Age-Related Increase in Plasma Urea Level and Decrease in Fractional Urea Excretion: Clinical Application in the Syndrome of Inappropriate Secretion of Antidiuretic Hormone

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This study confirms in humans an age-related increase in plasma urea levels ($r = 0.62$; $P < 0.001$; $y = 0.229x + 18.26$) and no correlation between plasma creatinine and age ($r = 0.06$; NS). Fractional urea excretion (FE urea) decreases with age ($r = -0.41$; $P < 0.001$; $y = -0.226x + 55$). Comparing urea and creatinine clearances, measured in 19 young and in 15 old women, a larger decrease of urea clearance (−56%) compared with the creatinine clearance (−43%) was observed as expected, explaining the lower FE urea in the elderly. In old women, the daily urea excretion was 27% and the daily creatinine excretion was 42% lower than in young women. An age-related decrease of same magnitude in both creatinine production and creatinine clearance explains why plasma creatinine remains stable with increasing age. The observation of a more important decrease in urea clearance (56%) than in urea production (27%) in older women led to an expected increase in plasma urea of 29%. These observations incited a comparison of biochemical profiles from younger and older patients with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Young patients with SIADH present lower mean plasma urea (18 ± 8 mg/dl) and higher mean FE urea (58 ± 14%), compared with both young control subjects (mean plasma urea 27 ± 7 mg/dl; mean FE urea 46 ± 10%) and old patients with SIADH (mean plasma urea 29 ± 8 mg/dl; mean FE urea 44 ± 15%). Physicians must realize that frankly low plasma urea values and high FE urea values can be expected only in young patients with SIADH, whereas old patients with SIADH will present values of plasma urea and FE urea in the same range than young control subjects. However, old patients with SIADH show still lower mean plasma urea values and higher mean FE urea values, compared with old control subjects (mean plasma urea 39 ± 8 mg/dl; mean FE urea 36 ± 9%), in whom plasma urea values between 40 and 50 mg/dl must be considered as usual.

Clin J Am Soc Nephrol 1: 909–914, 2006. doi: 10.2215/CJN.00320106

Both plasma urea and fractional urea excretion (FE urea) are considered as useful biochemical parameters in the differential diagnosis of salt-depleted hyponatremic and patients with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (1–3). Hyponatremia in SIADH is usually associated with a low plasma urea as a result of a high FE urea (4), whereas in hyponatremia that is caused by salt depletion (SD), plasma urea usually is increased as a result of an abnormal low FE urea (5) (prerenal uremia). Unfortunately, the usefulness of plasma urea and FE urea in discriminating SIADH and SD is limited by an important degree of "overlapping" values. In earlier work (6), we noted that plasma urea values >30 mg/dl were observed in 82% of patients with SD, whereas plasma urea values <30 mg/dl were seen in 79% of patients with SIADH. Eighty-two percent of the patients with salt-depleted hyponatremic presented FE urea values <50%, but only 52% of the patients with SIADH showed FE urea values >50%.

One of the explanations for such overlapping results in plasma urea and FE urea could be age, to which no attention was paid in this previous study (6). It is widely known that glomerular filtration decreases with age, but this is not associated with an increase in plasma creatinine, as a result of a concomitant age-related decrease in muscle mass and creatinine production (7). Some studies report an increase in plasma urea in the elderly (8–10).

We observed that whereas plasma creatinine did not increase with age, plasma urea did and that it was accompanied by a decrease in FE urea. Our study shows that old patients with SIADH have higher plasma urea and lower FE urea than young patients with SIADH but still lower plasma urea and higher FE urea than old normonatremic control subjects.

Materials and Methods

Study 1

We studied the relationship between plasma urea and age in 107 consecutive, ambulant, normonatremic subjects who were in good health (mean age 57 ± 23 yr) and did not have any illnesses or were

Received January 24, 2006. Accepted May 13, 2006.

Published online ahead of print. Publication date available at www.cjasn.org.

