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Metabolic Syndrome and Subclinical Atherosclerosis in Patients Infected with HIV

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Abstract

Background—The present study examines the association between carotid and coronary atherosclerosis and metabolic syndrome in human immunodeficiency virus (HIV)–infected adults.

Methods—We measured the common and internal carotid intima-media thickness (c-IMT) using B-mode ultrasonography, and we measured coronary artery calcium (CAC) using high-resolution, electrocardiographic, synchronized, computed tomography, for 314 HIV-infected men and women. Metabolic syndrome was defined by National Cholesterol Education Program/Adult Treatment Panel III criteria. We compared the c-IMT measurements and CAC scores of patients with metabolic syndrome with the scores of those without metabolic syndrome using a Wilcoxon test for continuous variables and a χ^2 test for categorical variables. To examine the association between surrogate markers and metabolic syndrome, we used logistic regression analysis.

Results—Participants with metabolic syndrome were more likely to have a common c-IMT measurement >0.8 mm than were those without metabolic syndrome (17% vs.7%; *P*=.009), but both groups were equally likely to have an internal c-IMT measurement >1.0 mm (20% vs. 13%; *P*=.15). Any positive CAC score was more likely to occur for participants with metabolic syndrome (80.3% vs. 46.7%; *P* < .0001). In a multivariate model adjusted for sex, age, ethnicity, and smoking status, participants with metabolic syndrome were more likely than those without metabolic syndrome to have an abnormal common c-IMT measurement (odds ratio [OR], 2.9; *P*= .020) and detectable CAC scores (OR, 4.9; *P* < .0001) but not a higher internal c-IMT measurement (OR, 1.6; *P*=.255).

Conclusion—Our study demonstrates that HIV-infected individuals with metabolic syndrome may be at increased risk for subclinical atherosclerosis and supports screening for metabolic syndrome among HIV-infected patients at risk for cardiovascular disease.

Metabolic syndrome is prevalent in both the general population and the HIV-infected population [1–3], and according to the National Cholesterol Education Program/Adult Treatment Panel III criteria, it is characterized by ≥3 of the following abnormalities: abdominal obesity, hypertriglyceridemia, a low high-density lipoprotein (HDL) cholesterol level,

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hypertension, and insulin resistance [4,5]. It is well established that individuals with metabolic syndrome have increased risk of cardiovascular morbidity and mortality [6]. Some abnormalities observed in HIV-associated lipodystrophy overlap with the components of metabolic syndrome, and there is increasing evidence that there is an elevated risk of premature atherosclerosis and adverse cardiovascular events among HIV-infected adults [7,8]. The metabolic and morphologic abnormalities associated with HIV infection include dyslipidemia (high triglyceride levels and a low HDL cholesterol level), insulin resistance, and visceral fat deposition; these abnormalities are more commonly observed in or are more extreme in patients treated with HAART than in treatment-naive patients. Additionally, hypertension is an important cardiovascular risk factor, and elevated blood pressure has been described in HIV-infected patients receiving antiretroviral therapy [9]. Proinflammatory and prothrombotic states also commonly occur in both metabolic syndrome and HIV infection and contribute to cardiovascular risk [10–12].

Subclinical carotid and coronary atherosclerosis are independent predictors of adverse cardiovascular events. Thus, measurement of atherosclerotic disease activity is important for early detection of cardiovascular disease [13,14]. Previous studies have shown a significant relationship between subclinical atherosclerosis assessed by carotid ultrasound or CT and metabolic syndrome among the general population [15,16]. It has also been shown that persons with metabolic syndrome have a faster rate of progression of carotid and coronary atherosclerosis and, hence, have an increased risk of cardiovascular morbidity and mortality [15]. The use of surrogate markers of atherosclerosis in HIV-infected adults is currently under investigation [17–27]. Recent studies have indicated that HIV-infected patients have more abnormal surrogate markers and faster rates of progression of atherosclerosis than do HIV-uninfected individuals [28,29]. It is unclear, however, whether this observation is associated with traditional and emerging cardiovascular risk factors or HIV-specific factors. We previously reported a high rate of abnormal carotid intima-media thickness (c-IMT) and coronary artery calcium (CAC) scores [30]. These surrogate markers of atherosclerosis were primarily associated with traditional and novel cardiovascular risk factors but not yet with HIV infection and treatment.

