Could FDG-PET imaging play a role in the detection of progressing atherosclerosis in HIV-infected patients?

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Important progresses in the management of patients with human immunodeficiency virus, in particular the advent of new anti-retroviral therapies (ART), have turned this rapidly fatal condition into a controllable chronic disease with a life expectancy that approaches the one from the general population. Cardiovascular diseases have now become one of the leading causes of non-HIV-related mortality in this population. Several factors including the presence of HIV in the vascular wall and the development of dyslipidemia and alteration in body fat distribution under ART might play a role the progression of atherosclerosis in HIV-infected patients. The use of imaging biomarkers may help to identify the factors associated with an increased risk of cardiovascular events and select high-risk patients who will benefit the most from the early implementation of preventive treatments.

Key Words: PET imaging • Atherosclerosis • Fluorodeoxyglucose (FDG)

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HIV AND ATHEROSCLEROSIS

Important progresses in the management of patients with human immunodeficiency virus (HIV), in particular the advent of new anti-retroviral therapies (ART), have turned this rapidly fatal condition into a controllable chronic disease with a life expectancy that approaches the one from the general population. Cardiovascular diseases (CVD) have become the leading cause of non-HIV-related mortality in the United States,[1] and the second cause after cancer in Europe.[2] HIV-infected patients have a higher number of cardiovascular risk factors than the general population,[3,4] but the increased risk of CVD persists even after adjustment for traditional cardiovascular risk factors.[4,5] At least two causes might explain why HIV infection and its treatments may contribute to the progression of atherosclerotic disease. First, the persistence of HIV in lymphocytes, smooth muscle cells, and macrophages causes the activation of these cells and promotes the development of chronic inflammation in the arterial wall.[6] In addition, HIV blocks the adenosine triphosphate-binding cassette transporter A1 pathway resulting in the inhibition of the reverse transport of cholesterol from macrophages to HDL particles and the accumulation of foam macrophages within the arterial wall.[7] Furthermore, the close link observed between concentrations of ultra-sensitive C reactive protein and the risk of cardiovascular events in these patients[8,9] pledges in favor of a role of chronic inflammation in the destabilization of atherosclerotic plaques in HIV-infected patients. Second, ART may also contribute to the development of atherosclerosis in patients with HIV infection. HIV protease inhibitors upregulate the scavenger receptor CD36 expressed on macrophages and involved in LDL phagocytosis leading

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to the accumulation of cholesterol in these cells.[10] ART have also been found to increase the levels of circulating plasminogen activator inhibitor 1 and fibrinogen enhancing arterial thrombosis.[11] In addition, protease inhibitors may cause important metabolic disorders. In the Data Collection on Adverse Events of Anti-HIV Drugs study, patients who developed the most severe dyslipidemia and diabetes among the 23,437 HIV-infected patients treated with protease inhibitors had the highest risk to present acute MI. In the Strategies for Management of Anti-Retroviral Therapy (SMART) trial,[12] two therapeutic strategies have been compared: in the first group, ART was interrupted when the disease was considered to be controlled (CD4 + > 350/mm^3); in the second group, ART was maintained regardless of CD4 + count. The group in which ART was halted had a progressive increase in HIV viral load and presented a higher number of cardiovascular events compared to patients in the drug conservation group. This study suggests that the control of HIV viral load with ART in atherosclerotic plaques seems to overcome the deleterious effects of metabolic disorders induced by these treatments.

