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Proximal Tubule Function and Free Water Clearance: Comparison between Healthy Elderly and Young HIV+ Patients

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Abstract

In previous studies it was documented that proximal tubule sodium reabsorption capability was preserved in healthy elderly, while Thick Ascending Loop of Henle (TALH) one was reduced.

Aim: Since, it has also been documented that senile changes are accelerated in HIV patients, we performed a prospective study in order to evaluate if there was a significant difference in proximal and TALH function between healthy elderly and HIV patients.

Methods: Proximal and TALH was analyzed by performing hyposaline infusion test in 10 young (≥ 18-≤ 40 years old) HIV volunteers under treatment with tenofovir, free of viral charge, and normal renal function: serum creatinine, urinary sediment, and renal ultrasound), with the control group made up of 10 healthy old volunteers (≥ 65 years old).

Results: During the test, it was observed that the HIV group had a significant reduction of natremia (HIV: 133 ± 1 mmol/l vs. healthy elderly: 139 ± 1 mmol/l, p=0.03), serum osmolarity (HIV: 276 ± 4 mOsm/l vs. elderly: 288 ± 3 mOsm/l, p=0.03) and free water clearance (HIV: 3.5 ± 3 ml/min/1.73 m² *vs*. elderly: 5 ± 8 ml/min/1.73 m², p ≤ 0.01). Besides, HIV patients showed an inadequate and significant increase in their urinary tonicity in comparison with the healthy elderly group: HIV: 170 ± 18 mOsm/l *vs*. elderly: 90 ± 10, p ≤ 0.01. Regarding proximal tubular function, it was found that it was preserved in both groups.

Conclusion: Proximal tubule sodium reabsorption was normal, while free water clearance was significantly reduced in young HIV patients in comparison with healthy elderly volunteers.

Introduction

In previous studies it was documented that proximal tubule sodium reabsorption capability was preserved in healthy elderly, while thick ascending loop of Henle (TALH) one was reduced in this population [1,2]. These evaluations were performed by applying a validated and specific physiological test for that, the hyposaline infusion test [3]. Senile TALH dysfunction has been attributed to a significant reduction in the number of TALH luminal sodium transporters secondary to ageing [4]. On the other hand, it has been documented that senile changes are accelerated in HIV+ patients, as is the case of atherosclerosis whose prevalence is increased even in young HIV+ patients [5,6]. We thought that it would be interesting to investigate if there would be a significant difference regarding proximal and TALH function between healthy elderly and young HIV+ patients. Thus, we performed a prospective study in order to evaluate, applying the hyposaline infusion test, if there was a significant functional difference in the above mentioned renal tubular segments between these two populations.

Material and Methods

In this prospective study, proximal tubule and thick ascending loop of Henle (TALH) were functionally evaluated by an adequate tests for this purpose, the hyposaline infusion test (Chaimovitz test) in 20 volunteers: 10 healthy elderly (≥65 years old) and 10 HIV young (18-40 years old) on tenofovir, with at least six month free of viral charge. All these volunteers had normal renal functional parameters: normal urinalysis, renal ultrasound imaging, and serum creatinine (Table 1). The hyposaline infusion test is based on the exploration of the kidney tubular response to an acute hyposaline load, which causes an expansion of the volume with which the release of aldosterone and vasopressin remains inhibited. In this way, it is possible to "functionally cancel" the collecting tubules and physiologically divide the proximal nephron in two segments: one going immediately after the glomerulus to the end of the ascending loop of Henle: named "proximal segment", and another one which encompasses the whole ascending loop of Henle, including its thin as well as thick segments: named "distal segment". Since this "distal segment" is normally responsible for the generation of free water

Age (years)	Healthy elderly 69 (66-71)	HIV patients 35 (22-40)	P <0.01	Normal values (healthy young)
Serum sodium (mmol/l)	142 ± 1	141 ± 1	NS	135 - 145
Serum osmolarity (mOsm/l)	294 ± 2	292 ± 2	NS	280 - 300
Serum creatinine (mg/dl)	0.7 ± 0.1	0.8 ± 0.05	NS	0.6-1.2
Urine osmolarity (mOsm/l)	820 ± 100	520 ± 150	0.03	900-1000
eGFR (ml/min/1.73 m²)	80 ± 11	114 ± 15	0.04	≥ 60

eGFR: estimated glomerular filtration rate by MDRD formula

Table 1: Basal parameters in both groups.