Currently, there are very limited data in the literature documenting the association between carotid or coronary atherosclerosis and metabolic syndrome in HIV-infected patients. The aim of the present study was to assess the frequency and degree of carotid and coronary atherosclerosis in HIV-infected adults defined as having metabolic syndrome, compared with those who do not have metabolic syndrome.

SUBJECTS, MATERIALS, AND METHODS

Subjects

We enrolled 314 HIV-infected men and women from a cardiovascular substudy of a longitudinal study, Nutrition for Healthy Living (NFHL), which examined nutritional and metabolic factors in HIV-infected patients. The NFHL cohort began in 1995 and followed participants at 6-month intervals until 2005. Additional details of this study have been reported elsewhere [31]. For this cross-sectional analysis, ultrasounds and CT were performed periodically during the period from 23 January 2002 through 31 March 2004. All patients provided informed consent for the NFHL study and for the cardiovascular substudy. All studies were approved by the Institutional Review Board at Tufts–New England Medical Center.

Clinical data

Demographic information from interview-administered questionnaires and clinical data were obtained within 3 months of the carotid ultrasound and the CT. Cigarette smoking and injection

drug use were classified as “past,” “current,” or “never.” Systolic and diastolic blood pressures were assessed (at the same time the laboratory measurements were assessed) with the Omron Regency digital automatic blood pressure monitor after participants had been seated for 5 min with their feet on the floor and their arms supported at heart level. Height (±0.1 cm), weight (±0.1 kg), and body composition (waist circumference and tricep skinfold thickness) were measured using standardized techniques by research personnel trained in anthropometry [32]. Body mass index was calculated as weight in kilograms divided by the square of height in meters. HAART was defined as the use of ≥3 drugs, with ≥1 protease inhibitor or a nonnucleoside reverse-transcriptase inhibitor. HAART, protease inhibitor, and nonnucleoside reverse-transcriptase inhibitor use and individual antiretroviral medications were reported as “current use.”

Laboratory values

Plasma total cholesterol, triglyceride, and HDL cholesterol levels were measured on a Hitachi 911 chemistry analyzer (Roche Diagnostics) using standard enzymatic methods [33]. Low-density lipoprotein cholesterol levels were measured directly using kits from Roche Diagnostics. Homocysteine, high-sensitivity C-reactive protein, fasting glucose, and insulin levels were measured at the same time the lipid levels were measured. QUICKI, a measure of insulin sensitivity, was calculated from insulin and glucose levels, using the formula [1/(log [insulin level] + log [glucose level])]. CD4 cell counts were measured by flow cytometry, and HIV RNA levels were obtained at the same time point using kits from Roche Diagnostics (limit of detection, 400 copies/mL).

Definition of metabolic syndrome

Metabolic syndrome was diagnosed in accordance with National Cholesterol Education Program/Adult Treatment Panel III criteria [2]. Participants with ≥3 of the following abnormalities were defined as having metabolic syndrome: (1) abdominal obesity (waist circumference, >102 cm for men and >88 cm for women), (2) hypertriglyceridemia (triglyceride level, >150 mg/dL); (3) a low HDL cholesterol level (<40 mg/dL for men and <50 mg/dL for women), (4) high blood pressure (≥130/85 mm Hg), and (5) a high fasting glucose level (≥110 mg/dL). Participants with a diagnosis of diabetes or who were receiving treatment for diabetes were classified as having a high fasting glucose level, and those receiving antihypertensive medications were defined as having high blood pressure.

