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Research paper

Epicardial adipose tissue and coronary artery calcium predict incident myocardial infarction and death in HIV-infected patients

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ABSTRACT

Background: Epicardial adipose tissue (EAT) and coronary artery calcium (CAC) have been associated with incident coronary artery disease (CAD) and all-cause mortality in the general population. Their prognostic impact in HIV is unknown.
Methods: Observational study of 843 consecutive HIV-infected patients receiving antiretroviral therapy for at least 6 months. Risk stratification was performed with coronary artery calcium (CAC) scoring and EAT screening. Patients were followed for CAD and all-cause mortality for a median of 2.8 years accounting for a total of 2572 patient-year follow-up.
Results: Mean patient age was 50 ± 8 years and 69% were men. At baseline EAT was associated with male gender, age, waist circumference, visceral adipose tissue, and lipodystrophy, while CAC score ≥100 was associated with male gender, age and total cholesterol. During follow-up 33 patients suffered an event (15 incident myocardial infarctions and 18 deaths); the EAT volume was larger and the CAC score was higher in patients with events ($p = 0.038$ and $p = 0.001$ respectively). Multivariable regression analyses demonstrated that the upper tertile of EAT (≥93 cc; OR 2.15, 95% CI 1.06 − 4.39, $p = 0.034$), and CAC score ≥100 (OR 3.37, 95% CI 1.49 − 7.60, $p = 0.003$) were independent predictors of events after adjusting for age and sex.
Conclusions: In this observational cohort of HIV patients, EAT and CAC were independent predictors of hard outcomes after a median follow-up of approximately 3 years.

1. Introduction

Recent developments in the field of metabolic disorders have identified visceral fat both in the abdominal cavity and the intrapericardial space as a source of inflammatory cytokines and as a marker of increased cardiovascular risk.[1] Epicardial adipose tissue (EAT) is in direct contact with the adventitia of the coronary arteries and is believed to have a direct proinflammatory activity through paracrine mechanisms that favour the development of atherosclerosis.[1] On the other hand coronary artery calcium (CAC) is a marker of subclinical atherosclerosis. [2] Both EAT and CAC have been associated with incident cardiovascular events and all-cause mortality in the general population.[3–10] Despite the fact that both EAT and CAC are predictors of subclinical atherosclerosis and lipodystrophy in HIV infected patients,[11–13] to date there are no data to demonstrate their prognostic significance in HIV infected patients. HIV infection is a state of chronic inflammation and HIV patients are known to have a greater relative risk of cardiovascular disease at a younger age than the general population.[14] In this prospective observational study of 843 HIV infected patients on stable anti-retroviral therapy we assessed the association of EAT and CAC with incident cardiovascular events and all-cause-mortality during a median follow-up of 2.8 years.

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2. Methods

Patients were recruited from the Modena HIV Metabolic Clinic at the University of Modena and Reggio Emilia in Italy between January 1, 2006 and June 30, 2013. Demographic and clinical data were collected by infectious disease specialists and stored in an electronic medical record linked to a database. None of the patients included in these analyses had a prior history of cardiovascular disease. Diabetes mellitus was defined as a self-reported medical condition or as a fasting glucose ≥126 mg/dl or the use of hypoglycemic drugs. Hypertension was defined as a self reported medical condition or the use of antihypertensive medications or a measured blood pressure higher than 140/90 mmHg. Smoking categories were non-smoking or currently smoking. Body mass index was assessed as the ratio of body weight in kg divided by height in meters^2. The HIV stage was defined according to the CDC categories [15] and lipodystrophy was defined according to the HOPS categories as lipoatrophy, lipohypertrophy or mixed type.[16] Cumulative time exposure to highly active anti-retroviral drug classes (in months) and duration of known HIV status were recorded. To enter the study patients had to have received stable HAART for a minimum of 6 months. The study was approved by the local institutional Ethical Review Board and was conducted in adherence to the principles of the Declaration of Helsinki for medical research involving human subjects. All patients provided a signed informed consent before study entry.

