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Non-calcified coronary plaque volume inversely related to CD4 count in HIV infection

Horacio Duarte, MD¹, Jatin R. Matta, PA-C, MPAS², Nancy Muldoon, RN, BSN³, Henry Masur, MD³, Colleen Hadigan, MD, MPH¹, and Ahmed M. Gharib, MD²

¹National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda MD

²Biomedical and Metabolic Imaging Branch, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda MD

³The Department of Critical Care Medicine, National Institutes of Health, Bethesda MD

Abstract

Background—Non-calcified coronary artery plaque (NCAP) may be an important predictor of cardiovascular events, however, few studies have directly measured NCAP in HIV-infected individuals.

Methods—We completed a prospective cross-sectional evaluation of NCAP and coronary calcium scores using CT angiography in HIV-infected subjects (n=26) without known coronary artery disease (CAD), but who had one or more CAD risk factor and compared them to controls matched on age, race, sex, body mass index and Framingham risk score (n=26).

Results—There was no difference in coronary calcium scores (114 ± 218 vs. 124 ± 298 p=0.89) or NCAP volume (65 ± 86 mm³ vs. 63 ± 82 mm³, p=0.38) between HIV-infected subjects and controls, respectively. Among HIV-infected subjects, lower CD4 count was associated with increased NCAP volume (r=-0.52, p=0.006). CD4 count remained a significant predictor of NCAP in a multivariate analysis that adjusted for age and duration of antiretroviral therapy.

Conclusion—Plaque burden is similar between HIV-infected and uninfected individuals when matched on traditional CAD risk factors, however immune function may mediate the development of atherosclerosis in HIV infection.

Keywords

non-calcified coronary plaque (NCAP) volume; HIV; cardiovascular disease

Introduction

There is a growing body of evidence demonstrating excess cardiovascular disease (CVD) among HIV-infected adults [1, 2]. This increased risk of CVD appears to be related not only to inflammation inherent in chronic viral infection, but also to cardiometabolic toxicity associated with antiretroviral (ARV) therapy [1, 3, 4]. Several studies have identified abnormalities in surrogate markers for coronary artery disease (CAD) in HIV, such as carotid intima thickness and endothelial function [5-7]. Non-calcified coronary artery plaque (NCAP) may be an important predictor of cardiovascular events, and in non-HIV

Corresponding Author: Colleen Hadigan, MD, MPH, 10 Center Drive, Bldg 10, Rm 11C103, Bethesda, MD 20892, Phone: (301) 594-5754, Fax: (301) 402-4097, hadiganc@niaid.nih.gov.

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populations NCAP has been implicated in acute coronary syndrome [8]. Prospective evaluation of NCAP volume and calcium scores, using CT angiography was performed to determine whether asymptomatic HIV-infected subjects have increased atherosclerosis compared to controls matched on traditional CVD risk parameters.

Methods

Study design

We conducted a prospective pilot study of 26 HIV-infected subjects and 26 uninfected controls matched on sex, age, race, BMI and Framingham Risk score at the National Institutes of Health Clinical Center. The protocol was IRB approved and all subjects gave written informed consent.

Study Population

Subjects were self-referred, 18 or older, without known CAD but with one or more risk factors for CAD (e.g. smoking, hypertension, dyslipidemia, first degree relative with early CAD). Participants were excluded if they had creatinine ≥ 1.3 mg/dl, allergy to CT contrast, contraindication to β -blockers, or were pregnant or breastfeeding. There were no a priori entry criteria related to HIV specific characteristics, such as CD4 count, viral load, or years of exposure to ARV therapy. HIV-infected subjects had a previously established diagnosis of HIV infection; controls were healthy volunteers not known to be HIV-infected.

Study procedures

A medical history was obtained, including a complete history of prior antiretroviral exposure in HIV-infected subjects. A detailed assessment of CAD risk was performed and included smoking history, family history of CAD and fasting determinations of total, high-density lipoprotein (HDL), low-density lipoprotein (LDL) cholesterol, triglycerides, and hs-C reactive protein were obtained. Framingham Risk Score (FRS) was calculated using the online National Heart Lung and Blood Institute (NHLBI) tool: <http://hp2010.nhlbi.nih.net/atpiii/calculator.asp>. Individuals with known diabetes were scored as FRS=20%.

