Original Article

Carotid intima-media thickness, flow-mediated dilatation and proteinuria in patients of human immunodeficiency virus-positive patients: A case–control study

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Abstract

Introduction: Endothelium-dysfunction (ED) is a surrogate marker of coronary atherosclerotic disease. Carotid intima-media thickness (CIMT), flow-mediated dilatation (FMD), and proteinuria are surrogate markers of ED. Few studies have shown that patients with HIV have impaired endothelial function and are thus at risk of accelerated atherosclerosis. **Materials and Methods:** The present study assessed ED in HIV patients by various biophysical parameters as brachial artery FMD, CIMT, and proteinuria. A total of 43 HIV-infected patients were compared with 25 healthy controls who were healthy. **Results:** Mean age of patients with HIV was 33.84 ± 5.61 years while that of healthy controls was 31.48 ± 5.40 years. Male to female ratio among cases was 24:19 while among controls was 17:8. Mean CIMT was significantly higher among cases than control (0.513 ± 0.079, 0.452 ± 0.050 mm, respectively, $P = 0.001$). Percentage change in FMD was significantly lower among cases than control (3.27 ± 2.01, 6.96 ± 1.28, respectively, $P = 0.001$). Urine protein grading was significantly different between cases and controls ($P = 0.007$), with stable HIV cases having significantly higher urine protein grading compared to healthy controls. However, no correlation was seen between CIMT, FMD, and proteinuria overall among cases and controls. **Conclusions:** HIV-infected patients have significant impairment of endothelial function, in the form of increased CIMT, impaired FMD, and more proteinuria as compared to healthy controls.

Keywords: Carotid intima-media thickness, endothelial dysfunction, flow-mediated dilatation, HIV, subclinical atherosclerosis

Introduction

HIV-infected patients are at higher risk for cardiovascular events.[1] Thus, we need to identify the patients at risk at the earliest using easily obtainable, noninvasive, and inexpensive markers. Endothelial dysfunction (ED) is an early step that leads to progression of atherosclerosis. Proteinuria is another marker which predicts future cardiovascular events.[2]

The development of systemic ED has been suggested as the link between the presence of proteinuria and development of cardiovascular disease.[3] Not only HIV, its therapies have also been associated with ED.[4] Endothelial function can be assessed by flow-mediated dilatation (FMD).[5] Carotid intima-media thickness (CIMT) is a measure of the extent of early arterial wall changes. Increased carotid IMT is a strong predictor of acute coronary events.[6] Thus, we conducted a study to look at the endothelial cell dysfunction in stable HIV patients and compare with healthy controls.

Materials and Methods

The study population included forty-three consecutive stable HIV patients attending Medical OPD and HIV clinic at a tertiary care hospital at New Delhi.

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The aims of our study were:

1. To study endothelial cell dysfunction in stable HIV patients as a marker of premature atherosclerosis by FMD, proteinuria, and carotid intima-media thickness
2. To study its correlation with healthy controls.

We included stable patients of HIV (confirmed by IGM ELISA).

Patients with age <18 years and >40 years, overweight (body mass index >25 kg/m^2), suffering from preexisting diabetes mellitus or hypertension, receiving highly active antiretroviral therapy, suffering from known renal disease (serum creatinine >1.4 mg/dl or >124 μmol/L), history of cardiovascular and ischemic heart disease, fever (temperature >38.0°C) currently or 2 days before enrolment in the study, suffering from any opportunistic infection, smokers, alcoholics, or other active substance abuse, on drugs such as growth hormone, systemic steroids, ketoconazole, any form of estrogen, progesterone, testosterone, or any anabolic agents within 3 months before enrolment in the study and pregnant women were excluded from the study.

Twenty-five apparently healthy controls were residents and nurses working in the same tertiary care hospital. Exclusion criteria for controls were same as that for the HIV cases.

All the patients and controls in the study group were subjected to detailed history and physical examination. Informed consent was taken from both cases as well as controls. The study protocol has been evaluated and approved by the hospital Ethical Committee.

Following investigations were carried out in all the patients and controls:

1. Brachial FMD using 10MHZ linear array transducer
2. Common Carotid Ultrasonography-Using 7.5MHZ B-mode ultrasound with high-density lipoprotein 3500 machine, (ATL, USA) equipped with color flow imaging and pulse Doppler and one examiner examined the result of all the patients
3. Urine examination-single spot urine sample for proteinuria and cells/casts was obtained.

