

Metabolic syndrome in HIV-associated lipodystrophy

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ABSTRACT

Abstract Objectives The aim of our study was to describe the interaction and the overlapping features of lipodystrophy and metabolic syndrome in HIV-infected patients and verify the role of HIV viremia (viral load) on the development of metabolic abnormalities related to these conditions. *Methods* Cross sectional study of consecutive HIV-patients attending the Metabolic Clinic (MC) of Modena University (Italy) using NCEP-ATP III MS criteria. *Results* 361 patients were evaluated for anthropometry, DEXA, Triglycerides (TG), HDL-Cholesterol (HDL), Glucose (Glu), Insulin, Waist circumference (WC), Blood pressure (BP). Patients with MS (25.4% of our sample) differed significantly from patients without MS for the following anthropometric and metabolic variables: BMI (mean 24.9 [SD 3.7] vs 22.6 [3]; $p < 0.0001$), WHR (0.99 [0.07] vs 0.94 [0.07]; $p < 0.0001$), WC (91.34 [10.3] vs 83.86 [8.8]; $p < 0.0001$), trunk fat (7021.05 [3765.06] vs 5736.00 [2845.23]; $p < 0.001$), HOMA-IR (6.9[8.86] vs 4.01[6.4]; $p < 0.001$), HDL (34.55[10.14] vs 44.25[14.15]; $p < 0.0001$) and TG (283.3 [217.48] vs 202.38 [196.85]; $p < 0.0001$). We elaborated a statistical interaction that showed HIV has an impact on HDL and TG values while ART seems to affect TG more than HDL. *Conclusion* In conclusion we described the overlapping features of lipodystrophy and metabolic syndrome in HIV-infected patients. Insulin resistance appears to be the most relevant interaction between common metabolic and morphologic variables. Both HIV VL and HAART appear to be associated to these clinical syndromes.

Introduction

Combination antiretroviral therapy (ART) has improved the natural history of HIV infection leading to a significant reduction in morbidity and mortality. However, ART produces a spectrum of metabolic complications, including dyslipidemia, insulin resistance and changes in body fat compartmentalization known as lipodystrophy characterized by peripheral lipoatrophy, central fat accumulation or a combination of the two.

Metabolic syndrome (MS) is an aggregation of central obesity and metabolic abnormalities that confer an increased risk of cardiovascular disease (CVD) and type 2 diabetes (T2DM)[1]. The prevalence of MS in HIV infected individuals varies from 15 [2] to 25.5% [3] considering populations very different in ethnicity and habits.

Lipodystrophy (LD) and metabolic syndrome share common features with regard to biochemical parameters and consequently cardiovascular risk. An association between lipodystrophy and metabolic syndrome has been described [2, 4-6], but few data are available to establish the role of HIV itself and/or HAART on the development of MS in HIV-infected subjects.

HIV viral load (HIV-VL) may produce lipid abnormalities and insulin resistance both in ART naïve [3] and experienced HIV-infected people [7]. Some studies found an association between HIV-VL and MS [8-10] whereas others failed to find any relation between MS and the level of HIV-VL [2-5, 11].

The aim of our study was to describe the interaction and the overlapping features of lipodystrophy and metabolic syndrome in HIV-infected patients and verify the role of HIV viremia (viral load) in the development of metabolic abnormalities related to these conditions.

Materials and Methods

This is a cross-sectional study of consecutive patients attending the Metabolic Clinic (MC) of the University of Modena and Reggio Emilia. The clinic is a tertiary level referral center where patients receive comprehensive metabolic and anthropometric diagnostic assessments free of charge to evaluate the presence of LD. Likewise multidisciplinary treatment interventions are provided to manage diagnosed metabolic conditions. These include lipid lowering therapy, modification of antiretroviral therapy, physical therapy, dietary counselling, psychological support, facial surgery and liposuction[12]. Healthcare workers involved in the

diagnosis and treatment of infectious diseases include physicians, nutritionists, personal trainers for physical activities, psychologists, and plastic surgeons.

Data collection and the establishment of a photographic archive was authorized by the local institutional review board (IRB).

Patients considered eligible for study were those who had a physician-confirmed diagnosis of lipodystrophy using the Multicenter AIDS Cohort Study (MACS) definition[13] with or without other metabolic alterations.

MS was diagnosed when three or more of the following were present: abdominal obesity (men >102 cm; women, >88 cm), hypertriglyceridemia of 150 mg/dL or higher, low high-density lipoprotein (HDL) cholesterol (men<40 mg/dL; women<50 mg/dL), blood pressure (BP) of 130/85 mm Hg or higher or current use of antihypertensive medication, and fasting glucose of 100 mg/dL or higher, or previously diagnosed diabetes mellitus according to Adult Treatment Panel III criteria [14].

Interview data

We collected data from the following categories: demographic characteristics (age, race, sex); HIV infection history events (i.e. duration of infection HIV, CDC classification, type and duration of specific antiretroviral therapies). We also used a visual analogue scale to assess patient satisfaction with regard to their own facial and body appearance.

