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Research paper

Low thigh muscle mass is associated with coronary artery stenosis among HIV-infected and HIV-uninfected men: The Multicenter AIDS Cohort Study (MACS)

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ABSTRACT

Background: HIV-infected individuals are at increased risk for both sarcopenia and cardiovascular disease. Whether an association between low muscle mass and subclinical coronary artery disease (CAD) exists, and if it is modified by HIV serostatus, are unknown.

Methods: We performed cross-sectional analysis of 513 male MACS participants (72% HIV-infected) who underwent mid-thigh computed tomography (CT) and non-contrast cardiac CT for coronary artery calcium (CAC) during 2010–2013. Of these, 379 also underwent coronary CT angiography for non-calcified coronary plaque (NCP) and obstructive coronary stenosis ≥50%. Multivariable-adjusted Poisson regression was used to estimate prevalence risk ratios of associations between low muscle mass (< 20th percentile of the HIV-uninfected individuals in the sample) and CAC, NCP and obstructive stenosis.

Results: The prevalence of low thigh muscle mass was similar by HIV serostatus (20%). There was no association of low muscle mass with CAC or NCP. However, low thigh muscle mass was significantly associated with a 2.5-fold higher prevalence of obstructive coronary stenosis, after adjustment for demographics and traditional CAD risk factors [PR 2.46 (95% CI 1.51, 4.01)]. This association remained significant after adjustment for adiposity, inflammation, and physical activity. There was no significant interaction by HIV serostatus (p-interaction = 0.90).

Conclusions: In this exploratory analysis, low thigh muscle mass was significantly associated with subclinical obstructive coronary stenosis. Additional studies involving larger sample sizes and prospective analyses are needed to confirm the potential utility of measuring mid-thigh muscle mass for identifying individuals at increased risk for obstructive CAD who might benefit from more aggressive risk factor management.

1. Introduction

With advances in treatment for HIV infection and subsequent declines in AIDS-related mortality,[1] cardiovascular disease (CVD) has emerged as a leading cause of death among HIV-infected individuals. HIV-infected individuals have higher rates of myocardial infarction[2,3]

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and increased prevalence of subclinical coronary atherosclerosis compared to HIV-uninfected individuals with similar risk factor profiles.[4,5] The pathogenesis of coronary artery disease (CAD) in HIV-infected individuals is complex and may be related to both traditional and non-traditional CVD risk factors.

Muscle wasting is a potentially modifiable risk factor for CAD among HIV-infected individuals that has not been well-studied.[6] HIV infection, particularly in persons with a history of advanced HIV disease, is associated with lean muscle mass loss[7] and sarcopenia.[8] In the general population, sarcopenia has been associated with insulin resistance and systemic inflammation, known risk factors for atherogenesis.[9,10] Sarcopenia has also been linked to measures of subclinical atherosclerosis including carotid intimal medial thickness,[11] arterial stiffness,[12] and coronary artery calcium (CAC).[13] Whether low muscle mass is also associated with non-calcified coronary plaque, which is more prevalent in HIV-infected compared to non-infected individuals,[4,5] as well as with the severity of obstructive coronary artery stenosis, is unknown. Furthermore, whether the association of low muscle mass with subclinical coronary atherosclerosis is affected by HIV serostatus has not been assessed.

The mid-thigh muscle mass cross-sectional area ascertained by computed tomography (CT) has proven to be a useful index of body composition and sarcopenia.[14] Prior work from the Multicenter AIDS Cohort Study (MACS) found that thigh muscle cross-sectional area was significantly, though weakly, correlated with grip strength, and that HIV-infected men had lower muscle quality and more pronounced decline in thigh muscle density with increasing age compared to HIV-uninfected men.[15] Low thigh muscle mass by CT has also been associated with increased risk of hip fractures in another cohort.[16] A single slice mid-thigh CT is noninvasive and easily obtained among individuals undergoing CT imaging for other indications, and may offer additional prognostic information.

Our study sought to investigate three questions: (1) whether low thigh muscle mass is associated with subclinical coronary atherosclerosis as measured by both CAC and non-calcified coronary plaque; (2) whether low thigh muscle mass is associated with the severity of coronary stenosis; and (3) whether such associations, if present, differ by HIV serostatus. We hypothesized that low thigh muscle mass area is independently associated with CAC, non-calcified plaque, and severity of stenosis, independent of traditional CVD risk factors. We also evaluated whether such associations are stronger among HIV-infected compared to HIV-uninfected individuals, and whether associations are additionally independent of adiposity, systemic inflammation, and physical activity – factors which may mediate any relationships found.

