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Prevalence of Peripheral Artery Disease is Higher in Persons Living with HIV Compared to Uninfected Controls

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Abstract

Objective

Ankle-brachial index (ABI) is an excellent tool for diagnosing peripheral artery disease (PAD). We aimed to determine the prevalence and risk factors for PAD in people living with HIV (PLWH)

compared to uninfected controls. We hypothesized that prevalence of PAD would be higher among PLWH than among controls independent of traditional cardiovascular disease (CVD) risk factors.

METHODS

PLWH aged ≥40 were recruited from the Copenhagen comorbidity in HIV infection (COCOMO) study. Sex and age matched uninfected controls were recruited from the Copenhagen General Population Study. We defined PAD as ankle-brachial index (ABI) ≤ 0.9 and assessed risk factors for PAD using logistic regression adjusting for age, sex, smoking status, dyslipidemia, diabetes, hypertension and hsCRP.

RESULTS

Among 908 PLWH and 11,106 controls, PAD was detected in 112 (12% CI [95% 10-14]) and 623 (6% [95% 5-6]), respectively (p<0.001); odds ratio (OR)=2.4 [95% 1.9-2.9], adjusted OR=1.7 [95% 1.3-2.3, p<.001]. Traditional CVD risk factors, but not HIV-related variables were associated with PAD. The strength of the association between PAD and HIV tended to be higher with older age (p=0.052, adjusted test for interaction).

CONCLUSION

Prevalence of PAD is higher among PLWH compared to uninfected controls, especially among older persons, and remains so after adjusting for traditional CVD risk factors. Our findings expand the evidence base that PLWH have excess arterial disease to also include PAD. The exact biological mechanisms causing this excess risk remain to be elucidated. Until then, focus on management of modifiable traditional risk factors is important.

Keywords: Peripheral Arterial Disease; HIV infections; Comorbidity; Peripheral Vascular Diseases; Cross-Sectional Studies

INTRODUCTION

People living with HIV (PLWH) now have life expectancies approaching that of the general population and may be more prone to age related comorbidities [1,2]. Among comorbidities, cardiovascular disease (CVD) with atherosclerotic lesions of the coronary and carotid vessels has received much attention as CVD is a leading cause of mortality in PLWH [3].

Peripheral artery disease (PAD) is a manifestation of atherosclerosis that may lead to decreased blood supply and ischemic calf pain. With time, occlusive disease may lead to vascular ulcerations, gangrene and ultimately amputation[4]. Although, PLWH are at higher risk of CVD in general, PAD has been comparatively less well-explored in this population [2,5]. Existing estimates of the prevalence of PAD in PLWH are conflicting and studies report both higher and lower disease burden among PLWH compared to that of the uninfected population [1,6–10]. PAD can easily and safely be assessed by calculating the ratio of systolic blood pressure (SBP) measured at the ankle to the SBP of the brachial artery. Validated against gold standard angiography, the ankle-brachial index (ABI) has been found to be a sensitive and extremely specific marker for occlusive PAD [11]. Using ABI, we sought to investigate the prevalence and risk factors of PAD in a well-characterized population of PLWH compared to an uninfected population from the same geographical area matched on age and sex. We hypothesized that the prevalence of PAD was higher in PLWH than in uninfected and that HIV is an independent risk factor for PAD.

METHODS

Study design

From the Copenhagen Comorbidity in HIV infection (COCOMO) study, participants older than 40 years of age were included. The COCOMO study is a longitudinal cohort study with the aim of assessing the burden and mechanism of non-AIDS comorbidities in PLWH. Inclusion criteria were a positive HIV test and 18 years of age or older. The procedures for recruitment and data collection have been described elsewhere [12,13].

From the Copenhagen General Population Study (CGPS) age and sex matched uninfected participants were included with the aim of 14 controls per PLWH. Due to population size limitations, those younger than 60 years of age were matched 1:11 while those older than 60 were matched 1:14.

Ethical approval was obtained by the Regional Ethics Committee of Copenhagen (COCOMO:H-15017350; CGPS:H-KF-01-144/01). Written informed consent was obtained from all participants.