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ISSN: 1555-9041/105-0909

taking drugs that influence water, electrolyte, or urea handling. All these subjects presented a plasma creatinine that was not higher than 1.1 mg/dl. In 87 of them, we searched whether a correlation existed between FE urea and age. Therefore, we analyzed only the subjects with a urinary-to-plasma creatinine ratio (U/P creat) between 50 and 150, to avoid "instability" of FE urea, as a result of a brisk change in diuresis, known as the exaltation phenomenon (11). All these patients were under a normal salt diet. A morning plasma sample and a urinary spot analysis for creatinine and urea were carried out after overnight fasting, allowing the calculation of FE urea (FE urea = U urea/P urea × P creat/U creat × 100), a useful biochemical parameter for physicians because it can be calculated without knowledge of precise daily urinary volumes, which are more difficult to obtain.

Study 2

We had the opportunity to measure in 19 young (<40 yr) women creatinine clearance, urea clearance, and their daily excretion of creatinine and urea. We compared the results with those of 15 old women (>70 yr).

Study 3

Finally, we compared the biochemical volume-related parameters of 14 young patients with SIADH (<60 yr; five women and nine women) and 18 old patients with SIADH (>70 yr; 10 women and eight men) with those of young and old control subjects of comparable age. Each patient with SIADH was matched to two normonatremic control subjects who were of the same gender, were of comparable age (within a range of 2 yr), and had similar diuresis, indirectly measured by the ratio U/P creat. All the patients with SIADH corresponded to the widely known characteristics of SIADH: True hyponatremia with high natriuresis, high urinary osmolality, and normal plasma cortisol and thyroid function.

The linear regression model was used for the relationships between plasma urea and age and between FE urea and age. Comparisons between young and old normonatremic women and between young and old patients with SIADH and young and old matched control subjects were judged on their significance level by *t* test.

Results

Study 1

We confirm an age-related increase in plasma urea in 107 patients without any illnesses or drugs that influence water, electrolyte, or urea handling ($r = 0.62$; $P < 0.001$; $y = 0.229x + 18.26$; Figure 1, top). Plasma creatinine, conversely, was not correlated with age ($r = 0.06$; NS; Figure 1, bottom). For 87 of these 107 patients, who had U/P creat ratios between 50 and 150, FE urea and age were inversely correlated ($r = -0.41$; $P < 0.001$; $y = -0.226x + 55$; Figure 2, top). Figure 2, bottom, shows also a mild increase in fractional sodium excretion values with increasing age ($r = 0.27$; $P < 0.02$; $y = 0.0046x + 0.365$).

Study 2

Table 1 presents the comparative results of 19 young and 15 old women for urea and creatinine clearances, as well as their daily urinary urea and creatinine excretion. As could be expected, creatinine clearance and urea clearance were significantly lower in old than in young women ($P < 0.001$ for each). Creatinine clearance was on the average 43% lower and urea clearance 56% lower. This greater fall of urea than creatinine clearance with age is consistent with the fact that FE urea is

