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T-Cell Activation and E-Selectin Are Associated with Coronary Plaque in HIV-Infected Young Adults

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Abstract

We evaluated immune activation and coronary artery plaque in young adults with HIV acquired in early life (n=31). Coronary plaque was positively associated with lipids, immune activation marker %CD8+CD38+DR, and E-selectin, a marker of endothelial inflammation. Immune activation and endothelial inflammation may drive coronary plaque formation during the early stages of atherosclerosis in the context of chronic HIV.

Keywords

perinatal HIV; coronary plaque; E-selectin; cardiovascular disease; immune activation

Introduction

Despite the extraordinary benefits of antiretroviral therapy (ART), cardiovascular disease (CVD) is increased in HIV and is possibly related to ART use. Traditional risk factors such as smoking and dyslipidemia may work in combination with immune activation, and chronic inflammation to increase the overall risk of cardiovascular injury. Immune activation is thought to be a leading contributor to non-AIDS morbidity in HIV-infected populations.

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Conflict of Interest

The authors have no financial conflicts of interest to report in relationship to this research or manuscript.

Adolescents and young adults infected with HIV early in life who face long term exposure to these factor may be particularly vulnerable to the development of CVD.

Previous research has shown an increased prevalence of coronary and carotid plaque in association with immune activation (1). However, there are limited data on coronary plaque burden and immune correlates in young adults with lifelong HIV. We hypothesized that noncalcified plaque in this setting may be due, in part, to systemic inflammation and immune activation. Therefore we evaluated coronary atherosclerotic plaque burden and its relationship to biomarkers of immune activation in young adults who acquired HIV in early life.

Methods

Subjects

Young adults who acquired HIV early in life (n=31) and healthy controls (n=11) completed cross-sectional cardiovascular imaging between April 2010 and April 2013 at the National Institutes of Health (ClinicalTrials.gov identifiers: NCT00924365, NCT01656564). Partial data from this cohort was published previously (2). Subjects were excluded for known CVD or contraindications to MRI and CT. Controls were required to be healthy, ≥18 years old, with targeted recruitment to match the age (+/− 5 years), and sex distribution of the HIV cohort. HIV-infected participants could be <18, and there were no restrictions related to ART or CD4 count. Written informed consent was obtained and the protocol approved by IRB of the National Institute of Allergy and Infectious Diseases. Fasting laboratory tests included chemistry, lipid panel, CD4 count, HIV RNA load, biomarkers of inflammation or vessel injury (hs-CRP, d-Dimer, lipopolysaccharide binding protein (LBP), P-selectin, E-selectin, sICAM-3, VCAM-1) and immune activation (flow cytometry e.g. %CD8+CD38+DR+, %CD4+CD38+DR+).

Coronary CT Angiography (CCTA)

Electrocardiography–gated CCTA was performed and analyzed similarly to previously described techniques (3,4). When necessary, a β-blocker was administered before imaging to lower heart rate. CCTA based scores were calculated to characterize coronary plaque burden (4,5). Plaque presence, site, size and degree of stenosis were determined by 2 investigators in consensus who were blinded to HIV status. If plaque was present, a composite score, which summed the size (scale 1–3) x the severity of stenosis (1-mild 2-mild to moderate; 3-moderate; 4-moderate to severe; 5-severe) for each plaque was calculated. If no plaque was present this score was zero.

Statistical Methods

Nonparametric Wilcoxon rank-sum tests and Chi-square tests were performed where appropriate. Univariate linear regression analyses were performed to evaluate associations between clinical variables and coronary plaque. To identify independent predictors of coronary plaque, variables identified as statistically significant on univariate analyses ($p<0.05$) were included in multivariable regression analyses which also adjusted for age and

smoking pack years. Statistical significance was determined at a P value of <0.05 using SAS JMP software version 11.0 (SAS Institute, Cary, North Carolina).

Results

HIV-infected subjects were younger, had lower BMI, higher blood pressure and higher total cholesterol compared to controls (Table 1). HDL cholesterol, total CD4 counts, and CD4/CD8 ratios were lower in the HIV group, but %CD8+CD38+DR+ was significantly increased relative to controls. Although 71% of the HIV cohort reported current ART use, only 45% had HIV RNA < 50 copies/mL.

