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Factors Associated with Metabolic Syndrome in Middle-aged Women with and without HIV

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Abstract

MetS is associated with an increased risk of cardiovascular disease, increases after menopause and it is probably more frequent in HIV women.

Objective: To assess MetS and associated factors in HIV seropositive and seronegative middle-aged women.

Methods: Cross-sectional study with 537 women (273 HIV seropositive and 264 HIV seronegative), between 40 and 60 years' old receiving follow-up care in two medical centers in Brazil. MetS was diagnosed based on IDF criteria. Sociodemographic, clinical, and behavioral factors were evaluated.

Results: The prevalence of MetS in the HIV group was 46.9% and 42.2% in the seronegative group (P=0.340). Multiple regression analysis showed MetS association with body mass index (BMI)>25 kg/m² (PR=2.34; 95% CI: 1.70-3.21; P<0.001), aging (PR: 0.05, 95% CI: 1.02-1.07; P<0.001), and the use of highly active retroviral therapy (HAART) (PR: 1.48; 95% CI: 1.13-1.94; P=0.005).

Conclusions: There was no association between MetS and HIV status overall. Although HAART was associated with MetS, it seems that HIV-positive women in good immunological status, after early institution of HAART and its effective use, have traditional factors associated with MetS like being overweight and having older age.

Keywords: Metabolic syndrome X; Menopause; AIDS; Overweight

Introduction

After the emergence of the human immunodeficiency virus (HIV) infection, and introduction of use of highly active antiretroviral therapy (HAART) in the 1990s, treatment of HIV patients has evolved considerably. There has been a drastic reduction in morbidity, mortality, and occurrence of opportunistic infections, and an increase in life expectancy [1].with HIV-infection acquiring the characteristics of a chronic disease [2]. With the increase in life expectancy, many HIV-infected women live to reach menopause [3], and the number of perimenopausal women with HIV infection is increasing in Brazil and elsewhere in the world [4].

Despite reducing morbidity and mortality, HAART is not without risk and is associated with some adverse effects [5-7], including metabolic abnormalities such as insulin resistance, diabetes, dyslipidemia, and body fat redistribution with increased waist circumference [8]. The natural course of HIV infection is characterized by low levels of high density lipoprotein (HDL) and low density lipoprotein (LDL), and increased levels of triglycerides (TG) [9]. With the introduction of HAART, more atherogenic changes in the lipid profile, including increased TG and LDL and decreased HDL have been observed [5-7].

The pathogenesis of dyslipidemia related to HAART is complex and involves multiple drug-induced effects, in combination with hormonal and immunological effects. Postmenopausal women who experience low estrogen levels have an increased risk of hypertension, dyslipidemia, diabetes, and cardiovascular disease (CVD) compared with premenopausal women [10]. Menopause is associated with lower energy consumption and consequent weight gain, with increased central fat deposition [10]. Thus, HIV-infected post-menopausal women have metabolic risks not only from HIV infection and HAART but also from the consequences of estrogen reduction. These metabolic changes can contribute to metabolic syndrome (MetS), defined as a complex disorder represented by a cluster of cardiovascular risk factors commonly associated with central fat deposition, insulin resistance, hypertension, and dyslipidemia [11].

There are many operational definitions for MetS [12-14]. The International Diabetes Federation (IDF) diagnostic criteria for MetS in women are: waist circumference ≥ 80 cm and two or more of the following factors: TG ≥ 150 mg/dL or treatment for this abnormality; HDL cholesterol<50 mg/dL or treatment for this abnormality; systolic blood pressure (BP) ≥ 130 mmHg or diastolic BP ≥ 85 mmHg or treatment for previously diagnosed hypertension; fasting plasma glucose (FPG) ≥ 100 mg/dL, or previously diagnosed type 2 diabetes [14].

MetS is associated with an increased risk of CVD both in HIV negative [11] and in HIV-infected individuals, [15,16] which is the main cause of death in men and women and its incidence in premenopausal women is lower than in men of the same age. This sex difference decreases with age, and women have the same risk as men after menopause [17]. Thus, ovarian failure appears to be an important cardiovascular risk factor. Hypoestrogenism leads to central adiposity and increased insulin resistance [18]. Several studies have reported a higher prevalence of MetS in postmenopausal women compared with premenopausal women [19-23]. The prevalence of MetS in postmenopausal women is 22% to 69%, varying from one country

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to another and with the criteria used to diagnose MetS [21-23]. The prevalence of MetS in Brazilian postmenopausal women ranges from 34.7% to 56.9% [24-26]. World data show a higher prevalence of MetS in HIV patients than in the general population, [27,28] with increased risk of death from CVD, independent of factors such as age, sex, dyslipidemia, exercise, and smoking. This presents a major challenge to professionals involved in the care of HIV-infected individuals.