FDG-PET AND ATHEROSCLEROSIS

Atherosclerosis has a long asymptomatic phase and multiple factors have been involved in its progression. The use of surrogate imaging biomarkers might facilitate the understanding of the precise role of each of these factors in the progression of atherosclerosis from its asymptomatic phase towards clinical events. Fluorine-18 radiolabeled fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) has demonstrated its value for the non-invasive evaluation of inflammation in atherosclerotic plaques.[13] In addition, patients with high FDG uptake in the vascular wall have a faster progression rate of atherosclerosis[14] and an increased risk of cardiovascular events at follow-up.[15,16] Several metrics have been developed for the quantification of FDG uptake in the vascular wall on PET. The most validated metrics is Target-to-background ratio (TBR) calculated as the ratio between the maximal SUV measured in the vascular wall and mean SUV of blood measured in the right atrium. TBR values have been shown to correlate strongly with the density of macrophages in carotid plaques[13] and to be predictive of future cardiovascular events.[17] The reproducibility of TBR has been evaluated in 20 patients with suspected or established vascular disease, who performed two ^{18}F-FDG-PET/CT acquisitions two weeks apart,[18] showing excellent intra-class correlation coefficients (ICC) for reproducibility between both acquisitions (ICC > 0.8 for inter-observer/intra-observer agreements and inter-scan variability). This high reproducibility allows for the identification of changes in the intensity of vascular inflammation in relatively small group of patients. TBR measured in vascular wall on FDG-PET represents thus an interesting surrogate marker to evaluate the impact of several factors on vascular inflammation in HIV patients. In this issue of the *Journal of Nuclear Cardiology*, Lawal et al.,[19] report the results of a study that aimed at evaluating the intensity of vascular inflammation using FDG-PET. They identified retrospectively 121 HIV-infected patients who underwent FDG-PET imaging in their department for oncological or inflammatory indications and paired them with 121 non-HIV patients. In these relatively young patients (mean age = 35 ± 5 years), they found that HIV-infected patients had slightly higher TBR values than non-HIV-infected patients suggesting that HIV infection might stimulate chronic vascular inflammation.

LIMITATIONS OF ATHEROSCLEROSIS IMAGING WITH PET IN YOUNG PATIENTS

The strength of this work is the relatively large size of the cohort that gives more statistical power to identify small differences in TBR values between the two groups, but its limitation is that the FDG-PET acquisition protocol was not optimized for vascular imaging due to the retrospective design of the study. The implementation of a dedicated acquisition protocol for vascular imaging is particularly important when imaging the arteries of relatively young patients that are at the early stages of atherosclerosis. The mean thickness of the aortic wall in young patients is close to 2 mm, about half the spatial resolution of current PET systems (4–5 mm). The quantification of FDG uptake in this relatively thin vascular wall is subjected to important partial volume effects (PVE). PVE occurs when the size of the studied structure is smaller than the spatial resolution of the imaging system, thus generating a blurring of the image[20] leading to an important underestimation up to 5- to 10-fold the true concentration of FDG in the vascular wall.[21] Consequently, differences in the intensity of FDG uptake between the two groups of patients are diluted by PVE and more difficult to evidence. Furthermore, small differences in the thickness of the aortic wall between patients might also result in changes in signal intensity on PET, even though the concentrations of FDG are similar. A second phenomenon that is associated with PVE is the inadequacies between anatomical boundaries, and the grid of voxels constitutive of the PET image, making different structures coexist in a same voxel. For instance, the uptake of the arterial wall spills over surrounding structures, like the blood pool or neighboring organs, the uptake in these

regions spilling also over the arterial wall. The blood signal is still relatively high and the variable between patients at 60 min p.i. and might have affected the quantification of FDG uptake in the vascular wall. The recommendation is thus to image at later time points after the administration of ^{18}F-FDG ($\geq$ 90 min) to reduce interactions between the vascular signal and the residual signal in the surrounding blood pool.[22]

CONCLUSIONS

In summary, PVE in the aortic wall might have led to underestimate the importance of differences in TBR between HIV-infected and non-infected patients measured with PET in the study of Lawal et al.,[19] and also hampered precise signal quantification in the vessel wall. The small increase in FDG uptake observed in HIV-infected patients in this retrospective study will thus need to be confirmed in prospective studies including patients with more advanced atheroma that is less affected by PVE and using PET acquisition protocols dedicated to vascular imaging. Non-invasive imaging of atherosclerosis represents certainly an attractive approach to unravel the factors associated with atherosclerosis progression in HIV-infected patients and to identify a high-risk population that will benefit the most from the early implementation of anti-atherosclerotic treatments.

Disclosure

N. Mikail, M. Sinigaglia and F. Hyafil have nothing to disclose in relation to this Editorial.

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