

Microalbuminuria in Children: A Comparative Study of HIV-Infected and Non-Infected Children in Jos, Nigeria

Marcia M Ihekaike^{1*},
Isaac E Ocheke²,
Stephen Oguche³

¹MBBS, Lecturer I, Department of Pediatrics, College of Medicine and Health Sciences, Bingham University/ Bingham University Teaching Hospital, Jos, Nigeria.

²MBBS, Professor, Department of Pediatrics, College of Medicine, University of Jos/ Jos University Teaching Hospital, Jos, Nigeria.

³BMBCH, Professor, Department of Pediatrics, College of Medicine, University of Jos/ Jos University Teaching Hospital, Jos, Nigeria.

*Corresponding Author

Dr. Marcia M Ihekaike,

Email: marciaihekaike@yahoo.com

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Abstract

Background and Aim: Kidney disease occurs frequently in human immunodeficiency virus (HIV) infected individuals and is a leading contributor to morbidity and mortality in patients with HIV. Early detection of kidney damage will aid in instituting interventional measures that could slow down or halt the progression of kidney disease. The aim of this study was to determine the prevalence and risk factors of microalbuminuria in HIV infected children in Jos, Nigeria and compare them with those of HIV negative children.

Methods: A total of 135 HIV infected and 135 HIV uninfected children aged 1-18 years were screened for microalbuminuria using microalbumin 2-1 combo test strips. Logistic regression analysis was used for determination of the association between microalbuminuria and various predicted risk factors.

Results: Thirty (22.2%) HIV infected and 13 (9.6%) uninfected children had microalbuminuria ($p = 0.001$). Logistic regression analysis showed that an increase in the WHO clinical stage was significantly associated with the presence of microalbuminuria in HIV infected children ($p = 0.004$).

Conclusion: The prevalence of microalbuminuria is higher in HIV infected children, as such the detection of microalbuminuria as early as possible in the course of the disease and prompt initiation of therapy are very important in our resource poor environment.

Keywords: Microalbuminuria; HIV; Children; Kidney.

Conflict of interest: The authors declare no conflict of interest.

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Introduction

HIV infection affects virtually every human organ including the kidneys (1). The prevalence of kidney disease in HIV infected populations ranges from 2.4% to 17%; hence, kidney disease is an important health issue in HIV infected patients (2). HIV-associated nephropathy (HIVAN) is the most common form of chronic kidney disease (CKD) in HIV infected patients, (3, 4) and is generally seen after five to eight years of infection with the virus (1). The condition was first reported in adults with HIV but has also been described in children (5, 6).

Proteinuria is the most common early manifestation of nephropathy in HIV infected individuals (3, 7). Thus, the measurement of urinary proteins, particularly albumin, is an important tool for the early detection of kidney injury in individuals with and without HIV (1). However, microalbuminuria, a term that describes urinary albumin concentrations below the threshold for traditional dipstick assessment of proteinuria, (8, 9) usually precedes proteinuria (3, 10). Thus, microalbuminuria is a pre-clinical marker of kidney damage (11, 12). A high

prevalence of microalbuminuria of 6.7% to 12% has been described in HIV infected Nigerian children (5, 8, 10). As an early indicator of glomerular injury, the presence of microalbuminuria indicates an increased risk of progressive renal damage and increased mortality; it is also widely accepted as a measurable marker of early kidney disease (13-15). Kidney disease in HIV infected individuals is now a leading contributor to morbidity and mortality in patients with HIV and acquired immune deficiency syndrome (AIDS) in the era of highly active antiretroviral therapy (15-17). The severity of HIV disease, duration of infection, and treatment with antiretroviral drugs are factors that could contribute to kidney damage and outcome (18, 19). In addition, kidney injury does occur with some of the antiretroviral agents such as tenofovir and ritonavir used in HIV (20).

Chronic kidney disease, particularly end stage renal disease (ESRD) pose enormous health challenges to patients and physicians (16, 17). Treatment of ESRD relies on dialysis and transplantation, which are very expensive and often inaccessible in the developing world. Consequently, preventive measures offer the greatest hope in the management of patients with chronic kidney disease (8, 21).

Early detection of kidney damage using microalbuminuria, a simple and relatively inexpensive procedure, will aid in instituting interventional measures that can slow down or halt the progression of renal disease (22, 23).

The findings of this work will add to the existing pool of knowledge on microalbuminuria in HIV infected children and could be used as an advocacy tool that could possibly lead to development of screening protocols for early detection of kidney diseases in the HIV infected children.

Alternate hypothesis: the risk factors for microalbuminuria are the same for both HIV infected and uninfected children in Jos.

Null hypothesis: there is no significant difference in the risk factors for microalbuminuria between HIV infected and uninfected children in Jos.

