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Study of association of urine albumin to creatinine ratio with endothelial dysfunction in HIV patients on HAART

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ABSTRACT

Background: In HIV (Human immunodeficiency virus) positive patients several factors have been proposed to explain the cardiovascular (CV) risk, which include pro-athero-thrombotic viral effect, infection-mediated immune dysfunction and possible effects of HAART(Highly active antiretroviral therapy). Presence of endothelial dysfunction, an early CV risk marker, in HIV-infected patients on long-term HAART. Endothelial dysfunction can be measured by bFMD (Brachial artery flow mediated vasodilatation). Urine albumin to creatinine ratio (UACR) is frequent in HIV patients and is predictor of cardiovascular risk. UACR and endothelial dysfunction are positively associated in HIV affected patients thereby increased UACR might help to identify endothelial dysfunction in HIV patients on HAART. **Aims and Objectives:** • To measure urine albumin to creatinine ratio in HIV patients on HAART. • To find out correlation between UACR and bFMD. **Materials and Methods:** Study was conducted on HIV Patients admitted to hospital, considering the inclusion and exclusion criteria. Detailed clinical history, examination and Blood investigations were done. Endothelial function was assessed by brachial artery flow mediated vasodilatation(bFMD). **Results:** Among 100 HIV patients, 14% had UACR <30 and 86% had UACR >30 and mean UACR is 90 ±06. Mean BFMD was 8.44 ± 7.65. We identified a significant Negative correlations were found between bFMD and UACR(r=- 0.832, P=<0.001). **Conclusion:** Use of urine albumin to creatinine ratio (UACR) as a routine screening tests in those who are HIV positive on HAART can be used to find out those cases of HIV who are progressing towards cardiovascular impairment so that newer approaches can be used in them to prevent further cardiovascular involvement.

Key words: HIV; HAART; Urine albumin to creatinine ratio

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INTRODUCTION

HIV is global pandemic, at the end of 2016 an estimated 36.7 million individuals were living with HIV infection.[1] With introduction of antiretroviral therapy, mortality among AIDS patients has declined substantially. With increase in life expectancy, chronic manifestations of HIV infections have been noticed, including coronary artery disease.[2] Cardiovascular disease has emerged as a relevant complication and as a cause of death among HIV-infected individuals. Several factors have been proposed to explain the cardiovascular risk in HIV positive patients, which include direct pro-athero-thrombotic viral effect, infection-mediated immune system dysfunction and deleterious effects of HAART.[3]

HIV-infected patients receiving Highly Active Antiretroviral Therapy (HAART) are exposed at an increased risk of future cardiovascular events. Hence it's important to identify reliable cardiovascular prognostic markers in HIV infected individuals. Primary event in atherogenesis is endothelial dysfunction which occurs long before the structural atherosclerotic changes, so endothelial dysfunction, can be used as an early surrogate cardiovascular risk marker, in HIV-infected patients on long-term HAART.[4]

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Microalbuminuria is frequent in HIV patients and is predictor of cardiovascular risk and renal dysfunction which can be easily and reliably expressed by urine albumin to creatinine ratio (UACR). Microalbuminuria and endothelial dysfunction are positively associated in HIV affected patients thereby increased UACR help to identify endothelial dysfunction in HIV patients on HAART.[4]

Use of urine albumin to creatinine ratio (UACR) as a routine screening tests in those who are HIV positive on HAART can be used to find out those cases of HIV who are progressing towards cardiovascular impairment so that newer approaches can be used in them to prevent further cardiovascular involvement.

Aims and objectives

The aims and objectives of the current study was to measure urine albumin to creatinine ratio in HIV patients on HAART and to find out correlation between urine albumin to creatinine ratio (UACR) and bFMD.

MATERIALS AND METHODS

A Cross sectional study conducted on 100 HIV Patients admitted to hospitals attached to Bangalore medical college and research institute, during the period of November 1st 2016 to august 30th 2018 would be taken for study. Detailed clinical history, examination and Blood investigations like UACR, RBS, fasting lipid profile, CD4 count were done for every patients. Endothelial function was assessed by brachial artery flow mediated vasodilatation (bFMD).

Inclusion criteria

All HIV patients aged above 18 years receiving HAART for more than 1 year.

Exclusion criteria

The exclusion criteria of the subjects under this study were, Pre-existing Renal disease, Patients with Diabetes, Patients with Hypertension,Glomerular Filtration Rate (eGFR)<60 ml/min, Patients on ACE inhibitors, NSAIDS, penicillamine, statins; Established cardiovascular diseases and history of smoking.