2. Methods

2.1. Population

MACS is an ongoing multi-center prospective cohort study of the natural and treated histories of HIV-infection in men who have sex with men. There were 7087 HIV-infected and HIV-uninfected participants enrolled across 4 time periods: 1984–85 (N = 4954), 1987–90 (N = 668), 2001–03 (N = 1350) and 2010+ (N = 115) at 4 sites: Baltimore, Maryland/Washington, DC; Chicago, Illinois; Pittsburgh, Pennsylvania; and Los Angeles, California.[17] Research visits occur every 6 months and include questionnaires, physical examination, blood testing (including long-term blood storage), and urine analysis. Detailed description of the MACS has been previously published.[17]

Of > 7000 men originally enrolled in MACS, 1006 were recruited between 2010 and 2013 into a CVD sub-study (MACS-CVD2). Inclusion/exclusion criteria for the CVD substudy have been published.[4] Briefly, MACS participants were included if they were aged 40–70 years, weighed less than 136 kg, and had no history of cardiac surgery or percutaneous coronary intervention.[4] Eligible men underwent non-contrast cardiac CT scanning to determine CAC score. Among

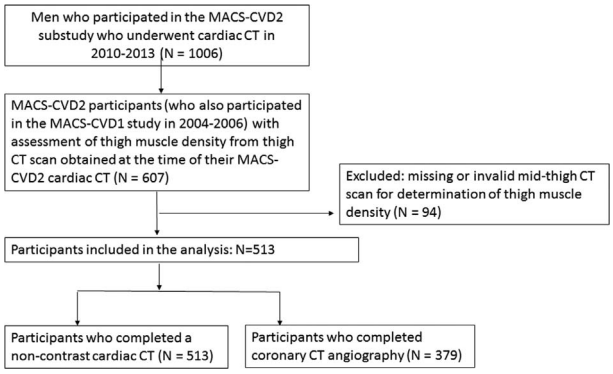

Fig. 1. Inclusion and exclusion of study participants.

participants who completed the non-contrast cardiac CT, a subset (n = 759) also underwent contrast coronary CT angiography (CTA) to measure total plaque burden, plaque composition and coronary stenosis. Exclusion criteria for CTA were contrast allergy, atrial fibrillation, or chronic kidney disease (estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2) within 30 days of imaging.

Of the 1006 MACS-CVD2 participants who were eligible for non-contrast cardiac CT scanning, 607 underwent measurement of muscle density from a mid-thigh CT scan obtained at the time of their MACS-CVD2 cardiac CT as part of another ancillary study evaluating measures of body composition.[15] These participants were selected because they had participated in an earlier MACS-CVD1 ancillary study in 2004–2006. Ninety-four participants had missing or invalid mid-thigh CT scans for the measurement of muscle density. The current analysis was conducted on 513 men with both thigh muscle mass area and non-contrast cardiac CT data for CAC analysis, and on 379 men with thigh muscle mass area and CTA data for analyses of non-calcified plaque and severity of coronary stenosis (Fig. 1).

The Institutional Review Boards of all participating sites approved the MACS and MACS-CVD2 studies, and all participants signed informed consent.

2.2. Measurement of muscle mass

For this analysis, low muscle mass measured by CT was the independent variable of interest. Thigh CT images were analyzed by trained, experienced readers at the core CT reading center (Los Angeles Biomedical Research Institute at Harbor-UCLA) who were blinded to participant characteristics and HIV serostatus. Details of the CT scanning equipment has been previously reported[4,18]; three centers used a 64-slice multidector CT at 3 sites and one center used a 320-row multidetector CT (Supplemental Methods).

The thigh CT scanning protocol is described in the Supplemental Methods and the methods for thigh muscle mass measurement have been published.[15] Briefly, mid-thigh CT scans were obtained with a 5–10 mm cross-sectional image for each subject at the midpoint between the anterior superior iliac crest and the patella. The right leg was typically scanned per protocol, unless unavailable, in which case the left leg was scanned instead. Manual tracings were performed to delineate thigh subcutaneous fat and muscle (Fig. 2). Muscle density in Hounsfield Units (HU) was measured within the region bound by the fascia lata (outermost fascia) of the thigh muscle. In image analysis, areas (cm^2) of thigh skeletal muscle and subcutaneous adipose tissue were measured by selecting the regions of interest defined by the following attenuation values described by Goodpaster et al. [19]: −35 to −190 HU for adipose tissue and 0 to 100 HU for muscle. The mean muscle attenuation was determined from all pixels within this range. Although reproducibility data was not available for our cohort, prior work by Goodpaster found the test/re-test coefficient of variation for assessment of skeletal muscle attenuation by mid-thigh CT was 0.51%,

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