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Mild Decrease in Renal Function in HIV-Infected Patients on Antiretroviral Therapy: A Neglected Diagnosis

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Abstract

Background: Renal impairment is increasingly reported among HIV-Infected patients and has been associated to an increased chance of cardiovascular disease and death. Therefore, early identification of this problem could help to reduce morbidity and mortality among these individuals. The objective of the study was to determine the prevalence and associated factors with mild decrease in renal function of HIV-infected patients on highly-active antiretroviral therapy (HAART) and undetectable viral load in Brazil.

Methods: Individuals between 18-70 years of age with time on HAART ≥ 12 months, viral load < 50 copies/mm^3, and CD4 ≥ 200 cells/mm^3, were consecutively enrolled at the outpatient clinic of Hospital de Clínicas de Porto Alegre, Brazil. Exclusion criteria were chronic kidney disease, pregnancy and known hepatic disease. Renal function was assessed by the Chronic Kidney Disease Epidemiology Collaboration equation. Mild decrease in renal function was defined as an estimated glomerular filtration rate between 89-60 mL/min/1.73m^2, for a period of at least 3 months.

Results: From the total of 213 enrolled volunteers, 193 were included in the final analysis. The mean age was 41.5 years, 102 were men (52.6%), and 156 (80.4%) were euro-descendants. Mild renal decline was diagnosed in 33.5% of the patients. Every other year of life (RR=1.05, 95%CI 1.03-1.06, p<0.001) and being euro-descendant (RR=1.94; 95%CI 1.07-3.78; p=0.049) were associated to mild decreases, whereas high body mass index (BMI) (RR=1.04, 95% CI 1.013-1007, p<0,001) was associated to normal function.

Conclusions: Mild decrease in renal function was extremely common and more than expected in our cohort (33.5%) which deserves further attention while assisting HIV-positive individuals.

Keywords: HIV; AIDS; Renal function; Kidney disease; HAART; CKD-epi; Brazil

Introduction

Although overall mortality attributable to HIV related complications have declined worldwide, the diagnosis of chronic degenerative disorders and deaths related to non-AIDS diseases have been increased [1-3]. In this scenario, renal disease is relatively common among HIV-Infected patients with a still rising number of different entities of kidney problems being reported [4-8]. Many guidelines recommend screening for factors associated to renal disease at the time of HIV diagnosis and regularly thereafter [9-11].

According to the literature, the overall frequency of any renal disease is around 35% in HIV population [5,12,13], and chronic kidney disease (CKD) prevalence varies from 4.0% to 8.4% [6,7,12,14,15]. Decreased renal function in HIV population has been associated with increased mortality and worse outcomes [1,5,16,17]. CKD is an established factor of cardiovascular disease in general population. Knowing that HIV-positive individuals are at an increased risk for cardiovascular events, the presence of CKD could further worse these risks, as some studies have already suggested [18-21].

Nevertheless, intervening in early stages of renal disease could lead to improvement in short and long term outcomes, even reverting the progression to CKD and to more advanced stages [19,22-24]. There is evidence that antiretroviral therapy (ART) can have a positive impact in renal injury caused by HIV, as demonstrated by studies comparing patients continuously exposed to ART against those with intermittent therapy [22,25]. Unfortunately, there is almost no reference regarding mild renal impairment, which is the beginning of renal dysfunction.

The diagnosis of mild renal decline is challenging, as it is silent and only detectable through laboratory analyses. The former equations, Cockcroft-Gault (CG) and modified diet in renal disease (MDRD) only accurately estimate renal function in individuals already with CKD [26-28]. With the validation of chronic kidney disease epidemiology collaboration (CKD-epi) equation for general population, it became more accurate to estimate glomerular filtration rate (eGFR) in individuals with normal or mild impairment of renal function [19,27,28].

Therefore, the objective of our study was to determine the prevalence of mild renal glomerular filtrated rate decline and its associated risk factors in a cohort of well-controlled HIV infected individuals on ART not severely immunosuppressed (CD4 count > 200 cells/mm^3) and with undetectable viral load in Brazil.

