Prevalence of Microalbuminuria and associated factors among HIV–infected ART naïve patients at Mulago hospital, Kampala, Uganda.

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Abstract

Background

The kidney is one of the common target organs for HIV infection. Early detection of microalbuminuria, the earliest marker of renal damage is critical to slowing down progression to end stage renal disease if appropriate intervention is made. The burden of microalbuminuria and its associated factors in HIV–infected ART naive patients has not been determined in Uganda.

Methods

A cross-sectional study was conducted in the Mulago Immune suppression syndrome (ISS) clinic on adult HIV–infected ART naïve outpatients. Data was collected on age, sex, level of education, marital status, religion, address, and history of alcohol intake, diabetes mellitus, hypertension, medications and smoking. Measurement of blood pressure, weight and height to determine body mass index (BMI) and investigations including complete blood count (CBC),serum urea and creatinine, Liver function tests(LFTs), CD4+ count, spot morning urine albumin and urine creatinine to determine microalbuminuria were conducted. Logistic regression was used to estimate the strength of association between variables.

Results

A total of 185 adult participants were consecutively enrolled into the study. The mean (SD) age was 34.2(±9.0) years and majority (63.8%) were female. The mean (SD) CD4+ count 466±357 cells/μL, and BMI 23.1 (±4.9) kg/m 2 . The prevalence of microalbuminuria was 18.9%. None of the participants had albuminuria. CD4+ count <350cells/μL and BM1<18.5kg/m 2 were associated increased risk of microalbuminuria OR 3.8 (95%CI 1.7-8.3) (p value=0.01) and OR 4.7 (95%CI 1.82-12.4) (p value=0.03) respectively. Diabetes mellitus, hypertension, smoking, alcohol intake were not found to be significantly associated with microalbuminuria.

Conclusion

Microalbuminuria was highly prevalent in adult HIV–infected ART patients especially those with low CD4+ count and low BMI. There is need to study the effect of ART on microalbuminuria in adult HIV–infected patients.

Key words: HIV, microalbuminuria, Uganda, ART naïve

Background

About 40 million people live with HIV with 2.1 million new infections occurring annually[1]. Almost 30 million of the world's HIV burden is in Africa with majority (26.1 million) in Sub-saharan Africa (SSA). Uganda's HIV prevalence is estimated at 7.3% and together with Nigeria and South Africa account for 48% of the world's new infections[1]. The kidney is one of the common target organs for HIV and has been

demonstrated as an important reservoir of HIV infection making renal disease one of the recognized complications [2–4].

Microalbuminuria is the earliest marker of renal dysfunction and predicts the development of proteinuria, a feature of renal disease[5]. Microalbuminuria therefore is the most effective way to identify increased risk of developing renal damage. Early detection of HIV associated renal disease is critical to slowing down progression to end stage renal disease which requires dialysis and renal transplantation both often not accessible in Uganda and sub-Saharan Africa at large. Prevalence of renal disease in HIV − infected antiretroviral therapy (ART) naïve patients in Uganda is unknown. There has not been any study on microalbuminuria in HIV-infected ART naïve patients in our setting.

We determined the prevalence of microalbuminuria and associated factors among adult HIV-infected ART naïve patients attending Mulago hospital ISS clinic using a cross-sectional design. We hope that this data generated will inform HIV care programs about the magnitude of microalbuminuria and perhaps incorporate its screening as one of the tests to assess kidney function in HIV-infected patients before ART initiation.

Methods

During the two months' period of March and April 2017, we conducted a cross-sectional study in the Mulago ISS clinic. It is one of the outpatient facilities for Mulago National Referral Hospital but also acts a research facility under the umbrella body of Makerere University Joint AIDS Program (MJAP). It is situated 2 kilometres from Kampala capital city, Uganda and receives an average of 5 new HIV − infected ART naïve patients daily. The Mulago ISS clinic was chosen for the study because it is accessed by the Kampala city residents but also represents a large portion of Ugandans all over the country that come to seek specialist care in Mulago National Referral Hospital. It runs five days a week (Monday to Friday) excluding public holidays, 8.00am to 5.00 pm.

Total sample size was 185. It was estimated using Kish Lesley (1965) formula on the basis of 14% prevalence of microalbuminuria based on recent estimates[6], 5% precision, 1.96 level of confidence and presumed prevalence of 19%. Only adults (18 years or older) who had had a confirmed positive HIV serological test with no prior ART and able to give written informed consent were consecutively enrolled. We excluded all participants who were either pregnant or had confirmed renal disease.