2.1. Laboratory and imaging procedures

Routine biochemical parametres assessed in the fasting state included glucose and lipids profile (total cholesterol, HDL and LDL cholesterol, and triglycerides). Immunological biomarkers included: complete blood cell count, CD4 + lymphocytes count, CD4 + nadir and HIV viral load. Chest computed tomography scans were performed without the injection of iodinated contrast to assess the presence and extent of coronary artery calcium CAC. All patients underwent CT imaging and measurement of CAC scores was performed according to the Agatston technique.[17] Briefly, a cranio-caudal sequence of 30–40 consecutive axial slices of the heart was acquired with a 64-slice Volume CT multidetector scanner (GE Medical Systems, Milwaukee, WI). All images were obtained during a single breath hold using 320 mAs and 120 Kv. Image acquisition was prospectively triggered at 80% of the R–R interval on the surface electrocardiogram. A section thickness of 2.5 mm, a field of view of 20 cm^2, and a matrix of 512 × 512 were used to reconstruct the raw image data, yielding a nominal pixel size of 0.39 mm^2 and a voxel of 0.4 mm^3. CAC quantification was performed with the "Smart Score" software on a dedicated workstation (GE Medical Systems, Milwaukee, WI). Epicardial adipose tissue (EAT) was measured on the same images used to quantify CAC as previously described.[18] EAT appears as a hypodense rim surrounding the myocardium and located within the visceral pericardium (Fig. 1). Quantification of EAT volume was performed on a GE workstation (Advantage, GE, Milwaukee, WI) with dedicated software (Volume Viewer, GE, Milwaukee, WI) as described by Gorter et al.[18] The visceral pericardium was traced manually from the mid left atrium to the left ventricular apex excluding all extra-pericardial tissue. The attenuation threshold was then set between −190 HU and −30 HU which highlighted the EAT volume in each slice. This excluded myocardium, coronary arteries, coronary artery calcium, aorta and blood pool from the images leaving the epicardial fat highlighted. The individual EAT volumes in each section were then summed to compute the total EAT volume. The reproducibility of this method is excellent as reported by Gorter et al.[18] The total estimated radiation dose for the chest CT was 1.1 mSv. Visceral adipose tissue (VAT) was measured on a single CT slice of the abdomen at the level of 4th lumbar vertebra and VAT was quantified on a standalone workstation with dedicated software (Advantage Windows 4.4, GE, Milwaukee, WI).

2.2. Clinical endpoint

The endpoint of interest was a composite of incident non-fatal myocardial infarction and all-cause mortality. All myocardial infarctions were adjudicated using the classification criteria used in the D.A.D study cohort [19] by an investigator blinded to the results of the imaging tests.

2.3. Statistical analyses

Baseline patient characteristics are presented as frequencies (proportions) for categorical variables and mean (SD) or median (range) for continuous normally or non-normally distributed variables. Differences between patients with and without events were analysed using Fisher's exact test for categorical variables and Student's T-test or Mann–Whitney U-test for normally and non-normally distributed continuous variables, respectively. Factors associated with EAT were analysed using univariable and multivariable linear or logistic regression where appropriate. EAT volume was normalized applying a square root transformation or categorized according to tertiles. The Akaike Information Criterion (AIC) was applied to choose the best fitting multivariable models both for EAT and CAC. The CAC scores were dichotomized as < or ≥100 because this threshold has been shown in prior publications to be associated with increased cardiovascular risk.[6] No patient was lost to follow-up; the outcome information was collected by chart review, follow-up phone calls for patients who did not return to the clinic and personal reporting for those who returned to the clinic for follow-up visits. Incidence rates of events were calculated as event/100 person-year follow-up. Cox regression analyses were performed to assess the association between hard outcome (myocardial infarction and/or all-cause mortality) and EAT as well as CAC. In survival analyses both EAT and CAC were considered as dummy variables (EAT ≥ 3rd tertile and CAC ≥ 100 Agatston units). The independent predictive value of EAT and CAC was assessed in 3 nested Cox models adjusted for factors significantly associated with the primary outcome in univariable analyses. Model 1 was adjusted for age and sex; model 2 was adjusted for age, sex and CAC (≥100 Agatston Units), and model 3 was adjusted for age, sex, CAC and EAT (≥3rd tertile). The AIC was applied to choose the best final multivariable model to predict hard outcomes. Statistical significance level was set as a p-value <0.05. All statistical analyses were conducted using STATA 13.1 for Mac (StataCorp, College Station, TX, US).

3. Results

The clinical characteristics of the 843 enlisted in the study are shown in Table 1. The median follow-up was 2.8 years and there were a total of 33 events: 15 non-fatal myocardial infarctions and 18 deaths. Overall the cohort was young (mean age 50 ± 8 years) and the majority were men (69%). At baseline, age, male prevalence, the absolute CAC score and the prevalence of CAC score ≥100 were significantly different between event-free survivors and patients suffering an event (Table 1). Additionally, patients who suffered an event had a borderline larger VAT volume (p = 0.071), and a significantly larger EAT volume (median (IQR): 97 cc (65–107) vs. 74 cc (50–98), p = 0.038) than event-free survivors, while there was no difference in BMI and waist circumference between event-free survivors and patients with events.