C-IMT assessment

To ensure the use of standardized methods for the scanning and interpretation of the c-IMT measurements, we used protocols adapted from the Cardiovascular Health Study, as developed by O’Leary et al. [34]. Centrally-trained and certified ultrasonography specialists performed the imaging, and a single reader at a central reading site read the c-IMT measurements. One longitudinal lateral view of the distal 10 mm of the right and left common carotid artery and 3 longitudinal views in different imaging planes (anterior, lateral, and posterior) of the right and left internal carotid artery were obtained. The mean of the peak of the near- and far-wall c-IMT measurements for both arteries were used for the final analysis, because these areas have been shown to have the strongest association with cardiovascular risk factors [35]. To quantify degree of carotid artery wall thickening, all measurements were summarized into 2 variables, 1 for the common carotid artery and 1 for the internal carotid artery. C-IMT measurements were used as a continuous measure or stratified as ≥0.8 mm and <0.8 mm for the common c-IMT measurement and ≥1.0 mm and <1.0 mm for the internal c-IMT measurement, to define incident nonstenotic atherosclerosis.

CAC score measurements

The CAC score was obtained using ultrafast computed coronary calcium scanning, as described in previous studies [36,37]. An electrocardiographic data file, acquired during the scan, was used to select a single image for each scan group, with the goal of minimizing image degradation due to heart motion. The initial image selection was performed automatically using rules based on the image position within the scan group. After the image selection was complete, the operator identified the particular pixel regions within the images that were to be considered for calcium scoring. The calcification scores were computed using standardized scoring techniques [38]. For our analysis, CAC scores were used as a continuous variable or stratified as 0, 1–100, and >l00. Any detectable score was defined as >0. CAC scores >100 were defined as significant atherosclerotic disease.

Statistical analysis

The present study was a cross-sectional analysis of 314 NFHL participants. Analyses were performed with SAS for Windows, version 9.0 (SAS Institute). After distribution assumptions were tested, nonnormally distributed variables were transformed by obtaining the natural logarithm prior to analysis. Log transformations of the c-IMT measurements and the CAC scores were used for significance testing, but all descriptive data were presented using nontransformed values. Because the normal CAC score value is 0, 1 was added prior to log transformation [*ln*(1 + CAC score)]. In univariate analysis, we evaluated the difference in the c-IMT measurement and the CAC score by the presence or absence of metabolic syndrome, using general linear models. The proportion of participants with abnormal surrogate marker cutoffs because of the presence of metabolic syndrome was assessed using a χ^2 test. In multivariate analysis, we determined the ORs and 95% CIs for each binary outcome among participants with or with-out metabolic syndrome—unadjusted and adjusted for age, sex, smoking status, and ethnicity—using generalized estimating equations. *P* values <.05 were considered to be statistically significant.

RESULTS

Sociodemographic and clinical characteristics

Sociodemographic and clinical characteristics of the HIV-infected participants with and without metabolic syndrome are shown in table 1. Of the 314 participants, 22.9% fit the criteria for having metabolic syndrome. The prevalence of each of the components of metabolic syndrome was as follows: abdominal obesity, 26.8%; high triglyceride level, 43.8%; low HDL cholesterol level, 58.8%; high blood pressure, 25.7%; and high glucose level, 5.8%. The prevalence of metabolic syndrome increased from 21.0%, among participants aged <50 years, to 31.2%, among those aged ≥50 years (*P*=.089). Of the various traits constituting metabolic syndrome, only the prevalence of hypertriglyceridemia increased significantly (from 39.4% to 61.7%; *P*=.002) with advancing age. Significantly more women than men had metabolic syndrome. In addition to the parameters defining the syndrome, participants with metabolic syndrome also had significantly higher body mass indices, tricep thickness measurements, apolipoprotein E levels, remnant lipoprotein cholesterol levels, and insulin levels. QUICKI was significantly lower in patients with metabolic syndrome. When QUICKI was compared among participants with normal glucose measurements only, QUICKI remained significantly lower in those with metabolic syndrome than in those without metabolic syndrome (0.33 ± 0.033 vs. 0.35 ± 0.032; *P* < .0001), indicating that there was more insulin resistance among those with metabolic syndrome, irrespective of hyperglycemia. There were trends for the apolipoprotein B and the high-sensitivity C-reactive protein levels to be higher in participants with metabolic syndrome. Of the HIV-specific factors, viral loads were higher in participants with metabolic syndrome than in those without metabolic syndrome (*P*=.032). All other HIV-specific factors did not differ between participants with and without metabolic syndrome.

