ORIGINAL ARTICLE

# Prevalence of Microalbuminuria and Proteinuria In Patients of HIV/AIDS in Jammu

**J.P. Singh, Sahil Kohli, Seema Jamwal, Rajkumar Sharma, Shazia Hamid, Sunil Raina, Aditya Singh Pawar**

**Abstract**

There is scarcity of Indian studies as far as the renal spectrum in HIV is concerned and there is no data regarding the detection of microalbuminuria and proteinuria in HIV positive patients in Jammu region. The present prospective study was conducted in the Postgraduate Department of Medicine, Government Medical College, Jammu over a period of 1 year on 108 HIV/AIDS patients, out of which 71% were males and 29% females with a male:female ratio of 2.48:1. Highest incidence of HIV/AIDS (55.56%) was found in the age group of 26-35 years. Microalbuminuria was present in 21% HIV patients with majority (60.87%) being in the age group 26-35 years. Prevalence of microalbuminuria among males was 65.22% and among females 34.78% with 83% patients having microalbuminuria/urinary creatinine ratio of >10 mg/mmol and 17% having this ratio <10 mg/mmol. There was a significant correlation between CD4 count <200/1 and presence of microalbuminuria ($p = 0.01$). Significant proteinuria (0.15-3 g/24 hour) was found in only 3 of those patients found positive for microalbuminuria. No patients had protein/creatinine ratio >3.5 (nephrotic range). Nephropathy is an important cause of morbidity and mortality in HIV positive patients. Use of microalbuminuria as a routine screening test in those who are HIV positive is recommended. Simple tests, like microalbuminuria, if applied in these patients in the very screening phase can help benefit the patients for years to come thereby helping in fighting the epidemic of HIV/AIDS in a better and a stronger way.

**Key Words**

HIV/AIDS, Microalbuminuria, Nephropathy

## Introduction

Survival among persons with HIV infection has improved significantly over last decade (1). Concurrent with the improvements in morbidity and mortality, there has been an increase in deaths among HIV infected patients attributed to liver and kidney disease (2). As a result, there has been increasing focus in research and clinical care on kidney conditions, which has improved our understanding of their pathogenesis as long-term complications of HIV infection.

Among the patients with diabetes mellitus, the presence of microalbuminuria is associated with risk of developing overt proteinuria and death and is considered a marker of progressive kidney disease. These associations suggest that microalbuminuria is probably a marker of early vascular damage related specifically to abnormal glycosylation in diabetes. Among HIV infected persons, the presence of proteinuria has been linked to CKD (chronic kidney disease), ESRD (end stage renal disease), new AIDS defining illness and mortality (3,4). The spectrum of renal involvement in HIV positive patients ranges from mild fluid and electrolyte disorders to acute renal failure and HIV associated nephropathy (HIVAN) leading thereby to end-stage renal disease (ESRD) (5). Hyponatremia has been reported in 30-60% of patients hospitalised with HIV infection (6,7). Volume depletion due to diarrhoea and vomiting is probably the cause of hyponatremia which is further contributed by syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (8). Both, hypokalemia and hyperkalemia are also seen commonly in patients infected with HIV. Cause of hypokalemia is usually the gastrointestinal losses of potassium in HIV-infected patients and is also contributed by tubular dysfunction caused by Amphotericin B used to treat fungal infection. Hyperkalemia is caused by high dose trimethoprim-sulfamethoxazole or intravenous pentamidine and can also result from acute or chronic

**From the PG Department of G. Medicine, Govt Medical College Jammu - J&K, India**

**Correspondence to :** Dr.J.P Singh, Associate Professor, PG Department of G. Medicine Govt Medical College, Jammu (J&K)-India.

kidney disease, or as a manifestation of mineralocorticoid deficiency due to adrenal insufficiency (9,10).

