Relation of Epicardial Fat and Alanine Aminotransferase in Subjects With Increased Visceral Fat

Gianluca Iacobellis[1], Adriano M. Pellicelli[2], Benvenuto Grisorio[3], Giorgio Barbarini[4], Frida Leonetti[5], Arya M. Sharma[1] and Giuseppe Barbaro[6]

Background: Increased visceral adipose tissue (VAT) is a risk factor for an unfavorable cardio-metabolic profile and fatty liver. Individuals with human immunodeficiency virus (HIV) on highly active antiretroviral therapy (HAART) can be associated with metabolic syndrome (MS) and higher visceral fat. However, the potential link between cardiac adiposity, emerging index of visceral adiposity, and fatty liver is still unexplored.
Objective: To evaluate whether echocardiographic epicardial adipose tissue, index of cardiac adiposity, could be related to serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity, surrogate markers of fatty liver, in HIV-infected patients with (HIV+MS+) and without HAART-associated MS (HIV+MS-).
Methods and Procedures: This was a cross-sectional observational study on 57 HIV+MS+ patients, 52 HIV+MS– and 57 HIV-negative subjects with MS (HIV–MS+), as control group. Epicardial fat thickness and intra-abdominal VAT were obtained by echocardiography and magnetic resonance imaging (MRI), respectively. Serum ALT and AST activity, plasma adiponectin levels, and MS biochemical parameters were measured.
Results: Echocardiographic epicardial fat thickness was correlated with MRI-VAT ($r = 0.83$, $P < 0.01$), AST/ALT ratio ($r = 0.77$, $P < 0.01$), ALT ($r = 0.58$, $P < 0.01$), AST ($r = 0.56$, $P < 0.01$), and adiponectin ($r = -0.45$, $P < 0.01$) in HIV+MS+. MRI-VAT and AST/ALT ratio were the best correlates of epicardial fat thickness ($r^2 = 0.45$, $P < 0.01$).
Discussion: This study shows for the first time a clear relationship of epicardial fat, index of cardiac and visceral adiposity, and serum ALT and AST activity, markers of fatty liver, in subjects with increased visceral adiposity and cardio-metabolic risk. This correlation seems to be independent of overall adiposity and rather function of excess visceral adiposity.

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INTRODUCTION

Increased visceral adipose tissue (VAT) and fatty liver are growing risk factors for an unfavorable cardio-metabolic profile. Individuals with human immunodeficiency virus (HIV) on highly active antiretroviral therapy (HAART) can be associated with metabolic syndrome (MS), regional fat redistribution, and higher visceral fat (1,2). Emerging evidences suggest a significant role of visceral adiposity and insulin resistance in inducing fatty liver disease rather than overall adiposity (3–7). High serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity are widely used as reliable surrogate markers of fatty liver (8–11). Increased ALT activity has been mainly associated with several components of the MS, such as abdominal visceral obesity, impaired insulin sensitivity, raised fasting glucose, and unfavorable lipid pattern (12–14).

However, if most of the attention was focused to the relationship between abdominal fat and elevated transaminases, the potential link between cardiac adiposity and fatty liver is still unexplored.

Increased cardiac visceral fat, particularly the epicardial adipose tissue, has been now recognized as new cardio-metabolic risk factor (15,16), and its echocardiographic measurement has been proposed as easy and reliable index of visceral adiposity and potential diagnostic tool in subjects with MS (17–21).

Hence, in this study we sought to evaluate the correlation between echocardiographic epicardial fat thickness and ALT

[1]Division of Endocrinology and Metabolism, Department of Medicine, McMaster University, Hamilton, Ontario, Canada; [2]Department of Internal Medicine, S. Camillo Hospital, Rome, Italy; [3]Infectious Diseases Unit, General Hospital, Foggia, Italy; [4]Department of Infectious and Parasitic Diseases, Policlinico S. Matteo, Pavia, Italy; [5]Department of Medical Sciences, University "La Sapienza", Rome, Italy; [6]Cardiology Unit, Department of Medical Pathophysiology, University "La Sapienza," Rome, Italy. Correspondence: Gianluca Iacobellis (gianluca.iaco@tin.it)

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and AST in HIV-infected subjects with and without HAART-associated MS.