Surrogate markers and metabolic syndrome

The unadjusted associations between metabolic syndrome and surrogate markers are shown in table 2. The mean common c-IMT measurement was significantly higher among participants with metabolic syndrome than among those without metabolic syndrome (0.66 mm vs. 0.59 mm; *P*=.005). There was a trend for the internal c-IMT measurement to be greater among participants with metabolic syndrome (0.79 mm vs. 0.70 mm; *P*=.072). When common and internal c-IMT measurements were compared using the previously defined thresholds (common c-IMT measurement, ≥0.8 mm; and internal c-IMT measurement, ≥1.0 mm), we found a consistently higher prevalence of incident atherosclerosis among participants with metabolic syndrome, compared with those without metabolic syndrome, but this difference was only significant for the common c-IMT measurement. When c-IMT measurements were compared using individual components of metabolic syndrome, participants with abdominal obesity had significantly greater common c-IMT measurement than those without abdominal obesity (0.65 mm vs. 0.59 mm; *P*=.009). In addition, participants with elevated blood pressure had significantly greater common c-IMT (0.65 mm vs. 0.59 mm; *P*=.002) and internal c-IMT measurements (0.81 mm vs. 0.69 mm; *P*=.002) than those with normal blood pressure. Participants with elevated triglyceride levels had a significantly greater internal c-IMT measurement than those with normal triglyceride levels (0.78 mm vs. 0.68 mm; *P*=.036), and there was a trend for a greater common c-IMT measurement in participants with elevated triglyceride levels, compared with those with normal triglyceride levels (0.63 mm vs. 0.59 mm; *P*=.051). For all other components, there was no significant difference in common or internal c-IMT measurements.

A detectable CAC score was significantly more common among participants with metabolic syndrome than among those without metabolic syndrome (80.3 % vs. 46.7%; $P < .0001$). Normal coronary arteries (score, 0) were more common in participants without metabolic syndrome than in those with metabolic syndrome (53.3% vs. 19.7%; $P < .0001$). When detectable CAC scores were compared using individual components of metabolic syndrome, participants with abdominal obesity had significantly more detectable CAC scores than did those without abdominal obesity (69.5% vs. 48.9%; *P*=.001). Furthermore, participants with elevated blood pressure had significantly more detectable CAC scores (68.3% vs. 49.8%; *P*=.004) than did those with normal blood pressure. For all other components, there was no significant difference in detectable CAC scores.

The multiple-adjusted ORs for cutoff values of surrogate markers in participants with metabolic syndrome, compared with those in participants without metabolic syndrome, are shown in table 3. After adjusting for age, sex, ethnicity, and smoking status, participants with metabolic syndrome were 2.9 times more likely to have abnormal common c-IMT (95% CI, 1.2–7.1; *P*=.020), 1.6 times more likely to have abnormal internal c-IMT (95% CI, 0.7–3.4; *P*=.255), and 4.9 times more likely to have a detectable CAC score (95% CI, 2.5–9.6; $P < .001$), compared with those without metabolic syndrome. The adjusted OR of having a CAC score >100 for participants with metabolic syndrome was not significant.

DISCUSSION

As previously reported by our group, metabolic syndrome was equally prevalent in this HIV-infected cohort and in the general US population [39]. There are very limited data on carotid ultrasound measurement and metabolic syndrome in HIV-infected patients. A recent, small study of 37 HIV-infected patients undergoing endothelial function testing found that the common c-IMT measurement was greater in patients with metabolic syndrome than in those without metabolic syndrome (*P*=.02) [40]. Another study showed that c-IMT measurements were not different in HIV-infected women with and without metabolic syndrome [41]. To our knowledge, our study provides the first report of both c-IMT measurements and CAC scores

and metabolic syndrome in subjects with HIV infection. In the present study, abnormal c-IMT measurements and CAC scores—2 surrogate markers of early atherosclerosis—were found to be more common in HIV-infected patients with metabolic syndrome than in those without metabolic syndrome. However, after adjusting for age, sex, smoking status, and ethnicity, only the common carotid artery and the detectable CAC score were significantly more likely to be abnormal in patients with metabolic syndrome than in those without metabolic syndrome. A possible explanation for this observation is that common c-IMT has less measurement variability than internal c-IMT. Generally, carotid ultrasound is a more established method for assessing atherosclerosis than is coronary CT, and internal c-IMT correlates more strongly with cardiovascular disease than common c-IMT [42].

