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Increased Epicardial Adipose Tissue Volume in HIV-Infected Men and Relationships to Body Composition and Metabolic Parameters

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Summary

Epicardial fat accumulation may have important clinical consequences, yet little is known regarding this depot in HIV patients. We compared epicardial fat volume in 78 HIV-infected men and 32 HIV-negative controls. Epicardial fat volume was higher in HIV than control subjects (p=0.04). In HIV patients, epicardial fat volume was strongly associated with visceral adipose tissue area (VAT)(ρ = 0.76, p<0.0001), fasting glucose (ρ = 0.41, p=0.001) and insulin (ρ = 0.44, p=0.0003). Relationships with glucose and insulin remained significant controlling for age, race, BMI, adiponectin, VAT, and antiretroviral therapy. Epicardial fat may be an important fat depot in HIV-infected patients.

Keywords

HIV; epicardial fat; visceral fat; glucose; atherosclerosis

Introduction

Epicardial adipose tissue is hormonally active tissue that releases adipokines and fatty acids [1, 2] and may be important in HIV patients as it shares an embryonic origin with visceral fat [3]. In non-HIV populations, prior studies have shown associations between pericardial or epicardial fat and VAT [4, 5], insulin resistance [6], the metabolic syndrome [4, 7] and coronary calcifications [7, 8]. Although prior studies have investigated epicardial fat thickness by echocardiography in HIV-infected patients [9, 10], no studies have compared epicardial fat volume by CT in HIV and non-HIV groups. In this study we investigate epicardial fat volume in HIV and non-HIV patients with similar cardiovascular risk factors and body composition indices to determine whether epicardial fat accumulation occurs and the relationship of epicardial fat to metabolic abnormalities, including glucose parameters, in this population.

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Methods

Design

In a prospectively recruited cohort of HIV patients and HIV-negative controls [11], we measured epicardial fat volume by MDCT and now present novel data comparing epicardial fat volume between the two groups, assessing the relationship of epicardial fat volume to body composition and metabolic parameters.

Participants

Subjects were recruited based on absence of known heart disease and cardiac symptoms with a goal to recruiting two groups with similar cardiovascular risk factors. Subjects were not recruited based on anthropometric or body composition parameters [11].

Assessments

Epicardial fat volume measurements were performed by a single experienced reader using a dedicated semiautomatic program (Siemens Medical Solutions) using similar methodology as previously described [12]. A region of interest was traced on the boundaries of the pericardial layers in every 10 mm with interpolation between the superior and inferior boundary. The top limit of the pericardium fat was the middle of the right pulmonary artery and the lower limit was the apex of the pericardial sac. Fat tissue was defined by voxels with Hounsfield unit (HU) between −30 HU to −190 HU [12]. Body composition and metabolic parameters were determined as previously described [11]. Lipodystrophy was scored as previously reported, rating face, extremities, neck or abdomen as 0–2 for each area[13].

Statistics

Comparisons between the groups utilized Student's T-test and Wilcoxon test as appropriate. Univariate and multivariate linear regression were performed using SAS JMP.

Results

Seventy-eight HIV-infected men and 32 HIV-seronegative men were studied (Table 1). Epicardial fat volume was higher in HIV patients (112.3 [81.9, 158.7] cm^3) compared to non HIV-infected controls (84.6 [57.7, 130.7] cm^3) (p=0.04). In contrast, VAT, waist circumference, BMI and total body fat were not different between the groups, although the HIV group tended to have less subcutaneous abdominal fat. A minority of subjects in each group met criteria for the metabolic syndrome and the proportions did not differ between the groups (Table 1). 16% of HIV-infected participants reported having a major feature of lipodystrophy (score of 2 at one or more sites).

Relationship of Epicardial Fat to Body Composition and Metabolic Parameters in HIV Patients

Body Composition—Epicardial fat was associated with BMI (ρ = 0.48, p<0.0001), VAT (ρ = 0.76, p<0.0001), SAT (ρ = 0.39, p=0.002), total fat mass (ρ = 0.62, p<0.0001) and lean mass (ρ = 0.37, p<0.004). In a model including BMI, VAT, SAT, total fat mass and lean mass, VAT was the only body composition measurement that remained significantly associated with epicardial fat (β = 0.30 cm^3/cm^2, p<0.0001, model r^2 = 0.57). Additional sensitivity analysis adjusting for body composition parameters as well as age, PI and NRTI use also demonstrated similar results. Among HIV-infected patients without the metabolic syndrome, similar results were seen.