Laboratory studies

Patient data analyzed included the following: plasma CD4+ T-lymphocyte counts/cc3 (CD4); nadir CD4;

quantitative plasma HIV RNA levels (viral copies/ml³) using the Roche Amplicor Monitor (Roche Molecular Systems) with a lower limit of detection of 50 copies/ml³; fasting serum biochemistries including total cholesterol (TC), low density lipoprotein cholesterol (LDL), triglycerides (TG), blood glucose (Glu). We also used fasting serum insulin measurements to calculate HOMA-IR as a measure of insulin resistance.

Physical examinations

All patients underwent thorough physical examinations. We measured weight (in kg) after a 5h fast, height in cm by stadiometer, and circumferential measurements of waist, hip and thigh as the average of three measurements.

Statistical analysis

We analyzed the role of virological and immunological parameters and their relationships with metabolic abnormalities by a statistical interaction model generated by the MIM software[15].

Graphic Modelling is a approach to data analysis based on statistical models that can be displayed as graphs. In these graphs, nodes represent variables, and edges drawn between nodes represent conditional dependences. That is to say, a line or arrow is drawn between two nodes unless the two variables are conditionally independent given some or all of the remaining variables. The graphs supply precise representations of the interrelationships between the variables in the model. Being able to work directly with the graphs promotes an understanding of the dependence structure of the data [15].

Results

361 patients were evaluated for triglycerides, total cholesterol, HDL-cholesterol (HDL), glucose, waist circumference, blood pressure.

The prevalence of metabolic syndrome was 25.4%. LD was present in 88.3% of patients and was strongly associated with MS ($p<0.01$). Patient characteristics are summarized in Table 1.

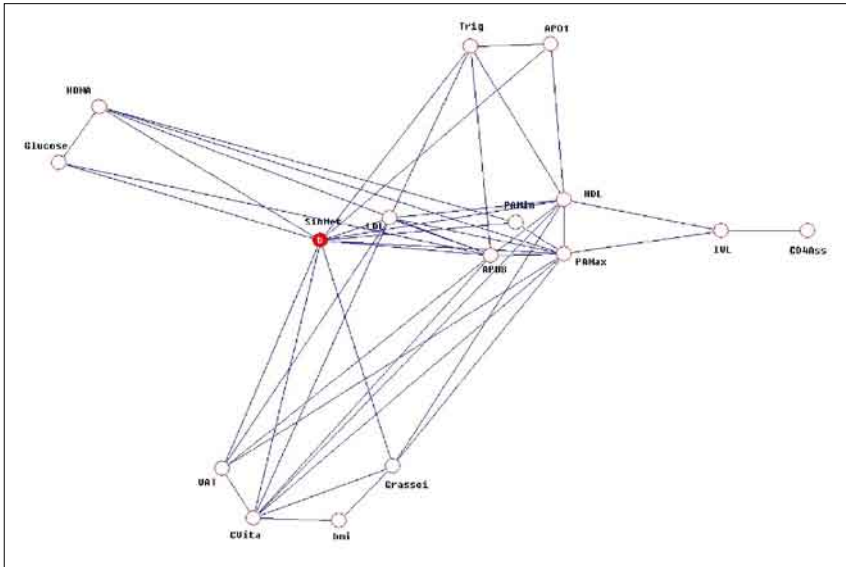
Patients with MS differed significantly from patients without MS for: metabolic variables (glucose, HDL cholesterol, triglycerides, ApoB, HOMA-IR, blood pressure), anthropometric variables (BMI, WC, LD phenotype) and HIV-VL and CD4 cell count.

Descriptive variables of lipodystrophy and diagnostic criteria for metabolic syndrome were plotted in the graphic model (Figure 1) to show the interaction and the overlapping features of metabolic and morphologic variables associated with

Table 1 Patients' demographics

	SM +, mean (SD)	SM -, mean (SD)	p
Female (%)	31.9	38.8	.266
Age, yrs	45.6 (7.77)	43.3 (7.2)	.009
CD4 nadir, cells/ μ L	181 (114)	177 (128)	.785
CDC group C (%)	18.1	25.0	.350
HOMA	6.90 (8.86)	4.01 (6.40)	.001
HDL (mg/dL)	34.55 (10.14)	44.25 (14.15)	<.0001
LDL (mg/dL)	109.22 (42.43)	111.11 (39.94)	.697
CH (mg/dL)	192.67 (53.97)	190.72 (53.52)	.761
TG (mg/dL)	283.30 (217.48)	202.38 (196.85)	.0001
BMI	24.9 (3.7)	22.6 (3.0)	<.0001
WHR	0.99 (0.07)	0.94 (0.07)	<.0001
Leg crf (cm)	47.8 (6.1)	46.7 (5.5)	.067
Leg Fat (cm)	2271.59 (1733.67)	2059.56 (1537.10)	.286
Trunk fat (gr)	7021.05 (3765.06)	5736.00 (2845.23)	<.001
Total fat (gr)	11605.16 (7007.13)	9650.08 (5238.71)	<.007
SAT (cm ²)	177.96 (156.10)	149.28 (116.06)	.174
VAT (cm ²)	183.04 (136.59)	144.07 (118.66)	.057
TAT (cm ²)	361.00 (218.0)	293.35 (165.33)	.024

FIGURE 1: Interaction model (grapho) between Metabolic and anthropometric variables.