HIVAN is the third leading cause of ESRD in African-Americans between the age of 20 and 64 and the most common cause of ESRD in HIV-1 seropositive patients (11). Patients typically present with renal insufficiency accompanied by proteinuria that is usually in the nephrotic range (12). Despite the presence of heavy proteinuria, peripheral edema is uncommon. Hypertension is also surprisingly rare in most patients of HIVAN (13).

Microalbuminuria is the excretion of >30 mg and <300 mg of albumin in the urine/day or 20-200 g/minute on first morning spot urine sample not detectable by standard dipstick test for albumin. It is the earliest indicator of impending nephropathy. Microalbuminuria urea predicts overt proteinuria among patients with HIV infection. For convenience and consistency, the American Diabetes Association and the National Kidney Foundation has recommended measurement of albumin to creatinine ratio (ACR) in a random spot urine collection for diagnosis of microalbuminuria (14).

There is scarcity of Indian studies as far as the renal spectrum in HIV is concerned and there is no data regarding the detection of microalbuminuria and proteinuria in HIV positive patients in Jammu region. The present study covering this aspect of the HIV spectrum will benefit not only the patients of HIV/AIDS but also the treating physicians and society as a whole.

**Material and Methods**

The present prospective study was conducted in the Postgraduate Department of Medicine, Government Medical College, Jammu over a period of 1 year. The patients were selected for study from - (a) Voluntary Counselling and Testing Centre (VCTC), Government Medical College (GMC), Jammu; (b) Patients detected to be HIV positive while being treated in GMC and Associated Hospitals; and (c) Patients referred from various peripheral health institution to immunodeficiency clinic. A written and informed consent was taken from the subjects included in the study after nature of study was fully explained to them. In case of children, parental consent was taken for getting enrolled in the study. Basic information and details of the patients were recorded as per the proforma of the study. HIV positive status was established by detecting specific antibodies or detecting HIV and/or its components. Screening tests employed were Direct Sandwich Elisa Test Method (3rd generation) and Combaids-RS Test for Detecting HIV-1 and 2.

The subjects underwent various laboratory investigations like complete blood count, urine examination, urea, creatinine, uric acid, blood sugar, electrolytes like Na+, K+, Ca2+, serum bilirubin, SGOT, SGPT, alkaline phosphatase, serum proteins, total cholesterol, chest radiographs, ECG and ultrasound abdomen (where feasible).

Microalbumin urine test (MICRAL test), a semiquantitative immunological method for the detection of urinary albumin, was used in this study. Glomerular filtration rate (GFR) was derived from creatinine clearance calculated by Cockcroft Gualt formula.

*Exclusion Criteria*

Patients with pre-existing diseases like diabetes mellitus, hypertension, congestive cardiac failure or previous renal disease and those having urinary tract infection were excluded from the study.

**Results**

The present study was conducted on 108 HIV/AIDS patients, out of which 77 (71%) were males and 31 (29%) females with a male:female ratio of 2.48:1 (*Fig. 1*). Highest incidence of HIV/AIDS (55.56%) was found in the age group of 26-35 years, followed by 25.93% in 36-45 years (*Table 1*). Microalbuminuria was present in 23 (21%) HIV patients (*Fig. 2*) with majority (60.87%) being in the age group 26-35 years (*Table 2*). Prevalence of microalbuminuria among males was 65.22% and among females 34.78%. Microalbuminuria was further evaluated by calculating the ratio of microalbuminuria to urinary creatinine, 83% patients had this ratio >10 mg/mmol and 17% had this ratio <10 mg/mmol (*Fig. 3*). Chi-square test was used to calculate the significance of the correlation between CD4 count with the presence of microalbuminuria in HIV patients (*Table 3*). There was a significant correlation between CD4 count <200/ l and presence of microalbuminuria (p = 0.01). Significant proteinuria (0.15-3 g/24 hour) was found in only 3 (13.05%) of those patients found positive for microalbuminuria (*Table 4*). Protein/creatinine ratio was <0.2 in 20 patients, 3 had ratio in the range of 0.2-3.5 and none in the nephrotic range (>3.5) (*Fig. 4*).