There was no significant difference in number of noncalcified plaque lesions between groups (HIV+ median 0, range 0–4, Control median 0, range 0–7, p=0.08). There were 5 controls and 6 HIV-infected subjects with at least one plaque lesion. The mean plaque score among the 5 control subjects with plaque was 3; the mean score was 2.8 among the 6 HIV-infected subjects with plaque. No calcified plaque was found in either group and no subject had a lesion that created severe stenosis. Among the HIV-infected subjects, there was no significant difference in viral load, CD4 count or duration of ART between those with and without plaque. Of those with plaque, 67% had a detectable VL while 52% of subjects without plaque had a detectable VL (p=0.5). Additionally, in the HIV-infected group, there was a trend for those with plaque to have lower CD4/CD8 ratios than those with no plaque (0.36 ± 0.30 vs 0.81 ± 0.45, p=0.06).

There was no association between plaque score and CRP, d-Dimer, homocysteine, or LBP in either study population. Although P-selectin, sICAM-3, VCAM-1, TIMP-1, and MCP-1 levels were significantly elevated in HIV-infected subjects compared to controls (data not shown), these biomarkers were not related to plaque score. None of the measured markers of inflammation or immune activation were associated with plaque in the control group.

Level of activated CD8 T cells in the periphery (%CD8+CD38+DR+) was associated with increased composite coronary plaque score in the HIV+ group (r=0.46, p=0.025) as was %CD8+CD38+ (r=0.56, p=0.005). Further, %CD4+CD38+ was correlated with increased plaque (r=0.49, p=0.02), but CD4/CD8 ratio (r=−0.38, p=0.07) and %CD4+CD38+DR+ (p=0.16) were not. Plaque was also correlated with %CD3+CD38+DR+ (r=0.56, p=0.004) and %CD3+CD38+ (r=0.61, p=0.002), LDL cholesterol (r=0.78, p<0.001), total cholesterol (r=0.50, p=0.049) and log triglyceride level (r=0.79, p<0.001).

E-selectin was significantly correlated with plaque score (r=0.48, p=0.006), LDL (r=0.48 p=0.004) and log triglycerides (r=0.51, p=0.002), but not HDL (p=0.09). In a multivariate regression analysis, which included age, smoking pack-years, E-selectin and %CD8+CD38+DR+ in the HIV-infected group, %CD8+CD38+DR+ was the only significant predictor of plaque (p=0.01). This observation persisted in subsequent analyses adjusting for LDL or triglyceride levels (adjusted p-value for %CD8+CD38+DR+ p=0.04 with LDL in the model, and p=0.02 with triglycerides in the model).

Discussion

In this study, we identify a significant association between coronary plaque burden and specific biomarkers of immune activation and inflammation in young adults with long-standing HIV infection. There were no significant differences in coronary plaque burden between healthy controls and HIV-infected subjects. However, in HIV-infected subjects the plaque composite score was associated with lipid levels, as well as immune activation marker %CD8+CD38+DR+, and E-selectin, a marker of endothelial inflammation, in this unique cohort.

These observations shed light on the complicated nature of cardiovascular disease risk among individuals living with HIV. Previous research of calcified and noncalcified plaque in HIV-infected individuals has been conducted predominantly in males and almost exclusively in adult populations. Lo and colleagues found that older age, longer duration of infection and lower CD4/CD8 ratio predicted coronary plaque in HIV-infected adult males (6). While CD4/CD8 ratio was not a significant predictor of plaque score (severity) in our cohort, those who had detectable noncalcified plaque had lower CD4/CD8 ratios overall. Given the younger age of our cohort, traditional CVD risk factors such as aging and smoking may not play as large of a role in observed coronary artery changes, thus our study group provides a unique sample for evaluation of immune activation as a potential contributor to atherosclerosis in the early stages of coronary artery disease in HIV.