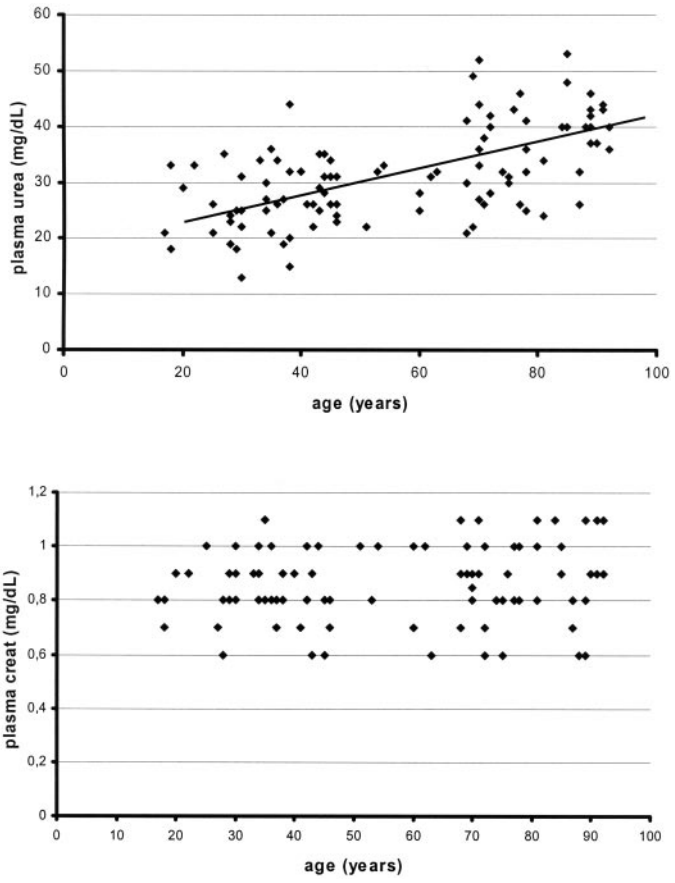

Figure 1. Relationships between plasma urea and age (top; $y = 0.229x + 18.26$; $r = 0.62$; $P < 0.001$) and lack of correlation between plasma creatinine and age (bottom) in 107 patients.

inversely correlated with age, as seen in study 1. The mean daily creatinine excretion was 42% lower ($P < 0.001$; Table 1) in older women, compared with younger women, whereas mean daily urea excretion in older women was only 27% lower ($P < 0.01$; Table 1). The daily excretion of osmoles was 53% lower in old compared with young women ($P < 0.001$; Table 1).

Study 3

These age-related differences in plasma urea and FE urea incited us to compare biochemical profiles from younger and older patients with SIADH. Table 2 summarizes the usual biochemical characteristics from both young and old patients with SIADH, compared with those of normonatremic control subjects matched for gender and age. Young patients with SIADH present lower mean plasma urea and higher mean FE urea compared with both young control subjects ($P < 0.01$ for both mean plasma urea and mean FE urea; Table 2) and compared old patients with SIADH ($P < 0.001$ for mean plasma urea and $P < 0.02$ for mean FE urea; Table 2). However, the 18 old patients with SIADH show a still lower mean plasma urea value ($P < 0.001$; Table 2) and a higher mean FE urea value ($P < 0.02$; Table 2), compared with the 36 old control subjects.

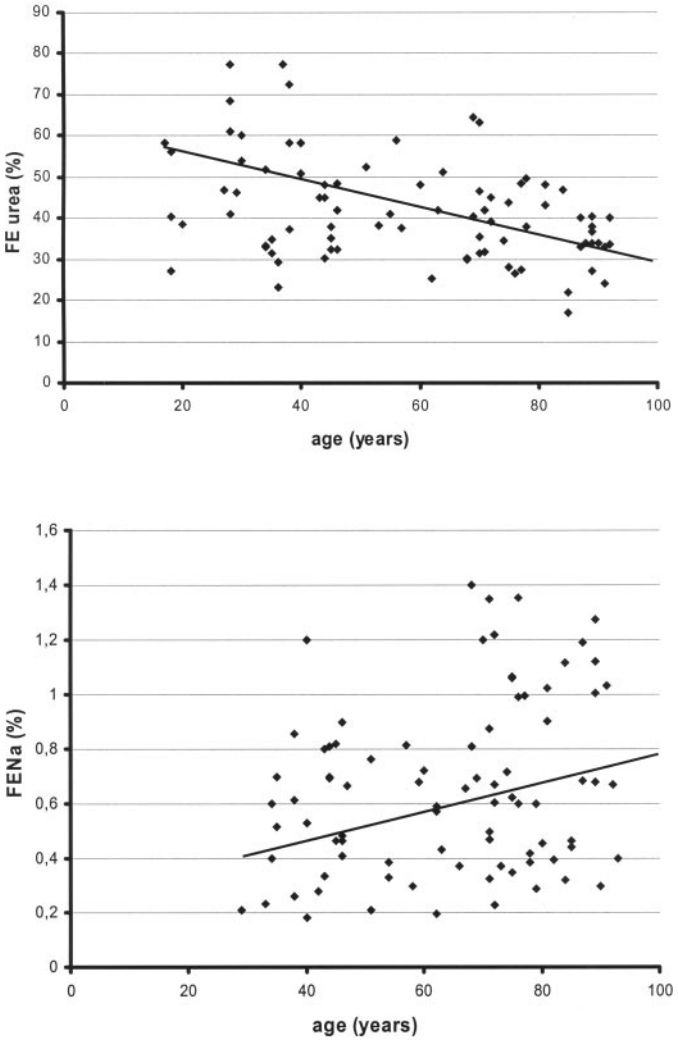

Figure 2. Relationship between fractional urea excretion (FE urea) and age (top; $y = -0.226x + 55$; $r = -0.41$; $P < 0.001$) and between fractional sodium excretion (FENa) and age (bottom; $y = 0.0046x + 0.365$; $r = 0.27$; $P < 0.02$) in 87 patients with an urinary-to-plasma creatinine ratio between 50 and 150.