After obtaining institutional ethics committee clearance and written informed consent, data was collected from outpatients and inpatients admitted in hospitals attached to Bangalore medical college and research institute, Bangalore. Patients will be selected according to inclusion and exclusion criteria mentioned above. For each patient the following data will be collected: Age, Sex, RBS, CD4 count, Duration of HIV, UACR, lipid profile, ultrasound Brachial artery flow mediated diameter.

Flow mediated vasodilatation: Baseline diameter of brachial artery is measured using vascular Doppler. Hyperaemia induced by inflation of pneumatic cuff(12.5cm wide) at 230 to 250 mm of Hg for 4 minutes on most proximal portion of the forearm. Arterial diameter measurement was repeated 45 to 60 seconds after sudden deflation of the cuff.

Calculation of bFMD

bFMD is calculated using the equation: FMD = (d2 −d1) × 100/d1; where d1 is the brachial artery diameter at baseline and d2 is the brachial artery diameter 60 s after cuff release. FMD is expressed as a percent change(FMD%).

Statistical analysis

Data were entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. **Chi-square test** were used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. Pearson **correlation** was done to find the correlation between two quantitative variables and qualitative variables respectively.

RESULTS

Mean age of the study subjects in the study was 41.5 ± 11.744 years. Fifteen percent were in the age group <30 years, 40% were in the age group 31 to 40 years, 22% were in the age group 41 to 50 years, 16% were in the age group 51 to 60 years and 7% were in the age group >60 years. Sex distribution male 63% and female 37%.

In the study 14% had UACR <30 and 86% had UACR >30. Mean UACR was 90.06 ± 43.4, and Mean BFMD was 8.44 ± 7.65, with minimum value is 1.04 and maximum value is 34 (Table 1).

In the study there was significant negative correlation between UACR and bFMD (**r= 0.832, P=<0.001**) i.e. with increase in UACR there was decrease in bFMD and vice versa (Table 2; Figure 1).

In the study there was significant positive correlation between bFMD and CD4 count(r=0.283, P=0.004) i.e. with increase in bFMD there was increase in CD4 count and vice versa and there was significant negative correlation between

Table 1: UACR and BFMD distribution in subjects

UACR	Count	%
<30	14	14.0%
>30	86	86.0%

BFMD						
N	Mean	SD	Minimum	Median	Maximum	Range
100	8.44	7.65	1.04	5.20	34.0	32.96

bFMD and Duration of HIV(r=-0.487, P=<0.001) i.e. with increase in Duration of HIV there is a decrease in bFMD and vice versa (Table 3).

In the study there was significant negative correlation between bFMD and Total Cholesterol(r=-0.558, P=<0.001), LDL(r=-0.469,P=<0.001) and Triglyceride (r=0.252,P=0.011). i.e. with increase in Total Cholesterol, LDL and Triglyceride there was significant decrease in bFMD and vice versa (Table 4).

There was significant positive correlation between bFMD and HDL(r=0.313, P=0.002) i.e. with increase in HDL there was increase in bFMD and vice versa (Figure 2).

There was significant positive correlation between bFMD and Albumin levels (r=0.222, P=0.027) i.e. with increase in Albumin there was increase in bFMD (Figure 3; Table 5).

DISCUSSION

HIV infection is global pandemic, with introduction of HAART; mortality among AIDS patients has decreased substantially. But with increase in life expectancy chronic manifestation of HIV increased mainly coronary artery

Table 2: Correlation between UACR (Urine albumin to creatinine ratio) and BFMD (Brachial artery flow mediated vasodilatation)

UACR	UACR	BFMD
Pearson correlation	1	-0.832**
P value		<0.001*
N	100	100

Table 3: Correlation between BFMD (Brachial artery flow mediated vasodilatation) and CD4 Count, Duration of HIV

BFMD	BFMD	CD4 Count	Duration of HIV
Pearson correlation	1	0.283**	-0.487**
P value		0.004*	<0.001*
N	100	100	100