Some studies in HIV-positive patients have evaluated MetS in men and women of different age groups, [1,27-30] and many studies have evaluated MetS in climacteric women without HIV [21-26]. However, there is a lack of information specifically with regard to the impact of HIV infection on MetS in climacteric women. The study aimed to determine the prevalence and the factors associated with MetS in women in women aged between 40 and 60 years, with and without HIV infection.

Methods

Subjects

This cross-sectional study recruited women aged 40–60 years who were receiving care at the Menopause Outpatient Clinic at the University of Campinas (UNICAMP) Clinical Hospital and at the Infectious Diseases and HIV Outpatient Clinic at the UNICAMP Clinical Hospital and the Eduardo de Menezes Hospital (HEM) in Belo Horizonte, Brazil. Determination of the sample size was based on the difference in prevalence of MetS between HIV-positive and HIV-negative groups of 13 percentage points [19-26]. Considering an α error of 0.05 and a β error of 0.20, the sample size required to evaluate MetS was calculated as 242 women in each group. All women who fulfilled the inclusion criteria were invited to participate in the study. Interviews were carried out with 537 women, 273 HIV-positive and 264 HIV-negative.

HIV seropositive status was confirmed by enzyme-linked immunosorbent assay or western blotting, while women recruited to the HIV-negative group had to have a negative HIV test. Menopause status was determined by state in relation to menopause, reported by women using the definition of Jaszmann and classified as: pre-menopausal (women with regular menstrual cycles or menstrual pattern similar to what they had during their reproductive life), peri-menopause (women with menstrual cycles in the past 12 months, but with change in menstrual pattern as the previous standards) and postmenopausal (women whose last menstrual period occurred at least 12 months before the interview). Menopausal status in women with previous hysterectomy was confirmed according to the serum levels of follicle stimulating hormone (FSH) on any day and classified as: premenopausal (<10 mIU/mL); menopausal transition (≥10 and <30 mIU/mL); and postmenopausal (≥30 mIU/mL). Bilaterally oophorectomized women, nursing mothers, pregnant women and those unable to answer the study questionnaire were excluded from the study.

Main outcome measures

A structured questionnaire was completed during an interview held in a private setting. Demographic and lifestyle data were collected, as well as information on hormone status and reproductive cycle. At the same visit, waist circumference, BP, weight and height were measured, and body mass index (BMI) was calculated. Blood samples were collected to measure fasting glucose, HDL cholesterol, TG, follicle-stimulating hormone (FSH), thyroid-stimulating (TSH), and free T4 levels. Diagnosis of MetS was based on the IDF criteria as mentioned above [14].

Independent variables

The main independent variable was HIV status. Other independent variables evaluated were age (years- continuous variable); skin color (white/other); physical activity in the previous month (none or up to twice a week/three times a week or more); schooling (<8/≥8 years); family income (≤US$ 750,00/>US$ 750,00); number of residents in the home (≤2/>2); smoking habit (none or past/current); current consumption of alcoholic beverages (yes/no or never drank); menopausal status (pre or perimenopausal/postmenopausal); weight gain (yes/no); use of hormone therapy (yes/no); self-perception of health (good or excellent/not so good or bad); use of HAART (yes/no); other chronic diseases (yes/no); BMI (normal/abnormal); FSH (normal/abnormal); TSH (normal/abnormal); and free T4 (normal/abnormal).

Data analysis

The association between the dependent variable MetS and predictive factors was evaluated. Yates and Fisher's chi-square tests were used to compare categorical variables between groups with and without MetS. Poisson multiple regression analysis was adjusted in the various models for each of the independent variables to evaluate the factors associated with MetS. The backward manual selection method was used in which all variables were initially included, with those that were not significant being excluded, one by one, until only variables with $P<0.05$ remained in the final model. The prevalence ratio (PR) with 95% confidence interval (CI) of MetS was determined according to each factor. Data were analyzed using SPSS, version 17.0 (SPSS Inc., Chicago, IL, USA) and Stata, version 7 (Stata Corp., College Station, TX, USA).