Table 1. Comparison of daily urea and creatinine excretion in 19 young women (<40 yr) and 15 old women (>70 yr)[a]

	Young Women ($n = 19$)	Old Women ($n = 15$)
Age (yr)	31 ± 7	75 ± 6
Weight (kg)	59 ± 15	64 ± 9
Diuresis (L/24 h)	1.3 ± 0.6	1.1 ± 0.7
P Na (mEq/L)	140 ± 2	141 ± 3
P urea (mg/dl)	25 ± 7	36 ± 7[b]
P creat (mg/dl)	0.8 ± 0.1	0.9 ± 0.1
P UA (mg/dl)	3.9 ± 1.5	4.2 ± 1
U osm (mOsm/kg)	684 ± 238	414 ± 119[b]
FENa (%)	0.7 ± 0.3	1.1 ± 0.5[c]
FE urea (%)	52 ± 15	42 ± 10[d]
V/CrCl (%)	0.9 ± 0.5	1.8 ± 0.7[b]
CrCl (ml/min)	107 ± 26	61 ± 16[b]
Urea clearance (ml/min)	57 ± 25	25 ± 8[b]
Cr excretion (mg/kg 24 h)	18.9 ± 2.3	10.9 ± 1.5[b]
Urea excretion (mg/kg 24 h)	270 ± 61	196 ± 50[c]
Osmole excretion (mOsm/kg 24 h)	13.9 ± 5.2	6.5 ± 3.9[b]

[a]Data are means ± SD. CrCl, creatinine clearance; creat, creatinine; FE, fractional excretion; P, plasma.
[b]$P < 0.001$ *versus* young women.
[c]$P < 0.01$ *versus* young women.
[d]$P < 0.05$ *versus* young women.

Discussion

Plasma urea and FE urea are frequently used parameters in the differential diagnosis of hyponatremia, but sometimes they fail in their predictive value of saline responsiveness in individual patients with hyponatremia (3,6). A first reason could be that using FE urea in the evaluation of the volemia state of a patient can be misleading when the urine spot sample is carried out just after a brisk change in urine flow rate. As urine flow rate is rapidly increased, a transient abrupt rise in urea excretion occurs before the new steady state in urea excretion is reached (11). This short period is limited in the time (60 to 90 min) but can induce misleading results in urea excretion, when urine spot samples (*e.g.*, to determine FE urea) are carried out, shortly after increasing urine flow rate. This is known as the exaltation phenomenon (11).

Another reason to explain why these biochemical parameters can fail in their predictive value of saline responsiveness could result from an influence on plasma urea and FE urea by age. How can we explain higher plasma urea levels in the elderly? Elderly individuals have lower protein intake (10). This could explain lower urea clearance (1,12), but in case of lower protein intake, we expect lower plasma urea values than in younger control subjects with higher protein intake. Reduction in urea excretion on a low-protein intake is achieved not only by reductions in GFR and plasma urea but also by a marked increase in net urea reabsorption along the distal parts of the nephron, without change in the intensity of urea reabsorption in proximal segments (1,13). Observations in rats, sheep, dogs, and humans suggest that in addition to an increase in passive urea reabsorption, an active urea reabsorption takes place in the collecting duct (1,13). This adaptation to a low-protein diet is slow. In rats, for example, the appearance of an active reabsorption in the collecting ducts requires 3 wk to become detectable (1). Murdaugh *et al.* (12) already demonstrated long ago that the healthy human kidney is able to reabsorb urea actively after several weeks on a low-protein diet, even if less intensely than in sheep and dogs. The exact mechanism remains unknown.

