Frequency and associated factors of proteinuria in Iranian HIV-positive patients

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Summary
Background: Screening HIV-positive patients for proteinuria would result in early recognition of HIV-associated nephropathy (HIVAN). This would allow diagnosis and treatment of HIVAN at an early stage and hence prevent further disease progression. This study was undertaken to determine the frequency of proteinuria and its associated factors in Iranian HIV-positive patients.

Methods: In this study, 171 HIV-positive patients were screened for proteinuria. Proteinuria was defined as ≥1+ protein on the urine dipstick. A questionnaire was used to collect patient sociodemographic and clinical data. Hepatitis B surface antigen (HBsAg), hepatitis C antibody (anti-HCV), serum albumin, and creatinine were tested in all patients. CD4 counts were obtained by flow cytometry.

Results: Out of 171 HIV-positive patients, 21 (12.3%) had proteinuria. There were no significant differences between patients with and without proteinuria with regard to age, sex, risk behaviors for HIV acquisition, stage of infection, concurrent antiretroviral therapy, systolic and diastolic blood pressure, serum albumin and creatinine, glomerular filtration rate (GFR), and presence of anti-HCV or HBsAg. Patients with proteinuria had a lower CD4 count and creatinine clearance than those without proteinuria.

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Introduction

Currently the total number of people living with HIV in the Middle East and North Africa is 540,000. Approximately 92,000 individuals were newly infected in 2004 and 28,000 people died of AIDS during the same time period. With the increasing spread of sexually transmitted infections (STIs), injection drug users (IDUs), numbers of unemployed youths, a conservative culture, and low awareness of HIV, the region is especially vulnerable to a large-scale epidemic. 1

A significant prevalence of renal disease exists in the HIV seropositive outpatient population. 2 The renal disorders in HIV infection can be broken down into three large groups including HIV-specific glomerulopathy, acute renal failure syndromes, and fluid/electrolytes and acid–base disorders of HIV. 3

Classic HIV-associated nephropathy (HIVAN) is characterized by nephrotic range proteinuria, renal dysfunction, and rapidly progressing renal insufficiency (before the introduction of highly active antiretroviral therapy [HAART]), the mean time from presentation to the onset of end-stage renal disease (ESRD) was less than 6 months. Eighty-eight percent of cases are in blacks in the 20–64 years age group. Hematuria, gross or microscopic, although described, is not a classic feature. Patients are often normotensive and normovolemic. 3

While an understanding of the epidemiology and clinical course of HIVAN is growing, little is known about the risk factors and clinical course of the other renal diseases that may also occur as a complication of HIV infection. 4 HIVAN can be an initial presentation of HIV infection; however, HIV is usually advanced when the diagnosis is made. Winston et al. studied 20 seropositive, predominantly African American patients presenting with proteinuria and azotemia. They found that the mean CD4 count was 60/mm³; none of the patients had a CD4 count greater than 200/mm³. They also reviewed six studies reporting CD4 counts in patients with a diagnosis of HIVAN, and found that the majority of patients had CD4 counts less than 200/mm³. 5 Many reports suggest that black race, 6–13 Haitian background, 14 male gender, 8 injection drug use, 6–14 and a decreased CD4 cell count 15 are risk factors for the development of HIVAN.

Microalbuminuria may be an early marker of HIVAN, and screening for its presence may be beneficial. Renal biopsy may be considered in seropositive patients who present with persistent microalbuminuria, especially with low CD4 counts irrespective of good renal function. This will allow diagnosis and treatment of HIVAN at an early stage and may prevent further disease progression. 16

Screening HIV patients for proteinuria would result in early recognition of HIVAN or precursor lesions. Therefore, screening asymptomatic patients for proteinuria and early intervention with angiotensin-converting enzyme (ACE) inhibitors and HAART should be considered. 3 However, there are no HIV/AIDS epidemiological data available specific for the Middle East, and surveys conducted in a large area including the Middle East are lacking. 1 This study was undertaken to determine the frequency of proteinuria and its associated factors in Iranian HIV-positive patients.

