

Adiponectin Levels and Coronary Artery Disease among HIV-Infected Men

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Abstract

Objective: HIV-infected persons frequently experience lipodystrophy and are at higher risk of cardiovascular disease, but the impact of adipose-related hormones, such as adiponectin, on Coronary Artery Disease (CAD) remains unclear. We evaluated the association of plasma adiponectin levels and the presence of CAD.

Design: A cross-sectional study among HIV-infected men in a large HIV clinic.

Methods: HIV-infected participants underwent CT scan imaging to determine CAD as measured by Coronary Artery Calcium (CAC) scores categorized as no detectable disease (0), minimum disease (1-100), and significant disease (>100). Factors associated with CAD, including adiponectin levels, were evaluated using multivariate logistic regression modeling.

Results: 213 HIV-infected men were evaluated with a median age of 43 years, median CD4 count of 583 cells/ mm³, and 69% had HIV RNA<50 copies/mL. Forty-nine percent had lipohypertrophy, 30% had hypertension, and 21% had a moderate/high Framingham risk score (FRS). Thirty-three percent (n=71) had positive CAC scores. Seventy percent (n=149) had a low adiponectin level (<4.0 μ g/ml), including 66% with CAC=0, 76% with CAC of 1-100, and 81% with CAC>100 (p=0.09). Adiponectin levels were inversely correlated with lipohypertrophy, hypertension, and triglyceride levels (p<0.05), while FRS was marginally correlated (X^2 =3.1, p=0.08). In the final multivariate model, increasing age (OR 3.8 per 10 year increase, 95% CI 2.56-5.71, p<0.001) was significantly associated with CAC, and adiponectin approached significance (OR 0.8 per 1 μ g/ml increase, 95% CI 0.69-1.00, p=0.05).

Conclusions: Low adiponectin levels are common among HIV-infected persons. Adiponectin is correlated with lipohypertrophy and lower levels approached significance with CAD. Understanding the role of adiponectin in the pathogenesis of CAD may allow for targeted treatment and prevention strategies among HIV-infected persons.

Keywords: HIV; Cardiovascular disease; Adiponectin; Coronary artery calcium scores; CAC

Introduction

Cardiovascular disease is a leading cause of morbidity and mortality among HIV-infected persons [1,2]. As HIV patients are living longer, they are increasingly developing cardiovascular and metabolic diseases, similar to the aging general population [1-4]. Additionally, some studies suggest that HIV patients are experiencing accelerated vascular aging [5,6], although further data are needed. The exact risk factors for the higher risk of cardiovascular disease among HIV patients are unclear, but likely related to complex interactions between the virus itself, antiretroviral medications, increased immune activation, and metabolic changes [3,4,7-13].

Further information on the pathogenesis of cardiovascular disease among HIV-infected persons is needed. The identification of novel markers may not only enhance the understanding of underlying pathogenic mechanisms of cardiovascular disease, but also serve as indicators of underlying disease. Recently, inflammatory markers, such as high-sensitivity C-reactive protein (hsCRP), have emerged as indicators of and risk factors for cardiovascular disease [14-16]. Since HIV-infected persons have altered patterns of fat distribution, whether markers associated with fat deposition are related to cardiovascular disease is currently unclear.

Adiponectin is a plasma protein secreted exclusively from the adipose tissue into the bloodstream, and levels are inversely correlated

with obesity [17,18]. The mechanism whereby obesity leads to low adiponectin levels is the result of increased oxidative stress on adipose tissue and down regulation of adiponectin receptors [19]. Further, in epidemiologic investigations, inverse associations have been reported between plasma adiponectin levels and the presence of type 2 diabetes mellitus, hypertension, and the metabolic syndrome [18,20]. Recently, adiponectin has attracted attention for its anti-atherogenic and antiinflammatory properties [21,22]. As such, hypoadiponectinemia has been associated with an increased risk of cardiovascular disease in the general population [20,23,24]. Little data, however, exists among HIV-infected persons with a single study associating low adiponectin levels with increased Framingham risk scores (FRS) [25]. Since HIV patients often have altered fat distribution patterns, which may result in lower adiponectin levels, and prior studies have linked lipodystrophy to cardiovascular disease [26-29], data on the association of plasma

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adiponectin levels and cardiovascular disease among HIV-infected persons are needed.

Understanding the potential role of plasma adiponectin in the pathogenesis of cardiovascular disease among HIV-infected persons may be important in the development of novel preventive and treatment strategies. Therefore, we conducted a study to evaluate the association of adiponectin levels and Coronary Artery Disease (CAD) as measured by Coronary Artery Calcium (CAC) scores among HIV-infected men. Additionally, we examined the association of adiponectin with Fatty Liver Disease (FLD), since it may share common risk factors to CAD.

Methods

Study population

We conducted a cross-sectional study to determine the factors associated with coronary atherosclerosis as detected by coronary artery calcium (CAC) [30] scores among HIV-infected men. The secondary objective examined the association between adiponectin levels and FLD as detected by Computed Tomography (CT) imaging. Our study population consisted of HIV-infected men (\geq 18 years of age) receiving care at the Naval Medical Center San Diego (NMCSD); all participants were military active duty members, retirees, or dependents. Of the 223 participants in the original study [31], 213 were included in the current analysis after excluding females (n=10). Only men were included in this study since the majority of the participants were male and adiponectin levels vary by gender [32]. All participants were confirmed HIVpositive by enzyme-linked immunosorbent assay and Western blot testing. Participants were enrolled between December 2008 and March 2010. The study was approved by the Institutional Review Boards at NMCSD and San Diego State University, and all participants provided written informed consent.

