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Prevalence and risk factors of peripheral arterial occlusive disease in adult Indian HIV positive patients– The PAODH study

KEYWORDS: HIV, peripheral arterial occlusive disease (PAOD), Ankle Brachial Pressure Index (ABPI), Toe pressure, risk factors, HAART

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ABSTRACT *Introduction: HIV causes arterial occlusive disease by atherosclerotic and non-atherosclerotic mechanisms. There are only limited studies assessing the prevalence and risk factors of peripheral arterial occlusive disease (PAOD) in these patients: treatment parallels that of vascular disease due to other etiologies as a clear understanding of the pathophysiology in HIV disease is lacking. As patients with HIV infection has near normal life expectancy with the current antiretroviral therapy, management of vascular disease in HIV assumes clinical importance. This is the first study from the Indian subcontinent which analyses the prevalence of peripheral arterial occlusive disease in patients with HIV and identifies the risk factors for its occurrence.*

Methods: A prospective observational study was conducted in the department of Vascular Surgery and Infectious Diseases Retroviral Clinic in the Christian Medical College, Vellore from November 2012 to September 2014. Following a direct interview; demography, clinical features (assessed with help of Edinburgh Claudication Questionnaire), ankle brachial pressure index and laboratory parameters assessing conventional risk were recorded in a proforma. The Ankle Brachial Pressure Index (ABPI), exercise ABPI and or Toe pressure (TP) was done to detect peripheral arterial disease in patients with HIV.

Results: Four hundred and three HIV infected patients were recruited in to the study. Average age of study population was 41.45. There were 238 males and 165 females (59.1% Vs 40.1%). The prevalence of PAOD was 7.69% (31 patients); 26 were asymptomatic and 5 were symptomatic. Use of protease inhibitors and the duration of its use were identified to be risk factors for PAOD in this population whereas the traditional risk factors like diabetes mellitus, tobacco use including smoking, hypertension, and dyslipidaemia were not. Duration of HIV infection, overall duration of HIV treatment and CD4 count < 300 were also associated with a higher rate of PAOD but these did not attain statistical significance in multivariate analysis as risk factors.

Conclusion: The prevalence of peripheral arterial occlusive disease in HIV positive patients is higher than in the general population. Protease inhibitor use and duration of its use can be strongly associated with development of PAOD. Traditional risk factors seem to be playing negligible role in the development of peripheral arterial occlusive disease in these patients.

Introduction

Today 33.4 million people are living with HIV of which 2.39 million are in India: the third largest number worldwide. The first reports of HIV in India were in 1986, [1-4] about five years after the recognition of the disease in the USA. The prevalence of AIDS in India in 2011 was 0.3% according to the National AIDS Control Organisation (NACO) estimates of the Department of Health and Family welfare India.[5] The average survival time of untreated HIV infection was about 9-11 years.[6] After the introduction of HAART (Highly Active Anti-Retroviral Therapy), the morbidity and mortality of HIV and associated opportunistic infections has reduced significantly. However, HAART does contribute to various other abnormalities like metabolic syndrome, insulin resistance, and dyslipidaemia: these overlap with the traditional risk factors for atherosclerosis. With an increase in life expectancy, these patients are likely to be at an increased risk for age related vascular diseases and cardiovascular events.

HIV vasculopathy was first described as an entity in 1987.[7] This occurs by atherosclerotic and non-atherosclerotic mechanisms. Three clinical syndromes are described with respect to HIV and vascular system, [8] - atherosclerotic occlusive disease, non-atherosclerotic disease (vasculitis and aneurysms) and prothrombotic states. Among these, atherosclerotic disease is the commonest and vasculitis is the least common (about 1%).[9] The prevalence of PAOD in HIV patients varies from 0.9% to 22.4% as estimated in limited studies.[10] Advanced HIV disease with low CD4 count and low albumin are considered poor prognostic factors for vascular disease.[17] The understanding of the pathophysiology of causation of HIV related vascular disease is not fully understood. Evidence pointing to persistent inflammation mediated by the direct effect of viral replication, expanded copathogen burden, loss of mucosal integrity, and chronic translocation of gut microbial products is emerging. Biomarkers like IL-6, hsCRP and D-dimer have been reported

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to be high in patients with HIV-associated inflammation and shown to be significantly related to CVD. However, treatment protocols continue to empirically parallel that of atherosclerotic vascular disease. As patients with HIV infection live longer with better medical treatment, management of vascular disease in HIV assumes clinical importance.