Data acquisition

Information about participants´ demographics, family history, smoking, and medication was collected using identically structured questionnaires in COCOMO and CGPS. Participants were asked if they experienced lower extremity pain after having walked some distance with no pain on onset of walking. If they responded affirmatively, they were further asked if symptoms regressed after standing. 'Symptoms of PAD' was defined as affirmative response to all of the above, irrespective of ABI.

Data regarding HIV infection were obtained from a review of medical charts of COCOMO participants.

All physical examinations were performed by trained medical staff, using an identical protocol in both COCOMO and CGPS.

Blood pressure (BP) was measured after 5 minutes rest and with the subject in sitting position, using an automatic Digital Blood Pressure Monitor.

Ankle-brachial index and PAD

ABI was measured in accordance with American Heart Association, American College of Cardiology and European guidelines [4,11]. In supine position with head and ankles fully supported using a Doppler instrument (Sonotrax Basic A 294534, Edan, San Diego, CA, US) the pressure at which the flow in the posterior tibial artery was clamped was determined in both lower extremities.

Continuous ABI was calculated as the ratio of the lower of the SBPs of the left and right leg to the highest brachial SBP.

High ABI (≥1.4) is frequently due to arterial non-compressibility with concomitant vessel stenosis but PAD cannot be diagnosed or excluded in these cases using ABI alone [14]. As such, ABI ≥ 1.4 was coded as non-compressible and excluded.

PAD was defined as ABI ≤0.9 in one or both legs regardless of symptoms.

Symptomatic PAD was defined as symptoms of PAD in a person with PAD.

Biochemistry

Non-fasting venous blood was collected and analyzed for low-density lipoprotein cholesterol (LDL-C), glycated hemoglobin (HbA1c), high-sensitivity C-reactive Protein (hsCRP) and glucose. All blood samples from both COCOMO and CGPS participants were analyzed at the same laboratory.

Hypertension, BMI and Lipids

In accordance with the Joint National Committee on High Blood Pressure [15], hypertension was defined as current anti-hypertensive treatment and/or SBP ≥ 140 and/or diastolic blood pressure ≥ 90 mmHg.

BMI was defined according to the WHO classification (<18.5 underweight, 18.5–24.99 normal weight, 25–29.99 overweight and ≥30 obese) [16].

Elevated LDL-C (eLDL-C) was defined as LDL-C ≥ 160mg/dl (4.14mM) and/or current lipid lowering treatment [17,18].

Statistics

A 95%-binomial proportion confidence interval (CI) for PAD was calculated. Student's t tests or Mann–Whitney U tests were used for comparison of continuous data and χ^2 tests were used for categorical data. Crude odds ratios (OR) were calculated. We assessed whether independent variables were associated with a PAD or symptomatic PAD using multivariable logistic regression analyses adjusted for known predictors for PAD in the general population. We pre-specified two models: **model 1** included known predictors of vascular disease: age, sex, hypertension, diabetes, eLDL-C and smoking status[19]; **model 2** included all covariates in model 1 and additionally contained hsCRP, a marker of inflammation. A priori, we aimed to assess the interaction between

PAD and HIV with age, hypertension and smoking status, in a fully adjusted model. To investigate the impact of setting a lower threshold for eLDL-C, we conducted a sensitivity analysis with eLDL-C defined as LDL-C ≥ 116mg/dl (3.00mM).

A P-value less than 0.05 was used to infer statistical significance. All analyses were generated using SAS software v9.4 (SAS Institute Inc., Cary, NC, USA.)

RESULTS

From the COCOMO study and CGPS, 908 PLWH and 11,106 uninfected controls included. PLWH were slightly younger, had a higher proportion of current smokers and persons of non-Scandinavian descent but a lower mean BMI, and a lower proportion with hypertension. PLWH were more likely to have symptoms of PAD (Table 1). Most PLWH were well-treated (Online Supplemental Digital Content Table, http://links.lww.com/QAI/B192).

