Creatinine, urea, uric acid, water and electrolytes renal handling in the healthy oldest old

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INTRODUCTION

Even nowadays the limits that separate the changes considered typical of the normal ageing process of those patients who suffer from high prevalent illnesses characteristic of this period are not clear. Therefore the study of the physiology of very old healthy people (aged ≥ 75 years old), constitutes an excellent opportunity to better understand the limits which separate the normal renal ageing. In the present review article, we explain in detail the characteristics of the creatinine, urea, uric acid, sodium, water, and potassium renal handling in the very old healthy people taking the younger group (18-40 years) as a parameter. Additionally, it is important to point out that there are no significant physiological differences related to gender in both age populations.

CREATININE HANDLING

Creatinine clearance measured without (CC) or with cimetidine (CCWC), which is almost the same as inulin clearance due to the blocking effect that cimetidine has on the proximal tubular secretion of creatinine, has proved to be significantly lower in the very old healthy people in comparison to that documented on the younger population

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glomerulosclerosis which accompanies ageing[3-5]. Even though, the above mentioned creatinine renal filtration difference between the age groups, there is no significant difference regarding their serum creatinine value between them. This phenomenon can be explained as the decrease in the creatine levels due to the senile diminution in lean body mass (tissues from where creatinine comes) [8].

The procurement of a ratio between the CC and the CCWC allows for the evaluation of the net tubular handling of this substance; thus a ratio > 1 (AC/ACC: 1.28) was observed in the young group, which confirms the existence of a net secretion of creatinine in this group, whereas on the contrary, a ratio < 1 was observed in the very old group (AC/ACC: 0.86), which could be interpreted as the presence of a net reabsorption of creatinine in this group [6].

When this phenomenon was explored in the context of over hydration, it was observed that there was practically no change in the AC/ACC ratio neither in the young (ratio: 1.26) nor in the oldest old (ratio: 0.87). However, when this phenomenon was explored in the context of dehydration, it was observed that while there was practically no change in the AC/ACC ratio in the young (ratio: 1.3), conversely there was a significant reduction in AC/ACC value in the oldest old (ratio: 0.76), P = 0.02. These finding could be interpreted as the fact that the dehydration over expresses the habitual senile creatinine back-filtration. It could be hypothesized that the phenomenon of net creatinine tubular reabsorption documented on very old people could be explained due to the senile structural tubular changes (atrophy, etc.) which would make the proximal tubule more permeable and thus more susceptible to present the observed creatinine back-filtration pattern. Something similar was documented in the newborns but in this case it was attributed to tubular immaturity since this finding disappeared as they grew older [5-9]. Renal reserve is defined as the ability of the kidney of increasing its basal glomerular filtration rate in at least 20% after a proteic overload, it has been reported that it is preserved in the very old people, although its magnitude is considerably lower in comparison with the one in the young, since the increase in CC between its basal value (fasting) and its post-prandial highest one (peak) is significantly lower in the very old (40%) respect to the young (90%) (P = 0.02) [10-12]. Clinical consequences [13]; (1) It is worth mentioning that the characteristic of the reduced glomerular filtration in the very old is one of the factors which fosters medicine intoxication, if the doses were not adjusted to the glomerular filtration; (2) During pre-renal acute renal failure secondary to dehydration, serum creatinine and urea values are usually equally high due to an augment in the habitual creatine back-filtration in the aged.

### UREA AND URIC ACID HANDLING

It is already known that there is a significant difference between urea and uric acid renal handling in very old healthy people. On one hand, it has been documented that fractional excretion of urea, in volume contraction as well as in volume expansion, was significantly higher than the one reached by the young: 40% vs 24% (P = 0.017) and 65% vs 53% (P = 0.04) respectively [14-16]. Due to the fact that a reduction in the number of urea channels (UT1) has been documented in the collecting tubules of very old rats, it could be suggested that the senile increase in urea excretion may be the consequence of a lower reabsorption of urea at the distal tubules [7]. Clinical consequences: This increase in the urea urinary excretion, as well as the low protein diet that aged people usually have, both explain the normal serum urea value characteristically found in the elderly, despite of their reduced glomerular filtration rate [7]. Additionally, the high urea urinary excretion documented in the very old could be one of the factors which explains the senile medullar hypotonicity (reduced urea medullar content) and the nocturia (urea osmotic diuresis) usually found in the very old patients [15,16]. On the other hand, serum uric acid level and fractional excretion of uric acid (FEUAc) do not differ between very old healthy people in comparison with healthy young ones. In a recent study the documented FEUAc values in oldest old and young volunteers were 6%, and 7% respectively (P = NS) [17,18]. Since uric acid is mainly handled in the proximal tubule, a segment that suffers practically no functional changes with ageing, perhaps this could explain the above mentioned phenomenon [8].

