EPICARDIAL FAT, IMMUNE ACTIVATION, AND CORONARY PLAQUE AMONG HIV+ AND HIV- WOMEN

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Background

- Mechanisms underlying the increased risk of myocardial infarction (MI) among HIV-infected women remain unclear.
- Previous studies have shown that asymptomatic HIV-infected women (versus non-HIV-infected women) have a significantly higher percentage of non-calcified, rupture-prone coronary plaque in relation to increased systemic levels of pro-inflammatory cytokines and immune activation markers.
- Indeed, persistent systemic immune activation among individuals with HIV is believed to contribute to heightened myocardial infarction.
- Immunomodulatory cytokines are known to be produced by ectopic fat depots, and HIV infection plus antiretroviral therapy predispose to ectopic fat deposition.
- The epicardial adipose tissue (EAT) depot has distinct pathophysiologic relevance to atherosclerotic cardiovascular disease (CVD) risk.
- EAT is an ectopic fat depot, which resides within the pericardial sac and shares a common blood supply with the coronary arteries it surrounds. (Figure 1)
- Cytokines secreted by EAT may be expected to exert deleterious vasocrine or paracrine effects on coronary arteries– increasing arterial inflammation and, in turn, engendering accelerated atherogenesis, plaque remodeling, and/or endothelial dysfunction. To this end, increased epicardial fat has been shown to relate to incident MI in the general population.

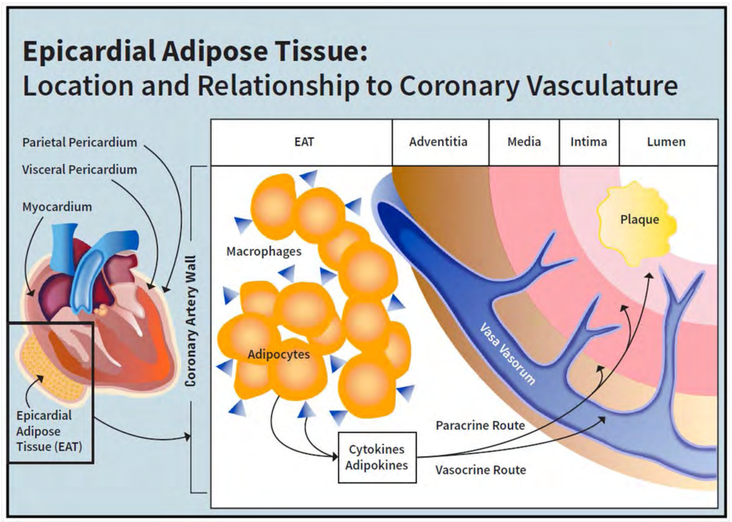

Figure 1. EAT encases and shares a blood supply with the coronary vasculature such that cytokines and adipokines produced by EAT may, through vasocrine and/or paracrine pathways, reach and act upon incipient, subclinical coronary plaque.

Objectives

- No prior studies have explored the epicardial fat depot in relation to immune activation and subclinical coronary atherosclerotic plaque among HIV-infected and non-HIV-infected women.
- In the present study, we measured EAT volume among HIV-infected and non-HIV-infected women without known CVD who had previously undergone cardiac computed tomography angiography (CCTA) as well as detailed immune/metabolic phenotyping.

Methods

Study Participants and Design

Fifty five HIV-infected and 27 non-HIV-infected women without known cardiovascular disease who underwent CCTA and metabolic/immune phenotyping were included. EAT volume derived from CT was related to systemic markers of immune activation and arterial inflammation, as well as composition of subclinical coronary plaque among groups stratified by HIV serostatus and high/low EAT (defined in reference to median EAT for each serostatus group).

Methods (cont.)

- Inclusion criteria for all subjects: female sex, age ≥ 18 and ≤ 60 years.
- Inclusion criteria for HIV subjects: stable ART regimen ≥ 3 months.
- Major exclusion criteria for all subjects: history of CVD or symptoms suggestive of CVD; contraindications to cardiac CTA

Assessment of Ectopic Fat Depots Using Cardiac Computed Tomography (CT)

- EAT volume was measured from the non-contrast calcium score CT performed as part of the Cardiac CTA. EAT was defined as tissue within the pericardial sac having an attenuation between -195 to -45 Hounsfield Units (HU). EAT volume in cubic centimeters (cm^3) was quantified using a dedicated semiautomated workstation (Multimodality Workplace (MMWP), Siemens Healthineers, Forchheim, Germany). Briefly, regions of interest were traced along the pericardium from the middle of the right pulmonary artery to the diaphragm at 10 mm intervals, with semiautomated interpolation. CCTA was used for assessment of coronary plaque type.

- Abdominal visceral and subcutaneous adipose tissue area were quantified on an axial noncontrast CT slice through the abdomen at the level of the L4 pedicle.

Laboratory Evaluation

After an overnight fast, subjects completed blood sampling for evaluation of systemic metabolic, inflammatory, immune activation, and cardiac markers.