Imaging was performed using a 16-MDCT scanner (Philips) in 41 subjects, 64-MDCT scanner (Philips or Toshiba) in 8 subjects (5 of whom were controls), and 32-MDCT Dual Source scanner (Siemens) in 3 subjects. When needed, metoprolol (50-100 mg) was given 30–60 minutes before imaging to lower the heart rate to 65 bpm. Coronary MDCTA was performed using a tube voltage of 120–135 kV and current of 400–700 mAs with a 220-mm field of view and retrospective ECG gating. Contrast material was injected through peripheral venous access at a rate of 4–5 mL/s followed by 50 mL of normal saline at the same rate. Post-processing, Agatston calcium scoring and interpretation of axial and multiplanar reformatted images were performed on a 3D software tool (Virtual Place, AZE). NCAP area was manually traced on CT images for each vessel by a single investigator blinded to subject clinical status. The volume of the NCAP was then calculated by multiplying the area by slice increment[9]. The degree of luminal narrowing was classified as mild ($<50\%$ stenosis) or moderate (50% – 70% stenosis) or severe ($>70\%$ stenosis).

Statistical Analysis

Student's t-tests and chi-square analyses were used to compare values between groups. Non-normally distributed variables were log transformed to approximate a normal distribution (e.g. triglycerides and NCAP volume). Due to the relatively small sample size, duration of ARV exposure was analyzed, but not individual ARV drugs or classes. Univariate linear and logistic regression analyses were performed to identify potential clinical variables associated

with plaque volume and coronary calcium scores. Data analyses were completed using SAS JMP Version 7.0 (SAS Cary, NC).

Results

Clinical characteristics of the study population are described in Table 1. Subject groups were similar in age, sex, race, FRS, and BMI. HIV-infected participants were more likely to have ever smoked, had a greater smoking pack years, had higher triglycerides, but had lower blood pressure compared to controls. There was no significant difference in hs-CRP, total, LDL, or HDL cholesterol values, calcium scores, or NCAP volumes between HIV-infected subjects and controls. There was no difference in NCAP volume between those on a statin versus those not on a statin.

Among HIV-infected subjects, 9 had evidence of coronary narrowing in one or more segments (Figure 1). Five HIV-infected subjects had regions of moderate or severe narrowing, and of these, 3 had involvement of all 3 major vessels. Among controls, 13 had coronary narrowing in one or more segments. Seven controls had regions of moderate or severe narrowing, and of these, 3 had involvement of all 3 major vessels. The distribution of calcium scores in the categories of 0, 50-100 and greater than 100 were similar between the two groups (HIV 38.5%, 11.5% and 50% versus Control 46%, 8%, 46% respectively; $\chi^2=0.42$, $p=0.8$).

Among all subjects, there were statistically significant correlations between plaque volume and age ($r=0.33$, $p=0.02$), plaque volume and calcium score ($r=0.35$, $p=0.01$), and calcium score and age ($r=0.38$, $p=0.005$). There was no correlation between FRS and plaque volume or calcium score. However, among the HIV-uninfected participants, there was a significant positive correlation between FRS and calcium score ($r=0.49$, $p=0.01$).

In univariate regression analyses among HIV-infected subjects, there was a significant inverse correlation between plaque volume and CD4 count ($r=-0.52$, $p=0.006$). There were no significant associations between plaque volume and duration of HIV or HIV viral load; however, there were non-significant trends between plaque volume and duration of ARV therapy ($r=0.37$, $p=0.06$) and nadir CD4 ($r=-0.36$, $p=0.07$). Using a multivariate regression which included duration of ARV therapy, statin use and age, CD4 count ($p=0.04$) remained a significant independent predictor of plaque volume.

Discussion

Few studies have characterized the degree of both calcified coronary artery plaque and NCAP in HIV-infected adults.[10, 11] In this study, we found a similar degree of coronary artery calcium and NCAP between HIV-infected adults and uninfected controls who were matched by Framingham CVD risk score.

In contrast to the present study, Lo et al. found increased NCAP volume in HIV-infected men compared to uninfected controls with a trend toward higher Agatston calcium scores among those with HIV (10). Within their HIV-infected group, plaque volume was associated with traditional markers of CVD risk such as age, FRS, and cholesterol in addition to HIV specific factors such as duration of HIV and CD4/CD8 ratio [10]. While our relatively small sample size may have limited our ability to detect differences observed by Lo and colleagues [10], older age, higher rates of hypertension and diabetes may also have contributed to increased NCAP in both HIV and control subjects in the current study.

While we did not identify an association between CD4/CD8 ratio and NCAP, we found that current CD4 count was inversely related to NCAP volume. Interestingly, Kaplan et al.

showed that current CD4 count <200 cells/mm³ was associated with an increased prevalence of carotid lesions among HIV-infected adults[12]. Also, Jericó et al. reported an association between nadir CD4 <200 cells/mm³ and increased carotid atherosclerosis[13]. Our findings of increased coronary artery plaque volume with lower CD4 counts complement these observations in carotid arteries and support the hypothesis that altered immune function and inflammation may contribute to coronary artery disease risk in this population [6, 10].

