Increased Coronary Artery Calcium Score and Noncalcified Plaque Among HIV-Infected Men: Relationship to Metabolic Syndrome and Cardiac Risk Parameters

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Objective: In this study, the effects of traditional cardiac risk factors on coronary artery calcium (CAC) score and presence of plaque, including noncalcified plaque, measured by computed tomography coronary angiography, were compared among HIV-infected and non–HIV-infected subjects, with respect to the presence of the metabolic syndrome (MS).

Design and Methods: HIV-infected men recruited for the presence of the MS (HIV + MS, n = 27) were compared with 2 control groups, HIV-infected men recruited without regard to metabolic criteria (HIV, n = 87), and HIV-negative control men (C, n = 40), also recruited without regard to any metabolic criterion.

Results: All 3 groups were similar in age, demographic parameters, and smoking. MS was seen in 100% of the HIV + MS group, compared with 28% in the HIV-infected control group and 11% in the HIV-negative controls. HIV + MS subjects had higher mean CAC score than HIV-infected controls (72 ± 25 vs. 30 ± 8, $P = 0.04$, HIV + MS vs. HIV) and HIV-negative controls (72 ± 25 vs. 18 ± 7; $P = 0.02$, HIV + MS vs. C). With respect to CAC, only the HIV + MS group had increased CAC compared with non-HIV. In contrast, both HIV groups demonstrated an increased prevalence of plaque [63% vs. 38%, $P = 0.04$ (HIV + MS vs. C) and 59% vs. 38%, $P = 0.02$, (HIV vs. C)] and increased number of noncalcified plaque segments compared with the HIV-negative group [1.26 ± 0.31 vs. 0.45 ± 0.16, $P = 0.01$ (HIV + MS vs. C); 1.02 ± 0.18 vs. 0.45 ± 0.16, $P = 0.04$ (HIV vs. C)]. Plaque and noncalcified plaque did not differ significantly between the HIV groups.

Conclusions: Metabolic abnormalities in HIV patients are specifically associated with increased coronary artery calcification, whereas HIV itself or other factors may be associated with the development of noncalcified lesions.

Key Words: Coronary artery calcification, HIV, metabolic syndrome

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INTRODUCTION

Recent studies have shown increased myocardial infarction rates in HIV patients,[1,2] which may relate, in part, to metabolic abnormalities such as dyslipidemia, diabetes mellitus, and hypertension. Rates of metabolic syndrome (MS) are increased among people living with HIV.[3,4] Non–HIV-infected patients with the MS have a faster rate of progression of coronary atherosclerosis and, therefore, increased risk of cardiovascular morbidity and mortality.[5] However, it remains unclear if the presence of MS is associated with coronary atherosclerosis in HIV-infected patients, and whether metabolic abnormalities are associated with specific types of coronary lesions.

METHODS

Subjects

One hundred fifity-four men are included in this analysis. The participants were recruited from HIV clinics and community health centers in the Boston area. Three groups were compared. Twenty-seven HIV-infected men, asymptomatic for and without known cardiovascular disease, were recruited specifically for the presence of MS (HIV + MS). Eligibility requirements for this group included aged 18–60 and demonstration of National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III)–defined MS. Eighty seven HIV+ (HIV) and 40 HIV-negative control men (C) without known cardiac disease and not recruited based on metabolic or anthropometric criteria were compared as control groups. Inclusion and exclusion criteria, with respect to known cardiac disease and age, were similar for all the groups. In both HIV groups, subjects receiving

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combination antiretroviral therapy (cART) were required to be on stable therapy for more than 3 months. Exclusion criteria for all 3 groups included known renal disease, creatinine more than 1.5 mg/dL, or estimated creatinine clearance less than 70 mL/minute. All participants gave informed consent to participate. This study was approved by the institutional review board of the Massachusetts General Hospital.

Study Procedures and Assessment of Coronary Atherosclerosis

Information on sociodemographic factors, medical history, family history, smoking, and medications was obtained, including duration of known HIV diagnosis and detailed history of prior antiretroviral therapy. Computed tomography (CT) imaging was performed using a Sensation 64 or a SOMATOM Sensation (Siemens Medical Solutions,) 64-slice CT-scanner as previously described.[6] In brief, coronary computed tomography angiography datasets were acquired with 64 × 0.6 mm slice collimation, a gantry rotation time of 330 ms, tube voltage of 120 kVp, and an effective tube current of 850 mAs using electrocardiogram-correlated tube current modulation when appropriate. Assessment of coronary atherosclerotic plaque, including number of segments with plaque and degree of stenosis, was determined by a consensus reading between 2 investigators, including a cardiologist and a radiologist with significant experience in the interpretation of cardiac CT. Agatston calcium score was calculated using the noncontrast CT images by standardized technique.[7] The presence of any coronary atherosclerotic plaque, whether calcified or noncalcified, was assessed. Noncalcified plaque was defined as any structure within the coronary wall with a CT attenuation below that of the lumen but above the surrounding connective tissue and epicardial fat.[8]

Body Composition Assessment and Metabolic and Biochemical Parameters

Abdominal visceral and subcutaneous adipose area (VAT and SAT), were assessed by CT as previously described.[6] Lipids, glucose, C-reactive protein (CRP), and CD4 were determined using standard techniques. Insulin was measured by immunoassay.