Ethics

The study was approved by the internal review board of CAISM (Integral Care Center for Women's Health)- UNICAMP- and was conducted in compliance with the current version of the Declaration of Helsinki and with Resolution 466/12 of the Brazilian National Committee for Ethics in Research (CONEP) and its subsequent revisions. This study forms part of a larger study evaluating menopausal symptoms, bone mass, sexual function and metabolic markers. Process: Committee for Ethics in Research (CEP): 407/2010, Certificate of Presentation for Ethical Consideration (CAAE): 0313.0.146.000-10. All women gave signed informed consent for participation in the study.

Results

The mean age was 47.7 years in HIV seropositive women and 49.8 years in HIV seronegative women ($P<0.001$). Most HIV seropositive women had a body mass index<25 kg/m^2 (51.6%), while in the HIV seronegative women with a BMI<25 kg/m^2 accounted for 29.3% ($P<0.001$). Other characteristics of the groups are shown in Table 1.

The prevalence of MetS in the HIV group was 46.9% compared with 42.2% in the HIV-negative group, a non-significant difference ($P=0.340$).

In the 273 patients with HIV, 91% were taking HAART, and approximately 74% had a nadir CD4 above 200/mm^3. The main risk factor for acquisition of the infection was heterosexual transmission, the mean duration of infection was 9.9 years, and the mean duration of therapy was 9.4 years (Table 1).

Table 2 shows the stratified analysis of women with MetS in relation to HIV infection. The factors significantly associated with MetS in HIV women were being postmenopausal ($P=0.032$), self-rated health considered excellent/good ($P=0.011$), and BMI>25 kg/m² ($P=0.005$).

Characteristics	Group		*p-value*
	HIV-seropositive (n=273)	HIV-seronegative (n=264)	
Age (years)			
40 – 44	36.60%	20.40%	<0.01
45 – 49	27.50%	28.00%	
50 – 54	19.00%	27.70%	
≥55	16.90%	23.90%	
BMI (kg/m²)			
<20.00	12.50%	1.50%	<0.01
20.00 – 24.99	39.10%	27.80%	
25.00 – 29.99	35.40%	36.90%	
≥30.00	12.90%	33.80%	
Skin color			
White	39.90%	48.10%	0.07
Non-white	60.10%	51.90%	
Schooling (years)			
≤7	58.20%	39.40%	<0.01
8-11	26.70%	37.90%	
≥12	15.10%	22.70%	
Menopausal status			
Premenopause	33.70%	22.00%	<0.01
Perimenopause	25.60%	20.00%	
Postmenopause	40.70%	58.00%	
Smoking			
Yes	28.60%	14.80%	<0.01
No	50.90%	58.00%	
Unknown	20.50%	27.20%	
Alcoholism			
Yes	29.70%	12.60%	<0.01
No	36.30%	78.60%	
Unknown	34.00%	8.80%	
Time since HIV diagnosis (years)	9.9 ± 5.4 y		
Nadir CD4 < 200 (%)	25.6		
In use of TARV (%)	91.0		
Time using TARV (years)	9.4 ± 4.8 y		
Previous or actual use of PI (%)	53.2		
Last CD4 cell count (cells/mm³)			
0-199	7.6		
≥200	92.4		
	76.9		
Quantitative viral load (copies/mL)	23.1		

Pearson's Chi-square; Yates's Chi-square; Mann-Whitney's test

Table 1: Characteristics of middle-aged women in HIV seropositive and seronegative groups (n=537).

Table 3 shows the prevalence of each of the MetS diagnostic criteria in postmenopausal women with or without HIV infection. Waist circumference ≥ 80 cm was present in all cases as it is the essential IDF criterion for MetS diagnosis. The other most prevalent factors in descending order were HDL<50 mg/dL, BP ≥ 130/85 mm Hg, TG ≥ 150 mg/dL, and blood glucose ≥ 100 mg/dL. The HIV-positive women had a worse lipid profile when compared to HIV-negative ones, with low HDL (P=0.019) and high TG (P=0.011).

In the multiple regression analysis of all women, MetS was significantly associated with BMI>25 kg/m² (PR: 2.34; 95% CI: 1.70–3.21; P<0.001), aging (PR: 1.05; 95% CI: 1.02–1.07; P<0.001), and use of HAART (PR: 1.48; 95% CI: 1.13–1.94; P=0.005) (Table 4).

