Leptin expression in HIV-infected patients during antiretroviral therapy

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Abstract

Background Leptin is an adipokine with complex metabolic, neuroendocrine and immune functions. Our objective was to evaluate leptin serum levels in a cohort of Romanian HIV-infected patients undergoing antiretroviral therapy in relation to their immune-virological status, lipid and glucose metabolic abnormalities and the presence of metabolic syndrome (MS).

Methods We enrolled consecutive non-diabetic HIV-infected patients aged 18 and over on stable cART for at least 6 months. Blood samples were tested for: leptin, CD4 T cells count, HIV viral load and lipid panel.

Results A total of 90 HIV-infected patients were included in the study: 50 males (55.6%) with a mean age of 33.3 years and 40 females with a mean age of 30.4 years. Most patients (74.4%) had HIV viral load below the limit of detection and the median CD4 count for the cohort was 476 (410) cells/cmm. More than one third of the patients (41.1%) had hypoleptinemia. The prevalence of MS was 13.3%. Hypoleptinemia was significantly more frequent in men. In a subset of patients with undetectable HIV viral load, the median leptin value was 0.6 (6.07) ng/mL in patients with poor immune recovery (CD4 count $\leq$ 200/cmm) compared to 2 (3.07) ng/mL for those with better immune response (CD4 count $>$ 200/cmm), without statistical significance. The median values of leptin were similar for persons with and without MS criteria. HDL-cholesterol values were positively correlated to leptin values in a linear regression model.

Conclusion A significant proportion of patients in our study presented low levels of leptin; this finding was not associated with immune and virological parameters or the presence of MS. Hypoleptinemia was significantly correlated with lower levels of HDL-cholesterol, a key cardiovascular risk factor.

Keywords Leptin, HIV, antiretroviral therapy, HDL-cholesterol

Background

Leptin is a hormone secreted mainly by the adipose tissue that regulates various immune, metabolic, neuroendocrine functions and

maintains energy balance.¹ The leptin-hypothalamic axis has an important role in regulating glucose and lipid metabolism by influencing pancreatic insulin secretion and

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concomitantly improving insulin sensitivity.² Leptin prevents fat accumulation by increasing thermogenic energy expenditure via the hypothalamic pathway. Leptin also has a significant contribution to maintaining normal weight by providing a satiety hypothalamic signal during and after a meal.^{2,3}

The introduction of combined antiretroviral therapy (cART) has markedly changed the evolution and prognosis of HIV-infected patients, by increasing CD4 T-lymphocytes count and thus restoring adaptive immune function. Chronic adverse effects of cART are complex and include fat redistribution (lipodystrophy) and alterations of fat metabolism. Lipodystrophy consists of increased visceral fat and loss of peripheral adipose tissue.⁴

Several authors have studied the relationship between serum leptin levels and the immune and virological status in HIV-infected individuals.^{5,6} The serum leptin level was lower in HIV patients with a lower CD4 count.⁵ Leptin levels may also be inversely correlated to HIV replication, independent of the amount of adipose tissue or disease progression.⁶

In HIV-infected patients insulin resistance and lipid metabolism abnormalities were reported before the cART era. A suppressed adaptive immune function may contribute to increased microbial translocation and consecutive inflammatory status that leads to hypertriglyceridemia and decreased insulin sensitivity, which further increases the risk of atherosclerosis.⁷ Some of these changes may be accentuated by antiretrovirals, through different pathophysiologic pathways. A complex of interactions involving increased inflammation

and antiretroviral drug-associated factors may determine metabolic abnormalities and alterations of hormone levels.⁸ Abnormal leptin levels may be associated to cART-induced lipodystrophy, decreased insulin sensitivity and metabolic syndrome.⁹

Our objective was to assess leptin serum levels in a cohort of Romanian HIV-infected patients undergoing cART, in relation to their immune status, virological replication and lipid and glucose metabolic abnormalities. We also evaluated the relationship between leptin levels and the presence of metabolic syndrome (MS).