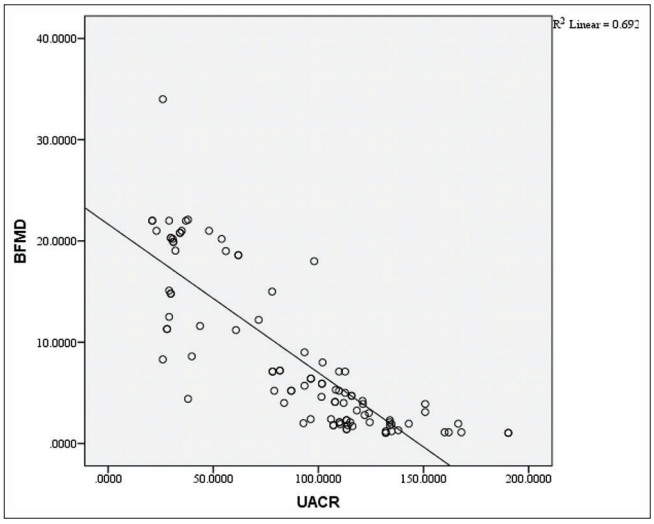

Figure1: Scatter plot showing significant positive correlation between UACR ((Urine albumin to creatinine ratio)) and bFMD (Brachial artery flow mediated vasodilatation)

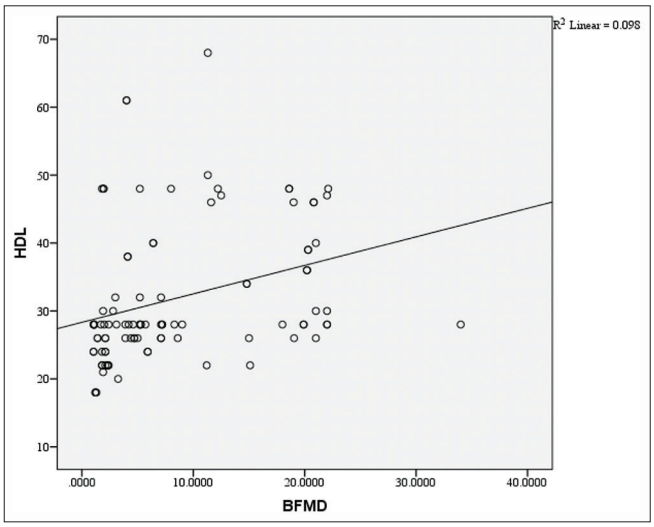

Figure 2: Scatter plot showing significant positive correlation between HDL and bFMD(Brachial artery flow mediated vasodilatation)

Table 4: Correlation between BFMD (Brachial artery flow mediated vasodilatation) and Lipid Profile

BFMD	BFMD	Total Cholesterol	HDL	LDL	Triglyceride
Pearson correlation	1	-0.558**	0.313**	-0.469**	-0.252*
P value		<0.001*	0.002*	<0.001*	0.011*
N	100	100	100	100	100

Table 5: Correlation between BFMD and laboratory parameters

Correlations								
BFMD	BFMD	Hb	TLC	Platelet	Total Protein	Albumin	Creatinine	RBS
Pearson correlation	1	-0.228*	-0.129	-0.107	0.172	0.222*	-0.079	-0.050
P value		0.023	0.201	0.291	0.087	0.027	0.433	0.618
N	100	100	100	100	100	100	100	100

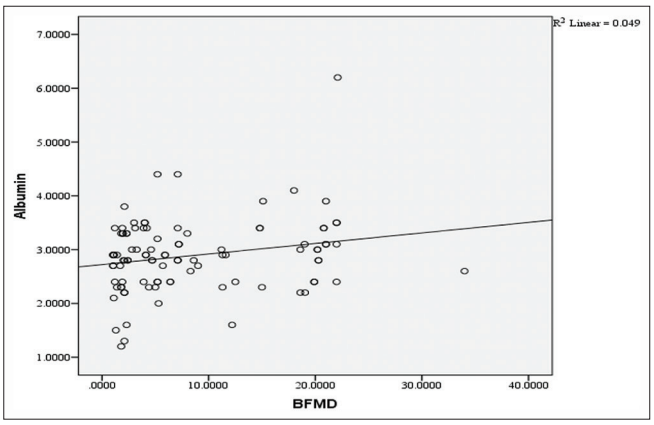

Figure 3: Scatter plot showing Positive correlation between bFMD (Brachial artery flow mediated vasodilatation) and Albumin

disease. Several factors have been proposed to explain the cardio-vascular risk in HIV positive patients, which include direct pro-athero-thrombotic viral effect, infection-mediated immune system dysfunction and possible deleterious effects of HAART.[3] As HIV patients exposed at an increased risk of future cardiovascular (CV) events. Hence it's important to identify reliable CV prognostic markers in HIV infected individuals