An attractive hypothesis to explain our results seems to be the widely known and progressive age–related reduction in GFR. The finding of considerably decreased creatinine clearance values without elevation of serum creatinine values in the elderly usually is explained by a great reduction with age in

Table 2. Comparison of usual biochemical parameters of 14 young patients with SIADH, 28 young control subjects, 18 old patients with SIADH, and 36 old control subjects[a]

	Young Patients with SIADH (n = 14; 5 W/9 M)	Young Control Subject (n = 28; 10 W/18 M)	Old Patients with SIADH (n = 18; 10 W/8 M)	Old Control Subjects (n = 36; 20 W/16 M)
Age (yr)	45 ± 9	43 ± 6	75 ± 5	77 ± 8
P Na (mEq/L)	126 ± 3	140 ± 2	125 ± 5	140 ± 2
P urea (mg/dl)	18 ± 8[b,d]	27 ± 7	29 ± 8	39 ± 8[c,d]
P creat (mg/dl)	0.7 ± 0.1[c]	0.9 ± 0.1	0.8 ± 0.2	0.9 ± 0.2
P UA (mg/dl)	2.4 ± 0.8[c]	5 ± 1.6	2.8 ± 0.9	5.4 ± 1.5[d]
U osm (mOsm/kg)	498 ± 162	515 ± 212	530 ± 153	582 ± 159
FE Na (%)	0.8 ± 0.4	0.6 ± 0.2	0.7 ± 0.3	0.7 ± 0.3
FE urea (%)	58 ± 14[b,e]	46 ± 10	44 ± 15	36 ± 9[c,e]
FE UA (%)	16 ± 6[c]	8 ± 4	14 ± 6	9 ± 4[f]
V/CrCl × 100 (%)	1 ± 0.3	1.1 ± 0.4	1 ± 0.4	1.1 ± 0.4

[a]Data are means ± SD. SIADH, syndrome of inappropriate secretion of antidiuretic hormone.
[b]$P < 0.01$, [c]$P < 0.001$ *versus* young control subjects.
[d]$P < 0.001$, [e]$P < 0.02$, [f]$P < 0.01$ *versus* old patients with SIADH.

lean body mass and thereby in creatinine production (14). Moreover, a reduction in the glomerular ultrafiltration coefficient contributes to GFR depression in aging individuals. This is due in part to structural changes that lower the glomerular ultrafiltration coefficient and in part to the reduction in the actual number of glomeruli (15). Aging humans therefore can been considered to present a "physiologic" degree of renal insufficiency. However, the ratio of plasma urea to plasma creatinine remains stable with decreasing creatinine clearance (5), whereas this ratio increased with age in our studied patients (study 1; Figure 1). The FE urea is expected to be high in renal insufficiency (16) but decreased with age in our observation (study 1; Figure 2). It suggests that the origin of a higher plasma urea and a lower FE urea in the elderly is not due to the age-related reduction in GFR. Moreover, the age-related decrease in urea clearance is sharper than the corresponding decrease in creatinine clearance (Table 1). Old women compared with young ones show a 43% reduction in creatinine clearance but a concomitant reduction in their urea clearance of 56% (Table 1), explaining lower FE urea values.

Figure 2 (bottom) shows that fractional sodium excretion mildly increases with age ($r = 0.27$; $P < 0.02$; $y = 0.0046x + 0.365$), indicating that the observed decrease of FE urea with age is not due to a mild solute depletion. If we apply the Cockcroft-Gault formula to estimate GFR in the 19 young and in the 15 old women shown in Table 1, we calculate the GFR at 93 ± 24 ml/min in the young women and GFR at 58 ± 13 ml/min in the group of the old women. These values are somewhat lower than the real measures of the GFR by means of the creatinine clearance, a method of appreciation of GFR near to that of inulin clearance (measured creatinine clearances 107 ± 26 ml/min for the young and 61 ± 16 ml/min in the old women). However, it is widely known that the Cockcroft-Gault formula underestimates GFR in individuals with normal kidneys (9).