The aim of the study was to determine the prevalence and risk factors of microalbuminuria in HIV infected children in Jos, Nigeria and compare them with those of HIV negative children.

Methods

This study was conducted in the Jos University Teaching Hospital (JUTH) Plateau State, a tertiary

center catering for patients in the north central part of Nigeria. The participants were enrolled from the Pediatric AIDS Prevention Initiative in Nigeria (APIN) and outpatient clinics of the hospital.

Ethical approval was obtained from the Institutional Health Research and Ethics Committee. Written informed consent was obtained from the parents/care givers and verbal assent from subjects who were ≥ 7 years of age as at the time of the study. This cross-sectional comparative study was conducted between October 2016 and April 2017. The study participants were children with confirmed HIV infection using western blot test, and the controls were children from pediatric outpatient clinic who screened negative for HIV using the Alere Determine HIV-1/2 rapid test kit (Massachusetts, United States of America, batch number 72690K100A).

Inclusion criteria for subjects

- 1) HIV infected children aged 1- 18 years
- 2) Parental consent and child assent (if age ≥ 7 years)

Inclusion criteria for controls

- 1) HIV negative children aged 1- 18 years
- 2) Parental consent and child assent (if age ≥ 7 years)

Exclusion criteria for subjects and controls

- 1) Dipstick hematuria or proteinuria \geq trace
- 2) Sickle cell anemia, diabetes mellitus or hypertension
- 3) Fever (temperature $\geq 37.5^{\circ}\text{C}$) at presentation
- 4) Overt clinical signs and symptoms of renal disease or children on follow-up at the Pediatric Nephrology Clinic.

On enrolment of the HIV infected children, further clinical information such as the date of HIV diagnosis and the date of HAART commencement were obtained. The socioeconomic class was scored and classified based on the parents' educational status and occupation as described by Olusanya et al. (24) All subjects had clinical staging done using the WHO clinical staging method (25). The CD4 count was estimated using the flow cytometry method. The CD4% was used for children less than five years of age and was considered severely low at $<15\%$, moderately low at $15-24\%$ and normal at $>24\%$ (26). The CD4 count was used for children

five years old and above and considered severely low at <200 cells/ μl , moderately low at $200 - 500$ cells/ μl , and normal at 500 cells/ μl and above (26). Weight in kilograms was measured using a weighing scale (Seca weighing scale, model 786) with a sensitivity of 0.1kg . The subject while lightly dressed stood upright, looking straight ahead, with feet flat and together at the center of the weighing scale with arms hanging loosely at the sides. Height was measured using a stadiometer (Seca stadiometer, model 786) with a sensitivity of 0.1cm . Subjects were asked to stand erect barefoot, looking straight ahead with the occiput, scapulae, buttocks and heel touching the vertical board. A horizontal board was placed on the vertex and measurement was done. Heights less than -2SD for age and sex were considered stunted while heights between -2SD and $+2\text{SD}$ were considered normal (27).

The body mass index (BMI) was calculated using the weight in kilograms divided by the square of height in meters and charted for participants using the WHO body mass index chart (28). A BMI between -3SD and -2SD for age and sex was considered underweight, a BMI between -2SD and $+2\text{SD}$ was considered normal, a BMI between $+1\text{SD}$ and $+2\text{SD}$ was considered overweight, and a BMI greater than $+2\text{SD}$ was considered obese (28). All participants had their urine tested for microalbuminuria using the same urine sample with the Microalbumin 2-1 Combo strip (Teco Diagnostics Anaheim, California, United States of America, batch number 64773). The strip is specific for the measurement of albumin, creatinine and microalbumin to creatinine ratio in a random urine sample. Microalbuminuria was defined as 30 to 300 mg albumin/g creatinine.

Clinical information (historical, physical examination and laboratory) were entered into the data collection form designed separately for HIV positive and negative clients. This was then analyzed using the Software Package for Social Science (SPSS) version 21.0 for Windows. Continuous variables such as age, duration of HIV diagnosis, and duration of HAART treatment were analyzed and the results are expressed as mean and standard deviation. Comparison of mean values was done using t test. Chi-square test was used for categorical variables. P values of <0.05 were considered significant.

Results

The male: female ratio was $0.875:1$. The mean age of the participants was 10.7 ± 3.9 years for subjects and 10.6 ± 3.9 years for controls. The majority of both subjects and controls were in the lower socioeconomic class (Table 1).

Thirty (22.2%) subjects and 13 (9.6%) controls had microalbuminuria ($p = 0.001$). There was no significant difference in the nutrition and growth status of participants between the two groups with or without microalbuminuria. There was a significant difference in the WHO clinical stage ($p = 0.01$) between subjects with and without microalbuminuria (Table 2).