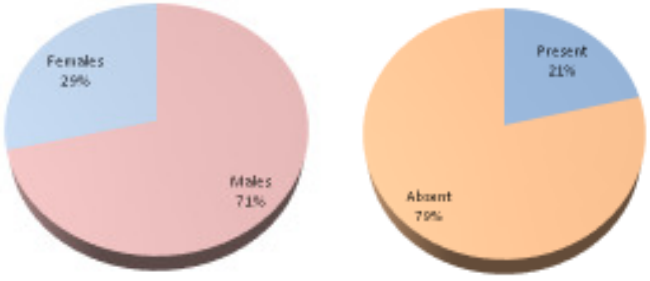


***Fig. 1. Sexwise Distribution of HIV/AIDS Patients &***
***Fig 2. Prevalence of Microalbuminuria in the Study Group***

*Fig. 3 Ratio of Microalbuminuria & Urinary Creatinine*

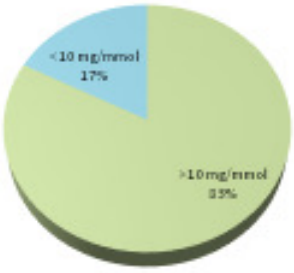


*Fig. 4 Urinary Protein/Creatinine Ratio*

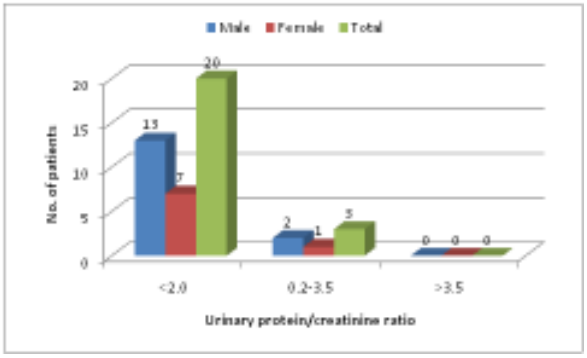


*Table 1 . Age & Sexwise Distribution of HIV/AIDS Patients*

| Age (in years) | Male No. (%) | Female No. (%) | Total No. (%) |
|---|---|---|---|
| 5 – 15 | 3 (2.78) | 2 (1.85) | 5 (4.63) |
| 16 – 25 | 1 (0.92) | 3 (2.78) | 4 (3.70) |
| 26 – 35 | 42 (38.89) | 18 (16.67) | 60 (55.56) |
| 36 – 45 | 22 (20.37) | 6 (5.56) | 28 (25.93) |
| 46 – 55 | 9 (8.33) | 2 (1.85) | 11 (10.18) |
| **Total** | **77 (71.29)** | **31 (28.71)** | **108 (100.00)** |

*Table 2. Agewise Distribution of Patients with Microalbuminuria*

| Age (in years) | HIV Patients No. (%) |
|---|---|
| 16 – 25 | 1 (4.35) |
| 26 – 35 | 14 (60.87) |
| 36 – 45 | 6 (26.09) |
| 46 – 55 | 2 (8.69) |
| **Total** | **23 (100.00)** |

*Table 3 . Correlation of CD4 cell Counts with the Presence of Microalbuminuria*

| $CD_4$ cell counts | Microalbuminuria (positive) No. (%) | Microalbuminuria (negative) No. (%) | Total No. (%) |
|---|---|---|---|
| <200/µl | 14 (12.96) | 28 (25.93) | 42 (38.89) |
| >200/µl | 9 (8.33) | 57 (52.78) | 66 (61.11) |
| **Total** | **23 (21.29)** | **85 (78.71)** | **108 (100.00)** |

*Table 4 . Urinary Protein Evaluation*

| Urinary protein | Male No. (%) | Female No. (%) | Total No. (%) |
|---|---|---|---|
| <0.15 g/24 hour | 13 (56.52) | 7 (30.43) | 20 (86.95) |
| 0.15 – 3 g/24 hour | 2 (8.70) | 1 (4.35) | 3 (13.05) |
| **Total** | **15 (65.22)** | **8 (34.78)** | **23 (100.00)** |

## Discussion

HIV associated nephropathy, the most common renal disease in HIV patients was first described in 1984 (15,16). Most patients present with nephrotic syndrome, progressive loss of renal function and without treatment progress to ESRD within weeks to months (17).