	Metabolic Syndrome (%)				
Variable	**HIV+ (%)**	**n**	**HIV- (%)**	**n**	***P(x)***
Age (years)					
40–49	39.3	64	31.0	35	0.199
50–60	60.2	56	52.4	65	0.314
Skin color					
Other	48.0	72	45.2	56	0.728
White	45.3	48	38.9	44	0.416
Physical activity (a)					
0–2 /week	46.5	93	39.8	74	0.220
≥3 /week	47.3	26	51.0	26	0.852
Formal education (years)					
0–7	55.0	83	49.0	48	0.427
≥8	35.2	37	37.4	52	0.830
Family income (US$) (b)					
≤750.00	48.4	78	44.4	48	0.603
>750.00	43.6	41	39.8	51	0.670
House residents ©					
≤2	52.0	53	46.0	29	0.562
>2	43.8	67	41.0	68	0.691
Smoking					
No/past	45.9	84	40.4	82	0.323
Yes	49.3	36	52.9	18	0.887
Alcohol use					
No/past	47.5	87	43.1	91	0.438
Yes	45.2	33	34.6	9	0.479
Menopausal status					
Pre or peri	37.3	57	35.8	34	0.823
Postmenopausal	61.2	63	46.5	66	**0.032**
Hormone therapy (d)					
No	46.2	115	44.8	87	0.853
Yes	80.0	4	28.6	12	**0.040(y)**
Self-perception of health (d)					
Excellent/good	47.6	78	32.6	46	**0.011**
Not so good/bad	45.6	41	55.8	53	0.213
Other chronic diseases (e)					
No	44.3	74	43.7	62	>0.999
Yes	48.8	40	41.1	37	0.392
BMI (kg/m²) (b)					
≤25	28.7	39	19.7	13	0.231
>25	68.1	81	50.6	86	**0.005**
FSH (mIU/mL) (f)					
<40	37.2	51	34.8	31	0.823
≥40	58.7	61	47.2	67	0.099
TSH (mIU/mL) (g)					
≤4.5	46.0	99	41.7	86	0.429
>4.5	54.8	17	46.4	13	0.701
Free T4 (ng/dL)					
<0.90 or >1.80	51.5	17	35.7	5	0.501
0.90–1.80	46.7	99	42.5	94	0.438

(x) Yates chi-square test, (y) Fisher's exact test.
BMI: Body Mass Index; FSH: Follicle-stimulating Hormone; TSH: Thyroid-stimulating Hormone.
Missing information: (a) One in the HIV group; (b) One in each group; (c) Eight in the control group; (d) One in the control group and two in the HIV group; (e) Five in the control group and seven in the HIV group; (f) Six in the control group and 15 in the HIV group; (g) Three in the control group and 10 in the HIV group.

Table 2: Bivariate analysis of patients with metabolic syndrome according to HIV status (n=220).

VARIABLES	HIV+ (%) (n = 187)	HIV- (%) (n = 201)	*P*(a)	TOTAL (n = 388)
Waist circumference				
<80 cm	0	0		0
≥80 cm	100	100		100
Blood pressure			0,833	
<130/85 mm Hg	48.7	50.2		49.5
≥130/85 mm Hg	51.3	49.8		50.5
High density lipoprotein			**0,019**	
<50 mg/dL	56.7	44.3		50.3
≥50 mg/dL	43.3	55.7		49.7
Triglycerides			**0,011**	
<150 mg/dL	57.2	70.1		63.9
≥150 mg/dL	42.8	29.9		36.1
Glucose			0,470	
<100 mg/dL	75.4	71.6		73.5
≥100 mg/dL	24.6	28.4		26.5

(a) Yates chi-square

Table 3: Prevalence of each metabolic parameter according to HIV status in climacteric women with metabolic syndrome (n = 388).

VARIABLES	PR	95%CI	*P*
BMI (>25 kg/m²)	2.34	1.70–3.21	<0.001
Use of HAART (Yes)	1.48	1.13–1.94	0.005
Age (years)	1.05	1.02–1.07	<0.001

PR: prevalence ratio; **95% CI:** 95% confidence interval.
Missing information: (a) 46 in the whole group.
Variables considered to backward selection: age (years); skin color (white / other); physical activity (0–2 times per week / ≥3 times per week); education (0–7 years / ≥8 years); family income (≤ US$ 750.00 / >US$750.00); house residents(up to 2 / >2); smoking (yes / no); alcohol consumption (yes / no); menopausal status (pre or perimenopause / menopause); weight gain (yes / no); hormone therapy (yes / no); self-rated health (excellent or good / not so good or bad); use of HAART (yes / no); other chronic diseases (yes / no); BMI (≤25 />25 kg/m²); FSH (<40 / ≥40); TSH (≤4.5 / >4.5); free T4 (<0.90 or >1.80 / 0.90 to 1.80); group (HIV / control).