METHODS AND PROCEDURES

Subjects

Men and women between 18 and 70 years of age with a documented HIV-1 infection were recruited over a 1-year period. We selected 109 consecutive HIV-infected white outpatients of whom 57 (45 males and 12 females, 44 years median of age (range 38–56)) with HAART-associated MS (HIV+MS+) and 52 (42 males and 10 females, 44.5 years median of age, (range 38–55)), without MS (HIV+MS−). All HIV+MS+ subjects were on HAART given either as nucleoside reverse transcriptase inhibitors and protease inhibitors in combination (80%) or as nucleoside reverse transcriptase inhibitor and non-reverse transcriptase inhibitor in combination (20%) for an average of 38 months. Regarding the CDC stage of HIV infection, no significant difference between the two HIV+ groups occurred (62% of the subjects in stage A1 and 38% in stage A2 in HIV+MS+ group and 66% of the subjects in stage A1 and 34% in stage A2 in HIV+MS−).

Fifty-seven white outpatients with MS, negative for HIV infection (HIV-MS+) (40 males and 17 females, 48.4 years median of age (range 38–55)), who referred to our clinic for routine clinical assessment, have been also selected to match HIV-positive patients for range of age and gender distribution and therefore to form the control group.

MS was identified in HIV+MS+ and HIV−MS+ by the presence of three or more of risk factors according to the NCEP-ATPIII guidelines (22). Exclusion criteria in all groups were the presence of signs, symptoms, and history of the following: alcoholic hepatitis, viral hepatitis, positive serum hepatitis B virus surface antigen, positive serum hepatitis C virus surface antibody autoimmune hepatitis, drug-induced hepatitis, history of fatty liver during pregnancy, portal hypertension, liver cancer, elevated serum transferring saturation, >2 drinks of alcohol per day. This study was conducted in accordance with the guidelines proposed in the Declaration of Helsinki and has been approved by local ethical committees. All patients gave their informed consent.

Methods

Anthropometric measurements. Weight and height were measured while the subjects were fasting and wearing only their undergarments. BMI was calculated as body weight divided by square of the height. Minimum waist circumference (in centimeters; minimum circumference between the lower rib margin and the iliac crest, midwaist) was measured while the subjects were standing with their heels together.

Analytical procedures. Serum ALT and AST activity were assayed using a Hitachi 737 analyzer (Boehringer Mannheim Diagnostics, IN). AST/ALT ratio was also calculated.

Plasma adiponectin concentrations were measured by RIA kit (reference range: 1.5–100 ng/ml; Linco Research, St. Louis, MO; intra- and interassay coefficients of variations 4.5 and 3%, respectively). Samples were diluted 500 times before assay.

Biochemical parameters were also examined. Plasma glucose was determined by the glucose oxidase method (Autoanalyzer, Beckman Coulter, Fullerton, CA). Plasma total (TC) and high-density lipoprotein-cholesterol, and triglycerides concentrations were measured using enzymatic kits (Ortho-Clinical Diagnostic, Milan, Italy). Low-density lipoprotein-cholesterol values were calculated according to the Friedwald formula. After centrifugation, plasma insulin concentrations were determined by RIA kit (Sorin Biomedical, Milan, Italy). Homeostasis model assessment of insulin resistance was calculated as previously described.

Blood pressure was measured using a standard manual mercury sphygmomanometer for at least three measurements.

Echocardiographic study. Hewlett-Packard Sonos 500 (Hewlett-Packard, Palo Alto, CA), with a 2.5-MHz transducer, was used for M-B-mode trans-thoracic echocardiography. Echocardiographic measurements were performed in both groups of patients according to the recommendations of the American Society of Echocardiography (23). Epicardial fat was identified as the space or layer anterior to the right ventricle with decreased echoreflectivity compared to the myocardium and pericardium as we previously showed (17,18). Epicardial fat thickness was measured in end-diastole on the free wall of right ventricle from both parasternal long- and short-axis views. Imaging constraints were used to make sure that the epicardial fat thickness was not measured obliquely. The maximum values at any site were measured, and the average value was considered. Epicardial fat on the right ventricle is recognized as the highest absolute epicardial fat layer thickness. Moreover, parasternal long- and short-axis views allow the most accurate measurement of epicardial adipose tissue on the right ventricle, with optimal cursor beam orientation in each view. Hypertrophy of the right ventricle trabecula and moderator band, even if it occurred, did not confound epicardial adipose tissue calculation.