Clinical data collection

Study participants completed a questionnaire including data on demographics (age, ethnicity, and gender); history of tobacco, alcohol, and illicit drug use; and medical history. Research coordinators reviewed participants' medical records for data on medical conditions, medication use, and HIV-specific information including CD4 cell counts (nadir and current) by flow cytometry, HIV RNA level (Roche Amplicor, undetectable <50 copies/ml), and years of HIV seropositivity [defined as the time from HIV seroconversion (midpoint between last negative and first positive test) or first seropositivity to enrollment]. The CD4 cell count and plasma HIV RNA level were obtained from the laboratory records given that they were collected in close proximity to study enrollment. Information collected on antiretroviral medications included cumulative use of nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and Protease Inhibitors (PIs). Current receipt of highly active antiretroviral therapy (HAART) was defined as the use of three or more antiretroviral drugs as per the guidelines [33]. Specific NRTIs (abacavir, tenofovir and didanosine) and PIs (ritonavir, atazanavir) were examined based upon the number of users as well as published studies showing that some antiretroviral medications may be associated with increased CAD risk [11-13].

Diabetes and hypertension were defined based on the participant's use of medications for these conditions, and excessive alcohol use was defined as >140 grams of ethanol/week [34]. The participant's 10-year cardiovascular risk was determined using the FRS [35]. Research coordinators measured the participants' weight and height for calculation of the Body Mass Index (BMI); overweight was defined as a BMI 25.0-29.9 kg/m², and obese as a BMI \geq 30 kg/m².

Additionally, measurements of body circumferences (hip, thigh, and waist circumference, and waist/hip ratio) and skin-fold thickness (subscapular, suprailiac, biceps, and triceps using a standardized Lange skin-fold calipers) were obtained on the participant's right side, as previously described [36,37]. Three measurements of each body site were taken, and the mean measurement was utilized for each body site. Percent body fat was calculated by caliper measurements [36,38].

The participant's physician conducted a visual assessment to estimate fat gain or loss in six locations (cheeks, neck, breasts, abdomen, buttocks, and legs) since the time of HIV diagnosis. The physician's visual assessment of the participant's lipodystrophy was ranked on a scale of -3 to +3, with negative scores indicating lipoatrophy, positive scores indicating lipohypertrophy, and 0 as no change [39].

Laboratory data

Laboratory data included fasting (≥ 10 hours) glucose, total cholesterol, High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), and triglyceride levels. Additionally, blood was obtained for plasma adiponectin (multimeric enzyme-linked immunosorbent immunoassay, ALPCO Diagnostics, Salem, NH), hsCRP (lower limit of detection <0.5 mg/dl, Particle Enhanced Immunoturbidimetric Assay, Roche, Indianapolis IN), and Erythrocyte Sedimentation Rate (ESR, Modified Westergren Method). All tests were performed at the NMCSD clinical laboratory [certified by Clinical Laboratory Improvement Amendments (CLIA)], except the adiponectin assay which was performed at the Analytical Translational Core Laboratory at Brigham and Women's Hospital Laboratory. Adiponectin levels were stored and run at the same time to ensure calibration. A low adiponectin level was defined as <4.0 µg/ml [40,41].

CT imaging

All participants underwent a Computerized Tomography (CT) scan, on the same day as laboratory testing, to determine the CAC score and assess for FLD. Participants underwent imaging using a single, multidetector CT scan (Siemens Definition Dual Source CT Scanner, Siemens Medical Solutions, Forsheim, Germany) without the administration contrast media. Prospectively gated axial 3 mm images were obtained at 120 kV during a single breath hold. The scanning protocol captured images with a 330-milisecond gantry rotation time, an individual detector width of 0.6 mm with a reconstructed section width of 3 mm, and temporal resolution of 165 milliseconds. CAC scores were performed on an Aquarius workstation (TeraRecon, San Mateo, California) and calculated as the sum of all lesions in each of the coronary arteries using Agatston units [42]. A CAC score of >0 was considered positive for detectable calcium, and a score of >100 was considered clinically significant. Limited 3 mm axial images were also obtained through the mid-liver, centered at the level of the portal vein, and spleen to estimate fat content [43]. FLD was defined as a liver-tospleen ratio of <1.0, using the mean values of three images taken in the right posterior, right anterior, and left lobe of the liver [44]. Images were processed on an Impax 6.3 workstation (AGFA).

Statistical analysis

The primary outcome of this study was to evaluate the association of adiponectin with the presence of CAD as defined by the CAC score categorized as no detectable disease (0), minimum detectable disease (1-100), and clinically significant detectable disease (>100). Our secondary outcome examined the relationship of adiponectin levels with FLD. Statistical analyses included descriptive statistics for all variables of interest. Frequency distributions of categorical variables are presented as numbers with percentages, and continuous variables as medians with interquartile ranges (IQR). Spearman correlation coefficients and chi-square tests were used to describe the correlations between adiponectin and continuous and categorical variables of interest, respectively. Univariate proportional odds logistic regression was used to determine the association of each variable with the threelevel CAC score (no detectable disease, minimum detectable disease, and clinically significant detectable disease), and then repeated with FLD as the secondary outcome.

