European Review for Medical and Pharmacological Sciences 2013; 17: 2660-2667

Kidney disease in HIV-infected patients

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Abstract. – The introduction of highly active antiretroviral therapy (HAART) has reduced mortality and improved life expectancy of HIV-positive patients. However, increased survival is associated with increased prevalence of comorbidities, such as cardiovascular disease, hepatic and renal disease. Kidney disease, including HIV-associated nephropathy, acute renal failure and chronic kidney disease, represents one of the main causes of morbidity and mortality, especially if associated to other risk factors, i.e. hypertension, diabetes, older age, black race and hepatitis C coinfection. Careful evaluation of renal function may help identifying kidney disease in its early stages. In addition, proper management of hypertension and diabetes is recommended. Even if HAART has changed the natural course of HIV-associated nephropathy, reducing the risk of End-stage Renal Disease (ERDS), some antiretroviral regimens have been related with the development of acute or chronic kidney disease. Further studies are needed to optimize the management of renal disease among HIV-infected patients.

Key Words:
ARF, CKD, HAART, HIV, HIVAN, Kidney.

Introduction

The introduction of highly active antiretroviral therapy (HAART) has reduced mortality and decreased HIV-related morbidities[1]. However, HAART cannot eradicate HIV infection. Nowadays, non-AIDS-related diseases, including cardiovascular disease, malignancies, bone and renal disease, represent the main cause of morbidity and mortality among HIV-positive patients[2-54].

Kidney disease is considered one of the most common complications of HIV infection[55]. Kidney function is abnormal in up to 30% of HIV-infected patients and has become a relatively common cause of end-stage renal disease (ESRD) requiring dialysis. Moreover, kidney disease has been associated with faster progression to AIDS and death[56-59]. Race is an important risk factor for chronic kidney disease (CKD), as black persons have a 11-fold increased risk compared with white patients[60]. Of importance, diabetes and hypertension, the two most frequent causes of CKD in the general population, are increasingly common among HIV-positive patients. Other important risk factors are represented by age, a family history of renal disease and hepatitis C virus coinfection. In addition, higher baseline HIV viral load (> 4000 copies/mL) and lower baseline CD4+ T-cell count (< 200 cells/μL) have been associated with decreased renal function in HIV-positive subjects[56].

In the present review, we sum up the current evidence about risk factors, screening and treatment of HIV-related renal disease.

HIV-Related Renal Disease

HIV-associated nephropathy (HIVAN), which is a collapsing form of focal glomerulosclerosis with tubulointerstitial injury, has been demonstrated in up to 60% of renal biopsies performed for patients with CKD and represents the most common cause of CKD in HIV-infected subjects.

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CKD severity is graded according to renal function, on the basis of estimated glomerular filtration rate (eGFR). The development of CKD in HIV-infected patients is due not only to HIVAN but also to comorbidities, such as diabetes and hypertension, which are important risk factors for CKD in the general population[61].

HIVAN is the third leading cause of ESRD in black people aged 20-64[62-64]. Approximately 50% of HIVAN patients have a history of intravenous drug use. Most patients present with proteinuria and reduced renal function. Biopsy may be useful to confirm histological diagnosis of HIVAN[65].

HIVAN is not the only cause of kidney disease in patients with HIV infection. Acute renal failure (ARF) is more common in HIV-infected persons than in the general population. ARF is a clinical syndrome defined as an abrupt decrease in GFR over days to weeks with an increase in serum creatinine level to values > 1.5 mg/dl (or > 1.3 times the laboratory upper limit of normal), which returns to baseline values within 3 months. Several studies have indicated underlying CKD, advanced HIV disease and HCV coinfection as risk factors for ARF[66-68].

Diagnostic Evaluation of Renal Disease

A useful indicator of kidney damage is represented by elevated urinary protein excretion, which indicates tubular damage and may be measured qualitatively with the use of urine dipstick or quantitatively with the use of spot urine protein/creatinine ratio. The presence of urinary albumin indicates glomerular damage and is a risk factor for cardiovascular disease[69].