There are only limited studies assessing the prevalence and risk factors of peripheral arterial occlusive disease in these patients: none from India to our knowledge. This is the first large scale study from the Indian subcontinent which analyses the prevalence of peripheral arterial occlusive disease and identifies the risk factors for its occurrence.

Materials and Methods:
HIV infected patients of >18 years, confirmed using fourth generation ELISA were prospectively recruited to assess the prevalence of peripheral arterial occlusive disease and to identify associated risk factors. Critically ill, those who could not perform post-exercise ABPI or those who did not consent were excluded. This was performed in patients presenting to a retroviral clinic at a tertiary care hospital in South India from December 2012 to September 2014. The study was approved by the Institutional Review Board.

Demography, traditional risk factor assessment, treatment details (diagnosis, enrolment for ART, drug regime, recent CD4 count) were recorded. The CD4 count recorded was at a single point in time. Clinical examination and non-invasive vascular lab testing were performed. Symptomatology was assessed with the help of Edinburgh Claudication Questionnaire. Peripheral arterial occlusive disease was diagnosed based on the American Heart Association (AHA) guidelines- Ankle Brachial Pressure Index (ABPI) <0.90. [28] In those patients with chronic kidney disease or diabetes where there is evidence of calcific, non-compressible vessels (ABPI >1.1); toe pressures (TP) <50 mm Hg and/or toe brachial index (TBI) < 0.7 were considered diagnostic. A post exercise reduction to <0.9 and/or >25% reduction from the baseline ABPI was considered significant. ABPI was measured for all patients using a single hand held Doppler and standard blood pressure cuff by the principal investigator to avoid inter observer variability.

Dyslipidaemia was diagnosed based on the history of lipid lowering drug intake, triglyceride >/= 150mg/dL, LDL cholesterol >/= 130 mg/dL, total cholesterol >/= 200 mg/Dl or HDL cholesterol <40 mg/dL.[25] Hypertension was diagnosed by history of antihypertensive intake or as defined by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) guidelines.[26] Diabetes mellitus was diagnosed based on history of use of anti-diabetic medications, fasting plasma glucose level >/= 126 mg/dl and/or 2 hours post prandial plasma glucose >/= 200 mg/dL.[27]

The reported prevalence of PAOD in HIV patients varied from 0.9% to 20.7%. [10] Using an expected prevalence of 20% and precision of 4%; the sample size calculated was 400. Following data collection statistical analysis using univariate and multivariate analysis was performed.

Results
Among 403 patients studied- 238 patients (59.1%) were males and 165 (40.9%) were females. Average age of the study population was 41.45 years. Peripheral arterial occlusive disease (PAOD) was identified in a total of 31 patients using ABPI (exercise/ resting) as the screening tool. Only 3 patients were found to have >25% reduction in post-exercise ABPI. 19 patients (5%) reported leg pain suggestive of claudication as per the Edinburgh Claudication Questionnaire. In the claudicants, mean claudication distance was 1.03 kilometres. No patient reported critical limb ischemia- rest pain or features of tissue loss (ulcers or gangrene).

The prevalence of peripheral arterial occlusive disease in this study was 7.69%. Among the patients with PAOD, 17 (54.8%) were females and 14 (45.2%) were males.

79 (19.6%) patients used tobacco in some form. Predominant form of tobacco use was smoking. Alcohol was used by 58 (14.4%) patients. 32 patients (7.9%) were diabetic and 371 (92.1%) were non-diabetic. 63 patients (15.63%) were hypertensive and 340 patients (84.37%) were not diagnosed with hypertension. Majority of the hypertensive patients in this population were on irregular treatment. Only 18 patients (4.5%) were diagnosed with dyslipidaemia- majority did not receive lipid lowering medications. 3 patients (0.7%) had prior history suggestive of ischemic heart disease/acute coronary syndrome/coronary artery disease/history suggestive of coronary angina. 1 patient (0.2%) had history of prior stroke from which the patient had recovered completely. 9 patients (2.2%) had history suggestive of vascular disease in the family. Mean duration since HIV was diagnosed was 59.35 months. 381 patients (95%) were currently on ART. 122 patients were on one of the protease inhibitors at least or had history of using one of the protease inhibitors in the past, 259 patients never had history of protease inhibitor use. Mean duration of protease inhibitor use was 16.57 months. Majority of patients had history of using protease inhibitors for less than 30 months. Among those who were not on ART, the immune status as assessed by CD4 count was good, with a mean of 456 cells/microliter (range 1-1363 cells/uL). Among 403 patients, almost equal percentages were of normal, overweight or underweight. Mean CD4 count was 456.04. Mean haemoglobin was 12.52 gm%. Mean albumin was 3.97 gm%.