In this study, age group ranges from 18-68 years. Majority of the age group belongs to 30 to 40 years (40%). Mean age 41.5 ± 11.744 years. The sex wise frequency was 63% (males) and 37% (females). Microalbuminuria defined as UACR>30, in our study 14% had UACR <30 and 86% had UACR >30 and mean UACR is 90 ±06.This shows high prevalence of microalbuminuria, which indicates HIV infection had a strong and independent association with microalbuminuria. The high prevalence of microalbuminuria among the HIV infected could be a harbinger of future increased risks of both kidney and cardiovascular disease. In the study by Lyna anne szczech et al showed MA (UACR>30 mg/g) was present in 11% of HIV infected patients.[5]

In our study we assessed endothelial dysfunction by bFMD. In the study Mean BFMD was 8.44 ± 7.65. Prevalence of severely impaired endothelial function in HIV-treated patients, using a bFMD cut-off point of 2.1%, which corresponds to the 25th percentile of bFMD in the population of HIV-treated patients, we find that 25.6% of patients had a severe impairment of endothelial function. Study done by Michael P. Dube et al showed that mean FMD in subjects on HAART was 5.5±4.1%.[6]

Baseline characteristics

The mean value of various components in the study population as follows: Total cholesterol 212.3±30.9, Triglyceride 158±24, HDL 31.8±10.2, LDL 147.3±24.5,CD4 count 168±30.9 ,duration of HIV 4.1±3.35.In our study there was significant negative correlation found between bFMD and Total Cholesterol **(r=-0.558,P=<0.001)**, FMD and LDL**(r=-0.469,P=<0.001)** and Triglycerides**(r=-0.252,P=0.011)**, i.e. with increase in Total Cholesterol, LDL and Triglycerides there was significant decrease in bFMD and Vice versa.

There was significant positive correlation between bFMD and HDL**(r=0.313,P=0.002)**, FMD and CD4 count (**r=0.283,P=0.004**) i.e. with increase in HDL,CD4 count there was increase in bFMD and vice versa.

Pearson's correlation analysis is done between bFMD and UACR, which showed significant negative correlation between UACR and bFMD (**r= - 0.832, P=<0.001**) i.e. with increase in UACR there was decrease in bFMD, which suggests that there was progressively lower vasodilator function with increasing in UACR. In the study by pirro et al showed that in HIV patients on HAART, the prevalence of increased UACR, defined by two cut-off levels (20 mg/g and 30 mg/g), was 29% and 17%. UACR was significantly higher while bFMD was lower ($r = -0.31$; $p < 0.001$).[4]

Study done J P Singh et al on prevalence of microalbuminuria in HIV Patients opined that Microalbuminuria was present in 21% HIV patients with majority (60.87%) being in the age group 26-35 years. There was a significant correlation between CD4 count <200/ l and presence of microalbuminuria ($p = 0.01$).[7]

Anthony Solages et al studied endothelial dysfunction in HIV patients observed that HIV-infected persons have substantial impairment in endothelial vasomotor Function and that this impairment is worse among those with elevated levels of HIV replication, particularly intravenous drug users.[8]

Study conducted by Morten Baekken showed the prevalence of microalbuminuria is 2-4.7 times higher in HIV patients than normal healthy patients and the cause of microalbuminuria is most probably endothelial dysfunction and microalbuminuria is a prognostic risk factor in CAD.[9]

Our findings of an association between UACR and bFMD might confirm the recent trend of the scientific literature suggesting a role of endothelial dysfunction in causing microalbuminuria. Although there is overwhelming evidence of an association between UACR and endothelial dysfunction in different clinical settings, this association was little explored in HIV positive patients. This result might have an important prognostic implication if we consider that endothelial dysfunction is a recognized early surrogate marker of atherosclerosis-mediated CV risk.

Our finding suggest that measurement of UACR might be proposed for a more accurate CV risk estimation in HIV infected patients receiving HAART, irrespective of the presence or the absence of either diabetes, hypertension or both conditions

CONCLUSION

Measurements of UACR might help to identify HIV-treated patients with an impaired endothelial function. Use of urine albumin to creatinine ratio (UACR) as a routine screening tests in those who are HIV positive on HAART can be used to find out those cases of HIV who are progressing towards cardiovascular impairment so that newer approaches can be used in them to prevent further cardiovascular involvement.

Limitations of the study

Small sample size and single centre study

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Author's Contribution:
SBH-Concept and design of the study; manuscript preparation; **AHR**- Interpretation of results, reviewed the literature and manuscript preparation; **NAG**- Statistical analysis and interpretation, preparation of manuscript and revision of the manuscript; **AML-** Concept, coordination, review of literature and manuscript preparation.

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