Peripheral artery disease

PAD was found in 112 PLWH (12% [95% CI: 10-14]) and in 623 controls (6% [95% CI: 5-6]), (p<.001). The mean ABI in PLWH and controls did not differ (1.1 [1.1-1.1] vs 1.1 [1.1-1.1], p=.942). In univariate analyses PAD was associated with HIV (OR: 2.4[95% CI: 1.9-2.9]), age (OR per decade: 1.4[95% CI: 1.3-1-6]), diabetes (OR: 2.0 [95% CI: 1.5-2.7]), smoking status (OR if current smoker: 3.1[95% CI: 2.5-3.9]), hypertension (OR: 1.9 [95% CI: 1.6-2.3]), kidney function (OR per 10 ml decrease in eGFR: 1.2 [95% CI: 1.1-1.3]) and symptoms of PAD (OR:11.6 [95% CI: 8.1-16.6]). Being overweight or obese (BMI≥25) compared to normal weight was negatively associated with PAD (OR: 0.8 [95% CI: 0.7-0.9]). After adjusting for CVD risk factors (model 1), these associations did not

change, and in addition we found female sex to be associated with PAD. Further adjustment for hsCRP (model 2) did not alter these findings (Figure 1), nor did lowering the threshold of eLDL-C from 160mg/dl to 116mg/dl. Reported outcomes in figure 1 are adjusted for model 2.

Each ten year increase in age doubled the risk of PAD among PLWH (OR 2.02 [95% CI: 1.48-2.76]), but raised it only by 36 % among uninfected controls (1.36 [95% CI: 1.23-1.50]) (p=.0517, test for interaction). There was no interaction between HIV and smoking or HIV and hypertension for PAD (p-values for interaction were .5668 and .8852, respectively). HIV was not associated with symptomatic PAD (p=.1189, adjusted p=.3216).

Within PLWH, age, female sex, smoking status, hypertension, intermittent claudication, and kidney function were associated with PAD (Figure 1). In contrast, HIV-related factors including a prior diagnosis of AIDS, CD4 nadir, CD4 count, CD4:CD8-ratio, HCV coinfection, duration of cART and duration of HIV infection were not associated with PAD (all p>.05).

DISCUSSION

PLWH had higher prevalence of PAD and symptoms of PAD than uninfected controls matched on age and sex and recruited from the same geographical area. HIV remained a risk factor for PAD after adjusting for traditional CVD risk factors. Regardless of HIV status, traditional risk factors of CVD were associated with PAD, but we did not find any associations between PAD and HIV-specific variables in PLWH.

From previous studies, no consensus has been reached on whether HIV infection poses an independent risk of PAD, and both higher and lower prevalence of PAD in PLWH compared to the general population has been reported [1,6–8,20–23]. However, few of these studies have included

controls, and as PAD prevalence increases with age, direct comparison to general population studies have been difficult. The present study uses a very well-characterized control population with all variables collected in identical fashion by trained medical staff, using the same equipment in PLWH and uninfected controls. Furthermore, both populations were enrolled over the same period of time, live in the same geographical area and are of the same age. As such, we have excellent comparability between the PLWH and the uninfected controls. Of note, PLWH and controls were asked *identical*, but *not validated* questions regarding symptoms of PAD. Hence, we may falsely have classified differential diagnoses (e.g neurospinal disease) as symptoms of PAD, but this misclassification would apply to both PLWH and controls equally. The Edinburgh claudication questionnaire [24] or similar would have allowed us to describe the level of symptomatic disease with a greater degree of certainty. Due to logistic reasons, it was not possible to include the Edinburgh claudication questionnaire in our study.

HIV-related variables have been shown to predict CVD including atherosclerotic carotid artery disease(18-20) but data are less clear with regards to lower extremity PAD[21,26]. We found traditional CVD risk factors but not HIV-related variables to predict PAD. This is in agreement with prior findings[6,10,21], although one study found a CD4+ T cell count of <200 cells/µL to predict PAD[8]. Few COCOMO participants have detectable viral replication or current CD4+ T cell count below 200 cells/µL. To elucidate why HIV-related factors predict coronary and carotid atherosclerotic disease and not PAD requires studies in populations that are less well-treated. Although hsCRP is an inflammatory marker often found to be associated with CVD in HIV,[27,28] additional adjustment for hsCRP did not alter the association between HIV and PAD in this study. Thus, we found no

evidence to support that inflammation explains the excess risk of PAD among PLWH, but we cannot rule out that unmeasured inflammatory indices may contribute to the pathogenesis.