Creatinine-based estimates of GFR include the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) equations. The estimation of renal function is based on several parameters, such as serum creatinine level, age, sex, race and anthropomeric data[70-71], but they have some limitations because they do not adjust for creatinine tubular reabsorption. A third equation, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), seems more accurate. New biomarkers have been introduced to estimate kidney function. Cystatin C is a cysteine protease inhibitor, which is freely filtered by the glomerulus, reabsorbed and then catabolized by renal tubules; cystatin C seems to be a good indicator of mild kidney dysfunction and a stronger predictor of death[72-77]. However, this biomarker is affected by some bias (age, gender and race) and is associated with an inflammatory state[78-80]. Neutrophil gelatin-associated lipocalin (NGAL), produced by neutrophils and epithelial cells, represents an early, sensitive marker of acute kidney injury. Serum NGAL levels are lower in HIV-infected patients and increase to normal levels after virological response to HAART[81].

Two other promising biomarkers, the asymmetric dimethylarginine (ADMA), a nitric oxide synthase inhibitor that reflects endothelial function, and the liver-type fatty acid binding protein (L-FABP), a marker of proximal tubule integrity, have been associated with faster progression to dialysis and death in HIV-negative subjects with CKD[82-83]. However, no studies evaluating urinary ADMA and L-FABP have been performed in HIV-positive individuals.

All HIV-positive patients should be assessed for existing kidney disease at the time of HIV diagnosis with a screening urinalysis; if there is no evidence of proteinuria at initial evaluation, patients should undergo annual screening for renal disease, including risk assessment, eGFR and urine dipstick analysis[65]. More frequent monitoring is recommended in the presence of CKD risk factors or treatment with nephrotoxic drugs. If there is significant proteinuria, haematuria, decreasing eGFR or eGFR < 60 ml/min, current guidelines suggest to perform renal ultrasound, discontinue or adjust drug dosages where appropriate and refer to a nephrologist, for further evaluation and potentially biopsy[65].

Treatment of Renal Disease in HIV-Infected Patients

Considering that HIV infection itself appears to be the cause of HIVAN, HAART represents the mainstay for the treatment of HIV-related renal disease. In fact, HAART has been associated with beneficial effects on both preservation and improvement of kidney function in patient with HIV infection[84-90]; lower levels of viral load after starting HAART have been related with an improvement of kidney function[91].

The beneficial effects of HAART on HIVAN have been supported by renal biopsy, showing a dramatic improvement of renal histological findings of patients receiving antiretrovirals[92-93].On the other hand, the long-term administration of HAART has been associated with increased risk of progression to ERSD[94]. However, CKD may reflect the prolonged survival and increased prevalence of hypertension and diabetes among HAART-treated patients[95].

Adequate management of diabetes and hypertension is fundamental. Blood pressure should

be monitored at each ambulatory visit and antihypertensive treatment started when appropriate to reach a target blood pressure < 130/80 mmHg[96]. Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers are the first-choice drugs, because they improve renal hemodynamics, reduce urinary protein excretion and slow the progression to ESRD[97]. Beta-blockers or non-dihydropyridine calcium channel blockers are alternative drugs, but their metabolism can be blocked by PIs[98]. Glycemic control is also important to slow down the progression of nephropathy. Patients with diabetes have to maintain glycated hemoglobin level < 7%, preprandial plasma glucose level of 90-130 mg/dl and peak postprandial plasma glucose level < 180 mg/dl (data from The American Diabetes Association).

Effect of Antiretroviral Therapy on Renal Function

Renal disease has been often associated with indinavir and TDF administration, even if isolated case reports of nephrotoxicity have been reported with almost all antiretroviral drugs.