The above factors were analysed by logistic regression analysis to determine if any of these could be potential risk factors for PAOD. Table 1 presents the results of the univariate regression analysis demonstrating relationships between PAOD in HIV patients and other variables. Univariate analysis revealed that duration of HIV, treatment duration, use of protease inhibitors, duration of use of protease inhibitors and CD4 count <300 positively correlated with PAOD. Then, stepwise method (forward-backward selection) was applied in order to select variables included in a multivariate regression model. Among variables listed in the Table 1, use of protease inhibitors (OR-2.64), low CD4 count <300 (OR-1.93) and prolonged duration of antiretroviral (ART) treatment (OR-1.002) remained as factors showing significant association with a higher risk of developing peripheral arterial occlusive disease in HIV positive population. The only risk factor which attained statistical significance for causation of peripheral arterial occlusive disease was protease inhibitor use (p = 0.014). In those with protease inhibitor use, duration of treatment with this agent was also found to be significantly associated (p = 0.018) with peripheral arterial occlusive disease (Table 2).

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Table 1: Results: risk factors for PAOD in HIV patients

Variable	Variable value		p value
	PAOD Present	PAOD Absent	
Age	40.71 ± 8.46	41.51 ± 8.25	0.603
Gender - Male	14 (45%)	224 (60%)	0.128
BMI	21.59 ± 5.187	22.20 ± 3.99	0.429
Tobacco use	4	75	0.364
Alcohol use	3 (10%)	55 (15%)	0.597
DM	1 (10%)	31 (15%)	0.494
HTN	5 (16%)	58 (16%)	1.000
BP (mm Hg)	124.39 ± 17.71	126.40 ± 18.25	0.554
Dyslipidaemia	1 (3%)	17 (5%)	1.000
Total Cholesterol	180.88 ± 38.63	164.82 ± 3.99	0.333
HDL Cholesterol	39 ± 12.67	37.16 ± 12.34	0.686
LDL Cholesterol	104.75 ± 27.71	96.27 ± 28.86	0.424
IHD/ACS/CAD	0	3 (1%)	1.000
CVA/TIA	0	1 (1%)	1.000
Family history of vascular events	1 (3%)	8 (2%)	0.517
Duration of HIV (months)	33.65 ± 61.50	35.08 ± 52.33	0.001
Duration of HAART	29.11 ± 36.11	47.05 ± 37.23	0.001
PI use	17 (57%)	105 (30%)	0.004
Duration of PIs	9.57 ± 9.84	17.70 ± 17.50	0.018
CD4 < 300	15 (48%)	109 (29%)	0.041

Table 2: multivariate analysis

Variables	Odds Ratio, (95% C.I)	P value
Treatment Duration	1.002, 0.98- 1.03	0.889
HIV Duration	0.984, 0.96- 1.08	0.189
CD4 count < 300	1.93, 0.88- 4.23	0.101
Duration of PI	2.64, 1.22- 5.74	0.014

Discussion

The prevalence of peripheral arterial occlusive disease in the general population is estimated to be 1% at the age of 50 years and 3% at the age of 60 years.[11] This is similar to what is reported from India with similar etiology, clinical presentation and natural history as reported in the West.[12]

Prevalence of peripheral arterial occlusive disease obtained in this study was 7.69%. Majority of patients were asymptomatic (83.9%). Patients from both sexes were nearly equally distributed. Though disease was present in all age groups; disease was seen at a relatively younger mean age than the general population. Risk factors associated with higher risk of PAOD in this population were not much different from that of western population. Smoking, DM and age which attained statistical significance in many studies in the west were not significant in this study, even in the bivariate analysis. A higher risk of developing PAOD was found in those patients with CD4 count <300 in comparison to those with CD4 counts >300. Our final analysis has showed that there is statistically significant association (p value- 0.011) between use of protease inhibitors and development of PAOD. Most of our patients who were receiving protease inhibitors were using tenofovir. Average duration of treatment with protease inhibitors in our study was 16.57 months. With respect to this, it is important to note that duration of HIV had showed some significant association to the development of PAOD in bivariate analysis. This could probably mean that repeated and persistent endothelial dysfunction could result from prolonged duration of HIV infection.