Methods

We enrolled a cohort of consecutive non-diabetic HIV-infected patients attending the National Institute for Infectious Diseases "Prof.Dr. Matei Balş", Bucharest, Romania between June 2010 and June 2011. We selected patients aged 18 and over on stable cART for at least 6 months. The patients with a known malignancy or with other immune inflammatory diseases and active drug users were excluded from the study. The local ethics committee approved the study protocol (no. 190/15.01.2009). All patients signed a written informed consent in order to participate in the study and they received a standard questionnaire for demographic parameters.

Blood samples were tested for: leptin (EASIA KAP2281, BioSource, Nivelles, Belgium), CD4 T cells count (FACSCanto II flow cytometer, Becton Dickinson, New Jersey, USA), HIV viral load (LightCycler® 480 Real-Time PCR System, Roche, Basel, Switzerland), fasting triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and fasting plasma glucose (dry slide technology, Vitros 950, Johnson & Johnson, New Jersey, USA). The values of serum leptin for each patient were compared to sex and age-adjusted reference values: 0.5-7.9 ng/mL (18-24 years), 4.1-14.5 ng/mL (25-29 years), 5.5-40.4 ng/mL (> 30 years) for females and 0.5-3.2 ng/mL (18-24 years), 0.5-14.6 ng/mL (25-29 years), 2.5-42.1 ng/mL (> 30 years) for males.

The diagnosis of MS was made according to the new criteria of the International Diabetes

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Federation (2013), that included central obesity (defined as waist circumference with ethnicity specific values) plus any two of the following four factors: raised triglycerides (≥ 150 mg/dL or specific treatment), reduced HDL-cholesterol (< 40 mg/dL in males, < 50 mg/dL in females or specific treatment), raised blood pressure (systolic BP ≥ 130 mmHg, diastolic BP ≥ 85 mmHg or treatment of preexisting hypertension) and raised fasting plasma glucose (≥ 100 mg/dL). The values of waist circumferences to define central obesity were ≥ 94 cm for men and ≥ 80 cm in women according to ethnic specificity.¹⁰

Statistical analysis

We used the Shapiro–Wilk test in order to test for normally-distributed variables. Means ($\pm$ standard deviation [SD]) were used to describe samples with parametric distribution and medians (interquartile range) for non-normally distributed continuous data. Differences in means or medians between groups were evaluated using independent-sample t-test or Mann–Whitney, respectively, according to samples' distributions. Chi-square or Fisher's exact tests were used to test for statistical significance in case of categorical variables. Linear regression and binary regression models were fitted to evaluate the impact of independent variables on selected dependent variables, in multivariate analysis. We used a forward selection stepwise approach, adding selected variables in order to improve the models. The linear correlation between the observed and model-predicted values of the dependent variables in linear regression was assessed by calculating the coefficient of correlation (R). Leptin values were natural log transformed (LogLeptin) in order to meet the assumptions for linear regression analysis. The total variability in the dependent variable was evaluated using Nagelkerke R-squared in binary logistic analysis. All analyses were performed with SPSS Statistics for Windows, version 17.0 (SPSS Inc., Chicago, Illinois, USA). Statistical significance was set at 5%. We computed two-tailed *p* values.

Results

Descriptive analysis

We enrolled 90 HIV-infected patients: 50 males (55.6%) with a mean age of 33.3 (± 13.7) years and 40 females (44.4%) with a mean age of 30.4 (± 13.9) years. The median time from HIV diagnosis was 63.5 (57.9) months and the median time on cART was 61 (73) months. Most patients (74.4%) had HIV viral load below the limit of detection. The median CD4 count was 476 (410) cells/cmm. Sixty-six patients (73.3%) had a current cART regimen based on protease inhibitors. Six patients (6.6%) had a body mass index (BMI) > 30 kg/sqm. The median serum leptin value was 1.89 (3.57) ng/mL. After adjusting values based on age and sex, more than one third of the patients (41.1%) had hypoleptinemia and 8.9% presented hyperleptinemia. The prevalence of MS was 13.3% (Table 1).

