

HIV-associated nephropathy in Saudi Arabia

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BACKGROUND AND OBJECTIVES: Human immunodeficiency virus-associated nephropathy (HIVAN) is the most common cause of chronic renal failure in HIV patients with African descent. It usually presents with proteinuria, enlarged kidneys, and rapidly progressive renal failure, often over several weeks to months. We conducted this study to determine the prevalence of HIVAN in our HIV population.

DESIGN AND SETTINGS: Cross-sectional observational study in a referral center covering the period of 1990–2010.

METHODS: Proteinuria and estimated glomerular filtration rate (e-GFR) were used to identify renal disease and suspicious cases of HIVAN with abnormal proteinuria and e-GFR of <60 mL/min/1.73 m².

RESULTS: Of 585 HIV-positive patients, 248 were eligible to inclusion criteria. Most of the patients were male, that is, 165 (67%) were male compared to 83 (33%) female with the mean age 39 years; 240 (96.7%) were on antiretroviral therapy. Thirty (12%) patients had abnormal proteinuria and 218 (88%) had normal urinary protein and e-GFR. No significant differences were observed in demographic data, CD4+ T-lymphocyte count, viral load, creatinine level, and e-GFR among both groups. Significant differences were observed in the prevalence of diabetes mellitus in the abnormal proteinuria group (10 patients [33.3%] compared to 30 patients [13.8%] in the normal group ($P=.0139$) and the prevalence of hypertension in the abnormal proteinuria group (11 patients [36.7%] compared to 22 patients [10%] in the normal group ($P=.002$)). Sixteen patients (6.6% of the cohort) met the study definition of HIVAN.

CONCLUSION: The prevalence of abnormal proteinuria and HIVAN among HIV-infected patients in Saudi Arabia is higher than that of non-African patients in developed countries.

Kidney disease in human immunodeficiency virus type 1 (HIV-1)-infected patients has been recognized since the early years of the acquired immune deficiency syndrome (AIDS).^{1,2} Various forms of the disease—that are directly related to the viral infection—have been described. HIV-associated nephropathy (HIVAN) is the most common cause of chronic renal failure in HIV-infected patients, characterized by collapsing focal segmental glomerulosclerosis. The peak incidence of HIVAN leading to end-stage renal disease (ESRD) requiring dialysis occurred in the mid-1990s and remained stable after an initial decline. In 1995, highly active antiretroviral therapy (HAART) became widely available, resulting in declining rates of AIDS-related morbidity and mortality. However, the number of patients who are at risk for developing HIVAN living with HIV infection or AIDS has increased.³ The 1- and 2-year survival of HIV-infected blacks undergoing hemodialysis during the HAART

era was 63% and 43%, respectively. These rates are significantly lower than the 1- and 2-year survival of 80% and 68%, respectively, among non-HIV-infected blacks undergoing dialysis.⁴

HIVAN is an almost exclusive disorder of individuals of African descent in reports from developed countries. This implied the existence of a genetic relation. The prevalence of HIVAN in this population has ranged from 3% to 12%.⁵⁻¹¹ Because of the lack of definitive diagnosis of HIVAN by kidney biopsy, most studies estimate renal involvement in HIV-1-infected individuals rather than true prevalence of HIVAN.

Patients usually present with proteinuria, enlarged kidneys, and rapidly progressive renal failure often over the span of several weeks to months.^{2,7,12} Lower-extremity edema and hypertension are uncommon, and their absence may contribute to delayed diagnosis. Detectable viremia is a typical feature, and the diagnosis is very unlikely if HIV-1 RNA level is <400 copies/

mL.⁴ It was previously thought to develop in those with advanced AIDS. In the post-HAART era, however, patients are presenting earlier in their course of HIV with CD4+ T-lymphocyte counts over 200.¹³ Screening tools for chronic kidney disease in HIV-infected persons are limited and predominantly center on glomerular filtration rate (GFR) estimation and proteinuria assessment.^{14,15} Regular screening is important because of the asymptomatic presentation of most kidney diseases. Although clinical diagnosis can be made in some patients, definitive diagnosis of HIVAN is only possible through kidney biopsy.

Data on HIVAN- and HIV-related kidney disease in Saudi Arabia and the region are lacking. Therefore, we chose to perform this study to determine the prevalence of proteinuria and HIVAN in our population by using simple an easy screening method for early detection of this disease that is associated with significant morbidity and mortality.

