Renal Functional Reserve in Naïve HIV Patients

Articoli originali

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ABSTRACT

Introduction. Renal functional reserve (RFR) is the kidney capability of increasing its basal glomerular filtration rate (GFR) at least 20% after an adequate stimulus. Renal disorders have been reported in seropositive HIV patients, particularly the decrease in glomerular filtration rate (eGFR), nephrotic syndrome, and proximal tubular deficiency associated with the disease itself or the use of some anti-retroviral treatments. Thus, it was decided to carry out a prospective study in order to evaluate if RFR test was preserved in naive HIV patients.

Material and Method. GFR was measured by using cimetidine-aided creatinine clearance (CACC), and RFR as described Hellerstein et al. in seropositive naive HIV patients and healthy volunteers.

Results. RFR was evaluated in 12 naïve HIV patients who showed positive RFR (24.8±2%), but significantly lower compared to RFR in 9 control individuals (90.3 ± 5%).

Conclusion. In this study was found that renal functional reserve was positive in naïve HIV patients, but significantly lower compared to renal functional reserve achieved by seronegative healthy individuals.

KEYWORDS: renal reserve, HIV, renal physiology

Abbreviations

Renal Functional Reserve (RFR)
Glomerular Filtration Rate (GFR)
Human Immunodeficiency Virus (HIV)
Tenofovir Disoproxil-Fumarate (TDF)
Thick Ascending Limb of Henle's Loop (TALH)
Tubular-Glomerular Feedback (TGF)
Cimetidine-Aided Creatinine Clearance (CACC)

Introduction

Renal functional reserve (RFR) is the renal capability of increasing its basal glomerular filtration rate (GFR) at least 20% after an adequate stimulus such as amino-acid infusion or oral protein overload. A positive renal reserve response requires the presence of both adequate glomerular and renal tubular function [1]. In order to evaluate GFR, one of the most simple and reliable method seems to be the cimetidine-aided creatinine clearance (CACC), particularly that which uses oral cimetidine supply. Since cimetidine inhibits creatinine secretion in the proximal tubules, the ratio of the CACC and GFR is about 1.1 [2–4]. The clinical spectrum of human immunodeficiency virus (HIV) infection associated disease has changed significantly, mainly due to the wide availability and improvement of combination antiretroviral therapy regiments [5]. Moreover, renal disorders have been reported in HIV patients, particularly the decrease in GFR, nephrotic syndrome, and proximal tubular deficiency associated with the disease itself (viral renal tissue damage) or the use of tenofovir disoproxil-fumarate (TDF) and some protease inhibitors such as lopinavir/ritonavir and atazanavir [5]. Renal damage by TDF is established from its accumulation in the proximal convoluted tubule. In fact, the most representative form of nephrotoxicity reported in cases and series by TDF is an incomplete form of Fanconi syndrome [6–9]. As far as we know, it has not been reported yet if HIV infection itself can alter the RFR. Therefore, it was decided to carry out a prospective study in order to evaluate RFR in stable seropositive HIV patients who had neither nephropathy nor anti-retroviral treatment yet (naïve HIV patients).

Material and Method

RFR was evaluated in 21 young adult (18-64 years old) stable individuals, 12 naïve seropositive HIV patients, and 9 seronegative healthy volunteers (control group). The study exclusion/inclusion criteria were as follows:

Patient group:

- Inclusion criteria
  a) Age between 18 and 64 years
  b) Documented HIV infection (Western Blot test or history of at least one detectable HIV viral load determination)
  c) not being on antiretroviral treatment yet
- Exclusion criteria
  a) Nephropathy defined as presence of abnormal urinalysis (proteinuria, and/or hematuria), abnormal renal ultrasound imaging (any structural alteration), and/or eGFR <80 ml/min (obtained by creatinine-based CKD-EPI equation)
  b) Undergoing opportunistic infection

c) Being on any nephrotoxic medication (AINEs, etc.) or anti renin-angiotensin-aldosterone system drugs (eg: enalapril, etc.)