Correlation of leptin with age, sex and BMI

The patients with hypoleptinemia had a significantly higher mean age, when compared to persons with normal serum leptin values (39.8 ± 14.2 vs. 28 ± 11 , $p = .000$) in univariate analysis. Hypoleptinemia was also significantly more frequent in men (60% vs. 17.5% in women, $p = .000$). BMI means were similar across all leptin expression categories. Serum leptin values were not correlated to the duration from HIV diagnosis or the time on cART (Table 1).

Leptin and immuno-virological parameters

The median values of leptin were 2 (3.4) ng/mL in patients with undetectable HIV viral load vs. 1.28 (5.8) ng/mL for persons with persistent viral replication ($p = .343$). The median CD4 count was 531 cells/cmm in patients with normal leptin values, compared to 436 cells/cmm in hypoleptinemic patients, without statistical significance ($p = .308$, as shown in Table 1).

In order to evaluate if leptin expression was correlated with poor immune recovery after achieving viral suppression we selected only undetectable HIV patients. In a simple linear regression model that included CD4 T-lymphocytes count as the dependent variable and

Table 1. Clinical and biological characteristics of study patients by leptin expression

Characteristics	Total patients	Hypoleptinemia	Normal leptin values	Hyperleptinemia	<i>p</i> value
	90	37	45	8	
Mean age $\pm$ SD ^a , years	32.1 $\pm$ 13.7	39.8 $\pm$ 14.2	28 $\pm$ 11	19.6 $\pm$ 1.5	.000*
Males, no (%)	50	30 (81.1)	17 (37.8)	3 (37.5)	.000*
Females, no (%)	40	7 (17.5)	28 (70)	5 (12.5)	.000*
Mean BMI ^a $\pm$ SD ^a , kg/sqm	23.7 $\pm$ 3.9	23.7 $\pm$ 3.7	23.4 $\pm$ 4	24.9 $\pm$ 4.4	.751
Median CD4 T (IQR) ^a , cells/cmm	476 (328)	436 (321)	531 (396)	749 (370)	.308
Patients with undetectable HIV viral load, no. (%)	67 (74.4)	25 (67.6)	36 (80)	6 (75)	.438
Time from HIV diagnosis (IQR) ^a , months	63.5 (57.9)	51.5 (54)	73 (105)	96 (98)	.359
Time on antiretroviral therapy (IQR) ^a , months	61 (71)	50 (51)	71 (105)	95 (98)	.245
Patients with metabolic syndrome, no (%)	12 (13.3)	7 (18.9)	4 (8.9)	1 (12.5)	.380
Abnormal waist circumference ^b , no (%)	13 (14.4)	8 (21.6)	4 (8.9)	1 (12.5)	.253
Hypertension ^c , no (%)	23 (25.6)	11 (29.7)	10 (22.2)	2 (28.6)	.951
Abnormal fasting glucose ^d , no (%)	5 (5.6)	3 (8.1)	2 (4.4)	0	.579
Raised triglycerides ^e , no (%)	53 (58.9)	19 (51.4)	29 (64.4)	5 (62.5)	.559
Median triglycerides ^a (IQR) ^a , mg/dL	166 (127)	181.5 (146)	165 (85)	173 (175)	.561
Reduced HDL-cholesterol ^f , no (%)	47 (52.2)	22 (59.5)	21 (46.7)	4 (50)	.427
Median HDL-cholesterol (IQR) ^a , mg/dL	43 (16)	37.3 (18)	43 (14)	50 (25)	.120
Leptin ^a , ng/mL	1.89 (3.57)	0.89 (1.28)	2.98 (4.55)	7.9 (15.5)	

Data are shown as mean $\pm$ SD or number (percent)