Variables with a p-value ≤ 0.20 in the univariate analyses were evaluated in the multivariate analysis. Multivariate analysis was conducted using ordinal logistic regression with forward stepwise addition of variables to derive the final model. The final regression model included all independent variables with a p-value <0.05 or variables which were confounders (changed the odds ratio of adiponectin >10%). Collinearity among variables of interest was assessed using Spearman's correlation coefficient, chi-square, and Fisher's exact tests; variables that were highly correlated with other independent variables in the multivariate model were eliminated from the final model, except the most significant and clinically relevant

variables. Separate final multivariate models for the outcomes of CAC score and FLD were created. In addition to the model for FLD as the outcome, an additional logistic regression analysis was performed for non-alcoholic fatty liver disease (NAFLD), by excluding participants with excessive alcohol intake. Odds ratios (OR) and adjusted odds ratios (AOR) with 95% confidence intervals (CI) are presented. A p-value of <0.05 was considered statistically significant and all statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

Results

Baseline study population characteristics

A total of 213 HIV-infected men were evaluated with a median age of 43 years (IQR 36-49); 51% were Caucasian, 22% African American, 14% Hispanic, and 13% other (Table 1). Thirty percent of participants had hypertension, 6% had diabetes, 2% were co-infected with hepatitis C virus (HCV), and 17% were current tobacco users. By FRS, 21% had a moderate/high risk score. The median BMI was 26.7 kg/m² (IQR 24-29); 98 (46%) participants were overweight and 42 (20%) obese. By physician's visual lipodystrophy assessment, 104 (49%) of the

| Characteristic ^a | Total Cohort N=213 | Clinically Significant Disease (CAC Score >100) N=16/213 | Minimum Detectable Disease CAC Score 1-100) N=55/213 | No Detectable Disease (CAC=0) N=142/213 | OR (95% CI) | P-value |
|---|-----------------------|--|--|---|-----------------|---------|
| Variable of Interest | | | | | | |
| Adiponectin, per 1.0 µg/ml increase | 3.1 (2.2-4.4) | 2.5 (2.0-3.7) | 2.8 (2.1-3.9) | 3.2 (2.3-4.4) | 0.8 (0.7, 1.0) | 0.06 |
| Demographics | | | | | | |
| Age, per 10 years | 43 (36-49) | 51 (49-55) | 49 (42-55) | 40 (31-45) | 3.7 (2.5, 5.5) | <0.0001 |
| Ethnicity | | | | | | 0.01 |
| Black | 48 (22.5%) | 1 (2.1%) | 9 (18.7%) | 38 (79.2%) | 0.3 (0.1, 0.7) | |
| Hispanic | 30 (14.1%) | 2 (6.7%) | 3 (10.0%) | 25 (83.3%) | 0.2 (0.1, 0.8) | |
| Other | 27 (12.7%) | 2 (7.4%) | 8 (29.6%) | 17 (63%) | 0.7 (0.3, 1.8) | |
| White | 108 (50.7%) | 11 (10.2%) | 35 (32.4%) | 62 (57.4%) | 1.0 | |
| Clinical Information | | | | | | |
| Hypertension | | | | | | |
| No | 150 (70.4%) | 9 (6%) | 26 (17.3%) | 115 (76.7%) | 1.0 | |
| Yes | 63 (29.6%) | 7 (11.1%) | 29 (46.0%) | 27 (42.9%) | 3.8 (2.1, 7.1) | <0.0001 |
| Diabetes | | | | | | 0.001 |
| No | 200 (93.9%) | 13 (6.5%) | 48 (24.0%) | 139 (69.5%) | 1.0 | |
| Yes | 13 (6.1%) | 3 (23.0%) | 7 (53.9%) | 3 (23.1%) | 5.9 (2.0, 17.2) | |
| CHD Risk Level by FRS | | | | | | <0.0001 |
| Low | 169 (79.3%) | 10 (5.9%) | 34 (20.1%) | 125 (74.0%) | 1.0 | |
| Moderate/High | 44 (20.7%) | 6 (14.0%) | 21 (48.0%) | 17 (38.0%) | 4.0 (2.0, 7.7) | |
| Tobacco Use | | | | | | 0.50 |
| Never | 106 (49.8%) | 5 (4.7%) | 28 (26.4%) | 73 (68.9%) | 1.0 | |
| Past | 70 (32.9%) | 7 (10.0%) | 16 (22.9%) | 47 (67.1%) | 1.1 (0.6, 2.2) | |
| Current | 37 (17.3%) | 4 (10.8%) | 11 (29.7%) | 22 (59.5%) | 1.5 (0.7, 3.3) | |
| HIV-specific Information | | | | | | |
| Duration HIV infection (years) | 11 (5-19) | 20 (14-23) | 17 (8-22) | 8 (4-15) | 1.1 (1.0, 1.1) | <0.0001 |
| CD4 count (cells/mm ³),per 100 cells | 583 (386-729) | 643 (464-836) | 480 (305-734) | 587 (425-713) | 1.1 (0.9, 1.3) | 0.09 |
| Nadir CD4 (cells/mm ³), per 100 cells | 260 (138-366) | 257 (103-346) | 170 (71-304) | 284 (187-382) | 0.7 (0.5, 0.8) | 0.001 |
| HIV RNA level (copies/ml) | | | | | | |
| <50 | 148 (69.5%) | 13 (8.8%) | 38 (25.7%) | 97 (65.5%) | 1.0 | |
| ≥50 | 65 (30.5%) | 3 (4.6%) | 17 (26.2%) | 45 (69.2%) | 0.8 (0.4, 1.5) | 0.50 |
| Current HAART Use | | | | | | |
| No | 37 (17.4%) | 1 (2.7%) | 4 (10.8%) | 32 (86.5%) | 1.0 | |
| Yes | 176 (82.6%) | 15 (8.5%) | 51 (29.0%) | 110 (62.5%) | 3.8 (1.4, 10.2) | 0.01 |
| Total months NRTI use, per 12 months | 76 (17.3-147) | 154.4 (99-180.3) | 125 (53-182) | 47 (9.1-117.2)) | 1.1 (1.0,1.1) | <0.0001 |
| Total months protease | 24.4 (0-71) | 78.1 (24.4-117) | 53 (3.3-105) | 3.05 (0-63) | 1.1 (1.0,1.2) | 0.0001 |
| | | | | | | 1 |