Statistical analysis

The data of all patients were entered into Microsoft Excel version 2007. The data analysis was done by the SPSS software for window version 17(IBM Corporation, New York, United States). Quantitative variables were reported as mean ± standard deviation and were compared by Student's *t*-test or Mann–Whitney test as appropriate. One-way analysis of variance (ANOVA) model was used to compare cases and controls for difference of urine protein grading. Qualitative variables were reported and compared by Chi-square test or by Fischer's exact test as appropriate. $P < 0.05$ was considered statistically significant. Continuous variables were correlated using Pearson's correlation coefficient.

Results

Our study included 43 cases and 25 healthy controls. Proteinuria was estimated by dip stick method which is represented in Table 1. Baseline characteristics of both cases and controls are shown in Table 2.

The studied parameters were compared which is shown in Table 3.

Urine protein was also compared among cases and controls which is shown in Table 4.

Urine protein grading was significantly different between cases and controls ($P = 0.007$), with stable HIV cases having significantly higher urine protein grading compared to healthy

Table 1: Dipstick proteinuria ranges

Dipstick grading	Semi-quantitative urine protein (mg/dl)
Negative/nil	0
Trace	15-30
1+	30-100
2+	100-300
3+	300-1000
4+	>1000

Table 2: Baseline characteristics of cases and controls

Characteristics	Cases (*n*=43)	Controls (*n*=25)
Age (years)	33.84±5.61	31.48±5.40
Sex (male:female)	24:19	17:8
BMI (kg/m^2)	20.67±2.63	21.52±1.16
ESR (mm at 1 h)	9.47±2.62	3.56±1.87
Hemoglobin level (g/dl)	12.46±1.18	13.51±0.45
Fasting blood sugar (mg/dl)	80.63±8.18	80.28±5.42
Blood urea (mg/dl)	23.23±5.32	23.48±2.61
Serum creatinine (mg/dl)	0.62±0.25	0.32±0.11
Serum uric acid (mg/dl)	5.10±0.99	3.62±0.57
Total cholesterol (mg/dl)	141.16±28.53	130.12±15.23
Serum triglyceride (mg/dl)	124.35±33.79	118.76±16.21
LDL cholesterol (mg/dl)	89.58±20.93	110.68±18.42
HDL cholesterol (mg/dl)	43.26±7.66	52.84±4.07
VLDL cholesterol (mg/dl)	29.37±4.25	25.68±4.03

BMI: Body mass index; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; VLDL: Very low-density lipoprotein; ESR: Erythrocyte sedimentation rate

Table 3: Comparison of studied parameters between cases and controls

Parameters	Patients (*n*=43)	Controls (*n*=25)	*P*
CIMT right (mm)	0.516±0.084	0.452±0.050	0.001
CIMT left (mm)	0.510±0.095	0.452±0.050	0.006
CIMT mean (mm)	0.513±0.079	0.452±0.050	0.001
Brachial artery diameter at rest (cm)	0.379±0.037	0.343±0.039	<0.001
Peak brachial artery diameter on hyperemia (cm)	0.392±0.040	0.366±0.042	0.02
Percent FMD	3.27±2.01	6.96±1.28	<0.001

CIMT: Carotid intima media thickness; FMD: Flow-mediated dilatation

controls (one-way ANOVA). In urine microscopy, cells and casts were absent both in cases and controls.

Table 4: Comparison of urine protein grading between cases and controls

	Urine protein grading				Total
	Nil	1+	2+	3+	
Cases	19	8	13	3	43
Controls	21	3	1	0	25
Total	40	11	14	3	68

Table 5: Association between various studied parameters overall in cases and controls

Parameters (both cases and controls)	Association	Level of significance (*P*)
CIMT versus percentage FMD	Not significantly associated	0.107
CIMT versus urine protein grading	Not significantly associated	0.764
Percentage FMD versus urine protein grading	Not significantly associated	0.177

CIMT: Carotid intima media thickness; FMD: Flow-mediated dilatation

The association between the parameters was calculated which is shown in Table 5.

Discussion

In this study, we studied forty-three stable HIV patients and twenty-five apparently healthy controls and looked for any significant difference between stable HIV patients and controls with respect to CIMT, FMD, and proteinuria and examined the relationship between CIMT, FMD, and proteinuria and their use as a marker of ED for premature atherosclerosis.

In our study, we found higher baseline mean CIMT in HIV-positive patients (0.513 ± 0.079 mm), as compared to controls (0.452 ± 0.050 mm) with a significant difference (P = 0.001). Table 6 summarizes previous major studies on CIMT in HIV patients.

In our study, we excluded the patients on HAART to prevent its effect on CIMT.