Control group:

- Inclusion criteria
  a) Age between 18 and 64 years
  b) Documented seronegative HIV test
  c) Not on any medication
- Exclusion criteria
  a) Nephropathy defined as presence of abnormal urinalysis (proteinuria, and/or hematuria), abnormal renal ultrasound imaging (any structural alteration), and/or eGFR <80 ml/min (obtained by creatinine-based CKD-EPI equation)

All the studied individuals (patients and volunteers) signed an informed consent approved by our institution's Ethics Committee.

In each studied individual, first, it was performed a resting GFR by using measuring a cimetidine-aided creatinine clearance (CACC), and second a RFR test as described by Hellerstein et al. [10].

To measure RFR the following protocol was followed: each volunteer was on a low protein diet (0.8 g/kg/day) for two weeks, and on oral cimetidine (1600 mg/day) for 48 hours before the RFR test. First, basal blood sample was obtained, and then oral hydration was initiated using tap water (20 ml/kg) during thirty minutes.

After bladder voiding, time and volume data from each micturition were documented for two periods. From these data CACC was calculated by applying the following formula:

CACC = [[urinary creatinine × urine volume (ml) / serum creatinine × time (min)]]

Finally, from these two CACC values an average CACC value was obtained for each volunteer (basal GFR). Then, each volunteer received an oral protein load of 1.5 g/kg body weight based on dairy products (milk and cheese): 30 minutes for ingestion and 40 minutes for digestion.

After bladder voiding four consecutive blood samples (30, 60, 90, 120 minutes), and urine samples (including their time and volume) from each micturition were obtained for a period two hours (volunteers´voiding was each 30-40 minutes).

From these data the maximum CACC value after protein load (pick GFR), delta CACC value (pick CACC – basal CACC), and RFR percentage were calculated.

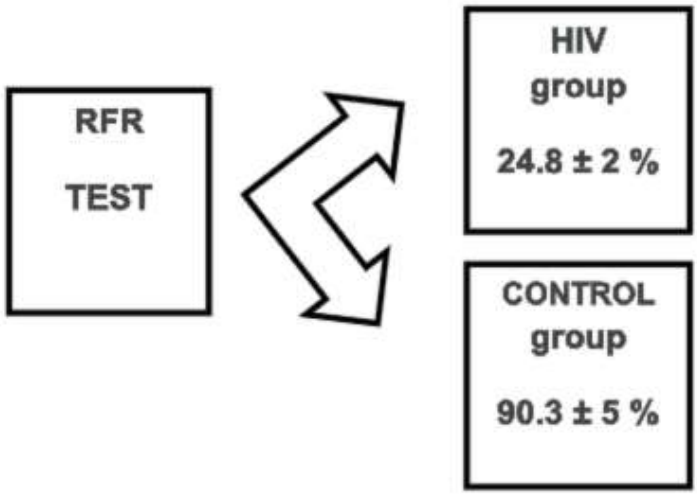
ANOVA test was applied for the statistical analysis.

	Basal CC mean ± SD ($ml/min/1.73m^2$)	**Basal CACC** mean ± SD ($ml/min/1.73m^2$)
HIV patients (n: 12)	129.2 ± 10	123.7 ± 40
Control (n: 9)	131.8 ± 15	122.5 ± 25
p value	NS	NS

Table 1. Basal 24 hours-creatinine clearance (CC) and basal cimetidine-aided creatinine clearance (CACC) in stable HIV patients and controls.