The present study was undertaken to detect the prevalence of microalbuminuria in 108 patients who were positive for HIV irrespective of the stage of illness. Out of these, 71.29% were males and 28.71%) females with male:female ratio of 2.48:1.

In a large Indian study done in Pune involving 2801 subjects over a period of 2 years, Ghate *et al.*(18) reported male:female ratio of 2.22:1. In another Indian study, Kumarasamy *et al.*(19) reported that out of 594 HIV/AIDS patients, 72.9% were males and 27.1% females, male:female ratio being 2.6:1, which is consistent with the present study.

Highest incidence of HIV/AIDS (55.5%) was found in the age group of 26-35 years in the present study, followed by 25.9% in 36-45 years age group. When the two age groups were clubbed from age 26 to 45 years, the incidence came out to be 81.47%. In a study by Ghate *et al.*(18), 88.1% HIV positive patients were in the age group of 21 to 40 years, which is almost consistent with the present study.

In the present study, prevalence of microalbuminuria was observed in 21.29% (23) patients after all 108 HIV/AIDS patients were screened for the presence of microalbuminuria. In a study on 72 HIV seropositive patients (3 symptomatic, 32 AIDS-related complex and 37 AIDS) screened for phase I clinical pharmacology studies, Luke *et al.*(20) found prevalence of microalbuminuria in 19.4% (14) patients.

However, Busch *et al.*(21) found 13% of the 90 HIV infected patients with an albumin excretion >20 mg/liter; Varma *et al.*(22) reported prevalence of 17.6% among 142 HIV patients over a 4 year period; and Monje *et al.*(23) identified prevalence of microalbuminuria in about 19% of the 48 HIV seropositive patients in different clinical states.

All 23 patients who tested positive for presence of microalbuminuria were further evaluated by 24 hour urinary protein evaluation and only 3 patients had proteinuria in the range of 0.15-3.0 g/24 hour. There was no patient with proteinuria >3 g/24 hour (nephrotic range). Further evaluation by urinary microalbumin to creatinine ratio on a spot sample of urine supported present study's finding of microalbuminuria in these patients. Nineteen patients had microalbumin:creatinine ratio >10 mg/mmol and 4 had this ratio <10 mg/mmol.

Clinical guidelines from KDOQI recommend that instead of a timed urine collection, a random urine sample for the microalbumin-creatinine or protein-creatinine ratio should be used to quantify proteinuria (14).

On initial evaluation, microalbuminuria was detected in only 16 (14.8%) patients. However, the test was repeated after 6 months and it was found that 7 new patients turned to be positive for microalbuminuria. The CD4 cell counts in these patients was evaluated and it was found that there was a fall in the CD4 cell counts in all of these 7 patients. The initial mean CD4 counts were 269.4 versus 174.71 at the time of a positive microalbuminuria i.e. a fall of 94.71/ l CD4 cell counts.

Mean CD4 cell counts was calculated in patients with positive micral test and 9 patients had mean CD4 cell counts > 200/ l, while 14 patients had mean CD4 counts <200/ l, average CD4 cell counts being 119.89/ l and 221.27/ l, respectively.In previous studies also, Szczech *et al*.(24) found decreased CD4 lymphocyte cell counts and increased HIV-RNA levels as predictors of proteinuria. Atta *et al.*(12) found that patients with HIV associated nephropathy had a significantly lower CD4 cell counts (158 l versus 349 l; $p < 0.01$) at the time of biopsy. Subclinical dysfunction is not uncommon in HIV positive patients and many of these patients with incipient nephropathy are not detected by routine laboratory tests. The patients at risk of developing renal dysfunction might, therefore, be detected by sensitive tests as early as possible. Current KDOQI guidelines recommend screening for kidney disease with a serum creatinine measurements for use in GFR estimatioin and analysis of a random urine sample for albuminuria.