Materials and Methods

Population

Patients attended in the HIV/AIDS outpatient clinic at Hospital de

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Clínicas (SoBrHIV cohort), Porto Alegre, Brazil, were consecutively enrolled from March, 2009 through September, 2009. The SoBrHIV cohort has already been described elsewhere [29]. Briefly, it is consisted of HIV individuals followed at the southernmost state of Brazil and by the time of the study there was enrolled about 2,500 individuals being followed-up. To be included, patients needed to be on ART and to have undetectable viral load (less than 50 copies/mL) for a period equal or greater than 12 months, CD4 counts higher than 200 cells/mm^3 and age between 18 and 70 years. CKD (eGFR< 60 mL/min or with proteinuria) or previous diagnosis of any kidney disease, pregnancy and hepatic insufficiency were exclusion criteria.

Methods

Data was collected at the moment of the appointment and included demographic variables (ethnicity, height, weight, BMI, sex and age); diagnosis of DM (according to "The American Diabetes Association" [30]), hypertension (according to the Joint National Comittee 7 [31]); a complete history of HIV treatment; use of drugs for prophylaxis against opportunistic infections; the most recent and nadir CD4 cell counts (cells/mm^3, measured by flow cytometry); plasma HIV-RNA level (copies/mL, measured by b-DNA; HIV-1 RNA 3.0 assay, with limit of detection of 50 copies/mL); serum creatinine (mg/dL, measured by Jaffé; calibrated method by isotope dilution mass spectrometry - IDMS); date of HIV diagnosis and other comorbidities.

Two measurements of CKD-epi and MDRD equations (collected at least three months apart) were performed to determine the eGFR. Mild decrease in renal function was defined as an eGFR between 60-89 mL/min/1.73 m^2, for a period of at least 3 months. Renal function was further classified in two stages depending on the level of the eGFR: normal (≥ 90 mL/min per 1.73 m^2) or mild decrease (between 60-89 mL/min per 1.73 m^2) [32].

The study was approved by the Research and Ethic Committee of Hospital de Clinicas and all patients signed the informed consent.

Statistical analysis

Statistical analysis included descriptive (mean and standard deviation), univariate and multivariate analysis. Absolute and relative frequencies were utilized for continuous and categorical variables respectively.

Poisson Regression was used to determine the factors associated with mild decrease in renal function in the multivariate model. Variables significantly associated with renal impairment in univariate analysis (p<0.05) were included in the multivariate model. Pearson coefficient and Bland-Altman graph were used to evaluate the correlation and the concordance between the two equations to eGFR (MDRD and CKD-epi). A p value of less than 0.05 was considered significant. Analysis was performed using the statistical package for the social sciences (SPSS) program, version 17.0 (SPSS Inc., Chicago, Illinois, USA).

Sample size

The sample size calculation was based on a prevalence of 30% of mild decrease in renal function in the cohort studied with a confidence level of 95%. A sample size of at least 163 individuals was calculated to have a power of 80%.

Results

From the initial 213 included patients, there were 20 losses (9.4%): 18, due to missing laboratory data; one lost to follow-up; and one additional patient died after signing the consent. The characteristics and clinical variables of the remained 193 patients are shown in Table 1. One hundred and two patients were men (52.6%), 156 were euro-descendants (80.4%), and the mean age was 41.5 ± 8.3 years. Body Mass Index (BMI)was 25.9 ± 3.99; mean time on ART was 5.8 ± 3.7 years, mean CD4+ count was 585 ± 179 cells/mm^3, and the mean nadir CD4 count was 161 ± 142 cells/mm^3. The prevalence of hypertension and Diabetes Mellitus (DM) was 7.2% (n=14) and 6.2% (n=12), respectively.