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| inhibitor use, per 12 months | | | | | | |
|--|----------------------|------------------|---------------|----------------|-----------------|---------|
| Abacavir | | | | | | |
| None | 139 (65.3%) | 6 (4.3%) | 29 (20.9%) | 104 (74.8%) | 1.0 | |
| Past or Current Use | 74 (34.7%) | 10 (13.5%) | 26 (35.1%) | 38 (51.4%) | 2.9 (1.6, 5.1) | 0.0004 |
| Didanosine | | | | | | |
| None | 153 (71.8%) | 8 (5.2%) | 33 (21.6%) | 112 (73.2%) | 1.0 | |
| Past or Current Use | 60 (28.2%) | 8 (13.3%) | 22 (36.7%) | 30 (50.0%) | 2.7 (1.5, 5.0) | 0.001 |
| Tenofovir | | | | | | |
| None | 61 (28.6%) | 4 (6.5%) | 9 (14.8%) | 48 (78.7%) | 1.0 | |
| Past or Current Use | 152 (71.4%) | 12 (7.9%) | 46 (30.3%) | 94 (61.8%) | 2.1 (1.1, 4.3) | 0.03 |
| Ritonavir | | | | | | |
| None | 109 (51.2%) | 3 (2.8%) | 19 (17.4%) | 87 (79.8%) | 1.0 | |
| Past or Current Use | 104 (48.8%) | 13 (12.5%) | 36 (34.6%) | 55 (52.9%) | 3.6 (1.2, 6.6) | <0.0001 |
| Atazanavir | | | | | | |
| None | 142 (66.7%) | 8 (6.0%) | 33 (23.0%) | 101 (71.0%) | 1.0 | |
| Past or Current Use | 71 (33.3%) | 8 (11.3%) | 22 (31.0%) | 41 (57.7%) | 1.8 (1.0, 3.3) | 0.04 |
| Laboratory Results | | | | | | |
| ESR , per 10 mm/hr | 10 (7-18) | 11 (9-24) | 13 (10-19) | 10 (7-18) | 1.1 (0.9, 1.4) | 0.12 |
| hsCRP level (mg/dL) | 0.2 (0.1-0.3) | 0.2 (0.1-0.4) | 0.2 (0.1-0.4) | 0.2 (0.1-0.3) | 1.2 (0.8, 1.8) | 0.24 |
| Total cholesterol, per 10 mg/dL | 183 (158-211) | 170 (161-220) | 192 (164-217) | 182 (157-204) | 1.0 (0.9, 1.1) | 0.18 |
| HDL, per 10 mg/dL | 40 (35-49) | 39 (33-46) | 41 (35-46) | 40 (34-50) | 0.9 (0.7, 1.1) | 0.37 |
| LDL , per 10 mg/dL ^₅ | 102 (86-129) | 102 (70-129) | 109 (92-136) | 98 (83-129) | 1.0 (0.9, 1.1) | 0.22 |
| Fasting glucose, per 10 mg/dL ^b | 92 (86-99) | 99 (89-109) | 93 (87-103) | 91 (85-97) | 1.2 (1.0, 1.4) | 0.01 |
| Triglyceride level, per 100 mg/dL | 143 (94-243) | 181 (115-270) | 178 (118-247) | 131 (79-235) | 1.2 (1.0,1.4) | 0.01 |
| Weight and Fat Measurements | | | | | | |
| BMI (kg/m²) | 26.7 (24.2- 29.4) | 27.2 (25.4-29.4) | 25.1 (24-28) | 27 (24.3-30) | 1.0 (0.9, 1.1) | 0.15 |
| Suprailiac measurement (mm) | 16 (11-23.3) | 16.4 (11-28) | 16 (10-21) | 17 (11.3-24) | 1.0 (0.9, 1.0) | 0.69 |
| Subscapular measurement (mm) | 21 (16-27.3) | 20 (17-27) | 22.3 (14-29) | 21.1 (16-26.3) | 1.0 (0.9, 1.0) | 0.66 |
| Biceps measurement (mm) | 8 (5-11) | 7.2 (5-11.2) | 7 (4-11) | 9 (5-11) | 1.0 (0.9, 1.1) | 0.20 |
| Triceps measurement (mm) | 16 (11.3-21) | 18 (10-22) | 15 (9-19.3) | 17 (13-21) | 0.9 (0.9, 1.0) | 0.24 |
| Waist circumference (cm) | 94 (86-99) | 96 (87-107) | 91 (84-98) | 94 (86-99) | 1.0 (1.0, 1.0) | 0.31 |
| Thigh circumference (cm) | 56 (52-60) | 53 (51-58) | 54 (50-57) | 57 (53-61) | 0.9 (0.9, 1.0) | 0.01 |
| Hip circumference (cm) | 93 (87-98) | 94 (87-100.2) | 93 (86-98) | 92.2 (87-98) | 1.0, 0.9, 1.0) | 0.72 |
| Waist/Hip ratio (cm) | 1.0 (0.9-1.0) | 1.0 (1.0-1.1) | 1.0 (0.9-1.0) | 1 (0.9-1.0) | 2.2 (0.3, 15.6) | 0.41 |
| Percent body fat ^b | 26 (23-30) | 29 (25.3-33.5) | 27.1 (23-31) | 26 (23-29) | 1.0 (1.0, 1.1) | 0.02 |
| Physician Visual Assessment | | | | | | |
| Lipohypertrophy | 104 (48.8%) | 11 (10.6%) | 37 (35.6%) | 56 (53.8%) | 3.1 (1.7, 5.6) | 0.0002 |
| Lipoatrophy | 81 (38.0%) | 11 (13.6%) | 28 (34.6%) | 42 (51.8%) | 3.0 (1.6, 5.3) | 0.0002 |

