Human immunodeficiency virus infection is associated with accelerated atherosclerosis

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Objectives: Cardiovascular risk is increased in HIV-infected individuals compared with the general population, making HIV disease an ideal model to investigate the pathogenesis and natural history of atherosclerosis. In this pilot study, we compared the progression of coronary artery calcium (CAC) between HIV-infected and uninfected patients.

Methods: Atherosclerosis progression was assessed in 25 HIV-infected men and 13 HIV-negative controls by means of sequential CAC scans using CT. A CAC score progression ≥15%/year was used as a surrogate marker of increased risk of cardiovascular events.

Results: During a median follow-up of 11 months, a CAC score increase ≥15%/year was detected in 14 HIV-infected patients (56%) and 4 HIV-negative individuals (31%). HIV infection, age and hypercholesterolaemia were independently associated with a CAC score increase ≥15%/year in an adjusted Cox regression model.

Conclusions: HIV infection, age and hypercholesterolaemia were independently associated with CAC progression. HIV as well as traditional risk factors contribute to accelerate atherosclerosis in HIV-infected patients.

Keywords: cardiovascular disease, coronary artery calcium, antiretroviral therapy, chronic HIV infection

Introduction

The risk of cardiovascular disease events is increased in HIV-infected compared with uninfected individuals, making HIV disease an ideal model to investigate the pathogenesis and natural history of atherosclerosis.1,2 Coronary artery calcium (CAC), a sensitive marker of subclinical atherosclerosis, can be accurately quantified by means of multidetector CT imaging. Prior extensive literature has shown that CAC improves the prediction of cardiovascular events and mortality in the general population, because of its strong association with total coronary atherosclerotic disease burden.3,4 The progression of CAC is therefore considered a surrogate marker of the progression of atherosclerosis, and it has been shown to be associated with an adverse outcome.4,5 The aim of this pilot study was to compare the progression of CAC between HIV-infected and non-infected individuals.

Methods

Study design

In an observational study, we recruited 25 HIV-infected and 13 HIV-negative men. Each subject was submitted to two CAC measurements separated by a median of 11 months (range 6–36 months). The controls were selected from a pool of the general population referred for CAC screening and sequential follow-up by their primary care physicians or cardiologists. The HIV-infected patients were followed in a metabolic clinic at the University of Modena and Reggio Emilia; they carried several risk factors for atherosclerotic heart disease, with a median Framingham 10 year risk of cardiovascular events of 12% (range 6%–30%), and were therefore advised to undergo screening for CAC and follow-up imaging by their infectious disease specialists.

Patients were recruited between January 2006 and July 2009. The inclusion criteria for HIV-infected patients were: age ≥18 years; male gender; antiretroviral therapy (ART) for ≥1 year; ability to sign informed consent; and at least two sequential CAC assessments at a minimum interval of 6 months. For patients with established diagnoses of hyperlipidaemia and hyperglycaemia, stable lipid-lowering and diabetes mellitus therapies for ≥6 months prior to enrolment were required. Cases and controls were excluded if they reported or had documented evidence of any of the following cardiovascular conditions: previous myocardial infarction; stroke; coronary artery bypass surgery; percutaneous angioplasty; and peripheral vascular disease.

A signed informed consent to participate in this study was obtained from each patient. For each patient we collected demographic, clinical and metabolic data, HIV history, biomarkers and exposure to ART drug classes.
Dyslipidaemia was defined as one or more of the following criteria: total cholesterol >240 mg/dL; low-density lipoprotein cholesterol >160 mg/dL; high-density lipoprotein cholesterol <40 mg/dL; triglycerides >200 mg/dL; or use of lipid-lowering medications.

The study was approved by the local Institutional Review Board.