We found that 33.5% (n=64) patients presented mild decrease in eGFR. The factors significantly associated in the univariate model and further used in the multivariate analysis were every other year of life, being euro-descendant, tenofovir (TDF) exposure, hypertension, DM, time on ART and body weight. After adjustment in the multivariate model (Table 2), every other year of age (RR=1.05, 95% CI 1.03 – 1.06, <0.001) and being euro-descendant (RR= 1.94 95% CI 1.07 – 3.78, p= 0.049) were significantly associated to mild renal decrease in filtration rate. On the other hand, high BMI (RR=1.04, 95% Cl 1.013-1.007, p<0.001) was a protection factor against renal impairment.

There was a significant correlation between the CKD-epi and MDRD equations (Pearson coefficient = 0.92; p<0.001), although there

	N=193 (%)
Age (years)	41.5 ± 8.3
Men	102 (52.6%)
Ethnicity	
Euro-descendants	156 (80.4%)
Creatinine (mg/dl)	0.87 ± 0.29
Urea (mg/dl)	33.51 ± 12.27
eGFR* (ml/min)	99.02 ± 29.5
Body Mass Index	25.9 ± 3.99
CD4 (cells/mm^3	585.9 ± 179.4
Hypertension	14 (7.2%)
Diabetes Mellitus	12 (6.2%)
Time on ART† (years)	5.8 ± 3.7

* Estimated glomerular filtration rate; † Antiretroviral therapy

Table 1. Main demographic characteristics (data are presented as mean ± standard deviation or percentage).

	Univariate analysis			Multivariate analysis		
	RR	95% CI†	p	RR‡	95% CI	p
Euro-descendants	**2.942**	**1.13-7.65**	**0.027**	**1.941**	**1.07-3.78**	**0.049**
Men	0.728	0.45-1.13	0.192			
Use of atazanavir	1.129	0.66-1.91	0.654			
Use of tenofovir	1.847	1.16-2.95	0.009	1.344	0.97-1.85	0.07
Use of ritonavir (100mg)	0.915	0.49-1.71	0.781			
Use of ritonavir (200mg)	0.728	0.37-1.43	0.357			
Hypertension	2.444	1.57-3.78	<0.001	1.170	0.789-7.742	0.44
Diabetes Mellitus	2.347	1.48-3.71	<0.001	0.874	0.58-1.30	0.5
Every other year of life	**1.066**	**1.05-1.08**	**<0.001**	**1.051**	**1.034-1.067**	**<0.001**
Time on ART (years)	1.054	1.006-1.104	0.026	1.012	0.97-1.05	0.505
Body Mass Index	**1.055**	**1.018-1.021**	**0.004**	**1.04**	**1.013-1.007**	**<0.001**
CD4 (cells/mm^3)	1.00	1.00-1.001	0.661			

* eGFR, estimated glomerular filtration rate; † CI, confidence interval; ‡ RR, risk ratio; All variables significant in univariate analyses (p<0.05) were included in a multivariate model.

Table 2. Risk factors associated to alteration in the renal function (eGFR *< 60 ml/minper 1.73 m^{2}by CKD-epi); univariate and multivariate analysis.

were no concordance between the CKD-epi and MDRD equations (Bland-Altman graph analysis p=0.048; 95% IC -19.36 ± 22.34).

Discussion

In our study we evaluated mild renal impairment and its associated factors in a well-controlled HIV population (< 50 copies/mL and > 200 CD4+ cells/mm^3 for at least one year). To our knowledge this is the first study that looked for early renal disease in controlled HIV population without previous known kidney disease. We found an extremely high and worrisome prevalence of 33.5% of mild dysfunction by eGFR, which merits further attention to this particular organ as a potential target in HIV infection. This finding is in accordance to study conducted in a different HIV cohort from France, although only about 60% of the individuals had undetectable viral load [14]. Another cohort (ICONA) found a prevalence of almost 24% of mild renal glomerular decline. Nevertheless, in this population HIV disease was not well-controlled [33].

