184.5) | <0.001 |
| SAT [$cm^2$, adjusted mean (95%CI)] | 120.4(103.2-137.6) | 174.6(156.1-193.1) | <0.001 |
| VAT/SAT ratio [adjusted mean (95%CI)] | 1.2(0.8-1.6) | 2.1(1.7-2,5) | 0.002 |
| Fat mass [%, adjusted mean (95%CI)] DXA Total | 19.9(18.4-21.4) | 25.5(23.8-27.1) | <0.001 |

| | | | |
|---|---|---|---|
| Trunk | 21.4(19.7-23.1) | 29.0(27.2-30.8) | <0.001 |
| Leg | 17.9(16.0-19.7) | 20.5(18.4-22.5) | 0.063 |
| Arm | 21.7(20.0-23.3) | 27.6(25.8-29.4) | <0.001 |
| Fat mass [Kg, adjusted mean (95%CI)] DXA | | | |
| Total | 12.9(11.4-14.4) | 18.6(17.0-20.3) | <0.001 |
| Trunk | 7.1(6.3-8.0) | 11.3(10.3-12.2) | <0.001 |
| Leg | 3.7(3.2-4.2) | 4.3(3.8-4.9) | 0.076 |
| Arm | 1.5(1.3-1.8) | 2.3(2.1-2.6) | <0.001 |

Note: HIV: human immunodeficiency virus; cART: combined antiretroviral therapy; BMI- body mass index; OGTT: glucose tolerance test; HOMA: homeostasis model assessment; QUICKI: quantitative insulin sensitivity check index; LDL- low density cholesterol; HDL: high density cholesterol; IGFBP-3: insulin-like growth factor-binding protein-3; IGF-1: insulin-like growth factor-1; CT: computed tomography; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; DXA: dual-energy X-ray absorptiometry

**Table 9: HIV risk factor, CDC classification and ART regime, according to presence of metabolic syndrome**

| MS | Without MS | With MS | p |
|---|---|---|---|
| n | 125 | 108 | |
| HIV risk factor [n (%)] | | | |
| Injecting drug user | 43(34.7) | 19(17.8) | |
| Homosexual contact | 12(9,7) | 13(12.1) | |
| Heterosexual contact | 65(52,4) | 74(69.2) | |
| Others | 4(3,2) | 1(0.9) | 0.012 |
| CDC [n (%)] | | | |
| A | 67(51.5) | 63(48.5) | |
| B | 1(50) | 1(50) | |
| C | 56(56) | 44(44) | 0.754 |
| ART [n (%)] | | | |
| IP | 63(51.6) | 59(48.4) | 0.410 |
| NNRTI | 65(57.5) | 48(42.5) | 0.454 |
| NRTI | 124(55.6) | 99(44.4) | 0.094 |

Note: CDC: Centers for Disease Control and Prevention criteria for staging; IP: protease inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor

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FMUP FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

# Anexos

março, 2018

FMUP

# Normas da revista BioMed Central Infectious Diseases

## Submission Guidelines

### Criteria

Research articles should report on original primary research, but may report on systematic reviews of published research provided they adhere to the appropriate reporting guidelines which are detailed in our editorial policies. Please note that non-commissioned pooled analyses of selected published research will not be considered.

The information below details the section headings that you should include in your manuscript and what information should be within each section.

**Quick points:**

- Use double line spacing
- Include line and page numbering
- Use SI units: Please ensure that all special characters used are embedded in the text, otherwise they will be lost during conversion to PDF
- Do not use page breaks in your manuscript

### Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:
    - "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"

    - or for non-clinical or non-research studies a description of what the article reports
- list the full names, institutional addresses and email addresses for all authors
    - if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the "Acknowledgements" section in accordance with the instructions below
- indicate the corresponding author

## Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Methods:** how the study was performed and statistical tests used
- **Results:** the main findings
- **Conclusions:** brief summary and potential implications
- **Trial registration:** If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be in stated in this section. If it was not registered prospectively (before enrollment of the

first participant), you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration

## Keywords

Three to ten keywords representing the main content of the article.

## Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

## Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate

## Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

## Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

## Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

### List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

### Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and material
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (optional)

# Comprovativo de Apresentação de Poster Congresso 'VIII Advanced Course of Endocrinology'


Exmo.(a) Senhor(a) Dr.(a)

Patrícia Lima

É com muito gosto que informamos que o seu trabalho:
**IGF-1, IGFBP-3, IGF-1/IGFBP-3 ratio and insulin resistance in HIV fat redistribution syndrome**

**Foi aceite** para apresentação sob a forma de ***e-Poster*** no decorrer do **"*VIII Advanced Course of Endocrinology*"** a decorrer nos dias 06 e 07 de abril, na sala Douro do Porto Palácio Hotel.

O tempo previsto de apresentação é de 5 minutos. O *e-poster* e sua apresentação deverão ser em inglês.

Em breve informaremos o período de apresentação do seu trabalho.

Em e-mail separado enviamos o *template* e as normas para elaborar o seu trabalho final que **deverá ser enviado** para o e-mail: geral@eposters.pt até ao dia **27 de março de 2018.**