Statistical Analysis

Variables were compared between the 3 groups by ANOVA for continuous variables and by likelihood ratio for categorical variables. For variables that were not normally distributed, the Wilcoxon rank sum test was used. Post hoc comparisons were made between individual groups by student's *t* test if the overall ANOVA was ≤ 0.05. Separate multivariate regression analyses were performed relating relevant CVD risk parameters to coronary artery calcium (CAC) score, overall presence of plaque and number of noncalcified segments among all HIV-infected and control participants. CVD risk parameters tested in the analyses included the MS parameters, age, race and smoking. For the HIV-infected patients, duration HIV, and duration of PI, NRTI, and NNRTI were also included in the models. One outlier from the control group and one from the HIV-infected group with calcium scores were 5 SD greater than the mean were removed in the calcium score analysis. Values are mean ± SEM unless otherwise indicated.

RESULTS

Demographic Data

All 3 groups were similar in age, race, and smoking status. Framingham risk score tended to increase across the groups, but this did not reach statistical significance. The presence of MS was higher in the HIV + MS group compared with the HIV and non-HIV control groups ($P < 0.0001$ by ANOVA). Subjects in both HIV groups were similar with respect to duration since HIV diagnosis, use of cART, and CD4 count. Abacavir use was similarly low in both HIV groups (9% and 7%). Use of lipid lowering drugs was generally higher among the HIV patients compared with controls but not different between the HIV groups. Few patients received antidiabetic drugs (Table 1).

Metabolic Parameters

MS parameters including triglyceride levels, waist circumference (WC), and high-density lipoprotein (HDL) cholesterol were significantly different between groups by ANOVA ($P < 0.0001$, Table 1). Systolic blood pressure, diastolic blood pressure, and fasting glucose levels were not different between the 3 groups. Body mass index, waist to hip ratio, and CRP were significantly different between all 3 groups and highest in the HIV + MS group (Table 1).

Markers of Subclinical Atherosclerosis

HIV + MS subjects had higher mean CAC score than HIV-infected controls (72 ± 25 vs. 30 ± 8, $P = 0.04$, HIV + MS vs. HIV) and HIV-negative controls (72 ± 25 vs. 18 ± 7; $P = 0.02$, HIV + MS vs. C) (Fig. 1). With respect to CAC, only the HIV + MS group had increased CAC compared with non-HIV. In contrast, both HIV groups demonstrated an increased prevalence of plaque [63% vs. 38%, $P = 0.04$ (HIV + MS vs. C) and 59% vs. 38%, $P = 0.02$, (HIV vs. C)] and increased number of noncalcified plaque segments, compared with the HIV-negative group [1.26 ± 0.31 vs. 0.45 ± 0.16, $P = 0.01$ (HIV + MS vs. C); 1.02 ± 0.18 vs. 0.45 ± 0.16, $P = 0.04$ (HIV vs. C)]. Plaque and noncalcified plaque did not differ significantly between the HIV groups. Similar CAC scores, percent with plaque and segments with noncalcified plaque were seen in an analysis excluding patients using lipid-lowering drugs, as in the analysis of the entire cohort (data not shown).

In a multivariate regression analysis among all HIV-infected subjects, triglyceride level ($\beta = 0.21$, $P = 0.001$), HDL cholesterol ($\beta = -0.15$, $P = 0.04$) and age ($\beta = 3.62$, $P = 0.03$) were significantly associated with CAC (r^2 for model = 0.39). By contrast, among control subjects, fasting glucose ($\beta = 1.51$, $P = 0.04$) was significantly associated with CAC. In contrast, among HIV-infected subjects, only age ($\beta = -0.18$, $P = 0.003$) was significantly associated with presence of plaque (r^2 for model = 0.28). Similarly, in the analysis for noncalcified plaque segments, age ($\beta = 0.09$, $P = 0.004$) was also the only predictor of noncalcified segments, whereas WC trended toward significance ($\beta = 0.03$, $P = 0.06$) (r^2 for model = 0.29). Among HIV+ subjects, markers of coronary atherosclerosis did not correlate with insulin and low-density lipoprotein (LDL). CRP and CD4 were not significant. VAT was not significant and did not improve upon the models using WC (data not shown).