This finding supports the kidney as a frequent target even in well-controlled HIV infection and is in accordance to the other studies [14,33]. Moreover, the mean age of our cohort was only 41.5 year of age and such alterations should be noticed in older individuals in the general population [19,34]. Likely, this also might reflect the process of early ageing being suggested in HIV infection as reported with other organs and tissues of the body [2,3,18,35]. Therefore, we could speculate that the beginning of renal disease would be earlier than expected in this particular group.

Among the traditional risk factors only age was significantly associated to mild decrease of eGFR, although being euro-descendant was also significantly associated to mild renal disease. Other well known risk factors for renal impairment, like hypertension and DM [8,36], were not associated after adjustment in the multivariate model. This could be due to the not large enough sample size of our study, as the prevalence of hypertension and DM was lower than expected (7.2% and 6.2% respectively) in contrast to 10% in DM and approximately 20% of hypertension among Brazilian adults [37-39]. The lower prevalence of both conditions was somewhat expected due to the relative youthness of our population.

Surprisingly, we found an association between ethnicity and mild decrease of eGFR. Previous studies, looking to chronic kidney disease (eGFR< 60 mL/min) did not identify any association between renal impairment with euro-descendant individuals [7,12,40]. In our population, utilizing afro-descendant as the comparator, those with an European ancestry were at risk for mild renal decrease. A possible explanation would reside in the fact that the equations used nowadays to eGFR were based according to other populations that not necessarily resembled the ethnic distribution of our cohort.

On the other hand, no specific antiretroviral or time on antiretroviral agents, which had been previously associated to CKD in our population, were associated to mild lost in renal eGFR [4-8,12-15]. This finding should be further explored since it could be related to the differences in age of the selected populations. For instance, in the CKD study [15], the mean age was 46 years opposed to 41.5 years in the present study. Therefore, although risky, it is possible to consider that this could reflect a continuum, in which renal disease progresses with antiretroviral exposition. Conversely, this could simply mirror the chronic inflammatory milieu associated to HIV infection and ageing [2,35].

Another intriguing finding was related to the BMI, which was significantly related to renal protection. Individuals with higher BMI were associated to normal eGFR. It is difficult to try to interpret the result as the equations utilized to eGFR (MDRD and CKD-epi) do not take in account body weight in their composition. In that circumstance, as the drugs are prescribed in fixed dosage for adults, individuals with higher body weight would have lower plasma concentrations to these drugs and consequently last exposure, as clearly demonstrated by efavirenz, for example [41]. Nevertheless, if we consider renal disease as a continuum, it would reflect that some antiretrovirals, in fact, could really be nephrotoxic [4,7,16,42-44]. Likewise for antiretroviral exposition, this would only reveal the continuum spectrum of renal disease in HIV infection, in which individuals with lower weight (meaning hypercatabolic despite well controlled disease) might have a more pro-inflammatory profile associated to greater risk of organ disease [19].

The study has several limitations that should be considered. The equations used to eGFR are still not validated to HIV-infected individuals and therefore could be not accurate enough. As previously considered, our sample size might have been limited some of our findings, as the prevalence of chronic diseases such as hypertension and DM were lower than expected. In addition, this was a cross sectional study and therefore we can only draw association of events and not establish temporal sequence. Lastly, although we tried to minimize HIV infection and its comorbidities selecting individuals with CD4 counts greater than 200 cells/mm^3 and at least one year with undetectable viral load, it is not possible to exclude any influence of HIV infection.

In conclusion, we have demonstrated that mild decrease in renal function is relatively common in our population. According to our findings, those with older age, euro-descendant and with low body weight were at higher risk to have mild decrease in renal function. We suggest that kidney disease begins earlier than expected and it is a continuum (despite adequately viral suppression) and it should be taken along with the process of ageing in HIV population.

Actually, due to the increase of life-expectancy of HIV individuals, we can expect an even higher prevalence of renal disease. Therefore it is very important to screen and aggressively treat mild renal impairment. Other prospective studies should confirm our findings [22,45].

Competing Interests

We certify that there is no competing interest regarding the material discussed in the manuscript.

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