Although HIV associated nephropathy is usually diagnosed late in the course of HIV infection, renal involvement can occur earlier, even during the acute retroviral syndrome prior to HIV antibody seroconversion. Until recently, the clinical course of HIVAN was one of inexorable progression to ESRD in 6-12 months, with limited treatment options. More options are now available to patients and include antiretroviral therapy, angiotensin converting enzyme inhibitors and steroid therapy.

HIV infection appears to be a risk factor for developing chronic kidney disease. Even in patients with normal kidney function, the presence of proteinuria may indicate early kidney disease. If initial urine analysis results are normal, annual follow-up urine analysis are recommended to screen for newly developed kidney damage for the following groups, which are at higher risk for the development of proteinuria and poor renal outcome - African-American persons, patients with diabetes, patients with hypertension, patient with hepatitis C virus coinfection and patients with HIV-RNA levels >4000 copies/ l or absolute CD4 lymphocyte counts <200/ l (25).An estimate of creatinine clearance for GFR is also recommended annually to screen for renal dysfunction that may develop overtime and that may herald worse overall prognosis.Recent reports have suggested that the baseline presence of proteinuria with or without concomitant elevations in the serum creatinine level, is a sensitive prognosticator of the eventual development of chronic kidney disease (26,27). Main limitations of the study were that firstly HIV-RNA levels would not be performed in all the cases due to the financial constraints and lack of the facility in the present institution. Secondly, those patients whose urine tested for positive for microalbuminuria could not be further evaluated due to absence of proper set-up for renal biopsy in the hospital.Once the diagnosis of HIVAN is made, various treatment options are there which can be started on an early basis to prevent further damage to the already compromised renal status of the patients. The various drugs available are HAART, ACE-inhibitors and steroid therapy.HAART appears to be the most powerful arsenal in the treatment of HIVAN (28). The ACE-inhibitors, captopril and fosinopril, have also been studied as a form of therapy for factor beta (TGF- ) which has been implicated in the pathogenesis of HIVAN. It has been suggested that ACE-inhibitors initiated early may offer renal survival benefits in HIVAN (29). The National Kidney Foundation have issued guidelines for the management of chronic kidney disease (CKD) in HIV-infected patients (30). They recommended that all the patients at the time of diagnosis of HIV be assessed for existing kidney disease with a screening urine analysis for proteinuria and a calculated estimate of renal function. Patients with HIVAN should be treated with HAART at diagnosis. Addition of ACE-inhibitors or angiotensin receptor blocking drugs should be considered if HAART alone does not result in improvement of renal function. Prednisolone should also be considered in those with refractory HIVAN.

Kidney disease is an important complications of HIV infection. Kidney function is abnormal in upto 30% of HIV infected patients. AIDS related kidney disease has become a relatively common cause of ESRD resulting in considerable morbidity and mortality in these patients. Thus, it becomes very important to identify these patients at risk for renal disease and implement potentially preventive and therapeutic strategies. Consequently, an understanding of the causes, epidemiology, screening methods and therapeutic strategies associated with CKD in HIV infected patients is required.

## Conclusion

Nephropathy is an important cause of morbidity and mortality in HIV positive patients. The routine laboratory measurements like serum creatinine and proteinuria fail to recognize the patients with early renal involvement. Use of microalbuminuria as a routine screening tests in those who are HIV positive are recommended. This will help in uncovering those cases of HIV who are heralding towards renal impairment so that newer approaches can be advocated in them to prevent further renal involvement. Simple tests, like microalbuminuria, if applied in these pattients in the very screening phase can help benefit the patients for years to come thereby helping in fighting the epidemic of HIV/AIDS in a better and a stronger way. More future studies are needed so that a systematic approach towards the management of these patients could be used in order to reduce the morbidity and mortality in those patients resulting from nephropathy.

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