Patients and methods

In this cross-sectional study, 171 HIV-positive patients referred to the behavioral disease consulting center in Tehran, Iran from December 2005 through December 2006, were screened for proteinuria. The study enrolled patients with HIV infection tested with two enzyme-linked immunosorbent assays (ELISA) and confirmed with Western blot.

Proteinuria measurement was done in the absence of pregnancy, menstruation, fever, or urinary tract infection. Informed consents were obtained from all subjects. A questionnaire was used to collect sociodemographic data, medical history, nephrotoxic and antihypertensive drugs consumption, antiretroviral medication, stage of the infection (HIV/AIDS), and high-risk behaviors for HIV acquisition. A physician checked systolic and diastolic blood pressures.

All patients were also tested for hepatitis B surface antigen (HBsAg) and hepatitis C antibody (anti-HCV) by ELISA. The commercial HBsAg and anti-HCV enzyme immunoassay kits were from Hepanosticka Biomerieux, The Netherlands and Biorad, Italy, respectively. A recombinant immunoblot assay (RIBA Innogenetics, Ghent, Belgium) was employed to confirm anti-HCV reactivity.

In all patients CD4 lymphocyte counts were done by flow cytometry and defined as cells/mm³. Serum albumin and creatinine were also tested in all patients. Estimated creatinine clearance and glomerular filtration rate (GFR) were calculated using the Cockcroft–Gault equation 17 and simplified MDRD (Modification of Diet in Renal Disease study), 18 respectively.

Proteinuria was defined as ≥1+ protein on the urine dipstick. Antiretroviral medication was coded as: (1) none, (2) antiretroviral medications from nucleoside reverse transcriptase inhibitors (NRTI), and (3) combination therapy (more than one antiretroviral agent including at least one PI [protease inhibitor]). None of our subjects had received nephrotoxic antiretroviral medications like indinavir and tenofovir.

Statistical analysis

Chi-square and t² tests were used with the SPSS 11.5 program for statistical analysis. Data are presented as means ± standard deviations or, when indicated, as absolute number and percentage. A p value of <0.05 was considered significant.

Results

A total of 171 HIV-positive patients were enrolled in our study; 80.7% of them were male and 19.3% were female with
a mean age 37 ± 9.16 years. None of them had a history of diseases that affect renal function such as diabetes mellitus. Also none of them had consumed nephrotoxic and/or anti-hypertensive drugs. Of the patients, 52% were HIV-infected and 48% had clinical AIDS. Their mean systolic blood pressure (SBP) was 113.46 ± 14.25 and mean diastolic blood pressure (DBP) was 71.64 ± 9.42. One hundred and four patients (60.8%) had received no antiretroviral medication; 4.1% and 35.1% had received NRTI and combination therapy, respectively. Their serum albumin ranged between 2.50 and 5.80 g/dl (mean 4.6 ± 0.60) and serum creatinine ranged between 0.4 and 1.8 mg/dl (mean 0.92 ± 0.2). The CD4 lymphocytes were between 30 and 985.4 cell/mm³ (mean 388.5 ± 220.7). HBsAg and anti-HCV were positive in 7.0% and 52.6% of patients, respectively. Of the patients, 68.4% were IDUs, 19.3% heterosexual, 0.6% homosexual, and 4.1% had received infected blood and blood products; for 7.6% the means of HIV acquisition was not identified.

Proteinuria was detected in 12.3% (n = 21; 95% CI 7.1–16.9) of the patients using the urine dipstick. Demographic and clinical characteristics of patients with and without proteinuria are summarized in Table 1.

There were no significant differences between patients with and without proteinuria with regard to age, sex, risk behaviors for HIV acquisition, stage of the infection, concurrent antiretroviral therapy, systolic and diastolic blood pressure, serum albumin and creatinine, GFR, and presence of anti-HCV or HBsAg. However, patients with proteinuria had a lower CD4 count (336.66 ± 196.40 vs. 494.90 ± 223.26 cells/mm³, p < 0.05) and creatinine clearance (84.9 ± 30.6 vs. 102.4 ± 28.8 ml/min, p < 0.05) than those without proteinuria.