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clearance, the functionality of this segment can then be assessed by calculating such clearance based on the parameters measured during the test: urinary and serum creatinine and osmolarity, as well as volume and micturition times [2,3]. The physiological parameters obtained by hyposaline infusion test were: osmolal clearance, proximal tubule function, free water clearance, and TALH sodium reabsorption. These were the applied formulas [7]:

•V=urine volume (ml/dl GFR)

•Osmolal clearance=urinary osmolarity×V/serum osmolaity (ml/min/1.73 m^2)

•Free water clearance=V-osmolal clearance (ml/min/1.73 m^2)

•Sodium clearance=V×urinary sodium/serum sodium (ml/min/1.73 m^2)

•Potassium clearance=V×urinary potassium/serum potassium (ml/min/1.73 m^2)

•Sodium+potassium clearance=[(urinary sodium+urinary potassium)×V]/(serum sodium+potassium) (ml/min/1.73 m^2)

•Proximal tubule function=free water clearance+sodium clearance+potassium clearance (ml/min/1.73 m^2)

• TALH sodium reabsorption=free water clearance×100/free water clearance+sodium clearance (%)

All volunteers (fasting) underwent an oral water overload which consisted of administering mineralized water (20cc/kg) in 30 minutes, and replacing each urinated volume administering equal amount of water (oral). Concomitantly, two liters of IV hypotonic solution (0.45%) was intravenously infused along the whole test. During test basal and all passed urine were collected for registering its volume and taking a sample for measuring creatinine, sodium, potassium, and osmolarity. Besides, three blood samples (hours 0, 60 and 120 minutes) were drawn for measuring the same parameters. Then, from the data which came from the urine sample with the lowest osmolarity (lower than 100 mOsm/l) and its corresponding blood sample, proximal and TALH functions were obtained applying the above mentioned formulas.

Results

There was no clinical complication during the tests, and there was no significant voiding volume among the studied volunteers

In this study proximal and TALH tubular functions were studied in 20 Caucasian males volunteers which had similar weight, and normal basal serum sodium, osmolarity, and creatinine values (Table 1). There was a significantly lower glomerular filtration rate in the aged group respect to the young HIV one, but this difference was the normally expected one secondary to kidney ageing (Table 1). It was documented that serum sodium (SNa), and Serum Osmolarity (SO) were significantly reduced during hyposaline infusion test in HIV patients compared to healthy old (O) volunteers: SNa 133 ± 1 mmol/l (HIV) vs 139 ± 1 mmol/l (O), p=0.03; SO: 276 ± 4 mOsm/l (HIV) vs 288 ± 3 (O), p=0.03 (Table 2).

There was no significant difference between the measured (serum and urine) osmolarity values and the calculated ones

Regarding, free water clearance (FWC), and TALH sodium reabsorption (NaR), it was documented that they were also significantly reduced in HIV patients compared to healthy old volunteers: FWC: 3.5 ± 3 ml/min/1.73 m^2 (HIV) vs 5.8 ± 1 ml/min/1.73 m^2 (O), p=<0.01; NaR: 68 ± 3% (HIV) vs 73 ± 3%(O), p ≤ 0.01 (Table 2). Urine osmolarity (UO) was significantly lower in the elderly group compared with the HIV one: UO 90 ± 10 mOsm/l (O) vs 170 ± 18 mOsm/l, p=<0.01, and even though, it was documented a normal proximal tubule function (proximal sodium reabsorption) in both studied groups, the function of this segment was significantly higher in the HIV patients: Proximal tubule function 1 ± 0.4 ml/min/1.73 m^2 (HIV) vs 8 ± 2 ml/min/1.73 m^2 (O), p=0.02 (Table 2).

Weight (kg)	healthy elderly 68.4 ± 1	HIV patients 70.2 ± 2	P NS	Normal values (healthy young)
Serum sodium (mmol/l)	139 ± 1	133 ± 1	0.03	135 -145
Serum osmolarity (mOsm/l)	288 ± 3	276 ± 4	0.03	280 - 300
Urinary osmolarity (mOsm/l)	90 ± 10	170 ± 18	≤ 0.01	40-60
Osmolal clearance (ml/min/1.73 m^2)	2 ± 1	1.7 ± 0.4	NS	2
Free water clearance (ml/min/1.73 m^2)	5.8 ± 1	3.5 ± 3	<0.01	8-12
Proximal tubular function (ml/min/1.73 m^2)	7.5 ± 1	1 ± 0.4		≤20
TALH sodium reabsorption (%)	73 ± 3	68 ± 3	<0.01	≥85
V (ml/dl GFR)	8 ± 2	5.3 ± 1	<0.01	14

V: urinary volume, TALH: thick ascending loop of Henle

Table 2: Hyposaline infusion test: results in both groups.