There was no significant difference in the duration of HIV infection between subjects with and without microalbuminuria (Table 3).

According to logistic regression analysis, WHO clinical staging was the only independent risk factor for microalbuminuria in the subjects (Table 4). There was no independent risk factor for microalbuminuria in the controls.

Discussion

The overall prevalence of microalbuminuria in HIV infected children in this study was 22.2%, which is consistent with previous studies from South Africa and Tanzania that reported prevalence rates of 25% and 20.4% respectively (29, 30). However, the observed rate was higher than that documented in earlier studies in Nigeria (3, 5, 8, 10). In Port Harcourt Nigeria, a study reported a prevalence rate of 12% (10). The difference in the prevalence rate between the present study and Port Harcourt study could be explained by the lower mean age and smaller sample size of fifty subjects in that study. The researchers in that study employed the use of early morning urine specimen whereas a spot urine specimen was used in the present study. Although transient causes of albuminuria are more likely to occur with a spot urine specimen, the measurement of urinary creatinine alongside the microalbumin test to obtain the ACR adjusted for these changes in this study. In another study in Kano, a prevalence of 6.7% was reported (8). This value is much lower than the prevalence in the present study. The difference may be because the Kano study was on the prevalence of persistent microalbuminuria unlike the present study where a single spot urine sample was used.

Table 1: General characteristics of the study participants

Age (years)	Subjects		Controls		χ^2/df^*	P
Factors	N (%) (n =135)	No. (%) with MA (n = 30)	N (%) (n =135)	No. (%) with MA (n = 13)		
Age in years					0.85/3	0.78
1-4	9 (6.7)	1 (11.1)	9 (6.7)	1 (11.1)		
5-9	40 (29.6)	7 (17.5)	42 (31.1)	5 (11.9)		
10-14	60 (44.4)	18 (30.0)	61 (44.4)	4 (6.6)		
15-18	26 (19.3)	4 (15.4)	23 (17.8)	3 (13.0)		
Sex					0.85/1	0.36
Male	63 (46.7)	17 (27.0)	63 (46.7)	6 (9.5)		
Female	72 (53.3)	13 (18.1)	72 (53.3)	7 (9.7)		
Social class					2.00/2	0.40
Lower	72 (53.3)	14 (19.4)	72 (53.3)	5 (6.9)		
Middle	35 (25.9)	6 (17.1)	32 (23.7)	6 (18.8)		
Upper	28 (20.8)	10 (35.7)	31 (23.0)	2 (6.5)		
Height					2.82/1	0.09
Normal	86 (63.7)	16 (28.6)	106 (78.5)	10 (9.4)		
Stunted	49 (36.3)	14 (18.6)	29 (21.5)	3 (10.3)		
BMI					0.90/2	0.55
Thinness	8 (5.9)	2 (25.0)	34 (25.2)	5 (14.7)		
Normal	118 (87.4)	27 (22.9)	94 (69.6)	8 (8.5)		
Overweight/obese	9 (6.7)	1 (11.1)	7 (5.2)	0 (0.0)		

(MA = microalbuminuria, * Prevalence of MA in Subjects versus Controls, df = degree of freedom, BMI = body mass index)

Table 2: Association between prevalence of microalbuminuria and severity of illness, and HAART status in subjects

Factor	Microalbuminuria		χ^2/df	P value
	Present No. (%) (n = 30)	Absent No. (%) (n = 105)		
WHO clinical stage[#]			11.8/1	0.01
Stage I	18 (16.4)	92 (83.6)		
Stage II	12 (48.0)	13 (52.0)		
CD4% /count			1.43/2	0.49
Severely low	3 (23.1)	10 (76.9)		
Moderately low	9 (30.0)	21 (70.0)		
Normal	18 (19.6)	74 (80.4)		
HAART status			0.018/1	0.89
On HAART	29 (22.1)	102 (77.9)		
Not on HAART	1 (25.0)	3 (75.0)		
Second line drugs			1.36/1	0.24
Yes	8 (30.8)	18 (69.2)		
No	22 (20.2)	87 (79.8)		

(NB: percentages add across, df = degree of freedom, HAART= highly active antiretroviral therapy, [#]no participant had stages 3 & 4, WHO= World Health Organisation.)