As evidenced by a borderline statistically significant interaction between HIV and age, age may influence risk of PAD to a greater extent among PLWH than among controls. Though we cannot rule out the impact of unknown confounders, this observation may support the notion of an accelerated or premature ageing/atherosclerotic process attributable to HIV status in itself [29,30].

CONCLUSION

Prevalence of PAD and symptoms of PAD was higher among PLWH compared to uninfected controls, and remained so after adjusting for common CVD risk factors. We found some evidence that this relationship was more pronounced among older individuals. Our findings expand the evidence base that PLWH have excess arterial disease to also include PAD. To explain the exact biological mechanisms causing this excess risk requires focused investigation, as does the clinical implications from our findings. Further understanding of the modifiable CVD risk factors remains important in reducing the burden of PAD among PLWH.

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Legend/Caption

Figure 1 Adjusted Odds Ratio of Peripheral Artery Disease

Odds ratio of peripheral artery disease, adjusted for a predefined model with known cardiovascular risk factors including age, sex, hypertension, diabetes, eLDL-C, smoking status and high-sensitivity C-reactive protein (adjusted for model 2).

hsCRP: high-sensitivity C-reactive protein; **PAD**: Peripheral artery disease; **eGFR:** estimated glomerular filtration rate.

Table 1 Demographic characteristics

Characteristics	PLWH (N = 908)	Uninfected controls (N = 11,106)	P-value
Age, median (IQR)	52(47-60)	53 (48-62)	.0007
Sex (Male), n (%)	770 (85)	9,174 (83)	.0918
Ancestry, n (%)			<.0001
• **Scandinavia**	674 (76)	9,808 (89)	
• **Other European**	101 (11)	785 (7)	
• **Middle-east or Indian subcontinent**	12 (1)	316 (3)	
• **Other**	105 (12)	67 (1)	
BMI (kg/m^2), mean (CI)	25 (24.8-25.5)	27 (26.7-26.8)	<.0001
• **Underweight, n (%)**	20 (2)	47 (0)	
• **Normal, n (%)**	463 (51)	3,921 (35)	
• **Overweight, n (%)**	323 (36)	5,123 (46)	
• **Obese, n (%)**	95 (11)	1,986 (18)	
Education level n (%)			<.0001
• **None**	95 (11)	262 (7)	
• **Short**	90 (10)	276 (7)	
• **Vocational**	253 (29)	1,420 (35)	
• **Middle Length**	208 (24)	1,115 (28)	
• **University**	213 (25)	956 (24)	
Hypertension, n (%)	415 (48)	6,690 (61)	<.0001
Elevated LDL-C, n (%)	219 (26)	2,694 (25)	.5819
Lipid-lowering medication, n (%)	142 (16)	1,310 (12)	.0006
Diabetes, n (%)	47 (5)	472 (4)	.1277
Smoking, n (%)			<.0001
• **Current**	259 (28)	1,414 (13)	
• **Former**	338 (37)	4,531 (41)	
• **Never**	295 (32)	5,105 (46)	
Pack years, Median (IQR)	20 (8-34)	15 (6-130)	<.0001
Family history of CVD, n (%)	328 (36)	4,446 (40)	.0206
eGFR, mL · min-^{1} · 1.73 m^2 mean (SD)	87 (86-88)	88 (88-88)	<.0001
hsCRP , median (IQR)	1.2 (0.6-2.5)	1.1 (0.5-2.0)	<.0001
Ankle-Brachial Index, mean (SD)	1.1 (1.1-1.1)	1.1(1.1-1.1)	.9416
Peripheral artery disease n (%)	112 (12)	623 (6)	<.0001
Symptoms of PAD, n (%)	16 (2)	112 (1)	.0334
Symptomatic PAD, n (%)	7 (0.8)	46 (0.4)	.1189
Non-compressible, n (%)	12(1)	122 (1)	.5383

Table 1

Demographic characteristics.

BMI: Body mass index; CI: Confidence interval; CVD: Cardiovascular disease; eGFR: estimated glomerular filtration rate; eLDL-C: elevated low density lipoprotein-Cholesterol; Family history: defined as first relative with myocardial infarction and/or stroke; hsCRP: high-sensitivity C-reactive protein; IQR: Interquartile range; n: number; Non-compressible: ABI≥1.4; SD: Standard Deviation;