^a Categorical variables expressed as number (percentage) and continuous variables as median (interquartile range)

^bAll values are n=213, except LDL (n=200), glucose (n=212) and percent body fat (n=212) due to missing values

BMI, body-mass index; CAC, coronary artery calcium score; CHD Risk level, coronary heart disease risk level; CI, 95% confidence interval; ESR, erythrocyte

sedimentation rate; FRS, Framingham Risk Score ; HAART, highly active antiretroviral therapy; HDL, high-density lipoprotein; hsCRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; OR, odds ratio

Table 1: Study Population Characteristics and Univariate Associations with Coronary Artery Disease by CAC Score among 213 HIV-Infected Men.

participants had lipohypertrophy and 81 (38%) had lipoatrophy; fiftyone patients (24%) had both lipodystrophy and lipoatrophy.

Regarding HIV characteristics, the median duration of HIV infection was 11 years (IQR 5-19), the median current CD4 count was 583 cells/mm³ (IQR 386-729), the median CD4 nadir was 260 cells/mm³ (IQR 138-366), and 69% had an undetectable HIV RNA level. One hundred seventy-six people (83%) were current HAART recipients, the median duration of NRTI use was 76 months (IQR 17-147), and the median duration of protease inhibitor use was 24 months (IQR 0-71).

Prevalence of coronary artery disease and fatty liver disease

Thirty-three percent (n=71) of HIV-infected participants had a positive CAC score, of which 8% (n=16) had a CAC>100 indicating

clinically significant disease. The median age among those with a CAC score >100 was 51 years (IQR 49-55) and for a CAC score of 1-100 was 49 years (IQR 42-55). Thirteen percent (28/211) were diagnosed with FLD using CT imaging. Of those with FLD, 17 (59%) had a CAC score >0. FLD was noted among 9% of HIV participants with a CAC score of 0, 19% with a CAC of 0-100, and 44% with a CAC>100. CAC and FLD were highly correlated (X^2 =11, p<0.001).

Adiponectin levels

Among the study population, the median adiponectin level was 3.1 μ g/ml (IQR 2.2-4.4). Seventy percent (n=149) had a low adiponectin level (<4.0 μ g/ml), including 66% with a CAC=0, 76% with a CAC of 1-100, and 81% with a CAC >100 (p=0.09). Regarding adiponectin

levels and CAC, the median level was 3.2 μ g/ml (IQR 2.3-4.4) for those with a CAC score of 0, 2.8 μ g/ml (IQR 2.1-3.9) for those with a CAC score of 1-100, and 2.5 μ g/ml (IQR 2.0-3.7) for those with a CAC score >100 (p=0.06). Median adiponectin level among those with FLD was 2.8 μ g/ml (IQR 1.9-3.5) and for those without FLD was 3.1 μ g/ml (IQR 2.3-4.4) (p=0.06).

Adiponectin levels were inversely correlated with hypertension, triglyceride levels, BMI, lipohypertrophy, duration of HIV infection, cumulative NRTI use, and use of didanosine (all with p<0.05) (Table 2). Higher HDL levels were correlated with higher adiponectin levels. FRS approached significance with adiponectin level, and of those with moderate/high FRS, 33 (75%) had a low adiponectin level (<4.0 μ g/ml).

Factors associated with coronary artery disease (CAD)

Among HIV infected persons: In the univariate models, adiponectin had a marginally significant association with CAD by CAC score (OR 0.8 per 1 μ g/ml, p=0.06). Other factors associated with CAD

CAD (OR 0.8 per 1.0 µg/ml, p=0.05). There were no significant associations with other variables including HIV-specific information, such as included increasing age, African American and Hispanic compared to Caucasian ethnicity, hypertension, diabetes, moderate/high FRS, higher fasting glucose levels, higher triglyceride levels, greater percent body fat, lipohypertrophy, and lipoatrophy (Table 1). Regarding HIV-specific factors, CAD was associated with longer duration of HIV infection, lower nadir CD4 counts, current HAART use, cumulative NRTI use, and cumulative PI use. Individual antiretroviral drugs associated with CAD in the univariate models are shown in Table 1.