MRI study of adipose tissue. Magnetic resonance imaging (MRI) studies were performed in both groups of patients with a 1.5-T system (Gyroscan ACS-NT 1000, Philips, Eindhoven, The Netherlands) using a body coil for signal transmission and reception. Respiratory triggering was used for the sequences, whereby repetition time was dependent on respiratory frequency. During the examination, patients were not given special breathing commands. The areas of abdominal VAT, subcutaneous adipose tissue (SAT), and total adipose tissue were measured at the L4–L5 level. We obtained TFET1-weighted sequences with axial and sagittal orientation, antero-posterior phase-encoding direction, 10-mm-thick section with 1-mm-intersection gap, with a 364 field of view and a 256 × 256 matrix. The entire VAT and SAT volumes were measured by MRI while the subjects were lying supine on their abdomens, with arms elevated above the head, as previoulsy described (17,18). The SAT and VAT volumes were summed to obtain the total adipose tissue volume. Then VAT was calculated as total adipose tissue minus SAT. Epicardial adipose tissue scans were obtained by TSET1-weighted sequences with oblique axial orientation for a correct study of the four cardiac chambers, 10-mm-thick section with 1 mm intersection gap, 370 field of view, 256 × 256 matrix. We measured epicardial fat thickness on the free wall of the right ventricle, following the same echocardiographic points and views, as previously described (17,18).

Statistical analysis

Data in the text and in the tables are expressed as mean and s.d. Comparisons for variables among the three groups of patients will be performed using one-way ANOVA. Linear regression analysis was performed to evaluate the relationship of epicardial fat with transaminases, anthropometric and metabolic variables in all subjects. Multiple linear regression models were used to examine the relationships after adjusting for covariates and identify the best independent correlates of epicardial fat in all subjects. Two-tailed $P < 0.05$ indicated statistical significance. Analysis was performed using Stata 5.0 (Stata, College Station, TX).

RESULTS

Adiposity parameters, transaminases concentration, clinical and metabolic parameters of the three groups of patients are summarized in **Table 1**.

HIV+MS+ showed higher MRI-VAT, waist circumference, epicardial fat thickness, transaminases ($P < 0.01$ for all) and lower MRI-SAT and adiponectin ($P < 0.01$ for both) than HIV+MS− and HIV−MS+ subjects. HIV+MS+ patients presented also higher fasting glucose, fasting insulin, homeostasis model assessment of insulin resistance index, TC, low-density lipoprotein-cholesterol, tryglicerides, diastolic, systolic blood

Table 1 Adiposity parameters, transaminases, clinical and metabolic features in HIV+ subjects with and without MS and HIV− subjects with MS

	HIV+MS+ (*n* = 57)	HIV+MS− (*n* = 52)	HIV−MS+ (*n* = 57)	*P*
BMI (kg/m^2)	35 ± 2.5	27 ± 3.5	35 ± 4	<0.01
Waist (cm)	110 ± 3	90 ± 5	104 ± 12	<0.01
MRI-VAT (cm^2)	691 ± 34	395 ± 40	390 ± 60	<0.01
MRI-SAT (cm^2)	230 ± 16	180 ± 30	456 ± 45	<0.01
Epicardial fat (mm)	7.1 ± 1	6.3 ± 2	6 ± 2	<0.01
ALT (U/l)	38.3 ± 2.4	31 ± 4	22 ± 9	<0.01
AST (U/l)	43 ± 2.8	39 ± 2	35 ± 8	<0.01
Adiponectin (mg/l)	14.3 ± 1.2	15 ± 2	16 ± 6.3	<0.01
Fasting glucose (mg/dl)	109 ± 3	95 ± 5	100 ± 8	<0.01
Fasting insulin (μIU)	30 ± 2	18 ± 3	25 ± 3	<0.01
HOMA-IR	7 ± 4	3 ± 2	5.5 ± 4	<0.01
Total cholesterol (mg/dl)	209 ± 18	185 ± 25	201 ± 15	<0.01
LDL-C (mg/dl)	139 ± 10	107 ± 10	131 ± 10	<0.01
HDL-C (mg/dl)	37 ± 4	53 ± 6	40 ± 5	<0.01
Triglycerides (mg/dl)	161 ± 10	135 ± 8	152 ± 10	<0.01
Systolic BP (mm Hg)	137 ± 5	130 ± 4	135 ± 5	<0.01
Diastolic BP (mm Hg)	89 ± 2	82 ± 2	85 ± 5	<0.01
Comorbidities				
IFG[a] (n)	38	/	37	ns
Dyslipidemia[b] (n)	39	/	39	ns
Hypertension[c] (n)	32	/	33	ns

Values are reported as mean ± s.d.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; LDL-C, low-density-lipoprotein cholesterol; MRI, magnetic resonance imaging; SAT, subcutaneous adipose tissue; VAT, abdominal visceral adipose tissue.
[a]Fasting glucose 100–126 mg/dl in accordance with the American Diabetes Associations updated criteria. [b]Triglycerides ≥150 mg/dl; HDL men: <40 mg/dl, women: <50 mg/dl. [c]BP ≥130/85 mm Hg, both in accordance with the NCEP-ATPIII criteria.

pressure and lower high-density lipoprotein-cholesterol than both HIV+MS− and HIV−MS+ subjects ($P < 0.01$ for all).