The prevalence of PAOD is reported to be greater among the HIV positive patients.[10, 13, 14]

In the Swiss HIV cohort study, [15] PAOD was found in 20.7% of patients with symptomatic disease in 15.2% detected using ABPI/ exercise ABPI as the screening tool. Age, diabetes, smoking, and low CD4 counts (<200) are independent predictors of PAOD in HIV positive patients.[15] Higher BMI, dyslipidaemia, use of protease inhibitors and higher cardiovascular risk are other reported predisposing factors. Though the prevalence in women is not as high, these risk factors seem to be equally important.[16]

Characteristics of HIV associated vasculopathy differs from general population in the following ways,[8, 17]: young age of onset, less prevalent traditional risk factors, more advanced disease at presentation, extensive disease with poor peripheral run off, higher rate of complications especially wound and graft related, increased perioperative and post-operative mortality and morbidity. Perioperative mortality rate was 6.95% with long term mortality approaching 20%. The primary amputation rate was 31.91%, secondary amputation rate 36.1%. Poor nutritional status was considered a predictor of poor surgical outcome.[17]

Surgical outcome has been found to be largely independent of the CD4 values and hence no patient should be denied an operation based on low CD4 count.[8, 17]

HIV infection itself as well as ART drugs can cause dyslipidaemia. Use of protease inhibitors has been associated with hypertriglyceridemia and hypercholesterolemia; dyslipidaemia varying with the type of protease inhibitors used.[18, 19] This is associated with other metabolic derangements- insulin resistance, metabolic syndrome and risk of future cardio vascular events including myocardial infarction- in HIV patients.[10, 20, 21] The duration of treatment with protease inhibitors also correlates with causation of PAOD. However, as most infected patients are on treatment, distinction of causation due to viral / drug side effects is often unclear.

Endothelial injury plays a major role in the development of HIV related cardiovascular and inflammatory pathologies.[8, 15, 22, 23] Different endothelial cells have variable permeability to HIV. Viral entry followed by cell activation cause activation of soluble adhesion molecules and procoagulant protein production. Inflammatory cytokines and viral proteins can act in synergy leading to endothelial injury. These dysfunctional or injured endothelial cells potentiate inflammation, tissue injury and tissue remodelling, and thereby accentuate the development of various cardiovascular diseases including peripheral arterial occlusive disease.[23] Immune suppression, direct viral injury of endothelium, vasculitis, metabolic derangements due to HAART therapy also contribute to disease. Other abnormalities: antiphospholipid antibodies, lupus anticoagulant, increased Von Willebrand factor (vWF), deficiency in protein C and S, AT-III (anti-thrombin) and heparin cofactor, opportunistic infections and HIV associated neoplasms may also contribute to the procoagulant state.[24]

This study has a few limitations. Consecutive patients could not be recruited into the study due to personnel constraints. However, a large sample size was obtained to be representative of the target population. Imaging of the arterial system after detection of PAOD was not done as a part of this study. Temporal ambiguity– peripheral arterial occlusive disease could have been present even before the patient acquired HIV infection- could also be present. Even so, this study is the first from India addressing the problem of PAOD in HIV patients.

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Conclusion

Our study helped prove the higher prevalence of PAOD in HIV positive patients. Prevalence of peripheral arterial occlusive disease in HIV positive patients is about 8 %. The risk factors associated with development of PAOD in HIV positive patients were use of protease inhibitors, duration of treatment with protease inhibitors. The duration of HIV infection, treatment (HAART) duration, CD4 count < 300 though more common in patients with HIV did not attain statistical significance. Traditional risk factors for peripheral arterial occlusive disease (like DM, HTN, dyslipidaemia, smoking) did not contribute significantly to the causation of peripheral arterial occlusive disease in HIV positive population.

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