Legend to figure

BMI= Body Mass Index, CD4Ass= Cd4 Absolute count, CVita=Waist circumference, GrassoI= total fat, PAmax= Systolic blood pressure, PAmin= Diastolic Blood Pressure, SinMet:Metabolic Syndrome, VAT= Visceral adipose tissue, IVL= HIV-VL

these conditions. HIV-VL, CD4 count and cumulative antiretroviral drug exposure were also added in the model.

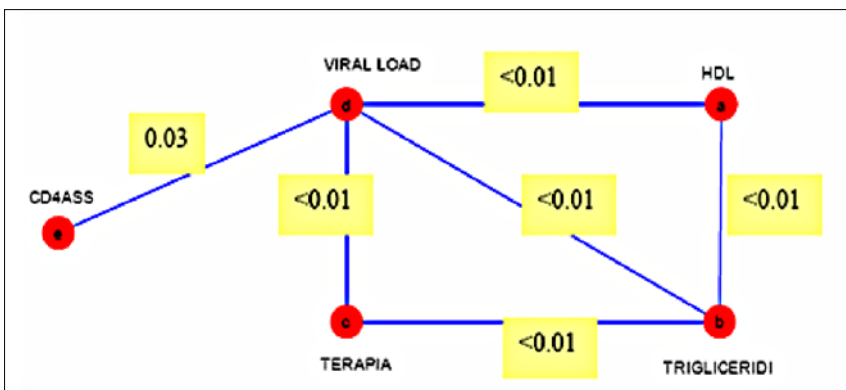
In our cohort metabolic syndrome was strongly related to high BMI and increased WHR as expected in the general population. In addition, it was associated with trunk fat mass evaluated by DEXA and lipohypertrophy.

No relationship was found between any class of antiretroviral drugs and CT measurements of adipose tissue and metabolic syndrome.

We found a strong association between fasting plasma insulin, HOMA-IR and Apo A1 and ApoB and diagnosis of metabolic syndrome (data not shown).

A second simplified Graphic model (figure 2) was built to better stress the impact of HIV viral load on HDL-cholesterol and triglycerides. ART seemed to affect triglycerides more than HDL.

FIGURE 2: Interaction model (Grapho) among HIV viral load, CD4 count, HDL-Chol (HDL), Triglycerides (TG) and ART.



MS was obviously associated with its diagnostic criteria; more interesting was the association of MS diagnosis with HOMA-IR, ApoB and total fat.

Discussion

MS prevalence in our population was 25.4%, higher than that reported by Bonfanti (20.8%) who studied a population similar in ethnic origin but very different in clinical characteristics. Our Metabolic Clinic selected people with LD (present in 88.3% of the sample) which may explain the higher prevalence of metabolic abnormalities in this population. Nevertheless LD co-morbidity was homogeneously distributed in patients with detectable or undetectable VL thus not influencing the objective of our study.

The statistical analysis disclosed a significant correlation between HIV-VL, HDL-cholesterol and triglycerides. Hypertriglyceridemia was a common feature in the wasting syndrome in the pre-HAART period and was probably related to the role of the cytokines network secondary to chronic viral infection [16-18].

Low HDL-cholesterol and high triglycerides are common features in insulin-resistant subjects with or without diabetes and are two alterations strongly correlated in the general population [19,20]. Our data confirm this evidence that was statistically significant.

As expected insulin resistance measured by HOMA-IR was much higher in patients with MS stressing the hypothesis of a possible common pathogenetic link between MS components. We stress the value of ApoB measure and its association with MS. This biochemical variable has recently been considered a better predictor of coronary heart disease than cholesterol and LDL-cholesterol, and it is not influenced by fasting at the time of blood testing [21].

The SMART study demonstrated a higher cardiovascular risk associated with CD4-guided treatment interruptions suggesting a role of HIV itself in increasing cardiovascular accidents [22].

Shrivastav et al. [23] recently showed in vitro that HIV-1 viral protein R (VPR) is a PPAR-γ suppressor inducing insulin resistance, and hypothesized a pathogenic driving force of metabolic syndrome.

We confirm higher BMI, VAT/TAT, trunk fat and total fat as expected in the general population. These results may help to explain the dual role of antiretroviral therapy on cardiovascular risk.

We can argue that ART reduces cardiovascular risk because it suppresses HIV replication that is a risk factor for the development of metabolic syndrome. On the other hand, therapy produces metabolic alterations such as insulin resistance which is the common

driving force of both lipodystrophy and metabolic syndrome.

In conclusion, we described the overlapping features of lipodystrophy and metabolic syndrome in HIV-infected patients. Insulin resistance appears to be the most important interaction between common metabolic and morphologic variables. Both HIV VL and HAART appear to be associated with these clinical syndromes.

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