Statistical Analysis

All normal data are presented as mean ± SEM, variables with non-normal distribution are reported as median [IQR] and categorical variables are represented as proportions. HIV and non-HIV-infected women were substratified into groups with high/low EAT (defined in reference to median EAT for each serostatus group). After determining there was no significant interactions between serostatus and EAT volume, a multiple group comparison was made using ANOVA for normally distributed variables after appropriate log transformation. Within each serostatus group, linear regression was performed using Pearson's correlation coefficient to evaluate parameters associated with EAT. Among the HIV-infected women, determinants of epicardial fat volume were evaluated in multivariate regression modeling using dependent variables of interests selected from univariate analyses with P<0.10 as well as age, a recognized correlate of ectopic fat deposition. Statistical significance was defined as P<0.05.

Results

Table 1. Characteristics of Non-HIV-Infected and HIV-Infected Women

	Non-HIV-Infected Women (n=27)	HIV-Infected Women (n=55)	P-value
Demographics			
Age, y	47 ± 1	47 ± 1	0.84
Caucasian Race, %	37	33	0.82
Hypertension, %	26	15	0.22
Dyslipidemia, %	7	15	0.33
Current statin treatment, %	4	9	0.35
Diabetes mellitus, %	15	16	0.86
Current smoker, %	56	49	0.58
Family history of premature CHD by NCEP, %	42	20	0.04
Total Framingham Point Score	11 ± 1	11± 1	0.93
Post-Menopausal, %	42	46	0.75
Metabolic Parameters			
Systolic blood pressure, mm Hg	123 ± 3	117 ± 2	0.16
Diastolic blood pressure, mm Hg	79 ± 2	75 ± 1	0.12
Fasting glucose, mg/dL	83 ± 3	91 ± 6	0.24
HDL cholesterol, mg/dL	60 ± 3	61 ± 3	0.79
LDL cholesterol, mg/dL	102 ± 5	106 ± 5	0.57
Triglycerides, mg/dL	110 ± 13	108 ± 8	0.90
AMH, ng/mL	<0.023 (<0.023,0.46)	<0.023 (<0.023,0.50)	0.90
Anthropometric Parameters			
Body mass index, kg/m^2	29 ± 1	28 ± 1	0.13
VAT area, cm^2	82 (50,103)	74 (35,118)	0.80
SAT area, cm^2	343 (246,508)	277 (186,408)	0.048
EAT volume, cm^3	65 (41,78)	54 (41,79)	0.31
HIV Disease Related Parameters			
Duration since HIV diagnosis, y	N/A	15 ± 1	N/A
Currently on antiretroviral therapy, %	N/A	98	N/A
Duration of antiretroviral therapy, y	N/A	8 ± 1	N/A
Duration of PI treatment, y	N/A	4 ± 1	N/A
Duration of NRTI treatment, y	N/A	7 ± 1	N/A
Duration of NNRTI treatment, y	N/A	2 ± 1	N/A
CD4+ T-lymphocytes, cells/μL	N/A	599 ± 42	N/A
Nadir CD4+ T-lymphocytes, cells/μL	N/A	193 ± 23	N/A
CD8+ T-lymphocytes, cells/μL	N/A	880 ± 58	N/A
Log HIV RNA viral load	N/A	1.79 ± 0.06	N/A
Undetectable HIV RNA < 50copies/mL, %	N/A	84	N/A

Results (cont.)

Table 2. Inflammatory, Immune and Cardiac Indices among Non-HIV-Infected and HIV-Infected Women by Within-Group Median EAT

	Non-HIV-Infected Below Median EAT (n=13)	HIV-Infected Below Median EAT (n=27)	Non-HIV-Infected Above Median EAT (n=14)	HIV-Infected Above Median EAT (n=28)	Overall P Value
Markers of Monocyte/Macrophage Activation					
Log MCP-1, pg/mL	2.20 ± 0.05	2.32 ± 0.04	2.35 ± 0.05	2.37 ± 0.04	0.10
Log CXCL10, pg/mL	2.06 ± 0.09	2.32 ± 0.06	2.15 ± 0.09	2.37 ± 0.06	0.02
Log sCD163, ng/mL	2.93 ± 0.07	3.14 ± 0.05	3.12 ± 0.07	3.24 ± 0.05	0.004
Log sCD14, ng/mL	3.02 ± 0.12	3.15 ± 0.09	2.87 ± 0.12	3.30 ± 0.09	0.03
Inflammatory Markers					
Log hsCRP, mg/L	-0.98 ± 0.19	-1.02 ± 0.13	-0.77 ± 0.18	-0.78 ± 0.13	0.50
Log hsIL-6, pg/mL	0.15 ± 0.07	0.13 ± 0.05	0.25 ± 0.07	0.25 ± 0.05	0.32
Log LPS, ng/mL	-1.86 ± 0.21	-1.42 ± 0.12	-1.66 ± 0.16	-1.86 ± 0.12	0.07
Cardiac Biomarkers					
Log hs-cTnT, ng/L	0.57 ± 0.06	0.54 ± 0.04	0.49 ± 0.06	0.56 ± 0.04	0.78
Log NT-proBNP, pg/mL	1.46 ± 0.13	1.59 ± 0.09	1.80 ± 0.13	1.57 ± 0.09	0.27
Log Galectin-3, ng/mL	1.08 ± 0.04	1.16 ± 0.03	1.20 ± 0.04	1.18 ± 0.03	0.10
Log sST2, ng/mL	1.45 ± 0.05	1.45 ± 0.03	1.40 ± 0.05	1.49 ± 0.03	0.38
Log Oxidized LDL, U/L	1.59 ± 0.04	1.62 ± 0.03	1.67 ± 0.04	1.63 ± 0.03	0.56
Log Lp-PLA_2, nmol/min/ml	2.10 ± 0.04	2.22 ± 0.03	2.22 ± 0.04	2.23 ± 0.02	0.04
Presence of coronary plaque, %	23	40	54	33	0.41
Segments with noncalcified plaque, %	33 ± 19 [0 (0,100)]	71 ± 10 [71 (63,100)]	19 ± 13 [0 (0,44)]	78 ± 12 [88 (54,100)]	0.009 (0.047)
Segments with mixed plaque, %	13 ± 16 [0 (0,40)]	27 ± 9 [25 (0,33)]	51 ± 11 [42 (31,75)]	17 ± 10 [0 (0,33)]	0.13 (0.13)
Segments with calcified plaque, %	53 ± 14 [60 (0,100)]	3 ± 8 [0 (0,0)]	40 ± 9 [33 (0,67)]	5 ± 9 [0 (0,13)]	0.003 (0.01)