No differences in comorbidities, considered as components of MS in accordance with the NCEP-ATPIII criteria (22), between HIV+MS+ and HIV-MS+ occurred. None of the patients had a diagnosis of overt diabetes while impaired fasting glucose was found in both groups of subjects with MS (Table 1).

Correlates of epicardial fat

Linear regression analysis. In HIV+MS+ patients the echocardiographic epicardial fat thickness was correlated with MRI-VAT ($r = 0.83$, $P < 0.01$), AST/ALT ratio ($r = 0.77$, $P < 0.01$), waist circumference ($r = 0.68$, $P < 0.01$), ALT ($r = 0.58$, $P < 0.01$), AST ($r = 0.56$, $P < 0.01$) (Figure 1), fasting insulin ($r = 0.55$, $P < 0.01$), BMI ($r = 0.49$, $P < 0.01$), and adiponectin ($r = -0.45$, $P < 0.01$), after adjusting for sex, HAART regimen, lipid lowering medications, and stage of HIV disease.

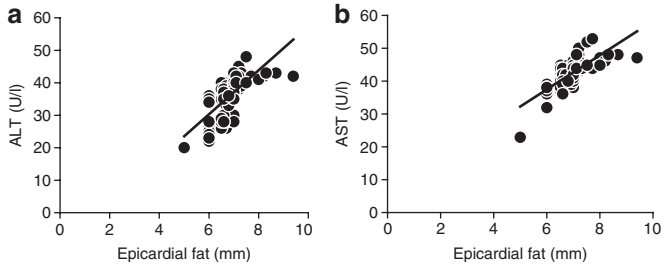

Figure 1 Relationship of epicardial fat thickness and (**a**) serum alanine aminotransferase (ALT), (**b**)aspartate aminotransferase (AST) activity. In HIV+MS+ patients the echocardiographic epicardial fat thickness was correlated with ALT ($r = 0.58$, $P < 0.01$) and AST ($r = 0.56$, $P < 0.01$).

Table 2 Relationships among epicardial fat thickness, transaminases, anthropometric and metabolic factors in HIV+ subjects with and without MS and HIV− subjects with MS

Epicardial fat	HIV+MS+ (*n* = 57)	HIV+MS− (*n* = 52)	HIV−MS+ (*n* = 57)
MRI-VAT	0.83[a]	0.82[a]	0.82[a]
AST/ALT ratio	0.77[a]	0.70[a]	0.48[a]
Waist circumference	0.68[a]	0.67[a]	0.75[a]
ALT	0.58[a]	0.57[a]	0.38[b]
AST	0.56[a]	0.56[a]	0.37[b]
Fasting insulin	0.55[a]	0.35[b]	0.59[a]
BMI	0.49[a]	0.47[a]	0.44[a]
Adiponectin	−0.45[a]	−0.48[a]	−0.43[a]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; MRI, magnetic resonance imaging; VAT, visceral adipose tissue.
[a]<0.01. [b]<0.05.

After adjustment for potential metabolic and anthropometric confounding factors of the relationship, as well as tryglicerides, low-density lipoprotein-cholesterol, fasting glucose, fasting insulin and BMI, epicardial fat thickness still showed a very good correlation with transaminases, ALT ($r = 0.57$, $P < 0.01$), AST ($r = 0.54$, $P < 0.01$) in HIV+MS+ patients.

Relationships among epicardial fat thickness, transaminases, anthropometric and metabolic factors in all subjects (HIV+ subjects with and without MS and HIV− subjects with MS) are reported in details in Table 2.

Multiple regression analysis. In a model ($r^2 = 0.45$) with epicardial fat as dependent variable and MRI-VAT, AST/ALT ratio, waist circumference as independent correlates, after adjusting for age, sex, and BMI, MRI-VAT ($t = 5.4$, $P < 001$) and AST/ALT ($t = 2.2$, $P < 0.01$) were the best correlates of epicardial fat thickness in HIV+MS+ subjects. When fasting glucose, tryglicerides, low-density lipoprotein-cholesterol and fasting insulin were included in the model, MRI-abdominal visceral adiposity and transaminases were still the best independent correlates of epicardial fat. Correlations were substantially unchanged in HIV+MS− subjects.