After an informed consent, a structured questionnaire was administered to the participants in a special recruitment room within in the clinic so as to provide utmost confidentiality. The data collected included social demographics (age, sex, address, occupation, level of education, marital status), alcohol intake, smoking and medical history of diabetes mellitus, hypertension and any other medications. We took physical measurements height and weight to determine BMI and blood pressure. Hypertension was defined by two blood pressure readings of a systolic of ≥ 140 mmHg and diastolic of ≥ 90mmhg taken 30 minutes apart by the triage team. Blood samples were obtained using venous phlebotomy for investigations including complete blood count, liver function tests for liver transaminases (Aspartate

aminotransferase [AST], Alanine aminotransferase [ALT]), and serum urea, serum creatinine and CD4 + count. Spot morning mid-stream urine was obtained in plain screw cap urine containers for urine albumin and urine creatinine analysis.

All blood samples were immediately taken for analysis to the Makerere Joint AIDS program laboratory which is ISO certified. Urine samples were transported in an ice packed cooler, transported every day to the Mulago hospital laboratory and stored in microvials. Microalbuminuria was estimated using the urine albumin creatinine ratio (UACR) formula. Urine albumin and urine creatinine were measured using the SELECTRA ProXL® chemical analyzer (ELITech group solutions, France).

Statistical analysis

All data was double entered into Epidata version 3.1, validated and cleaned. It was then exported to and analysed using SPSS software package version 19.0 (SPSS, Inc, Chicago, IL, USA).To determine the prevalence of microalbuminuria, we used the proportion of HIV-infected ART naive patients with microalbuminuria as the numerator and the total number of HIV-infected ART naïve patients in the study as the denominator. Microalbuminuria was taken as a random UACR of more than 30 mg (but less than 300 mg) of albumin per gram of creatinine [5]. The continuous variables (age, blood pressure, CD4 + count, BMI, urea, creatinine, AST, ALT) were explored, assessed for normality and summarised using means and standard deviations (SD). BMI and CD4 + count were further categorised into:

- BMI (kg/m^2)
  - <18.5
  - 5<25
  - ≥ 25
- CD4+ count (cell/μL)
  - <350
  - ≥350

Logistic regression was used to identify factors associated with microalbuminuria and the p values < 0.05 together with the odds ratios and their 95% confidence intervals as measures of association.
Ethics

Ethical approval was obtained from Makerere University School of Medicine Research and Ethics Committee as well as administrative permission from the Mulago ISS clinic management to conduct the study. All patients provided a written informed consent to take part in the study.

Results

Characteristics of participants

The 185 participants enrolled in the study were relatively younger with a mean (SD) age of 34.2(9.0) years, majority (63.8%, n = 118) of them being female, more than three quarters (84.3%, n = 156) from rural areas, with 91.9% holding informal jobs, 63.2% were not married and only 18(9.7%) having attained tertiary education. The baseline demographic and clinical characteristics of all study participants are summarised in Table 1.

Table 1
Baseline demographic and clinical characteristics of study participants (N = 185)

Variable	
Age (years) mean (SD)	34.2(9.0)
CD4 + count (cells/μL) mean(SD)	466(357)
BMI (kg/m^2) mean (SD)	23.1(4.9)
Haemoglobin (g/dL) mean (SD)	12.8(2.3)
Sex n (%)	
Female	118(63.8)
Address n (%)	
Urban	29(15.7)
Rural	156(84.3)
Occupation n (%)	
Informal	170(91.9)
Formal	15(18.1)
Level of education n (%)	
None	14(7.6)
Primary	91(49.2)
Secondary	62(33.5)
Tertiary	18(9.7)
Marital status n (%)	
Married	68(36.8)
Not married	117(63.2)
BMI (kg/m^2) n (%)	
< 18.5	21(11.4)
18.5 < 25	113(61.1)
≥ 25	51(27.6)

Prevalence of microalbuminuria

The prevalence of microalbuminuria in our study population was 18.9% (n = 35). None of the participants had albuminuria. The overall mean (SD) UACR of all the participants was 21.8 (20.6) mg/g. Among normal participants, the mean (SD) UACR was 14.7(6.6) mg/g while the mean UACR among participants with microalbuminuria was 51.9(31.0) mg/g.