In the final multivariate analysis, older age (OR 3.8 per 10 years, p<0.0001) was significantly associated with the presence of CAD as detected by CAC scores. Low adiponectin levels were marginally

| Variableª | Chi Square (X ²) | Correlation Coefficient ^b (<i>r</i>) | P-value |
|--------------------------------|-----------------------------|--|---------|
| Clinical Information | | | |
| Hypertension | 7.6 | | 0.01 |
| CHD Risk Level by FRS | 3.1 | | 0.08 |
| HIV-specific Information | | | |
| Duration HIV infection (years) | | -0.2 | 0.003 |
| Total months NRTI use | | -0.2 | 0.001 |
| Abacavir | 2.9 | | 0.09 |
| Didanosine | 13.9 | | 0.0002 |
| Laboratory Results | | | |
| Triglyceride level (mg/dL) | | -0.3 | <0.0001 |
| Fasting glucose (mg/dL) | | -0.1 | 0.05 |
| hsCRP (mg/dL) | | -0.2 | 0.003 |
| HDL (mg/dL) | | 0.2 | 0.0005 |
| Weight and Fat Measurements | | | |
| BMI (kg/m ²) | | -0.2 | 0.01 |
| Waist circumference (cm) | | -0.1 | 0.06 |
| Waist/hip ratio (cm) | | -0.1 | 0.06 |
| Percent body fat | | -0.1 | 0.09 |
| Physician Visual Assessment | | | |
| Lipohypertrophy | 9.2 | | 0.002 |

^a Table shows only the variables significantly correlated with adiponectin. All variables were inversely correlated with adiponectin, except for HDL in which higher HDL levels were correlated with higher adiponectin levels

^b Spearman correlation coefficient

Table 2: Factors Correlated with Low Plasma Adiponectin (<4.0 $\mu\text{g/ml})$ among HIV-infected Men

associated with antiretroviral medications, in the final multivariate model (data not shown).

Factors associated with fatty liver disease (FLD): In the univariate analyses with FLD (n=211; two patients were excluded due to missing liver/spleen ratio data) as the outcome, FLD was inversely associated with HDL and adiponectin approached statistical significance (OR 0.7 per 1.0 μ g/ml, p=0.06). Higher levels of triglycerides, fasting glucose, waist circumference, BMI, percent body fat, and lipohypertrophy were positively associated with FLD (Table 3). In the final multivariate analysis, FLD was associated with elevated triglycerides (OR 1.3 per 100 mg/dL, p=0.01) and increased waist circumference (OR 1.1 per 1 cm, p<0.0001). Low adiponectin levels were not significantly associated with FLD in the final multivariate model (OR 0.8 per 1.0 μ g/ml, p=0.33) (data not shown).

Since FLD may be secondary to NAFLD or excessive alcohol use, we conducted additional analyses excluding those with excessive alcohol use (n=12), and observed similar findings. In the final multivariate model, adiponectin was not significant (OR 0.8 per 1.0 μ g/ml, p=0.18), but elevated triglycerides (OR 1.3 per 100 mg/dL, p=0.007) and waist circumference (OR 1.1 per 1 cm, p=0.0002) were significantly associated with NAFLD.

Discussion

To our knowledge, this is the first study to examine adiponectin levels among HIV-infected men and evaluate its association with CAD as determined by CAC scores. Our study found that low adiponectin levels are common (70% prevalence) among HIV-infected men. We also demonstrated that CAD was marginally associated with low adiponectin levels, and noted a dose relationship between higher CAC scores and lower adiponectin levels. These data suggest that low adiponectin levels may play a role in the pathogenesis of cardiovascular disease among HIV-infected persons.

Adiponectin is a plasma protein secreted from adipose tissue with anti-inflammatory, anti-oxidative, and vasodilator effects. Obesity is associated with reduced plasma adiponectin levels, and rates of obesity are increasing among HIV-infected persons [45,46]. Further, HIV patients are predisposed to lipodystrophy, likely an effect of both HIV itself and antiretroviral agents [17,47]. Studies have shown that certain antiretroviral agents (e.g., NRTIs such as stavudine and PIs such as ritonavir) accumulate in adipocytes and down-regulate Peroxisome Proliferator-Activated Receptor-gamma (PPAR- γ) and adiponectin secretion [48-52]. Hence similar to hypoadiponectemia associated with obesity, dysfunctional adipose tissue in the setting of lipodystrophy and antiretroviral agents may lead to reduced secretion of adiponectin, with resultant adverse cardiovascular effects [53-57].

Regarding CAD, reduced circulating levels of adiponectin in the bloodstream contribute to endothelial vascular dysfunction [18,21]. Further, adiponectin prevents atherosclerosis by its anti-inflammatory and anti-oxidative activities in both cardiac and vascular cells, and by preventing the uptake of cholesterol [19,55]. In a case-control study of males in the general population who underwent coronary angiography, males with hypoadiponectinemia had a 2-fold increase in CAD prevalence, independent of traditional CAD risk factors [40]. Although lower levels of adiponectin have been associated with vascular diseases in the general population [40,58,59], there is a paucity of data regarding the relationship of adiponectin levels and CAD among HIV-infected persons.