TABLE 1. Demographic and Clinical Characteristics of Study Population

	Controls, n = 40	HIV, n = 87	HIV With MS, n = 27	Overall *P* Value by ANOVA
Demographics				
Age (yrs)	45 ± 1.2	46 ± 0.7	46 ± 1.5	0.38
Race (%)				0.41
White	63 (25)	67 (59)	78 (21)	
Non-white	38 (15)	33 (29)	22 (6)	
Framingham risk score	6.3 ± 0.9	7.8 ± 0.6	9.2 ± 1.0	0.08
MS (%)	11	28	100	<0.0001
Current smoker (%)	30	38	44	0.47
Lipid-lowering medications (%)	10	31	22	0.05
Diabetes Medications (%)	3	6	0	0.36
HIV disease-related parameters				
Duration since HIV diagnosis (yrs)	N/A	14 ± 1	13 ± 1	0.87
Ever on antiretroviral therapy (%)	N/A	91	89	0.73
Currently on antiretroviral therapy (%)	N/A	94	85	0.12
Duration of antiretroviral therapy (yrs)	N/A	6.9 ± 0.6	6.2 ± 1.0	0.57
Duration of PI use (yrs)	N/A	3.7 ± 0.5	4.0 ± 1.0	0.84
Duration of NRTI use (yrs)	N/A	6.7 ± 0.6	3.9 ± 1.0	0.01
Duration of NNRTI use (yrs)	N/A	2.6 ± 0.4	1.5 ± 0.4	0.17
CD4 T lymphocytes (#/mm^3)	N/A	525 ± 31	549 ± 46	0.70
MS parameters				
Systolic blood pressure (mm Hg)	118 ± 2	120 ± 1	122 ± 2	0.41
Diastolic blood pressure (mm Hg)	76 ± 1	77 ± 1	80 ± 2	0.34
WC (cm)	96.0 ± 2.5	96.3 ± 1.4*	105.1 ± 2.5†	0.01
Fasting glucose (mg/dL)	92 ± 2	94 ± 1	98 ± 2	0.16
HDL cholesterol (mg/dL)	48 ± 2	47 ± 2*	33 ± 2†	<0.0001
Triglycerides (mg/dL)	101 ± 9‡	165 ± 14*	241 ± 30†	<0.0001
Additional metabolic parameters				
Anthropometric parameters				
BMI (kg/m^2)	26.8 ± 0.8	26.3 ± 0.5*	29.5 ± 1.1†	0.01
WHR	0.93 ± 0.01	0.96 ± 0.01	0.98 ± 0.01†	0.01
SAT area (cm^2)	209 ± 20	178 ± 12	236 ± 32	0.10
VAT area (cm^2)	148 ± 17	171 ± 13	185 ± 18	0.37
Glucose parameters				
Fasting insulin (μU/mL)§	5.0 ± 0.7‡	8.4 ± 1.0	5.8 ± 0.8	0.05
2-hr glucose (mg/dL)	113 ± 5	125 ± 6	134 ± 10	0.21
Lipid panel				
Total cholesterol (mg/dl)	178 ± 6	181 ± 5	185 ± 7	0.77
LDL cholesterol (mg/dl)	110 ± 5	102 ± 3	109 ± 6	0.31
Inflammatory parameters				
CRP (mg/L), median (IQR)‖¶	2.0 (0.7–3.4)	1.6 (0.7–3.9)*	21.4 (12.9–34.2)†	<0.0001

Data reported as mean ± SEM or percentage, except for C-reactive protein, which is reported as median (IQR).
*$P < 0.05$ HIV vs. HIV with MS.
†$P < 0.05$ HIV with MS vs. controls.
‡$P < 0.05$ controls vs. HIV.
§Controls N = 29, HIV N = 73, HIV with MS N = 27.
‖Controls N = 33, HIV N = 79, HIV with MS N = 27.
¶The *P* value by Wilcoxon rank-sum test.
BMI, body mass index; IQR, interquartile range; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NNRTI, non-nucleoside analog; NRTI, nucleoside analogs; PI, protease inhibitor; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; WHR, waist to hip ratio.

DISCUSSION

In the present study, HIV-infected men with MS demonstrate a higher prevalence of subclinical atherosclerosis as indicated by increased CAC score when compared with HIV-infected and non HIV-infected control groups with similar demographic parameters, age, and smoking rates but differences in critical metabolic variables that constitute the MS. However, presence of plaque and number of noncalcified plaque segments were increased among both HIV-infected groups compared with HIV-negative controls and not significantly different between the HIV-infected men with MS and HIV-infected control subjects despite a significant difference in prevalence of MS.