Patients treated with zidovudine, didanosine or integrase inhibitors can develop ARF and the possibility of rhabdomyolysis with pigment-related kidney injury has to be considered[99-101].

Indinavir has been reported to cause nephrolithiasis and chronic interstitial nephritis[102-104]. Renal adverse effects may occur even after discontinuation of indinavir therapy and may be prevented by adequate hydration.

The typical presentation of TDF toxicity is proximal tubulopathy, possibly due to inhibition of mitochondrial DNA polymerase γ, which may cause in turn decreased mitochondrial DNA replication and subsequent renal function impairment[105-106]. In a cross-sectional study comparing patients treated with TDF with patients never treated with TDF, TDF use was associated with proteinuria, mostly of tubular origin[107]. Similarly, Labarga et al[108] reported that exposure to TDF was associated with an increased risk of kidney tubular abnormalities over time in the absence of impaired glomerular function. Gallant et al[109] evaluated the changes in renal function in patients taking TDF compared with those taking other nucleoside reverse-transcriptase inhibitors. They found that TDF was associated with a greater decline in GFR; other risk factors for renal disease included a lower CD4+ T-cell count, lower renal function at baseline and diabetes. Furthermore, a mild-to-moderate renal toxicity of TDF seems to be related to long-term therapy, as reported in a retrospective analysis conducted in HIV-infected patients with baseline CKD stage 0 or 1, who were started on either TDF or abacavir from 1998 to 2008. Progression to CKD 2 occurred in 48.8% vs. 23.7% of patients receiving TDF and abacavir respectively; progression to CKD 3 was reported in 5.8% of the TDF group vs. 0% of the abacavir group[110]. TDF use has been associated with Fanconi syndrome, a proximal tubule disease characterized by proteinuria, hypophosphatemia, euglycemic glycosuria, hypouricemia, hypokaliemia and metabolic acidosis. However, case reports of Fanconi syndrome have also been described with the administration of lamivudine, stavudine, abacavir and didanosine[111-113]. In a recent meta-analysis, TDF-containing regimens were associated with a significantly greater loss of kidney function and with higher risk of acute renal injury. Although the observed differences were statistically significant, their clinical magnitude was modest[114]. Recently it has been shown that urinary β_2 microglobulin and $\alpha 1$ microglobulin are potentially suitable screening tools for TDF-induced kidney tubulopathy. Monitoring these two markers should be useful in early detection of TDF nephrotoxicity[115].

Ritonavir-boosted protease inhibitors (PIs/r) have been associated with an increased risk of TDF toxicity, probably due to the fact that PIs/r compete with TDF for the same renal transporters, reducing its secretion and potentiating its nephrotoxicity. In a prospective observational cohort, patients receiving TDF and PI/r had a greater median decline in GFR than those taking TDF and a NNRTI at 6 months ($p = 0.01$), with trends at 12 ($p = 0.08$) and 24 months ($p = 0.08$). There was no difference in median GFR decline between patients receiving NRTI and PI/r compared with those taking NRTI and NNRTI[116]. In another observational longitudinal cohort of patients on a TDF-based regimen, renal dysfunction was more common when TDF was associated with PI/r than NNRTI (9.44% vs. 5.01%, $p = 0.003$)[117]. In the D:A:D cohort, which included 22,603 patients on HAART with normal baseline kidney function, the authors found that the decline in eGFR was associated with the use of TDF, ritonavir-boosted atazanavir and ritonavir-boosted lopinavir[118]. Further prospective studies are warranted to evaluate the long-term effect of antiretrovirals on kidney function.

Conclusions

Renal disease is an increasing cause of morbidity and mortality in HIV-positive patients.

Careful evaluation of renal function may help identifying kidney disease in its early stages. Clinically management includes monitoring of serum creatinine and urinary albumin or protein and treatment of comorbidities, including hypertension and diabetes. Longitudinal studies are needed to establish the impact of antiretroviral drugs on renal disease.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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