Metabolic Parameters—Epicardial fat was positively associated with fasting glucose (ρ = 0.41, p=0.001), fasting insulin (ρ = 0.44, p=0.0003), 2-hour insulin (ρ = 0.25, p=0.04) and negatively associated with adiponectin (ρ = −0.26, p=0.04), CD4 (ρ = 0.28, p=0.02) and CD8 (ρ = 0.39, p=0.001), but not with CRP (ρ = 0.09, p=0.47), monocyte chemoattractant protein-1 (ρ = 0.08, p=0.55), or IL-6 (ρ = −0.05, p=0.73).

Coronary Atherosclerosis and Ventricular Function—No correlation was found between epicardial fat and plaque volume (ρ = −0.12, p=0.35), segments with plaque (ρ = −0.06, p=0.64), nor with calcium score (ρ = −0.02, p=0.89). All but 3 HIV patients had normal left ventricular function assessed by cardiac CT. Median epicardial fat volume was 156.7 [107.0, 241.1] cm^3 in the 3 patients with decreased ventricular function and 110.6 [81.1, 158.7] cm^3 in HIV patients with normal cardiac function.

Multivariate Modeling in HIV Patients

Epicardial fat remained significantly associated with fasting glucose (β = 0.10 cm^3/mg/dL, p=0.02) in a model including age, race, BMI, adiponectin, VAT, current PI use and current NRTI use. Similar results were seen in modeling with fasting insulin (β = 0.07 cm^3/μU/mL, p=0.03). Self-reported nadir CD4 count was available for 58 HIV-infected patients. After controlling for nadir CD4 count, epicardial fat volume remained significantly associated with fasting glucose (β = 0.08 cm^3/mg/dL, p=0.005) and insulin (β = 0.09 cm^3/μU/mL, p=0.0002).

Relationship of Epicardial Fat to Metabolic Parameters in Non HIV-Infected Patients

Among HIV-negative controls, epicardial fat was associated with age (ρ = 0.51, p=0.01), Framingham score (ρ = 0.55, p=0.005), diastolic blood pressure (ρ = 0.57, p=0.003), 2-hour glucose (ρ = 0.59, p=0.002), BMI (ρ = 0.81, p<0.0001), total fat (ρ = 0.88, p<0.0001), SAT (ρ = 0.78, p<0.0001), and VAT (ρ = 0.85, p<0.0001).

Discussion

The current study demonstrates that epicardial fat volume was significantly higher in HIV patients compared to a well-matched control group that did not differ significantly with respect to other body composition parameters. Among HIV patients, epicardial fat volume correlated most highly with visceral obesity, more so than overall adiposity or other body composition parameters.

In a prior study of HIV patients on HAART with lipodystrophy and the metabolic syndrome, epicardial fat thickness measured by echocardiography correlated with VAT and IMT [9]. In contrast, patients in our study were not recruited based on the presence of fat redistribution or the metabolic syndrome. Moreover, the majority of patients did not have the metabolic syndrome and the relationships with epicardial fat volume were similar and remained highly significant when analysis was limited to only those without the metabolic syndrome.

In this study we present novel data among HIV patients demonstrating a moderate but significant relationship between glucose parameters and epicardial fat volume that appears to be independent of other factors known to regulate glucose homeostasis, including VAT. Additional studies are needed to determine whether development of excess epicardial adipose tissue contributes to the insulin resistance in this population and whether reducing epicardial fat should be targeted in this regard.

Our current data demonstrate that CD4+ and CD8+ T-lymphocytes are associated with epicardial fat. T-lymphocytes are increased in the adipose tissue of obese humans,

potentially playing a role in obesity-related inflammation [14, 15]. Studies are needed to assess if there is an independent relationship between epicardial fat and immune function in HIV-infected patients.