Table 4: Multiple regression analysis of the variables associated with the presence of metabolic syndrome in the total sample -HIV positive and negative women [n = 537 (a)].

Discussion

The prevalence of MetS was 46.9% and 42.2% in HIV-positive and HIV-negative women, respectively, and was similar to the rates of 22% to 69%, reported in studies that included individuals in different age groups who were HIV-positive [1,27-30].

Although there are many reports of adverse metabolic changes in HIV-positive patients in general, the effect of such changes on the development of MetS is still controversial [27,28]. No studies specifically evaluating the prevalence of MetS in HIV-infected climacteric women were found. The present study was based on the hypothesis that the prevalence of MetS would be higher in HIV-positive than in HIV-negative climacteric women. Nevertheless, in the present study HIV infection was not associated with MetS or any single parameter of MetS. The absence of an association between HIV and MetS could be related to the specific characteristics of our study population, such as good immunological status after early institution of HAART and its effective use. Krishnan et al. evaluated MetS before and after the introduction of HAART, and reported that virologic suppression and maintenance of high CD4 levels could reduce the risk of MetS [30].

There was a significant difference in the prevalence of MetS in HIV-seropositive women compared with seronegative women who perceived their health as excellent/good in the present study. The stigma of HIV infection is related to thinness and lipodystrophy, [31,32] and it is possible that overweight could be considered a sign of health in these women rather than associated with MetS.

In the stratified analysis of factors associated with MetS according to HIV status, it was observed that HIV-positive women had a significantly higher prevalence of MetS if they were postmenopausal and had BMI>25 kg/m². This BMI association remained in the multivariate analysis, which showed that BMI>25 kg/m² was associated with a 1.34-fold increased risk of MetS.

In present study, the HIV study population was composed mostly of HAART users, and multiple regression analyses showed that the use of HAART was associated with more than twice the risk of MetS. The use of HAART has been well documented in the literature as an independent risk factor associated with MetS [1,33,34]. Signorini suggested that longer exposure (mean duration of therapy of 54 (± 36) months to HAART appeared to be associated with MetS [1]. Cahn also observed an association between long-term exposure to HAART and MetS in a study conducted in seven Latin American countries [34]. These studies included patients of both sexes aged over 18 years, in contrast to the present study, which evaluated only middle-aged women. Although MetS has been attributed to the effect of HAART, we cannot forget that aging is an important contributing factor. As HIV-seropositive patients grow older, the risk of MetS seems to increase [1,35,36]. Ramírez-Marrero conducted a study in Hispanic patients and found that older HIV patients were more likely to have MetS than younger patients, and that there was a higher prevalence in females [35]. Freitas also reported a higher prevalence of MetS in HIV patients aged older than 40 years in Portugal [36]. Signorini observed an association between MetS and aging in a study in a Brazilian HIV-infected population [1]. This study has limitations. It is a cross-sectional study, so causal relationships cannot be attributed. There were differences between the groups of HIV seropositive and seronegative women that undermined the homogeneity of the samples. Furthermore, there were some differences in the clinical characteristics of the seropositive and seronegative women. These differences could be attributed to the fact that the seronegative women were selected in outpatient clinics specialized in providing care to menopausal women, and 78% were peri or post menopause. On the other hand, in the HIV positive group 66.3% were peri or post menopause. The HIV-negative women also had greater BMI, older and had higher scholarity. However, these differences have been controlled in the multivariate analysis. In addition, the HIV-positive group had good immunological status as demonstrated by viral suppression and high CD4 levels. As these women were treated at multidisciplinary referral centers for HIV infection, the results cannot be extrapolated to the general population infected with HIV.

Conclusions

In this study, there was no association between MetS and HIV status among middle-aged women. However, HIV-positive women who were postmenopausal or had a high BMI showed a significantly higher prevalence of MetS with otherwise similar characteristics. It seems that HIV-positive women in good immunological status, after early institution of HAART and its effective use, have traditional factors associated with MetS like being overweight and having older age. There is a need for a better approach, awareness, and education of both HIV-positive and HIV-negative women to prevent and MetS. For HIV-positive middle-aged women, using effective HAART with fewer adverse effects on metabolism is an important aspect to prevent MetS.

This should be considered in clinical practice to reduce the risk of MetS in this population.

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Conflict of Interest

None declared.

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