It seems a logical deduction to consider that plasma creatinine remains at a same level, when by the effect of age, a fall in glomerular filtration of 43% is accompanied by an almost equal fall in creatinine production of 42%, estimated by the creatinine excretion in steady state (Table 1). However, the same reasoning for urea shows us that an age-related fall in urea clearance of approximately 56% is counteracted only by a much smaller fall in urea excretion of approximately 27% (Table 1), resulting in an increase in plasma urea of approximately 29%. Hence, we could expect that the mean plasma urea of old women should be 29% higher than mean plasma urea of young ones. Compared with the mean plasma urea of 25 mg/dl in young women, a mean plasma urea of 32.3 mg/dl has to be expected in old women (observed mean plasma urea 36 mg/dl; Table 1).

Increased tubular reabsorption is involved in some pathologic increases of plasma urea. For example, the mechanisms of increased plasma urea after diuretic therapy in uremic patients and renal handling of urea in individuals with persistent azotemia and normal renal function are explained by an increased tubular reabsorption of urea, presumably in the distal part of the nephron (17,18). To our knowledge, increased tubular reabsorption in the elderly has not been reported. The association of higher plasma urea levels and lower FE urea values in the elderly could reflect a preservation of the tubular effect of vasopressin on urea reabsorption, which possibly differs from the widely known age-related decrease in water reabsorption in the elderly (19–21), despite an enhanced osmoreceptor sensitivity to vasopressin release (7,22) and higher vasopressin levels (7,23–25). In rats, age-associated defects in urine concentration are accompanied by a downregulation of renal vasopressin V_2 receptors and aquaporin-2 expression (26). Some urea transporter expressions have been studied in the aging kidney of rats. Markedly reduced kidney UT-A1, UT-A2, and UT-B1 abundances have been reported in senescent rats (27,28). Moreover, a different regional expression for UT-B1 within the inner medulla has been disclosed in the course of aging. Senescent rats have a much lower abundance of the transporter in the base of the inner medulla, whereas their UT-B1 protein content compared with younger adult rats is

higher in the tip of the inner medulla (27). It was shown recently in transgenic mice with a selective deficiency in UT-B (the urea transporter protein expressed in descending vasa recta and red blood cells) that lack of UT-B in normal conditions leads to a 44% elevation in plasma urea and to a 25% decrease in urea clearance (29).

Recently, it was suggested that just like for uric acid, an active urea secretion does exist somewhere along the renal tubule (1,30). An age-related decrease in urea secretion could be another possible mechanism to explain our findings. This urea secretion necessitates an active transport. It could be understood that such active transport could be less effective when age increases. Further fundamental research is required to study the exact mechanisms of the higher plasma urea and lower urea clearance in the elderly.

Which are the practical implications of these findings? In healthy elderly, physicians must not be surprised to observe plasma urea in the range of 40 to 50 mg/dl. Such values must been considered as usual values and do not implicate slight volume depletion. Another implication does exist in the differential diagnostic field of hyponatremia. Plasma urea and FE urea are commonly used parameters to distinguish patients with SIADH from salt-depleted patients with hyponatremia. Age-related changes in these parameters probably explain why their discriminating accuracy is not optimal. Using plasma urea as a biochemical parameter to recognize patients with SIADH, we observe that plasma urea values <30 mg/dl are the rule in young patients with SIADH (13 of 14 patients) but not in old patients with SIADH, in whom only 56% (10 of 18 patients) presented such plasma urea levels <30 mg/dl. In the same way, FE urea >55% is observed in 64% (nine of 14 patients) of young patients with SIADH but only in 22% (four of 18 patients) of the old patients with SIADH.

Physicians must realize that frankly low plasma urea levels and high FE urea levels can be expected only in young patients with SIADH, whereas old patients with SIADH will present values of plasma urea and FE urea in the same range as those of young control subjects. However, old patients with SIADH show still lower plasma urea values and higher FE urea values compared with old control subjects. This influence of age on plasma urea and FE urea has to be kept in mind when physicians judge kidney function of healthy elderly or would use these parameters to discriminate patients with SIADH from salt-depleted patients with hyponatremia.

Acknowledgments

This work was supported by a grant from the Fonds National de la Recherche Scientifique; Convention 3.45.09.03.

We thank Lise Bankir for helpful advice and for the constructive review of this manuscript.

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