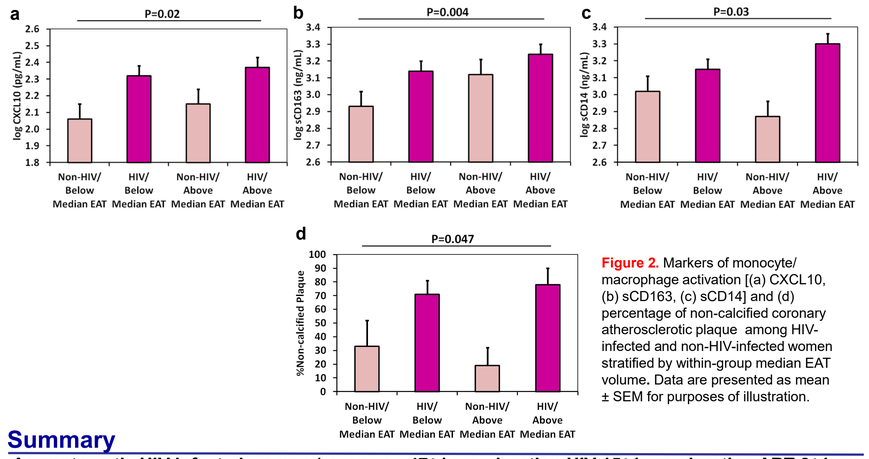

Figure 2. Markers of monocyte/ macrophage activation [(a) CXCL10, (b) sCD163, (c) sCD14] and (d) percentage of non-calcified coronary atherosclerotic plaque among HIV-infected and non-HIV-infected women stratified by within-group median EAT volume. Data are presented as mean ± SEM for purposes of illustration.

Summary

- Asymptomatic HIV-infected women (mean age 47±1 yrs, duration HIV 15±1 yrs, duration ART 8±1 yrs, $CD4^+$ count 599±42 cells/ml, undetectable VL 84%) and age-matched non-HIV-infected women with comparable BMI (28±1 vs. 29±1 kg/m^2) had similar median volumes of EAT(54[41,79] vs. 65[41,78]cm^2) (P>0.05). (Table 1)
- Markers of monocyte activation and arterial inflammation differed by [HIV serostatus/EAT volume] subgroup (sCD163 (P=0.004), sCD14 (P=0.03), CXCL10 (P=0.02), Lp-PLA2 (P=0.04)) and were highest among HIV-infected women w/ excess EAT compared to HIV-infected women w/o excess EAT, non-HIV-infected women w/ excess EAT, and non-HIV-infected women w/o excess EAT. (Table 2, Fig 2)
- The percent of non-calcified coronary atherosclerotic plaque also differed by [HIV serostatus/EAT volume] subgroup (P<0.05) and was highest among HIV-infected women w/ excess EAT. (Table 2, Fig 2)
- Among HIV-infected women, EAT was not related to traditional CVD risk factors and was instead related to unique HIV-specific parameters, including duration of NRTI use (r=0.27, P=0.045) and VAT area (r=0.58, P<0.0001). VAT(β est=0.2527, P=0.0002) remained an independent predictor of EAT in HIV after controlling for age and NRTI duration (overall multivariate model R^2=0.37, P<0.0001).

Conclusion

Among women with HIV, excess epicardial fat is associated with immune activation and arterial inflammation, as well as non-calcified plaque. Future treatment strategies aimed at reducing ectopic fat among HIV-infected women may have potential to dampen systemic immune activation and favorably influence plaque morphology.

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