We also found that in stable HIV patients have increased in brachial artery diameter in response to passive hyperemia

Table 6: Summary of previous major studies on carotid intima media thickness in human immunodeficiency virus patients

Authors	Patients (*n*)	Results
Kaplan *et al.*[7]	1931 cases 859 controls	CIMT was not significantly different in HIV-infected versus uninfected patients after adjustment for metabolic risk factors
Lorenz *et al.*[8]	292 cases 1168 controls	CIMT was higher in HIV infected compared to uninfected patients (absolute difference 0.044 mm, 95% CI 0.021-0.066 mm, *P*=0.0001) Use of HAART had an independent effect on CIMT
Currier *et al.*[9]	89 cases 45 controls	CIMT progression at 3 years was not significantly different between PI treated and non-PI treated patients and between HIV infected and matched uninfected controls
de Saint Martin *et al.*[10]	154 cases	CIMT predictors included age, SBP, and triglyceride value (<0.001, <0.001 and 0.02 respectively). Duration of PI, especially that of lopinavir, was also correlated with CIMT after adjustment (*P*=0.01)
Hsue *et al.*[11]	93 cases 36 controls	CIMT was higher in HIV infected versus uninfected patients (0.95 vs. 0.68 mm, *P*<0.001)
Jericó *et al.*[12]	132 cases	CIMT >0.8 mm or presence of plaque was found in 41.7% of patients. Risk of carotid atherosclerosis was increased in patients on HAART compared to treatment naive patients (OR 10.5, 95% CI 2.8-39)
Maggi *et al.*[13]	133 cases	PI use appeared associated with a more rapid onset of carotid lesions compared to patients treated with NNRTIs, with more rapid evolution of previous lesions
Mangili *et al.*[14]	327 cases	CIMT did not differ by HAART regimen For men age and waist circumference predicted common CIMT, for women, age and BMI were predictors
Currier *et al.*[15]	89 cases 45 controls	CIMT was not significantly different in HIV-infected patients on PI treatment for >2 years compared with those without prior PI use or uninfected controls (0.690 vs. 0.712 vs. 0.698 mm)
Hsue *et al.*[16]	143 cases 63 controls	CIMT progression at 1 year was higher in HIV infected versus uninfected patients (0.074±0.13 mm vs. 20.006±0.05 mm, *P*=0.002). Predictors of progression included age, latino race, and nadir CD4 count ≤200
Depairon *et al.*[17]	168 cases 68 controls	HIV infected patients had more carotid or femoral plaques when compared with uninfected patients (61% vs. 46%, *P*=0.03).Independent predictors of plaque included age, male gender, LDL cholesterol, and smoking. PI use was not associated with the presence of plaque
Maggi *et al.*[18]	102 cases 104 controls	Carotid plaque was higher than expected in patients receiving PI therapy, when compared with those without PI use and noninfected controls (52.7% vs. 14.9% vs. 6.7%)

CIMT: Carotid intima media thickness; HIV: Human immunodeficiency virus; CI: Confidence interval; HAART: Highly active antiretroviral therapy; PI: Protease inhibitor; SBP: Systolic blood pressure; OR: Odds ratio; NNRTIs: Nonnucleoside reverse transcriptase inhibitor; BMI: Body mass index; LDL: Low-density lipoprotein

which was significantly lower as compared to healthy controls (3.27 ± 2.01 mm vs. 6.96 ± 1.28 mm, $P < 0.001$). Furthermore, significantly lower HIV cases had percent FMD ≥4.5% as compared to controls (23.3% vs. 100%, $P < 0.001$). Table 7 summarizes previous major studies of FMD in HIV patients.

Our finding of unequal percentage FMD in HIV patients and non-HIV participants is in agreement with previous studies that found decreased FMD in HIV patients compared to HIV-uninfected controls[21,22] but in contrast to other studies[19,20] that found equal FMD in HIV patients and non-HIV participants. Various explanations have been proposed for conflicting results regarding brachial FMD in the literature. These include heterogeneity in patient populations being studied, different measurement protocols or inadequate sample sizes.

We also found significant difference in urine protein grading between stable HIV cases and healthy controls, with overall urine protein grading significantly higher in HIV cases compared to healthy controls ($P = 0.007$). Table 8 summarizes the previous major studies on proteinuria in HIV patients.

The high prevalence of proteinuria in this cohort of HIV-infected patients in our study is similar to earlier reports[23,24] from HIV-infected children and adults. The implication of this observation is that markers of kidney damage such as proteinuria should be searched for in HIV-infected patients with advanced clinical and or immunological stage of HIV disease.