**Imaging of CAC**

All subjects underwent CAC imaging with a 64 slice multidetector CT scanner (VCT; GE Medical Systems, Milwaukee, WI, USA). The imaging tests were completed during a single breath hold using 320 mA and 140 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 cm² and a matrix of 512×512 were used to reconstruct the raw image data, yielding a nominal pixel size of 0.39 mm² and a voxel volume of 0.4 mm³. The estimated radiation dose was 1.1 mSv. Images were then transferred to an off-line workstation that enabled CAC score quantification using ‘Smart Score’ software (GE Medical Systems). The CAC score was calculated according to the Agatston method, as previously described.6 In our experience, and that of others, the median inter-scan and inter-reader variability vary between 8% and 10%.7

**Statistical analysis**

A change in CAC score ≥15%/year was used as a surrogate marker of increased cardiovascular risk; in fact, this threshold has been shown to be predictive of an unfavourable outcome in the general population.4,5 Predictors of CAC progression were investigated with a stepwise multivariable logistic regression analysis that included HIV status, age, hypercholesterolaemia, hypertension, diabetes mellitus and baseline CAC score. Since CD4+ T lymphocytes were not measured in the HIV-negative individuals, the CD4+ cell count was not included in the model.

Kaplan–Meier curves were drawn to describe CAC progression in HIV-negative and HIV-infected patients. Curves were compared using the log-rank (Mantel–Cox) test. All analyses were conducted using STATA (Version 14; StataCorp LP, College Station, TX, USA); a two-sided P value <0.05 was considered significant.

**Results**

We enrolled 25 HIV-infected and 13 HIV-negative asymptomatic men. The baseline characteristics as well as the results of the univariable and stepwise multivariable logistic regression analyses are shown in Table 1. A CAC score increase ≥15%/year was reached by 14 HIV-infected patients (56%) and 4 HIV-negative individuals (31%) (P=0.182). Atherosclerosis was accelerated in HIV-infected patients, as demonstrated by a shorter time to reach a CAC score increase ≥15%/year, although the difference with HIV-negative individuals was only borderline significant (P=0.082; Figure 1).

HIV infection was independently associated with a CAC score increase ≥15%/year in a Cox regression model [hazard ratio (HR) = 3.99; 95% confidence interval (CI) 1.11–14.37, P=0.034] adjusted for age and smoking. This result was confirmed by a stepwise multivariable logistic regression analysis. HIV infection, age and hypercholesterolaemia were independently associated with a CAC score increase ≥15%/year, as shown in Table 1.

Lipodystrophy phenotypes were not associated with CAC progression (comparison of no lipodystrophy versus lipodystrophy, P=0.178).

**Discussion**

The findings of this study suggest that HIV infection is an independent risk factor associated with progression of subclinical atherosclerosis.

Assessment of CAC progression is challenging because of differing analytical strategies. Absolute change, percentage change considering the baseline CAC score, change in log-transformed CAC scores and change of square root-transformed CAC scores have all been used for reporting purposes; however, none of them is universally accepted as the preferred method to perform progression studies.5 We aimed to give clinical significance to atherosclerosis acceleration, comparing patients with and without HIV infection; therefore, we used a CAC score progression ≥15%/year as a categorical endpoint, because of its purported prognostic impact.4,5

Of note, our results confirm the role of traditional cardiovascular risk factors as independent predictors of CAC progression, namely age and total cholesterol. In the general population there is a weak association between baseline cholesterol levels and baseline CAC as well as CAC progression. However, randomized clinical studies have not demonstrated that lowering

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**Table 1.** Univariable and stepwise multivariable logistic regression analyses comparing patients with and without HIV infection