Our study is novel as it's the first to evaluate the relationship

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| Characteristic ^{a,b} | Fatty Liver Disease N=28 (13.27%) | No Fatty Liver Disease 183 (86.73%) | OR (95% CI) p-value | |
|---|--------------------------------------|--|------------------------|---------|
| Variable of Interest | | | | |
| Adiponectin, per 1.0 µg/ml increase | 2.8 (1.9-3.5) | 3.1 (2.3-4.4) | 0.7 (0.5, 1.0) | 0.06 |
| Demographics | | | · · · | |
| Age, per 10 years | 45 (40-50) | 43 (34-50) | 1.3 (0.8, 1.9) | 0.24 |
| Ethnicity | | | | 0.20 |
| Black | 2 (4.3%) | 45 (95.7%) | 0.2 (0.04, 0.9) | |
| Hispanic | 4 (13.3%) | 26 (86.7%) | 0.7 (0.2, 2.3) | |
| Other | 3 (11.1%) | 24 (88.9%) | 0.6 (0.1, 2.1) | |
| White | 19 (17.8%) | 88 (82.2%) | 1.0 | |
| Clinical Information | | | | |
| Hypertension | | | | |
| No | 17 (11.4%) | 132 (88.6%) | 1.0 | |
| Yes | 11 (17.7%) | 51 (82.3%) | 1.7 (0.7, 3.8) | 0.22 |
| Diabetes | | | | |
| No | 25 (12.6%) | 173 (87.4%) | 1.0 | |
| Yes | 3 (23.1%) | 10 (76.9%) | 2.1 (0.5, 8.0) | 0.29 |
| Tobacco Use | | | | 0.48 |
| Never | 12 (11.4%) | 93 (88.6%) | 1.0 | |
| Past | 9 (12.9%) | 61 (87.1%) | 1.1 (0.4, 2.9) | |
| Current | 7 (19.4%) | 29 (80.6%) | 1.9 (0.7, 5.2) | |
| HIV-specific Information | | | | |
| Duration HIV infection (years) | 11 (6-22) | 11 (5-19) | 1.0 (0.9, 1.0) | 0.61 |
| CD4 count (cells/mm ³),per 100 cells | 601.5 (394-766) | 578 (384-713) | 1.0 (0.9, 1.2) | 0.56 |
| Nadir CD4 (cells/mm ³), per 100 cells | 252.50 (95-368) | 260 (144-356) | 0.9 (0.7, 1.2) | 0.73 |
| HIV RNA level (copies/ml) | | | | |
| <50 | 19 (13.0%) | 127 (87.0%) | 1.0 | |
| ≥50 | 9 (13.9%) | 56 (86.1%) | 1.1 (0.4, 2.5) | 0.87 |
| Current HAART Use | | | | |
| No | 5 (13.5%) | 32 (86.5%) | 1.0 | |
| Yes | 23 (13.2%) | 151 (86.8%) | 1.0 (0.3, 2.8) | 0.96 |
| Total months NRTI use, per 12 months | 89.1 (17-157.1) | 74.3 (17.3-145.4) | 1.0 (0.9, 1.1) | 0.68 |
| Total months protease | 36 (0-78.1) | 23.40 (0-71) | 1.0 (0.9, 1.1) | 0.33 |
| inhibitor use, per 12 months | | | | |
| Ritonavir | | | | |
| None | 10 (9.3%) | 97 (90.7%) | 1.0 | |
| Past or Current Use | 18 (17.3%) | 86 (82.7%) | 2.0 (0.9, 4.6) | 0.09 |
| Laboratory Results | | | | |
| ESR , per 10 mm/hr | 11 (10-17) | 10 (7-19) | 1.1 (0.9, 1.4) | 0.37 |
| hsCRP level (mg/dL) | 0.2 (0.1-0.4) | 0.1 (0.1-0.3) | 0.8 (0.4, 1.9) | 0.69 |
| Total cholesterol, per 10 mg/dL | 200.5 (162-238) | 183 (157-204) | 1.1 (1.0, 1.2) | 0.17 |
| HDL, per 10 mg/dL | 36 (31-43) | 40 (35-50) | 0.6 (0.4, 0.9) | 0.02 |
| LDL , per 10 mg/dL ^c | 104 (76-132) | 101 (87-129) | 1.0 (0.9, 1.2) | 0.46 |
| Triglyceride level, per 100 mg/dL | 188 (145-399) | 135 (87-235) | 1.4 (1.1, 1.7) | 0.002 |
| Fasting glucose, per 10 mg/dL° | 97 (92-105) | 91 (85-98) | 1.3 (1.0, 1.5) | 0.01 |
| Weight and Fat Measurements | | | | |
| BMI (kg/m ²) | 30 (27-32) | 26 (24-29) | 1.2 (1.1, 1.3) | <0.0001 |
| Waist circumference (cm) | 104 (95-107) | 92 (84-98) | 1.1 (1.0, 1.1) | <0.0001 |
| Percent body fat ^o | 28 (24-33) | 26 (23-29) | 1.1 (1.0, 1.1) | 0.01 |
| Physician Visual Assessment | | | | |
| Lipohypertrophy | 20 (19.6%) | 82 (80.4%) | 3.1 (1.3, 7.3) | 0.01 |
| Lipoatrophy | 10 (12.5%) | 01 (87.5%) | 0.9 (0.4, 2.0) | 0.75 |