The association of increased risk of cardiovascular disease in persons with HIV infection and exposure to antiretroviral therapy is not completely understood. Protease inhibitors, in particular, have been implicated in causing premature atherosclerosis and have been found to be associated with metabolic syndrome [1]. Our study found that participants with metabolic syndrome had higher viral loads than did those without metabolic syndrome and that a trend to have received HAART for a longer duration of HIV disease and to have higher CD4 cell counts did not significantly differ between persons with and without metabolic syndrome. Protease inhibitor use was not more common among participants with metabolic syndrome than among those without metabolic syndrome. A recent study testing the strategy of intermittent antiretroviral therapy found the rate of cardiovascular disease to be slightly higher in the drug interruption group (drug conservation) than in those receiving continuous antiretroviral medications (viral suppression) [43]. In a previous report, we found that surrogate markers correlated mainly with traditional cardiovascular risk factors but not yet with HIV-specific parameters [30]. There was no difference in surrogate marker measurements among patients receiving or not receiving protease inhibitors. Current guidelines state that dyslipidemia and insulin resistance in HIV-infected persons receiving antiretroviral therapy should be treated to reduce the risk of cardiovascular morbidity and mortality, but control of the HIV infection should not be jeopardized [11,44–46].

As the HIV-infected population ages, metabolic syndrome will likely become increasingly prevalent, and more HIV-infected patients will be at increased risk for cardiovascular disease. Atherosclerosis most likely appears early in the course of metabolic syndrome. Noninvasive screening tools, such as carotid ultrasonography and coronary imaging by CT, will be paramount for the early detection of subclinical cardiovascular disease and for the effectiveness of intervention programs. But because screening all HIV-infected patients with metabolic abnormalities for early atherosclerosis would not be clinically feasible or cost-efficient, metabolic syndrome criteria can be used to stratify those at increased risk for future cardiovascular events through the addition of prognostic information. Through early identification of subclinical atherosclerosis, we may be able to reduce the risk of cardiovascular morbidity and mortality in HIV-infected patients by preventing metabolic syndrome using lifestyle or medication interventions.

In conclusion, abnormal surrogate markers of early carotid and coronary atherosclerosis are more common in HIV-infected individuals who also fulfill the criteria for metabolic syndrome. The concurrent presence of metabolic syndrome and subclinical atherosclerosis in HIV infection may help direct appropriate therapy to prevent future cardiovascular events among this population.

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Table 1

Characteristics of HIV-infected patients with and without metabolic syndrome (MSX).

Characteristic	Patients with MSX (*n* = 72)	Patients without MSX (*n* = 242)	*P*
Sociodemographic characteristic			
Age, years	45.3 ± 7.7	43.9 ± 7.1	.135
Sex			
Male	46 (63.9)	188 (77.7)	.018
Female	26 (36.1)	54 (22.3)	
Ethnicity			
African American	28 (38.9)	79 (32.6)	.770
Latino/Hispanic	6 (8.3)	19 (7.9)	
White	35 (48.6)	131 (54.1)	
Other	3 (4.2)	13(5.4)	
Smoker			
Current	35 (48.6)	120 (49.6)	.884
Ever	54 (75.0)	183 (75.6)	.915
IDU			
Current	3 (4.2)	12 (5.0)	.782
Ever	5 (7.0)	35 (14.5)	.093
Clinical data			
Systolic BP, mm Hg	126 ± 16.8	116 ± 15.8	<.001
Diastolic BP, mm Hg	81 ± 10.0	74 ± 10.0	<.001
BMI[a]	31 ± 5.7	25 ± 4.0	<.001
Tricep skinfold thickness, mm	18 ± 14	11 ± 9	<.001
Cholesterol level, mg/dL			
Total	188 ± 55.2	187 ± 49.1	.907
HDL level	33 ± 11.3	45 ± 18.4	<.001
LDL level	101 ± 43.5	112 ± 37.0	.027
Triglyceride level, mg/dL	278 ± 169.8	155 ± 163.6	<.001
ApoA1 level, mg/dL	120 ± 25.6	131 ± 29.8	.005
ApoB level, mg/dL	89 ± 20.0	83 ± 20.9	.067