^aBMI body mass index; IQR interquartile range; SD standard deviation

^bAbnormal waist circumference: ≥ 94 cm for men and ≥ 80 cm in women

^cHypertension was defined as systolic BP ≥ 130 mmHg, diastolic BP ≥ 85 mmHg or treatment of previously diagnosed hypertension

^dAbnormal fasting glucose was defined as plasma glucose ≥ 100 mg/dL

^eSerum triglycerides ≥ 150 mg/dL or specific treatment for this abnormality

^fHDL-cholesterol < 40 mg/dL in males, < 50 mg/dL in females or specific treatment for this abnormality

* $p < 0.05$

leptin as the explanatory dependent variable we found no significant correlation ($R=0.02$, $p = .860$). In this subset of patients with undetectable HIV load, the median leptin value was 0.6 (6.07) ng/mL in patients with poor immune recovery (CD4 count ≤ 200 /cmm) compared to 2 (3.07) ng/mL for those with better immune response (CD4 count > 200 /cmm), without statistical significance ($p = .617$).

Leptin and metabolic syndrome

The prevalence of MS was 18.9% in hypoleptinemic patients and 8.9% for those with normal leptin values ($p = 0.380$, Table 1). The median values of leptin were similar for persons with and without MS criteria (1.96 vs. 1.8 ng/mL, respectively), $p = .752$. We evaluated all five components of MS in relation to leptin distribution. Leptin values were not correlated to

waist circumference ($R=0.07$, $p = .971$) or triglycerides ($R=0.04$, $p = .703$). The subjects with abnormal fasting glucose had a median value of serum leptin of 2 vs. 1.8 ng/mL for patients without glucose metabolic imbalances ($p = .979$). Similarly, hypertension did not influence leptin distribution (median values of 1.36 ng/mL in patients with elevated blood pressure vs. 1.97 ng/mL in the non-hypertensive group, $p = .671$).

HDL-cholesterol values were positively correlated to leptin values in a linear regression model ($p = .025$), with mild coefficients of correlation and determination (Table 2).

Multivariate analysis

In order to evaluate factors that may influence leptin we fitted a stepwise forward selection regression model. Several regression models were fitted, in which the dependent variable was LogLeptin and independent variables (BMI, abdominal circumference, age, time from HIV diagnosis, time on cART, CD4 count, serum lipids) were added in order to improve the statistical significance. After this stepwise forward selection, the best model included only HDL-cholesterol and BMI. Both variables were positively associated with LogLeptin variation with a moderate correlation coefficient (Table 3).

Discussion

We found a significant prevalence of leptin deficiency in our cohort of young HIV-infected

patients, which was not correlated to the duration from HIV diagnosis or the time on cART. Most males had hypoleptinemia and age increase was associated with leptin deficiency. We found no correlation between leptin expression and immune and virological parameters or the presence of MS. HDL dyslipidemia was the only component of MS that was influenced by leptin – lower levels were significantly correlated to the decrease of HDL-cholesterol.

Azzoni et al. reported in 2010 that leptin was inversely associated with HIV replication, independent of disease progression, in a cohort of patients without cART.⁶ Our observations do not support this association, but the two cohorts are not similar, as our patients were on stable cART for more than 6 months. Leptin may have important immune functions and in HIV-infected patients may be positively correlated to CD4+ T lymphocytes count. In a recent study published in 2015, Koethe et al. reported that higher pretreatment BMI in HIV patients is associated with a better immune CD4 count recovery (36 cells/cmm in women and 19 cells/cmm in men with BMI of 30 kg/sqm, compared to the reference BMI of 22 kg/sqm).¹¹ Leptin may be involved in this differentiated recovery, as this hormone seems to represent the link between the energy and nutritional status to the T helper immune response.¹² Matarese et al. have recently reported that administration of recombinant methionyl human leptin

Table 2. Linear regression model: effect of selected variables (leptin) on HDL-cholesterol (dependent variable)

Independent variable	Unstandardized coefficients (B)	95% confidence interval for B	Standardized coefficients (beta)	R	R square	<i>p</i> value
Leptin	0.724	0.094 – 1.355	0.238	0.238	0.057	.025

Table 3. Multiple linear regression model: effect of selected variables (BMI, HDL-cholesterol) on LogLeptin (dependent variable)

Independent variable	Unstandardized coefficients (B)	95% confidence interval for B	Standardized coefficients (beta)	<i>p</i> value	R	R square
BMI	0.051	0.022 – 0.079	0.399	.001		
HDL-cholesterol	0.011	0.003 – 0.019	0.294	.001	0.43	0.18

BMI body mass index.