<table>
<thead>
<tr>
<th>HIV− controls (13 patients)</th>
<th>HIV+ cases (25 patients)</th>
<th>P value</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
<th>Adjusted odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>58.1 (9.0)</td>
<td>55.4 (7.5)</td>
<td>0.331</td>
<td>1.10 (1.01–1.21)</td>
<td><strong>0.035</strong></td>
<td>1.18 (1.03–1.34)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>3 (23.08)</td>
<td>12 (48.00)</td>
<td>0.176</td>
<td>0.38 (0.10–1.49)</td>
<td>0.166</td>
<td>—</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>5 (38.46)</td>
<td>20 (80.00)</td>
<td><strong>0.028</strong></td>
<td>2.86 (0.69–11.82)</td>
<td>0.146</td>
<td>—</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>3 (23.08)</td>
<td>9 (36.00)</td>
<td>0.486</td>
<td>1.91 (0.48–7.63)</td>
<td>0.361</td>
<td>—</td>
</tr>
<tr>
<td>Hypercholesterolaemia, n (%)</td>
<td>7 (53.85)</td>
<td>12 (48.00)</td>
<td>1.000</td>
<td>6.06 (1.48–24.74)</td>
<td><strong>0.012</strong></td>
<td>12.96 (1.96–85.48)</td>
</tr>
<tr>
<td>Baseline CAC score, median (IQR)</td>
<td>97 (46–304)</td>
<td>43 (3–128)</td>
<td>0.299</td>
<td>1.00 (0.99–1.00)</td>
<td>0.434</td>
<td>—</td>
</tr>
<tr>
<td>HIV infection</td>
<td>—</td>
<td>—</td>
<td>2.86 (0.69–11.82)</td>
<td>0.146</td>
<td>10.12 (1.23–82.74)</td>
<td><strong>0.031</strong></td>
</tr>
</tbody>
</table>

IQR, interquartile range.
The bold formatting indicates the statistically significant comparisons in the univariable analysis and the statistically significant predictors in the unadjusted and adjusted multivariable analysis.

Stepwise logistic regression analysis; smoking, hypertension, diabetes mellitus and baseline CAC score were automatically removed from the model.
Atherosclerosis progression in HIV

Figure 1. Kaplan–Meier curves of progression of CAC in HIV-infected patients and controls.

cholesterol levels slows the progression of CAC. In a previous study, lipodystrophy phenotypes were associated with CAC. In the current analyses, we did not find an association of lipodystrophy with CAC progression, but we cannot rule out that the lack of association was the result of the small sample size.

Both cases and controls displayed a high number of cardiovascular risk factors. They were probably chosen by their treating physicians for CAC screening based on a moderate to high risk for cardiovascular disease (as demonstrated by their Framingham risk score). In this light, CAC imaging may have been justifiable, as suggested by the recent recommendations of the American Heart Association. However, there is currently no recommendation for sequential CAC screening in the general population and, consequently, in HIV-infected patients. Our study must therefore be interpreted as an attempt at objectively demonstrating the tendency toward accelerated atherosclerosis development in HIV rather than an intent to advocate a new clinical pathway in the management of HIV-infected patients.

Study limitations include the observational nature of the study that does not allow the establishment of a cause and effect link, the small number of subjects and the inclusion of men only. CAC assessment is not recommended before the age of 40, given the low prevalence of CAC in younger age groups. Since women develop CAC on average 10 years later than men and since we could resort to a very small number of women in the CT pool of the general population, we decided to exclude women from this study. Lastly, we investigated only the calcified component of the atherosclerotic plaque. Lo et al., in a recent cross-sectional study of 78 HIV-positive and 32 HIV-negative men, reported an increased burden of atherosclerosis defined both as calcified and non-calcified plaque. Nonetheless, CAC remains a sensitive marker of the total coronary atherosclerotic burden, and can be measured without injection of iodinated contrast and with a smaller radiation exposure for the patient than would be required for acquisition of CT angiographic studies. However, sequential CAC scans impose a sizeable radiation dose, and some reports have raised concern about an increase in the risk of cancer when the total dose is in excess of 2.3 mSv. In our study, patients received 1.1 mSv per scan and were therefore below the threshold of 2.3 mSv for total exposure. Of note, with current technologies the radiation dose can be reduced to <1 mSv per scan.

In conclusion, we believe that this study has useful clinical implications; it provides evidence of rapid atherosclerosis progression in HIV-infected patients and suggests that HIV infection per se may contribute to this accelerated process.

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Transparency declarations
None to declare.

References