^a Categorical variables expressed as number (percentage) and continuous variables as median (interquartile range) other weight and body measurements were not included due to collinearity

^b Variables FRS, family history of CAD, and all other ART medications were removed from the table due to lack of significance with FLD;

°All values are n=211, except LDL (n=198), glucose (n=210) and percent body fat (n=212) due to missing values

BMI, body-mass index; CI, 95% confidence interval; ESR, erythrocyte sedimentation rate; HAART, highly active antiretroviral therapy; HDL, high-density lipoprotein; hsCRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; OR, odds ratio

Table 3: Study Population Characteristics and Univariate Associations with Fatty Liver Disease among HIV-infected Men

between adiponectin levels and CAD as detected by CAC scores among HIV-infected persons. To our knowledge, only two prior studies have evaluated measures of cardiovascular disease and adiponectin levels among HIV patients. The first study examined 56 HIV patients and found that a high FRS score was related to hypoadiponectinemia, but no cardiac imaging was performed [25]. The second study (n=45) noted a relationship between low adiponectin levels and coronary flow reserve by echocardiography [56]. Our results are concurrent with these studies suggesting a potential association between hypoadiponectemia and CAD [26,59]. These data provide an additional potential pathogenic mechanism (i.e., low adiponectin levels) for the increased risk of cardiovascular diseases noted among HIV patients.

Low adiponectin levels in our study were also correlated with lipohypertrophy, increased BMI, elevated triglyceride levels, and hypertension, concurrent with prior reports [25,51,54,56]. Additionally, our study noted inverse correlations between adiponectin and duration of HIV infection, cumulative NRTI use, and didanosine. These HIVrelated factors have been associated with progressive lipodystrophy and cardiovascular disease, and our findings may provide insight into interrelated pathogenic mechanisms.

The importance of understanding the potential role of adiponectin in the pathogenesis of cardiovascular disease among HIV-infected persons may include the development of novel preventive and treatment strategies. For example, treatment with growth hormone-releasing hormone analogues has been associated with increased adiponectin levels and decreased Visceral Adipose Tissue (VAT) [57]. Studies have also evaluated the use of PPAR- γ agonists, such as thiazolidinediones, for lipoatrophy since altered adipogenesis and PPAR- γ signaling may reduce adiponectin levels. In small studies, rosiglitazone increased adiponectin levels, but had variable results on altering fat distribution [60,61]. Finally, in mice models, direct administration of adiponectin has been shown to ameliorate some of the adverse metabolic effects of PIs [50]. Understanding the potential benefit of increasing adiponectin levels, including on cardiovascular disease, should be a focus of future research studies.

In addition to treatment strategies, adiponectin levels could also represent an important marker for patients at higher risk of cardiovascular disease. Other markers of inflammation and kidney reserve have already been shown to correlate with future cardiovascular risk including hsCRP, D-dimer, and cystatin C levels [4,25,62-64]. Interestingly, inflammatory markers themselves (such as hsCRP) can down-regulate adiponectin production, potentially explaining some of the predictive capabilities of these markers [65]. Whether the detection of altered marker levels (e.g., low adiponectin levels) should result in intensified cardiovascular screening is currently unknown, and prospective studies are needed especially among HIV-infected persons who are at higher risk for these outcomes.

We examined factors associated with FLD and found that increased triglyceride levels and waist circumference were significantly associated, similar to other studies in both HIV-infected and HIV-uninfected persons. We did not find an association with adiponectin levels; this may be due to the small number of patients with FLD in our cohort, since the pathogenesis of CAD and FLD appears to overlap [66].

Our study had some limitations including the cross-sectional study design; hence we could not assess the temporality between low adiponectin levels and the development of CAD. Second, CAC is surrogate for CAD and we did not evaluate clinical cardiovascular events. However, CAC scores are increasingly utilized in this population for detection of CAD [67] and have been shown to predict future cardiovascular events [30]; hence, our study may have important clinical implications. Third, our study was solely among HIV-infected men, hence our results may not be applicable to women. Fourth, we did not differentiate adiponectin into low- and high-molecular forms, but rather examined total levels. Additionally, the diagnosis of lipodystrophy was by visual assessment and did not include DEXA scans. Finally, our results should be contextualized to the population studied; our cohort had a high prevalence (~60%) of lipodystrophy, hence our results may not be applicable among other HIV-positive groups.

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There were several strengths of our study. Our study is one of the first to examine the association of adiponectin and CAD, and had a more robust sample size compared to prior studies [25,56]. Additionally we examined several clinical, laboratory, and anthropometric/body measurements in addition to adiponectin levels with CAD. Finally, the findings from this study add to the existing literature on CAD and HIV-infected men; since HIV patients appear to be at higher risk for coronary events, early assessment of risk using novel markers and a better understanding of the pathogenesis may ultimately help increase the lifespan of patients.

In summary, low adiponectin levels are common among HIVinfected men and are correlated with the presence of lipohypertrophy. Hypoadiponectinemia had a marginal association with CAD, and may represent a novel marker and target for future treatment strategies among HIV-infected persons.

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