Characteristic	Patients with MSX (*n* = 72)	Patients without MSX (*n* = 242)	*P*
ApoE level, mg/dL	6 ± 3.3	4 ± 2.0	<.001
Lp(a) level, mg/dL	27 ± 28.5	28 ± 30.2	.859
RLPC level, mg/dL	22 ± 21.4	13 ± 18.5	.001
Glucose level, mg/dL	95 ± 31.3	81 ± 16.1	<.001
Insulin level, mU/L	24 ± 30.2	11 ± 9.1	<.001
QUICKI[b]	0.32 ± 0.04	0.35 ± 0.03	<.001
Hs-CRP level, mg/L	3.9 ± 8.4	2.6 ± 3.4	.059
Homocysteine level, mg/L	9.2 ± 4.4	8.9 ± 3.6	.559
HIV infection status			
Duration of HIV infection, years	9.8 ± 4.9	9.9±4.7	.878
Duration of HAART, months	30 ± 27	25 ± 26	.198
CD4 cell count, cells/mm^3	505 ± 384	441 ± 257	.103
Log HIV RNA level, copies/mL	3.3 ± 1.2	3.0 ± 1.0	.032
Receiving HAART	55 (76.4)	175 (72.3)	.493
Current NRTI use	54 (75.0)	176 (72.7)	.702
Current NNRTI use	24 (33.3)	80 (33.1)	.965
Current PI use	35 (48.6)	106 (43.8)	.471

NOTE. Data are no. (%) of patients or mean ± SD. Apo, apolipoprotein; BP, blood pressure; BMI, body mass index; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IDU, injection drug user; LDL, low-density lipoprotein; Lp(a), lipoprotein (a); NNRTI, nonnucleoside reverse-transpriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; RLPC, remnant lipoprotein cholesterol.

[a] Calculated as weight in kilograms divided by height in meters.

[b] Calculated as [1/(log [insulin level]+log [glucose level])].

Table 2

Surrogate markers in patients with and without metabolic syndrome (MSX).

Surrogate marker	Patients with MSX (*n* = 72)	Patients without MSX (*n* = 242)	*P*
Carotid artery			
c-IMT measurement, mean mm ± SD			
Common	0.66 ± 0.24	0.59 ± 0.13	.005
Internal	0.79 ± 0.46	0.70 ± 0.34	.072
c-IMT measurement cutoff[a]			
Common	12 (16.7)	16 (6.6)	.009
Internal	14 (19.7)	31 (12.9)	.149
Coronary artery			
Calcium scores			
0	14 (19.7)	128 (53.3)	<.001
1–100	48 (67.6)	95 (39.6)	
>100	9 (12.7)	17 (7.1)	

NOTE. Data are no. (%) or patients, unless otherwise inicated. c-IMT, carotid intima-media thickness.

[a] The cutoff for common c-IMT was ≥0.8 mm, and the cutoff for internal c-IMT was ≥1.0 mm.

Table 3

ORs (95% CIs) of abnormal surrogate markers comparing patients with and without metabolic syndrome.

Surrogate marker	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)[a]	*P*
Common c-IMT measurement: ≥0.8 mm vs. <0.8 mm	2.8 (1.3–6.3)	.011	2.9 (1.2–7.1)	.020
Internal c-IMT measurement: ≥1.0 mm vs. <1.0 mm	1.7 (0.8–3.3)	.152	1.6 (0.7–3.4)	.255
CAC score				
≥0 vs. 0	4.7 (2.5–8.8)	<.001	4.9 (2.5–9.6)	<.001
≥100 vs. <100	1.9 (0.8–4.5)	.14	1.6 (0.6–4.4)	.348

NOTE. CAC, coronary artery calcium; c-IMT, carotid intima-media thickness.

[a] Adjusted for age, sex, smoking status, and ethnicity.