Table 3: Mean duration of infection, HAART usage and eGFR in microalbuminuria positive versus negative subjects

Variables	Microalbuminuria		T value	P value
	Present Mean \pm SD	Absent Mean \pm SD		
HIV infection duration (years)	8.6 \pm 3.9	7.7 \pm 3.4	1.2	0.22
Duration of HAART use (years)	8.4 \pm 3.3	8.4 \pm 3.3	1.4	0.16
eGFR	143.6 \pm 31.6	130.2 \pm 36.8	1.8	0.08

(eGFR= estimated glomerular filtration rate, HAART= highly active antiretroviral therapy)

Table 4: Logistic regression of microalbuminuria and predicted risk factors in subjects

Variables	OR (95% CI)	S.E	df	Coefficient	P value
Age	0.94 (0.65, 1.36)	0.189	1	-0.061	0.746
Sex	1.48 (0.55, 4.02)	0.509	1	0.394	0.439
Social class	0.45 (0.11, 1.81)	0.705	1	-0.790	0.262
BMI	1.80 (0.66, 4.93)	0.513	1	0.590	0.250
WHO stage	0.18 (0.05, 0.57)	0.593	1	-1.730	0.004
CD4 count	1.00 (1.00, 1.00)	0.001	1	-0.001	0.392
HAART status	2.58 (0.17, 40.08)	1.400	1	0.947	0.499
Duration of HIV infection	1.03 (0.69, 1.50)	0.197	1	0.015	0.938
Duration of HAART use	1.08 (0.72, 1.61)	0.203	1	0.076	0.708
Calculated GFR	1.01 (1.00,1.02)	0.070	1	0.010	0.139

(OR (95% CI) = Odds Ratio (95% Confidence Interval), S.E.= standard error, df= degree of freedom, BMI= body mass index, GFR= glomerular filtration rate, HAART= highly active antiretroviral therapy, WHO= World Health Organization)

Although the Kano study did not document the prevalence of microalbuminuria on the first contact, a similar study done by Hadigan et al (31) in Washington DC reported a prevalence of 17.6% for microalbuminuria on the first visit whereas only 8.2% had microalbuminuria on subsequent re-evaluations. The methodology in the Kano and Washington studies excluded transient causes of microalbuminuria such as postural changes and vigorous exercise, which were not excluded in this study.

The prevalence of microalbuminuria in HIV negative children was 9.6% in the present study, which was higher than the prevalence reported from other studies (6, 29). The difference in the rate between this study and the South African study (29) could be due to the lower mean age in that study. The observed prevalence rate of 9.6% was however lower than 33.2% reported by Okpere et al (14) among apparently healthy secondary school pupils in Port Harcourt. This difference could be due to a comparatively lower mean age in this study.

There was a significant difference in the prevalence of microalbuminuria between HIV infected and uninfected children in the current study (12.6%),

which was similar to a study on adults in Jos (14.5%) (21). This difference was however much lower than the difference of 24% reported from a study on South African children (29). This difference further confirms the understanding that HIV infection is a risk factor for microalbuminuria (19). Socioeconomic status did not affect the prevalence of microalbuminuria in this study, which was consistent with the findings of Okpere et al (14) in Port Harcourt. However, Isezuo et al (32) reported a higher prevalence of microalbuminuria in children from the upper socioeconomic class in Sokoto.

Microalbuminuria was significantly associated with an increase in the WHO clinical stage in both univariate and multiple logistic regression analyses in this study. This is comparable to the results of a study by Mistry et al (29) in South Africa who reported a higher prevalence of microalbuminuria in children with WHO clinical stages 2 and 3. On the contrary, Mudi et al (8) found no association between the clinical stage and microalbuminuria in their study in Kano.

In agreement with previous studies (8, 13), this study showed no significant association between

microalbuminuria and CD4% and CD4 count. Being that microalbuminuria has been reported in patients with low CD4 counts, it is noteworthy that there was a negative correlation between microalbuminuria and CD4 count in the present study. This is comparable with findings from previous studies (7, 33, 34).

The time since HIV diagnosis was longer among subjects with microalbuminuria than those without microalbuminuria but the difference was not significant. This longer duration was similar to findings from another study (31) and suggests that there could be progression of renal damage with longer duration of HIV infection.

Multiple logistic regression analysis showed that the odds of developing microalbuminuria decreased with an increase in the WHO clinical stage in HIV infected children. Similarly, Mosten et al (35) found that the presence of microalbuminuria was significantly associated with the severity of HIV disease progression according to WHO disease stage. No other factor was significantly associated with development of microalbuminuria in subjects or controls in this study.

Conclusion

The prevalence of microalbuminuria in HIV infected children was higher than that of HIV negative children in Jos, Nigeria. There was a significant association between the prevalence of microalbuminuria and the clinical stage of infection in the HIV infected children. We recommend routine screening of children with HIV infection for microalbuminuria for early detection and prevention of renal damage.

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Conflict of Interest

The author declares no conflicts of interest.

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Ethics

Ethical clearance was obtained from the Institutional Health Research and Ethics Committee

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