Factors associated with microalbuminuria

Bivariate analysis of factors associated with microalbuminuria

The mean BMI was higher among participants with normal UACR than those with microalbuminuria. This difference was statistically significant, p value = 0.006. There were statistically significant differences among normal weight, underweight and overweight/obese participants (p value = 0.002). The odds of microalbuminuria among those with BMI < 18.5 kg/m^2 were 4.7 times (95%CI 1.82 – 12.4) those of normal weight. The mean CD4 + count was higher (500 cells/μL) among participants with normal UACR than those with microalbuminuria (320cells/μL). This difference was statistically significant, p value = 0.007. There were statistically significant differences between CD4 + count < 350 and ≥ 350 cells/μL (p value = 0.001). The odds of microalbuminuria among those with CD4 + count < 350cells/μL were 3.8times (95% CI 1.7 – 8.3) those of CD4 + count ≥ 350 cells/μL. There were no statistically significant differences in age, sex, urea, creatinine, AST, ALT, diabetes mellitus blood pressure, haemoglobin, alcohol use and smoking among those normal UACR and those with microalbuminuria. The factors associated with microalbuminuria were lower BMI and lower CD4 + count (Table 2)

Table 2

Bivariate analysis of factors associated with microalbuminuria

Variable	Normal UACR	Microalbuminuria	Chi-square	p value	Unadjusted OR(95% CI)
Age (years) mean (SD)	34(8.6)	35.1(10.5)		0.51	
BMI (kg/m^2) mean (SD)	23.6(5.0)	21.1(3.7)		0.006	
CD4 + count (cells/ µL)mean(SD)	500(362)	320(298)		0.007	
Urea (mmol/L)mean(SD)	2.5(0.5)	2.8(1.1)		0.30	
Creatinine mean(µmol/L) (SD)	59.1(16.0)	62.3(28.4)		0.08	
AST (IU/L)mean(SD)	29.2(14.1)	32.1(16.9)		0.28	
ALT (IU/L)mean(SD)	22.0(16.0)	21.9(12.8)		0.97	
Sex n (%)			3.3	0.07	
Male	59(39.3)	8(22.9)			Ref
Female	91(60.7)	27(77.1)			2.2(0.9–5.1)
Current alcohol use n (%)			0.1	0.83	
No	77(63.1)	17(65.4)			Ref
Yes	45(36.9)	9(34.6)			0.9(0.4–2.2)
Smoking n (%)			0.2	0.64	
No	143(95.3)	34(97.1)			Ref
Yes	7(4.7)	1(2.9)			0.6(0.1-5.0)
Blood pressure (mmHg) n (%)			0.6	0.43	
< 140/90 (Normal)	135(90)	33(94.3)			Ref
≥ 140/90 (High)	15(10)	2(5.7)			0.5(0.1–2.5)
BMI (kg/m^2) n (%)			12.7	0.002	
18.5 – 24.9 (normal)	93(62.0)	18(51.4)			ref
< 18.5(underweight)	12(8.0)	11(31.4)		0.002	4.7(1.8–12.4)
≥ 25 (overweight/obese)	45(30.0)	6(17.1)		0.4	0.7(0.3–1.9)

Variable	Normal UACR	Microalbuminuria	Chi-square	p value	Unadjusted OR(95% CI)
$CD4^+$ count (cells/μL) n(%)			11.8	0.001	
< 350	95(63.3)	11(31.4)			ref
≥ 350	55(36.7)	24(68.6)			3.8(1.7–8.3)

Multivariate analysis of factors associated with microalbuminuria

Factors found statistically significantly associated with microalbuminuria at multivariate logistic regression analysis were BMI < 18.5 kg/m^2 and CD4 + count < 350cell/μL, p value = 0.03 and 0.01 respectively with the adjusted OR 3.5 (95%CI 1.3 – 9.6) BMI < 18.5 kg/m^2 and 2.9 (95% CI 1.2 – 6.6) for CD4 + count < 350cell/μL (Table 3)

Table 3
Multivariate logistic regression analysis of factors associated with microalbuminuria

Variable	p value	Adjusted OR(95%CI)
BMI (kg/m^2)	0.03	
18.5 – 24.9 (normal)		Ref
< 18.5(underweight)	0.01	3.5(1.3 – 9.6)
≥ 25 (overweight/obese)	0.73	0.8(0.3 – 2.3)
CD4 + count (cells/μL)	0.01	
≥ 350		Ref
< 350		2.9(1.2 – 6.6)

Discussion

We found a high prevalence of microalbuminuria at 18.9% in HIV-infected ART naïve outpatients attending the Mulago ISS clinic. This high prevalence of microalbuminuria highlights the magnitude of early renal dysfunction in HIV-infected patients before ART initiation. This was different from most of the studies conducted in recent times [5–13].