METHODS

In a cross-sectional study of all adult (more than 14 years) HIV-infected patients followed at King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, from 1990 till 2010, we aimed to determine the prevalence rate of proteinuria and HIVAN among HIV-infected Saudi patients. For the purpose of this study, we defined a suspicious case of HIVAN according to National Kidney Foundation practice guidelines for definition of chronic kidney disease¹⁶ as follows: abnormal proteinuria, either a protein/creatinine ratio above 0.2 (equal 200 mg/day) or albumin/creatinine ratio above 0.02 and 0.03 for male and female, respectively, renal dysfunction with estimated GFR (e-GFR) <60 mL/min/1.73 m² for 3 months or more, and no other reason for proteinuria. The e-GFR was calculated according to the Modification of Diet in Renal Disease method. Inclusion criteria were: HIV infection, age more than 14 years, and follow-up data available between 1990 and 2010. However, patients known to have chronic kidney disease (e-GFR <60 mL/min/1.73 m²) before the diagnosis of HIV infection were excluded. Patients' demographic data, HIV viral load, infection risk factors as diabetes which defined according to American Diabetic Association as: symptoms of diabetes plus random plasma glucose concentration ≥200 mg/dL (11.1 mmol/L) or fasting plasma glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours or 2 hours post load glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test. Hypertension is defined according to American Heart Association as blood pressure of 140

over 90 or higher. Viral hepatitis B and C and CD4+ T-lymphocyte cell count were collected from main database for the HIV Program or the hospital electronic record and/or the patients' medical records.

The statistical analysis of data was done by using the software package SAS version 9.3 (Statistical Analysis System, SAS Institute Inc., Cary, NC, USA). Descriptive statistics for the continuous variables were reported as mean (standard deviation) and categorical variables were summarized as frequencies and percentages. All continuous values were compared by using independent *t* test, and categorical variables were compared by chi-square test and Fisher exact test. Univariate and multivariate logistic regression analyses were used to define the major risk factors that contribute significantly to the development of proteinuria and HIVAN. The level of statistical significance was set at *P*<.05. The project was approved by the Institutional Review Board, (RAC # 2101044).

RESULTS

Between 1990 and 2010, 585 HIV-infected patients were enrolled in the HIV Program at King Faisal Specialist Hospital and Research Centre, Riyadh. A total of 13 patients were not eligible by inclusion criteria. Of these, 10 patients were aged less than 14 years and 3 had ESRD before the diagnosis of HIV infection. A total of 324 patients were excluded because the data on proteinuria were not available due to either normal renal function, loss to follow up, transfer of care, or death. A total of 248 patients who were eligible by inclusion criteria constituted the cohort of this report. The male to female ratio was 1.99:1. The mean age was 39 years (10.5) (median 40, range 15-68 years) (Table 1). All but 8 patients (240 or 97%) received HAART. A total of 159 (64%) patients had the plasma HIV RNA level below the limit of detection, and all of them were on HAART.

Thirty patients (12%) had abnormal proteinuria, and only 2 patients had e-GFR below 60 mL/min/1.73 m², while 218 patients (88%) had normal urinary protein and e-GFR. All the variables, i.e., age, CD4+ T-lymphocyte cell count at diagnosis of HIV, creatinine, e-GFR, viral load, and current CD4+ T-lymphocyte cell count were compared between the 2 groups, and there were no significant difference (Table 2). The risk factors of chronic kidney diseases (diabetes mellitus, hypertension, hepatitis B virus, and hepatitis C virus) were compared between the 2 groups. Diabetes mellitus was significantly higher in the proteinuria group that included 10 patients (33.3%), while the non-proteinuria group included 30 patients (13.76%) with

significant *P* value .0139 (Table 3). Hypertension was also significantly higher in the proteinuria group that included 11 patients (36.7%), while the non-proteinuria group included 22 patients (10%) with significant *P* value .0029. Seven patients had both diabetes and hypertension. The odds ratio of proteinuria among hypertension patients was fourfold with 95% CI of 1.6–10.3. On multivariate logistic regression of the risk factors, we found hypertension alone to have significant impact on proteinuria. Sixteen patients (6.6%) of the entire cohort had proteinuria without any specific reason, and could be related to HIVAN. No biopsy was done for any patient in this observation study.