Discussion

Healthy kidney has an enormous capacity to excrete free water, and this capacity depends on the following physiological variables:

•an adequate GFR, since it delivers urine to the diluting segment (TALH),

•a preserved TALH function (free water clearance), and

•an impermeable collecting tubules (absence of vasopressin).

As a consequence of that, a patient suffering from a severely reduced GFR (<10 ml/min), and/or a critically low free water clearance (<5 ml/min), can easily develop a free water excess (hypoosmolar hyponatremia) in a context of a high water supply [8-10]. In our study was documented that both groups (healthy elderly and HIV) showed a reduced FWC, and urine dilution capability (Table 2). However, FWC was more severely altered in HIV patients, since it was around three times lower than the normal one: FWC 3.5 ± 3 ml/min/1.73 m^2 in HIV group *vs.*10 ml/min/1.73 m^2 in healthy young people. That explains why HIV patients, despite their normal GFR, were not able to maximally dilute their urine during hyposaline infusion test (water load: 1700cc/hour), nor being able to **avoid** developing hyponatremia during this physiological test. Healthy people, young or old, do not develop hyponatremia during hyposaline infusion test since they are able to dilute adequately their urine which means to achieve a UO lower than 100 mOsm/l. It may propose that hyponatremia developed by HIV patients during hyposaline test could be secondary to an inappropriate (non-osmolar) antidiuretic hormone release (SIADH). However, against this interpretation we have the fact that on one hand, HIV patients showed normal serum sodium basal levels (Table 1); and on the other hand, SIADH syndrome usually runs with urine osmolarity higher than serum one, while in our hyponatremic HIV

patients their urine osmolarity was markedly lower than their serum osmolarity (SO): UO 170 ± 18 mOsm/l vs SO 276 ± 4 mOsm/l, $p \leq 0.01$. It is important to point out that even though there are previous reports of hyponatremia in HIV patients, all these cases are explained as induced by medications (opiods, anti-seizures drugs, etc.), concomitant diseases (pneumia, encephalitis, etc.), or SIADH in AIDS patients [9,11]. Conversely, our HIV patients were not on any hyponatremia inducing drugs, concomitant diseases, nor suffering from AIDS. Besides, even though they were on tenofovir, which can induce proximal tubule damage, this renal function was preserved in our volunteers as it was documented by Chaimovitz test's results and their pre-test renal screening [12,13]: normal serum and urine electrolytes values, urinalysis and kidney ultrasound. Thus, as long as we know, this is the first study that has described a urine diluting incapability in stable HIV patients. Regarding tubular sodium handling in the healthy old, it has been documented that the selective reabsorption of sodium at the proximal tubule, evaluated using the Chaimovitz test, shows that it remains in the normal range, and even significantly higher than in the healthy young. Conversely, tubular sodium handling in the thick ascending loop of Henle (TALH) is reduced in the aged healthy people respect to the young one. As a consequence, there is a decreased free water clearance, with the subsequent inability to dilute urine in healthy old people. It has been documented in old rats that the number of co-transporters sodium-potassium-2 chloride (NKCC2) in TAHL is significantly reduced. Perhaps, this phenomenon could explain the lower sodium reabsorption at the TALH which was observed in healthy old people [1,2,14]. Since these renal physiological changes have been explained as a consequence of the senescence process in the elderly and it has been proposed that ageing is accelerated in the HIV patients, thus it can hypothesize that this premature ageing process suffered by HIV patients could explain the reduced TAHL function documented in this people despite their young age. One of the limitations of this study is the small number of studied HIV patients (n:10). However, despite of that, obtained data were able to find statistically significant differences between the compared groups. Additionally, even though serum vasopressin was not measured, this is not a biochemical variable required by the physiological tests (hyposaline test) chose for being applied in this research study.

Conclusion

In this study, it was documented that proximal tubule sodium reabsorption was normal, while free water clearance was significantly reduced in young HIV patients in comparison with healthy elderly volunteers.

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