Higher prevalence of microalbuminuria found in other areas of SSA; in South Africa the prevalence of microalbuminuria was found to be 24.0%[9], however, they included in-patients who have been reported to be at higher risk of microalbuminuria due to advanced HIV[14] compared to our study participants who

were outpatients. Another study in Tanzania demonstrated that advanced HIV disease was significantly associated with microalbuminuria at 28.8%, however, they included patients who were already on ART[12]. The only study done in Africa that looked at participants with similar characteristics (adult HIV ART naïve patients attending an outpatient clinic was in Tanzania demonstrated the highest recorded microalbuminuria at 70.2%[13]. However, they used test strips that have been found to have poorer validity and reliability[15] than spectrophotometry we used in our study and their patients had relatively lower mean CD4 + count compared to our study (200 versus 466 cells/μL). Notably, there were two studies in adults that demonstrated lower prevalence 8.9% [11]and 14% [6] in Democratic Republic of Congo (DRC) and USA respectively. Overall, the differences in screening methodologies and the clinical characteristics of study participants probably explain the varied results among studies in relation to our study.

We found that lower CD4 + count and low BMI were independently associated with microalbuminuria. Several studies have shown microalbuminuria being associated with reducing CD4 + counts. Our study looked at CD4 + count as continuous variable with microalbuminuria being associated with lower mean CD4 + count compared to normal UACR (320 versus 500 cells/μL, p value = 0.007). A prospective cohort study by Hadigan et al, those with microalbuminuria were more likely to have a CD4 + count < 200 cells/μL (p = 0.0003)[6]. In our study, when CD4 + count was analysed as a categorical variable, those with microalbuminuria were more likely to have CD4 + count < 350 cells/μL (p value = 0.001) even after adjusting for BMI. The relationship between microalbuminuria and underweight has not been established among adult HIV − infected patients. In our study microalbuminuria was associated with being underweight, a finding that was evident in other populations[16]. Hypertension, diabetes mellitus, smoking, alcohol consumption were not associated with microalbuminuria in our study yet they well known risk factors for renal disease. This perhaps would be due to the fact that majority of our participants didn't report or record any of the above or our sample size was not powered enough to find another association.

Our study is the first of its kind to document the burden of microalbuminuria in HIV-infected ART naïve outpatients in Uganda. Our study population was both from the urban and rural areas within Uganda and therefore the results can be generalised to HIV-infected outpatients before ART initiation elsewhere in Africa especially in SSA which has the highest burden of HIV infection. However, we had some limitations. Data on viral load used as a surrogate marker to assess viraemia in HIV disease and which has been cited as one of the predictors of microalbuminuria in HIV-infected patients[5], was not done due to financial constraints. Nevertheless, viral load is not routinely done for HIV-infected patients before ART initiation and only used in monitoring care. Furthermore, the magnitude of microalbuminuria may have been affected by microscopic haematuria and leucocyturia which were not assessed, although this has not well documented.

Conclusion

We found the prevalence of microalbuminuria in HIV − infected ART naïve patients was 18.9% and the associated factors were low BMI and low CD4 + count. We believe this study has enlightened the magnitude of the earliest form of renal dysfunction in HIV − infected ART naïve outpatients in Uganda. Therefore we recommend that all HIV-infected patients with CD4 + count < 350 cells/μL and BMI < 18.5 kg/m² should be assessed for microalbuminuria before ART initiation. Further studies are needed to assess the progression of microalbuminuria in HIV patients after initiation of ART.

List Of Abbreviations

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

ART: Antiretroviral therapy

BMI: Body mass index

CD: Cluster of differentiation

DRC: Democratic Republic of Congo

HIV: Human immunodeficiency virus

ISS: Immune suppression syndrome

MJAP: Makerere University Joint AIDS Program

UACR: Urine albumin creatinine ratio

USA: United States of America.

Declarations

Competing interest

The authors declare that they have no competing interests.

Authors' contributions

TK conceived and designed the study, participated in collection and supervision of clinical and biological data and drafting of the manuscript. TK, PBK, RK, IAB, GM performed analysis and interpretation of data.

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Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethical approval was obtained from Makerere University School of Medicine Research and Ethics Committee.

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