Additionally, we found a trend toward higher plaque volume with increased duration of ARV therapy. Exposure to ARV therapy has been associated with subclinical carotid atherosclerosis[13]. Similarly, Lai et al. found a significant association between the use of ARVs for >18 months and the presence of NCAP[11]. However, this study was conducted primarily in HIV-infected subjects with a history of cocaine use, which was also identified as a risk factor for increased calcified plaque. Our observation of similar degree of multivessel disease between HIV-infected subjects and controls is consistent with a prior study [14] which showed no difference in angiographic plaque distribution between HIV-infected patients and controls who experienced acute coronary artery syndrome. Lai et al. (11) identified increased NCAP in association with HIV viremia, but no such association was found in our study or that of Lo et al. (10). The latter studies included participants with substantially more ARV exposure which may obscure potential relationships between viremia and atherosclerosis.

The present study is limited by small sample size. For example, the lack of association between plaque volume and traditional CVD risk factors such as smoking history or lipids may be due to our small size. Sample size may have also limited our ability to detect differences between groups. Additionally, we were not able to evaluate the independent contribution of ARV agents or classes on coronary plaque. Use of more than one CT scanner may have introduced some variability, but all scans were performed and analyzed by a single radiologist to minimize variability. Both HIV-infected participants and controls were required to have one or more known CVD risk factor to enroll, and therefore our observations may not be directly generalizable to other clinical populations not enriched for these risk factors. However, our study is strengthened by inclusion of controls well-matched for CVD risk and by the use of high quality non-calcified plaque burden determinations. Large cohort studies with longitudinal assessments, hard clinical endpoints, and appropriate controls are needed to more fully elucidate the relationship between HIV associated CVD risk factors, immune profiles, ARV exposure, and coronary artery disease in this unique at-risk population.

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Figure 1. Representative non-calcified soft plaque of coronary artery (white arrows) in a subject with HIV, FRS 20% and Calcium Score=11.4

Table 1
Demographic and Clinical Characteristics

Characteristics	HIV-Infected (n=26)	Non-HIV (n=26)	P value
Age (yrs)	53.0 ± 5.1	52.3 ± 11.6	0.78
Sex (male), n (%)	22 (85%)	22 (85%)	1.00
Race, n (%)			0.08
White	11 (42%)	14 (54%)	
Black	14 (54%)	7 (27%)	
Hispanic	0 (0%)	2 (8%)	
Asian	1 (4%)	1 (4%)	
Other	0 (0%)	2 (8%)	
Framingham Risk Score	11.8 ± 6.7	9.7 ± 7.3	0.28
BMI (kg/m ²)	27.7 ± 4.9	28.6 ± 4.0	0.44
Hypertension (%)	65	54	0.40
Hypertension Meds (%)	54	54	1.00
Diabetes mellitus (%)	35	15	0.11
Hyperlipidemia (%)	58	38	0.16
Statin (%)	58	35	0.09
Fibrate (%)	8	8	1.00
Ever smoked (%)	81	38	0.002
Current smoker (%)	31	31	1.00
Pack Years	17.5 ± 20.1	6.2 ± 12.1	0.02
Total Cholesterol (mg/dl)	167 ± 32	176 ± 32	0.30
LDL (mg/dl)	97 ± 31	108 ± 37	0.25
HDL (mg/dl)	44 ± 15	47 ± 11	0.38
Triglycerides (mg/dl) *	195 ± 106	146 ± 99	0.03
hs-CRP (mg/L)	0.5 ± 0.9	0.4 ± 0.7	0.85
Systolic BP (mmHg)	126 ± 12	135 ± 12	0.009
Diastolic BP (mmHg)	77 ± 8	83 ± 10	0.02
Plaque Volume (mm ³) *	65 ± 86	63 ± 82	0.38
Coronary Calcium Score	114 ± 218	124 ± 298	0.89
HIV Characteristics			
Duration of HIV (yrs)	14.0 ± 7.03	-	-
Current ARV (%)	81	-	-
Duration ARV (yrs)	7.7 ± 4.5	-	-
CD4+ T-lymphocytes (cells/μl) (current)	582.0 ± 224.7	-	-
CD4 nadir (cells/μl)	269.2 ± 171.4	-	-
HIV Viral Load			
< 50 copies/ml (%)	65	-	-

* p-values for triglycerides and plaque volume based on log-transformed values