DISCUSSION

The improvement in survival of HIV-infected patients means more people are living with HIV. It also resulted in more chronic diseases among people living with HIV. One of the common chronic illnesses in the HIV-infected population is chronic kidney diseases. Renal disease in HIV-infected patients was noted in 1984, only few years after the first cases of AIDS were reported.³ Chronic kidney disease and HIVAN have negative impact on HIV patients. One of the earliest signs for HIVAN is abnormal protein in the urine. By using simple non-invasive screening methods, early detection, and subsequent intervention may alter the course of renal disease in HIV-infected patients. The Infectious Diseases Society of America has published guidelines for the management of chronic kidney disease in HIV-infected patients. Screening for renal disease and proteinuria is recommended for the diagnosis of HIV infection and follow-up.¹⁴

Our report using proteinuria and e-GFR as a screening method for the detection of HIVAN is the first from our country and the region as a whole. The data obtained were as follows: 12% of the HIV-infected cohort was with abnormal proteinuria, and 6.6% with possible HIVAN. These values obtained for the Saudi population were comparatively higher than those for non-African Westerns and lower than those for Africans. Msango et al looked for prevalence of renal dysfunction among HIV patients in Tanzania without risk factors for chronic kidney disease such as hypertension, diabetes mellitus, or hepatitis C infection. They found 85% of patients had evidence of renal dysfunction as defined by an e-GFR below 90 mL/min/1.73 m² or an e-GFR above 90 mL/min/1.73 m² with proteinuria or microalbuminuria. For e-GFRs of 30–59 mL/min/1.73 m², the prevalence was 25%. The prevalence of microalbuminuria was 72% and that of proteinuria was 36%.¹⁶ These high rates were found

Table 1. Basic demographics of study population.

Variable	Mean	SD
Age (in y)	39.9	10.52
CD4 + T-lymphocytes at HIV diagnosis	307	270
Current CD4 + T-lymphocytes	641	781
Current viral load ^a (copies/mL)	47 317	137 639
Urine protein/creatinine	0.16	0.393
Urine albumin/creatinine	0.071	0.266
Creatinine (mmol/L)	66.0	16.64

HIV: Human immunodeficiency virus.

^aAmong 89 patients who had detectable HIV viral load on last follow-up.

Table 2. The means of different variables in patients with and without proteinuria.

Variable	Proteinuria n=30	No Proteinuria n=218	<i>P</i> value
Mean age (in y)	42	39	.1950
Mean CD4+ T-lymphocytes at HIV diagnosis	304	307	.9601
Urinary protein/creatinine	0.689	0.092	.0087
Urinary albumin/creatinine	0.449	0.009	.1407
Creatinine (mmol/L)	74	65	.0831
Mean eGFR mL/min/1.73 m ²	58	60	.2415
Mean viral load (copies/mL)	102 531	35 215	.2079
Mean current CD4+ T-lymphocytes	850	612	.5285

HIV: Human immunodeficiency virus, e-GFR: estimated glomerular filtration rate.

Table 3. Proportions with risk factors in patients with and without proteinuria.

Risk factor	Proteinuria n=30 n (%)	No Proteinuria n=218 n (%)	<i>P</i> value
Diabetes mellitus	10 (33.3)	30 (13.8)	.01
Hypertension	11 (36.7)	22 (10)	.002
Hepatitis B virus infection	0	4 (1.9)	NS
Hepatitis C virus infection	3 (10)	18 (8.3)	NS

NS: Not significant.

even when risk factors of chronic kidney disease were excluded. Whether the high prevalence rate of renal dysfunction among HIV patients in Tanzania was because of genetic predisposition (as HIVAN was more prevalent in Africans) or because they were HAART-naïve was not clear.

Given the high prevalence rates of diabetes mellitus and hypertension in our population, and the recent recommendations to use tenofovir as one of the first antiretroviral agents in HIV-infected patients, renal disease in HIV-infected patients is a real concern. The current health care system in Saudi Arabia is strained by the ever-increasing demands on renal replacement therapy.^{17,18} To add HIV-infected patients would definitely increase the burden.

Our report had a few limitations. The lack of renal biopsy precluded the exact measure of HIVAN based on histopathology. Since all the patients with isolated proteinuria had mild proteinuria (less than 1.5 gm/day) and normal e-GFR, renal biopsy was not just-

fied. Besides, other reports used "clinical criteria" to define HIVAN when renal biopsy was not performed.¹⁹ Another limitation is that our patient population was relatively small. As the excluded patients had normal e-GFR, the actual rate of HIVAN could be significantly lower than 6.6%. We currently care for almost 20% of the reported HIV-infected Saudis. We have no reason not to consider our data generalizable to the rest of HIV-infected Saudi patients. Finally, the majority of our patients were on antiretroviral therapy, and the mean CD4+ T-lymphocyte count was above 200/ μ L. So the rates of proteinuria and HIVAN may be higher in treatment-naïve and advanced HIV-infected patients.

In conclusion, the prevalence of proteinuria and HIVAN among HIV-infected patients in Saudi Arabia is higher than non-African patients. Screening HIV-infected patients for proteinuria and initiating antiretroviral therapy is essential for early detection and preventing further damage to the renal function.

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