Results

RFR test was performed to 21 caucasian individuals in this study. Of these individuals, twelve had a recent diagnosis of HIV infection (1 female) and were not on antiretroviral treatment yet (naïve HIV patients), while the rest (9 individuals) were seronegative healthy volunteers (all males) who had been selected as control group. Regarding their age, median age was 48 (range: 20-51) years in HIV positive group, while median age was 46 (range 28-50) years in the seronegative control group (the two groups were age-matched). No volunteer was on chronic medication except for two patients in the HIV group who were on amlodipine 10 mg/day, and rosuvastatin 10 mg/day. RFR was evaluated in 12 naïve HIV patients, and in 9 seronegative healthy individuals (control group). The positive HIV group showed a normal basal GFR value (123.7±40 ml/min/1.73 m^2), and a positive RFR (24.8±2%), and the control group also showed a normal basal GFR value (122.5 ± 25 ml/min/1.73m^2), and a positive RFR (90.3 ± 5%) (Graphic 1). However, even though there was no significant difference in basal GFR value between the studied groups, the RFR value was significantly higher in the control group respect to the positive HIV group ($p < 0.001$). The time of RFR pick value was at 30 minutes since the beginning of the test in both groups (Table 2).



Graphic 1. Renal functional reserve (RFR) in HIV and control groups.

	CACC basal mean ± SD (ml/min/1.73m^2)	CACC pick (ml/min/1.73m^2) mean ± SD	Delta (ml/min/1.73m^2) mean ± SD	RFR (%) mean ± SD
HIV patients (n: 12)	123.7 ± 40	155.7 ± 48	36.2 ± 32	24.8 ± 2
Control (n: 9)	122.5 ± 25	226.0 ± 49	103.6 ± 53	90.3 ± 5
p value	NS	**<0.001**	**<0.001**	**<0.001**

Table 2. Basal and peak values of cimetidine-aided creatinine clearance (CACC) during the renal functional reserve (RFR) test in stable HIV patients and controls.

Discussion

Nephropathy is increasingly recognized as morbid-mortality cause in seropositive HIV patients. Renal disease risk factors, such as hypertension, diabetes mellitus, and dyslipidemia are more prevalent in HIV-positive population. Additionally, exposure to combined antiretroviral therapy can also induce renal damage [11]. In our study, all the evaluated volunteers (seropositive HIV patients and control individuals) had normal renal assessment (normal GFR value, urinalysis, and renal

ultrasound imaging). Even though a positive value of RFR (24.8 ± 2%) was documented in naïve HIV-positive patients, as they managed to increase their baseline GFR by more than 20% according to one of the most recognized definitions of positive RFR, the value achieved was significantly lower than the one achieved by the healthy control group (90.3 ± 5%). This relatively lower hyperfiltration response observed in HIV-positive patients, who were free of chronic kidney disease and retroviral treatment, compared to healthy controls renal reserve response, could be explained by a subclinical deleterious effect of HIV virus on kidney tissue. In this sense, HIV virus has been detected in tubular cells suggesting that either the infection or the associated inflammatory process could produce direct tubular damage [11].

It is known that positive RFR response depends not only on adequate GFR but also on preserved proximal tubule, and thick ascending limb of Henle's loop (TALH) function. This phenomenon is explained because GFR increase induced by protein or amino acid load is attributed to tubular-glomerular feedback (TGF) activity. It has been hypothesized that *macula densa* cells sense some tubular flow rate indicator (eg: urinary sodium or chloride), and signal to the afferent arterioles to vasoconstrict or vasodilate in response to changes in this indicator urinary concentration. Then, an increase in serum amino-acid levels after protein oral load would result in an increase in amino acids filtration and their further reabsorption. Since amino acids and sodium are co-reabsorbed (cotransported) in the proximal tubule, proximal sodium reabsorption would also increase, resulting in a decrease in sodium delivery to the *macula densa*. Therefore, TGF mechanism results in afferent arteriolar vasodilatation and GFR increase [2]. Since renal reserve response depends on the adequate interaction among GFR, proximal tubule and TALH function, and Belloso et al. have already documented TALH functionally diminished in HIV positive patients, this phenomenon could explaine why RFR was significantly lower in these patients compared to healthy controls [11, 12].

Conclusion

In this study was found that renal functional reserve was positive in naive seropositive HIV patients, but their renal functional reserve was significantly lower compared to the one achieved by seronegative healthy individuals.

Limitations

One of the limitations of this study was the small representation of woman and small number of studied individuals (n: 21, 12 cases and 9 controls). Despite this limitation, the data obtained were sufficient to find statistically significant differences between the compared groups.

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