HIV infection is thought to accelerate aging of the immune system, giving adolescents an immune profile similar to elderly patients (7). It has been noted that CD38 expression on CD8 cells can be used as a prognostic tool given observations that higher levels of CD38+ CD8 cells indicated an increased risk for developing AIDS (8). Our results underscore the potential role of CD8 activity in cardiovascular disease. In particular, we provide evidence of %CD8+CD38+DR+ as significantly associated with coronary plaque along with E-selectin in this population of young adults with long-term HIV. These observations suggest that endothelial inflammation and immune activation may drive coronary plaque formation. In contrast, coronary calcium progression was associated with monocyte activation but not markers of T-cell activation in a large cohort of HIV-infected adults (9). The differences between our observations and these prior findings may represent differences in the underlying pathophysiology of the continuum from early plaque formation to progression.

In general, endothelial biomarkers are often observed to be elevated in HIV-infected individuals compared to controls (10), but levels of E-selectin are not consistently elevated in studies of HIV. Similar to previous observations, E-selectin was not significantly different between HIV and controls in our study (10). Yet, within the HIV-infected subjects, E-selectin was a significant predictor of coronary plaque. In addition, we observed a positive correlation between E-selectin and lipid levels, which is consistent with prior findings in non-HIV-infected adults (11). Hwang et al. showed E-selectin was associated with coronary artery atherosclerosis but not coronary heart disease and hypothesized that E-selectin might reflect the *early* steps of atherosclerosis (11). E-selectin has not been studied extensively in the context of HIV but may provide insight into the evolution of coronary disease in HIV in future investigations.

The small sample size of our study and the cross-sectional design precludes broad generalizations to larger HIV populations and we cannot attribute causality to observed associations. Due to age inclusion criteria, the control group was slightly older but the key observations in this study are made within the HIV-infected group independent of the control sample. In summary, the detailed coronary artery imaging of this very unique cohort with two decades of HIV infection provides potential insight into the nature of coronary disease in the context of lifelong HIV. Larger prospective studies are needed to more fully appreciate the potential cardiovascular disease impact of HIV infection acquired in early life as these individuals approach the third and fourth decades of life.

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Table 1

Demographic and clinical characteristics

	HIV+ (n=31)	Control (n=11)	P-value
Age, years	22 ± 3	25 ± 2	**0.006**
Sex: Male/Female (n/n)	19/12	3/8	0.05
BMI (kg/m^2)	23.7 ± 5.4	26.1 ± 4.8	**0.034**
Ever Smoked, n (%)	10 (32)	2 (18)	0.37
Smoking Pack years	0.9 ± 2.3	0.07 ± 0.2	0.26
Systolic BP (mmHg)	124 ± 13	116 ± 6	**0.01**
Diastolic BP (mmHg)	74 ± 7	67 ± 7	**0.01**
Hypertension, n (%)	4 (11)	0 (0)	0.13
Total Cholesterol (mg/dL)	152 ± 31	177 ± 28	**0.02**
LDL Cholesterol (mg/dL)	89 ± 35	98 ±26	0.15
HDL Cholesterol (mg/dL)	47 ± 13	65 ± 12	**0.0003**
E-Selectin (ng/ml)	7.20 ± 4.54	7.41 ± 1.36	0.73
%CD8+CD38+DR+	31.62 ± 17.20	7.30 ± 1.27	**0.0001**
Current CD4 (cells/μL)	499 ± 277	781 ± 185	**0.009**
CD4/CD8 ratio	0.74 ± 0.46	1.73 ± 0.55	**0.001**
Number of coronary plaque lesions	0.3 ± 0.8	1.3 ± 2.2	0.08
Composite Plaque Score	0.5 ± 1.9	1.4 ± 2.5	0.09
			HIV + (n=31)
Current ART use, n (%)			22 (71)
Duration ART use, years			15 ± 5
CD4 < 200 (cells/μL), n (%)			5 (14)
Nadir CD4 (cells/μL)			194 ± 187
HIV RNA <50 copies/mL, n (%)			14 (45)

*BMI = body mass index, BP = blood pressure, LDL = low density lipoprotein, HDL = high density lipoprotein, ART = antiretroviral therapy