When we considered HIV−MS+ subjects epicardial fat thickness was best predicted by MRI-VAT and waist circumference, consistently with our previous studies.

DISCUSSION

This study shows for the first time a clear relationship of epicardial fat, index of cardiac adiposity, and serum ALT and AST activity surrogate markers of fatty liver in subjects with regional fat redistribution and higher visceral fat. The correlation between epicardial fat and liver enzymes seems to be independent of overall adiposity and rather function of excess visceral adiposity. We believe that this finding is of novelty and could be of help in stratifying the cardio-metabolic risk among individuals with increased visceral adiposity , as well as HIV-infected subjects with HAART-associated MS.

The use of HAART for the treatment of HIV infection is associated with the development of HAART-associated MS, characterized by adipose tissue redistribution, increased intra-abdominal fat and a complex disarray affecting both glucose and lipid metabolism. Increased lipid storage in the liver is one of several detrimental effects of such impairment. There is now increasing evidence that VAT is a causative risk factor for fatty liver, rather than overall obesity (3–7). Also weight loss after gastric surgery has been associated with a preferential visceral fat loss and significant reduction in liver volume (24).

Similarly, we and others have emphasized the role of epicardial adipose tissue as active actor in developing an unfavourable cardio-metabolic profile in both HIV-uninfected (18–21) and HIV-infected subjects (25). Epicardial fat has been described as very active endocrine organ and therefore source of several pro- and anti-inflammatory cytokines that can modulate and affect the heart (15,16). Epicardial fat has also the potential to be a diagnostic tool, as it can be easily obtained and measured by standard echocardiography (17,18). Of particular interest, epicardial fat thickness is significantly related to intra-abdominal visceral fat, measured by MRI (17,18).

In this study we found that increased epicardial fat thickness is associated with increased transaminases, widely used as surrogate markers of fatty liver. The relationship of cardiac fat and liver enzymes is stronger in HIV-infected subjects, independently of the MS, suggesting a possible direct effect of HIV infection and HIV-related increased visceral fat.

Some possible mechanisms could be evoked to explain, at least partially, this relationship. First, we know that epicardial fat, fatty liver, and ALT are all related to intra-abdominal visceral fat (15) and visceral adiposity in general. Consistently with these previous observations, in our study the correlation was stronger in subjects with increased intra-abdominal visceral adiposity rather than in individuals with prevalent subcutaneous fat distribution. Additionally, both epicardial and intra-abdominal fat evolve from brown adipose tissue during embryogenesis, suggesting a potential explanation for similar biomolecular properties between the two tissues (15). Free fatty acids could also play a role in this relationship. In fact, epicardial fat was recently found to correlate with free fatty acid levels in humans (26). It is assumed that adipose tissue acts as a sink for lipids, removing circulating triglycerides from plasma and storing them as large amounts of fat droplets, in order to maintain triglyceride content of non-adipocyte cells within a narrow physiological range. The increased flux of free fatty acids to the liver impairs hepatic handling of fat inside the hepatocyte. Moreover our data indicate that subjects with HIV infection and HAART-associated MS have significantly higher visceral adiposity and both serum ALT and AST activity than HIV-negative individuals with MS, independently of BMI and potential confounding factors that can affect liver enzymes concentration. Although the development of fatty liver in HIV subjects is still multi-factorial (27,28), our study may suggest that HIV and HAART play an independent role in inducing increased visceral adiposity and liver enzymes concentrations. The finding that HIV-positive subjects without MS presented higher transaminases and epicardial fat thickness than HIV-negative patients with MS, despite a higher BMI in the latter group, seems to be supportive of a specific role of HIV infection in liver enzymes abnormalities and regional fat redistribution, as previously suggested (27,28). Potential confounding effects of comorbidities, as well as glucose and lipids abnormalities, on the relationship of epicardial fat and transaminases were considered in this study and therefore excluded.

In conclusion, the relationship between the cardiac fat and ALT and AST as markers of fatty liver is of absolute novelty. Given the fact that both epicardial fat and transaminases can be easily measured, they could be used as markers of HAART-associated increased visceral adiposity and cardio-metabolic risk.

Nevertheless, we recognize that the present data have some limitations and should be considered with caution. We studied only serum ALT and AST activity that cannot be used as a marker for histological diagnosis. Therefore, our conclusions are based solely on liver enzymes. Furthermore causality can not be determined from this cross-sectional study. Future studies exploring a potential relationship between cardiac adiposity and morphological parameters of fatty liver in high cardio-metabolic risk subjects are warranted.

DISCLOSURE

The authors declared no conflict of interest.

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