### WATER AND SODIUM HANDLING

Regarding tubular sodium handling in the oldest old, it has been documented that the selective reabsorption of sodium at the proximal tubule, evaluated using the Chaimowitz test, shows that it remains in the normal range: sodium clearance < 20 mL./min per 1.73 m², in both age groups, even though it is significantly lower in the very aged one: 8 mL./min per 1.73 m² (oldest old) vs 18 mL./min per 1.73 m² (young), P = less than 0.01 [14]. Additionally, it has also been documented a decrease in sodium reabsorption in the thick ascending loop of Henle in very old healthy people [8,19]. This lower local sodium reabsorption, leads to the following alterations [14]: (1) Decreased free water clearance, with the subsequent inability to dilute urine; And (2) Reduced medullar tonicity, with the subsequent inability to reabsorb free water by the collecting tubules in a state of antidiuresis (vasopressin release).

The thick ascending loop of Henle (TALH) has a co-transporter sodium-potassium-2 chloride (NKCC2). Studies in old rats have documented a significant reduction in the number of co-transporters NKCC2 in comparison with young ones. This phenomenon could explain the lower sodium reabsorption at the TALH in very old healthy people [14,20-22].

Besides, it has been documented that free water clearance (a marker of TALH function) is considerably lower in the very old in comparison with the young: 6 mL./min per 1.73 m² vs 15 mL./min per 1.73 m², respectively (P = 0.01) [24].
As regards the maximum tubular dilution capacity, another of the parameters which Chaimowitz test can evaluate, it has been reported that such dilution is significantly reduced in the very old in comparison with the young: 90 mOsm/L vs 40 mOsm/L, respectively ($P = 0.01$)[14].

Finally, as regards the evaluation of the urinary concentration capacity (using the 16 h water restriction test) urinary osmolality was significantly lower in the very old group (690 mOsm/L) in comparison with the young (980 mOsm/L), $P = 0.03$. This has been attributed to the senile medullar hypotonocity$^{[3,24]}$. The lower reabsorption of sodium in TALH is translated into a lower medullar concentration of sodium, which causes senile medullar hypotonocity and as a consequence to a reduction in the urinary concentration capacity, which can be the cause of dehydration in the old in situations of high loss of water or low intake$^{[11]}$.

Furosemide intravenous infusion (furosemide test) shows that fractional excretion of sodium (FENa) post-furosemide infusion is significantly lower in the very old group in comparison with the young one: FENa: 5.5% (very old) vs 8% (young), $P = 0.05$. Since furosemide stimulates sodium loss due to the inhibition of its reabsorption at the level of the TALH, the lower increase in soduria after furosemide infusion in the very old in comparison with the young could be explained by the functional reduction in the TALH (furosemide blocking site) due to the senescence process$^{[23-29]}$. Clinical consequences: From the clinical point of view, the above mentioned reduction in the tubular capacity to reabsorb sodium fosters sodium depletion and its clinical consequences: hypovolemia, hyponatremia caused by a sodium deficit (senile sodium loss) in old people on hyposodic diets and/or diuretic treatment.

**POTASSIUM HANDLING**

The collecting tubules are the nephronal segment where potassium secretion, and sodium and water reabsorption take place$^{[9]}$. Aldosterone bioactivity in this segment is studied using the furosemide test, which ultimately generates a discrete hypovolemia that stimulates the release of this hormone, which in turn stimulates the secretion of potassium in the collecting tubules. In this test, it is observed that the basal fractional excretion of potassium (FEK) (before furosemide infusion) is not significantly different in the young and the very old group, whereas the highest FEK post-infusion of furosemide is significantly lower in the very old group in comparison with the young one: 27% (very old) vs 35% (young), $P = 0.04$, with the very old group reaching this peak of excretion later than the young one: 120 min vs 30 min, respectively. The values of aldosterone (post-infusion of furosemide) are significantly higher in the very old group in comparison with the young: 113 ng/dL vs 70 ng/dL ($P < 0.001$), in spite of the lower potassium excretion observed in the very old, suggesting the existence of a kind of resistance to aldosterone by the senile collecting tubules$^{[29]}$.

The previously described physiological alterations also show that the characteristic senile sodium urinary loss depends not only on the reduced sodium reabsorbed in the TALH but also in the collecting tubules$^{[24]}$. The information obtained by means of the furosemide test (senile hyposecretion of potassium) explains why the tubular handling of potassium (measured as FEK and transtubular potassium gradient: TTKG) in basal situation, does not show any significant difference between the very old group and the young one, despite the existence of lower glomerular filtration in the very old, which ultimately accounts for the relatively reduced cation excretion in the very old, since it is known that the potassium excretion tends to increase paralelly to the reduction of glomerular filtration: FEK: 10% (young) vs 8% (very old); TTKG: 4 (young) vs 4 (very old), $P = NS$[29]. Clinical consequences: the reduced potassium secretion capability usually found in very old people explains how easy it is for this aged group to develop hyperkalemia when administered drugs which promotes potassium saving, such as converting enzyme inhibitors and/or angiotensin II receptor blockers$^{[57-59]}$.

**CONCLUSION**

Renal handling of many substances (creatinine, urea, sodium, water, potassium) significantly differs between very old healthy people and young one, while there is no change in uric acid renal handling between these groups.

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