Our data demonstrate for the first time that epicardial adipose tissue, assessed volumetrically by MDCT, is increased in HIV patients and related to visceral adiposity. Epicardial fat is significantly associated with fasting glucose and insulin in HIV-infected patients, independently of traditional factors affecting glucose homeostasis. Investigation of the mechanisms, clinical significance, and potential therapeutic strategies for epicardial fat accumulation in HIV patients is needed.

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Table 1

Demographic and Clinical Characteristics of Study Population

	Controls (n=32)	HIV Positive (n=78)	*P*-value
Demographics			
Age, y	45.4 ± 7.2	46.5 ± 6.5	0.44
Race, %			0.17
White	59	68	
Black	19	18	
Asian	9	1	
Hispanic	3	9	
Native American	6	4	
Metabolic syndrome by NCEP criteria, %	11	19	0.28
Framingham risk score	7.0 ± 4.6	7.7 ± 5.1	0.50
Hypertension, %	16	29	0.14
Diabetes mellitus, %	3	9	0.23
HIV Disease Related Parameters			
Duration since HIV diagnosis, y	N/A	13.5 ± 6.1	N/A
Ever on antiretroviral therapy, %	N/A	95	N/A
Currently on antiretroviral therapy, %	N/A	95	N/A
Duration of antiretroviral therapy, y	N/A	7.1 ± 4.6	N/A
Current protease inhibitor (PI) treatment, %	N/A	53	N/A
Duration of PI treatment, y	N/A	3.8 ± 4.2	N/A
Current NRTI treatment, %	N/A	91	N/A
Duration of NRTI treatment, y	N/A	6.8 ± 4.5	N/A
Current NNRTI treatment, %	N/A	49	N/A
Duration of NNRTI treatment, y	N/A	2.6 ± 3.5	N/A
CD4+ T-lymphocytes (cells/mm^3)	N/A	523 ± 282	N/A
HIV RNA viral load (copies/mL)	N/A	<50 (<50, <50)	N/A
Undetectable HIV RNA < 50 copies/mL, %	N/A	81	N/A
Body Composition parameters			
Body mass index, kg/m^2	26.9 ± 5.2	26.1 ± 4.3	0.43
Waist circumference, cm	96.1 ± 15.8	95.8 ± 13.5	0.91
Hip circumference, cm	102.1 ± 9.6	99.4 ± 8.5	0.15
Total body fat, kg	19.8 ± 11.4	17.7 ± 7.7	0.27
Visceral adipose tissue area (VAT), cm^2	149 ± 111	172 ± 121	0.35
Subcutaneous adipose tissue area (SAT), cm^2	212 ± 138	167 ± 98	0.06
Epicardial fat volume, cm^3	85 (58, 131)	112 (82, 159)	0.04
Metabolic parameters			
Fasting glucose, mmol/L (mg/dL)	5.1 ± 0.5 (92 ± 9)	5.2 ± 0.6 (94 ± 11)	0.40
2-hr glucose, mmol/L (mg/dL)	6.2 ± 2.3 (112 ± 41)	6.8 ± 2.6 (123 ± 47)	0.27
Fasting insulin, μU/mL	5.1 ± 3.6	8.2 ± 8.4	0.05
Hemoglobin A1c, %	5.5 ± 0.4	5.3 ± 0.6	0.17

	Controls (n=32)	HIV Positive (n=78)	*P*-value
Adipocytokines and Inflammatory Markers			
Adiponectin (μg/mL)	4.6 (3.5, 7.2)	4.0 (2.1, 9.0)	0.41
MCP-1 (pg/mL)	240 (195, 312)	282 (192, 367)	0.17
CRP (mg/L)	1.8 (0.6, 3.5)	1.6 (0.7, 4.0)	0.82

Data reported as mean ± standard deviation (SD) or percentage, except for variables with non-normal distributions, which are reported as median (interquartile range). NCEP, National Cholesterol Education Program; NRTI, Nucleoside/Nucleotide Reverse Transcriptase Inhibitors; NNRTI, Non-nucleoside Reverse Transcriptase Inhibitors.