Utilizing CAC score as an indicator of subclinical atherosclerosis among individuals with HIV is a relatively new

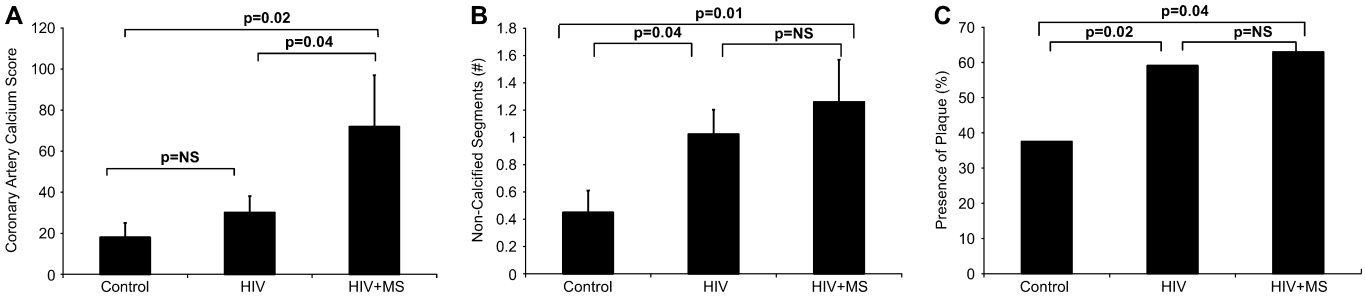

FIGURE 1. A, Coronary artery calcium score (18 ± 7 vs. 30 ± 8 vs. 72 ± 25, mean ± SEM); B, number of noncalcified segments (0.45 ± 0.16 vs. 1.02 ± 0.18 vs. 1.26 ± 0.31, mean ± SEM); C, prevalence of plaque (38% vs. 59% vs. 63%) among control participants vs. HIV patients and HIV patients with metabolic syndrome (presence of plaque overall *P* Value by ANOVA = 0.05, calcium score overall *P* Value by ANOVA = 0.02, number of noncalcified segments overall *P* Value by ANOVA = 0.05) NS, nonsignificant; HIV + MS, HIV with metabolic syndrome.

method. Among dyslipidemic individuals, Acevedo et al[9] found the percentage of HIV-infected participants with detectable CAC to be high. Talwani et al[10] did not find clinically significant differences in CAC score between HIV-infected individuals on short-term cART when compared with historical age, sex, and race-matched controls. In the MACS Study, there was a slight increase in prevalence of CAC among HIV-infected men on cART.[11]

There are very limited data on CAC scores in HIV-infected men with MS. A recent study by Magnili et al[12] found presence of CAC to be significantly more common among HIV-infected patients with MS compared with those without it, however an HIV-negative control group was not included, and factors that could be related to increased CAC were not evaluated.

Elevated triglyceride levels and low HDL cholesterol levels were independent predictors of CAC score among the HIV-infected men in this study. The DAD Study showed an association between increased myocardial infarction and triglyceride levels. However, this association was attenuated adjusting for HDL and total cholesterol[13]. Our studies complement the recent DAD studies by showing for the first time that increased triglyceride and low HDL are specifically associated with increased subclinical atherosclerosis, and CAC, controlling for other metabolic variables and traditional risk factors including smoking. In contrast to triglyceride and HDL, we did not see a relationship between LDL and subclinical atherosclerosis, likely because our population was not chosen to have known heart disease and had normal LDL levels.

The number of noncalcified plaque segments was elevated among both groups of HIV-infected subjects when compared with HIV-negative control subjects in this study. Noncalcified plaques develop early in plaque formation and are lipid rich.[14] This type of plaque is thought to be more vulnerable and, therefore, more prone to rupture than calcified lesions, which are more stable.[15] Factors associated with HIV infection, such as inflammatory or immunological factors, may be contributors to noncalcified plaque formation in this population, though we did not see associations with CRP or CD4 count in the current study. CTA is sensitive enough to detect and quantify overall presence of plaque, including noncalcified lesions. The use of CTA to distinguish the types of lesions in HIV patients may therefore add value to the use of coronary CT for CAC alone. Future studies are needed to determine the factors contributing to the increase in noncalcified plaques among HIV patients.

This study has limitations including the cross-sectional design from which causality cannot be determined. Also, because the study only includes men, the results cannot be generalizable to women living with HIV. We were unable to include a non HIV group with MS, and thus, we can not comment on whether coronary atherosclerosis is more severe in HIV vs. non HIV groups with MS. In addition, the number of HIV patients with MS was relatively small. However, our purpose was to compare lesion type in HIV with and without MS, and we characterized an adequate number of patients using the sensitive CTA technique to make this assessment.

This study suggests that traditional cardiac risk factors encompassing MS may be associated with increased coronary artery calcification, whereas HIV infection itself may be associated with the development of overall and noncalcified plaque formation of the coronary arteries. Among HIV-infected men with the MS, identification and treatment of risk factors, such as elevated triglyceride and low HDL levels, may be warranted. However, HIV patients without significant metabolic abnormalities may develop noncalcified plaque and be at increased risk for CAD.

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