### Discussion

This study examined the frequency and associated factors of proteinuria among Iranian HIV-positive patients. Proteinuria was present in 12.3% of the patients. It was associated with lower CD4 counts and creatinine clearance, but was not related to age, sex, risk behaviors for HIV acquisition, stage of the infection, concurrent antiretroviral therapy, systolic and diastolic blood pressure, serum albumin and creatinine, GFR, and the presence of anti-HCV or HBsAg. This relatively high prevalence of proteinuria shows that renal disorders are prevalent in HIV-positive patients. Because we did not perform renal biopsy, it is not possible to determine whether proteinuric subjects had HIVAN or some other type of nephropathy. A study by Ghahramani et al. showed significant proteinuria (>1 g/dl) among 4.4%, and proteinuria of >150 mg/dl among 33.1% of Iranian kidney donors. However, the explanation of these findings needs further study with more sensitive methods, in different Iranian groups. We used a single measurement method for proteinuria (urine dipstick), and hence the prevalence of proteinuria could change in the study cohort if a different method was used.
HIV infection is associated with several renal syndromes, including acute renal failure. Chronic renal failure directly linked to HIV infection includes thrombotic microangiopathic renal diseases, immune-mediated glomerulonephritides, and HIVAN. The most common cause of chronic renal failure in HIV-1 seropositive patients is HIVAN. It is known that the screening of all HIV-infected patients for proteinuria would result in early recognition of HIVAN or a precursor lesion.2

Hailemariam et al. showed clinical signs of nephropathy in 36% of HIV-infected patients, including proteinuria (18%), abnormal urinary sediment (19.5%), and renal insufficiency (11%).20 Gardner et al. reported that of 64 HIV-positive women with renal abnormalities, 46 had proteinuria and 32 had high serum creatinine. HIV-infected women with renal abnormalities did not differ from those without renal abnormalities with regard to percentage using antiretroviral therapy, mean log viral load, or mean CD4 cell count.21

Atta et al. showed that patients with HIVAN had significantly higher creatinine and lower CD4 counts at the time of biopsy than those without HIVAN. Injection drug use, presence of hepatitis C, and hypertension were not associated with HIVAN.22 Crowley et al. showed that 14% of HIV-infected patients had >1+ persistent proteinuria. The average CD4 count in the proteinuria group was 180 vs. 280 in the group without proteinuria.24 Szczech et al. reported that in HIV-positive women, the prevalence of asymptomatic proteinuria was 32%. Predictors of proteinuria included increasing viral load, black race, CD4 count <200/mm3, and presence of hepatitis C. HBsAg positivity and serum creatinine levels were not significantly different between patients with and without proteinuria.24

Some reports have suggested that injection drug use8—11 may be a risk factor for HIVAN, but this likely represents confounding with other epidemiologic factors from the early stages of the HIV epidemic.25 Although male sex has also been reported as a risk factor,6 the incidence of HIVAN in black women is increasing proportionately to the escalating rate of HIV infection in this group36,27 strongly suggesting that HIVAN is not sex-specific.23 A large series of patients with HIVAN confirmed that sex, risk factors for HIV acquisition, and CD4 lymphocyte count at the time of diagnosis are not as significant as previously described.28

These conflicting results may be related to various factors such as the HIV infection rate in the general population, the size of the study group, and the demographic and clinical features of the patients. As mentioned before, data on the incidence and prognostic significance of renal dysfunction in HIV disease are limited,21 and there were no HIV/AIDS epidemiological data available specific for the Middle East, especially regarding renal complications of HIV infection.1 So our study could define some epidemiological aspects of renal disorders in HIV-positive patients in this important area. Our findings support the hypotheses regarding the need for better monitoring and more aggressive treatment of HIV-infected patients with lower CD4 counts.29

In conclusion, proteinuria was relatively high in Iranian HIV-positive patients. The group at higher risk was that of patients with lower CD4 counts and creatinine clearance. A greater understanding of the risk factors and clinical modifying factors for HIV-related renal diseases is essential.

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Conflict of interest: No conflict of interest to declare.

References