We also found a weak inverse relationship between carotid IMT and brachial percent FMD but not significant ($r = -0.197$, $P = 0.107$), when data were combined both for HIV cases and healthy controls. There is only one previous study by Odueyungbo *et al.*[29] (257 HIV patients), that has validated this correlation in HIV patients with borderline significance ($r = -0.126$, $P = 0.043$).

We did not find any significant correlation between percentage FMD and proteinuria, overall in HIV cases and healthy controls ($P = 0.177$). After an extensive review of literature, we could find only one pilot study of its kind to study the relation between FMD and proteinuria in stable HIV patients. This study by Gupta *et al.*[30] of 34 stable HIV patients (28 nonproteinuric and 6 proteinuric), also could not establish any significant correlation between proteinuria and FMD.

We did not find any significant correlation between CIMT and proteinuria ($P = 0.764$), overall in HIV cases and healthy controls and also, separately for HIV cases ($P = 0.178$). To the best of our knowledge, this is the first study of its kind to study the association between CIMT and proteinuria.

Although HIV infection appears to be associated with substantial impairment of endothelial function, the degree to which this impairment translates into increased risk for cardiovascular disease in persons with HIV infection is still largely unknown. Large prospective, well-controlled studies are required to demonstrate that impaired endothelial functions translate into increased cardiovascular events and premature death in stable HIV patients.

Several limitations of our study need attention. First, the sample size of our study was small, limiting our ability to detect potentially clinically important associations. Second, proteinuria was determined by a semi-quantitative measure of urine protein concentration (dipstick), which is inferior to quantitative measures such as protein-to-creatinine ratio from a random or 24-h sample. Third, other potential confounders that were not accounted for include diet, physical activity, duration of HIV infection, and CD4 count.

Table 7: Summary of previous major studies on flow-mediated dilatation in human immunodeficiency virus patients

Authors	Patients (*n*)	Results
Blanco *et al.*[19]	28 patients 12 controls	Treated HIV patients had significantly lower percentage FMD (5.93±3.56) than healthy controls (10.64±3.08, P=0.008). Naive patients had an intermediate FMD but this was not statistically significant
Nolan *et al.*[20]	24 patients 24 controls	FMD was not significantly different between HIV patients and controls
Stein *et al.*[21]	37 patients	Use of PIs in HIV is associated with atherogenic lipoprotein changes and impaired FMD
van Wijk *et al.*[22]	37 HIV patients 13 type 2 diabetic patients 14 controls	The FMD was impaired in HIV-infected patients without the MS and the diabetic patients (5.1%±0.4% and 4.9%±0.6%, respectively) compared with controls (8.8%±0.7%). The HIV-infected patients with the MS had even more impaired FMD (2.5%±0.3%)

MS: Metabolic syndrome; HIV: Human immunodeficiency virus; FMD: Flow-mediated dilatation; PIs: Protease inhibitors

Table 8: Summary of previous major studies on proteinuria in human immunodeficiency virus patients

Authors	Patients (*n*)	Results
Chaparro *et al.*[23]	286 HIV children	The occurrence of proteinuria was 33% overall, with 11% having nephrotic range proteinuria
Szczech *et al.*[24]	2059 HIV women	32% had proteinuria on initial evaluation
Esezobor *et al.*[25]	88 HIV children 50 controls	20.5% of HIV-infected children had proteinuria, compared with 6% of the 50 controls, with significant difference (P=0.026)
Eke *et al.*[26]	250 HIV children	18.8% prevalence of proteinuria
Emem *et al.*[27]	400 HIV patients	Dipstick positive proteinuria was 1+ in 82 (20.5%) patients, 2+ in 39 (9.8%), 3+ in 17 (4.3%), and 4+ in 14 (3.5%) patients
Agaba *et al.*[28]	79 HIV patients 57 controls	20 (25.3%) HIV patients had proteinuria compared to 7 (12.2%) of controls, which was significantly different. The mean protein excretion/24 h was significantly higher in the AIDS group compared to controls, (2.99±0.54 g and 0.56±0.12 g respectively, P=0.001)

HIV: Human immunodeficiency virus

Conclusions

Indian stable HIV patients have increased ED, as evidenced by increased carotid intima-media thickness, impaired FMD, and higher proteinuria. This subclinical ED would probably translate into premature atherogenesis and increased vascular events in these patients. However, the correlation between these various surrogates of endothelial cell function was poor in Indian stable HIV patients.

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Conflicts of interest

There are no conflicts of interest.

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