(metreleptin) in women with acquired chronic hypoleptinemia and T-cell deficiency restored both T helper lymphocytes counts and in vitro proliferative responses.¹² We did not find a significant correlation between CD4 variation and leptin levels in our study. We also tested the hypothesis that leptin deficiency may be associated with poor immune status in persons with undetectable HIV load – a subset of patients that represents one of the most important current challenges in HIV management. The median leptin value was lower in patients with poor immune recovery when compared to those with CD4 lymphocytes counts above 200/cmm, but this result lacked statistical significance, probably due to the relatively low number of patients – a limitation of our study.

As leptin is associated with the regulation of fat storage it may influence key lipid and glucose metabolic parameters. The leptin/adiponectin imbalance may be correlated in the general population to an increased waist circumference and may elevate the risk of MS, a cluster of cardiometabolic risk factors in which excess adiposity and decreased insulin sensitivity are central features.¹³ In seropositive patients leptin deficiency was studied mainly in relation to HIV-associated lipodystrophy, in which leptin replacement may improve insulin sensitivity and decrease fat mass redistribution.¹⁴ Leptin deficiency did not increase the risk of MS in our patients and after analyzing each of the individual components in relation to this adipokine we found that HDL-cholesterol significantly decreased proportionately with leptin levels. Animal studies suggest that leptin may be involved in the regulation of lipid excretion pathways. Lundasen et al. studied in leptin-deficient *ob/ob* mice the expression of the hepatic HDL receptor, the scavenger receptor class B type I (SR-BI), and the LDL receptor. Compared to wild-type controls, *ob/ob* mice had reduced levels of SR-BI and short-term treatment with leptin led to a dose-dependent increase of this protein. The authors suggested that leptin was an important inducer of SR-BI and thus influences the levels of HDL-cholesterol.¹⁵ To our knowledge, available data for the assessment

of this relation in the general population is scarce and somewhat inconsistent. A study that evaluated non-diabetic subjects found that HDL-cholesterol was independent of serum leptin concentrations.¹⁶ Conversely, a study that assessed the influence of maternal diabetes on male offsprings reported that leptin is one of the most important determinants of HDL-cholesterol metabolism.¹⁷ A pilot study published by Mulligan et al. found that leptin therapy in lipoatrophic HIV patients increases HDL-cholesterol levels¹⁸. Our results support the hypothesis that at least in patients with HIV infection leptin is an important regulator of HDL-cholesterol metabolism and we speculate that this effect is mediated through hepatic SR-BI expression.

Despite some limitations of our study, such as the relatively low number of patients enrolled and the fact that correlations were small to moderate in magnitude, we consider that it brings relevant information to the HIV research field. Our cohort consisted mainly of young HIV-infected patients; a significant proportion of males had low levels of leptin, despite normal values of BMI, which may suggest adipose tissue dysfunction. Lower leptin levels were significantly correlated to decreased HDL-cholesterol, an observation that was rarely reported by previous studies for HIV-positive patients. We hypothesize that the treatment options for this type of dyslipidemia in HIV-infected patients should also include the management of leptin deficiency.

Conclusions

A significant proportion of our young HIV-infected cohort undergoing cART presented low serum levels of leptin. Leptin levels were not associated with immune and virological parameters or the presence of MS. Leptin influenced only one component of MS – HDL-cholesterol, which is an important factor for predicting major cardiovascular events.

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Conflicts of interest: All authors – none to declare.

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