Urotensin II is an inverse predictor of death and fatal cardiovascular events in chronic kidney disease

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Urotensin II (UTN), a cyclic vasoactive peptide expressed in multiple organs, had higher plasma levels that was previously shown to predict longer survival in dialysis patients. We sought to determine if this association exists in earlier stages of chronic kidney disease (CKD) by studying a cohort of 122 incident clinically stable pre-dialysis patients. Linear models were used to determine associations of UTN with baseline characteristics such as renal function and traditional and nontraditional cardiovascular risk factors. We used Cox regression analysis to model time-to-death as a function of UTN and the same variables for adjustment including a time-varying covariate that indicated progression to end-stage renal disease. No correlation was found between baseline glomerular filtration rate and plasma UTN. In adjusted analysis, UTN correlated directly with serum albumin and, inversely, with history of previous coronary events. During a mean follow-up of 41 months, 43 patients died – 29 from cardiovascular events. After adjusting for potential confounding factors, increased UTN predicted lower risk of death from all-cause and cardiovascular causes. In patients with moderate-to-severe CKD, plasma UTN was found to be an inverse predictor of overall and cardiovascular mortality.

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Urotensin II (UTN) is a highly conserved cyclic undecapeptide expressed in disparate species from teleost fish to mammals.[1–3] In humans, UTN is intensely represented in various organ systems including the nervous system, the gastrointestinal system, the kidney, and the cardiovascular system. Interest on this peptide was generated by a series of observations showing that the plasma concentration and/or the gene expression at tissue level of UTN is altered in a large series of diseases including atherosclerosis,[1] hypertension,[4] cardiac ischemia,[5] heart failure,[6,7] diabetic nephropathy,[8–10] and advanced renal insufficiency.[11,12] Although high levels of this compound are generally considered as potentially noxious to the heart and the kidney, it is presently unknown whether high UTN determines adverse clinical outcomes.[2] Indeed this peptide emerged as a potentially vasoprotective substance in some experiments in human vessels *in vitro*,[13] whereas other experimental data indicated that UTN either does not produce measurable changes in systemic and peripheral hemodynamics in healthy humans[14] or that it may induce a sustained vasoconstriction in the forearm.[15] UTN dilates cutaneous vessels in healthy subjects,[16,17] whereas it produces an opposite effect in patients with hypertension[16] and in heart failure.[17] Investigating the implications of UTN, derangements for human health is recognized as a much challenging problem because experiments performed so far in animal and *in vitro* models have shown that the effect of this peptide depends on species, administration route, vascular bed, organ system, and physiological or pathophysiological condition.[3] At this stage of knowledge well-conceived prospective studies in patients with cardiovascular and renal diseases may offer important interpretative clues for understanding the relationship between UTN and disease states and to generate scientific hypotheses to be tested in mechanistic and intervention studies.

Chronic kidney disease (CKD) represents a useful model to explore the potential role of UTN in human diseases because it was shown that the plasma concentration of this substance is increased both in patients with diabetic nephropathy and moderate-to-severe renal insufficiency and in patients with end-stage renal disease (ESRD). In recent studies in ESRD, we found that UTN is inversely, rather than directly, related with cardiovascular stress hormones such as

norepinephrine and plasma brain natriuretic peptide,[18] and that high plasma levels of this peptide predict better clinical outcomes, that is reduced cardiovascular complications, in this population.[11] To explore further the implications of raised UTN in renal diseases, we have now extended our observations to a well-characterized, incident cohort of stage 2–5 CKD patients. In this cohort, we performed a detailed analysis of the relationship between UTN with death and fatal cardiovascular events. The results of this study indicate that high UTN levels signals a situation of relatively lower risk for death and atherosclerotic complications in these patients.

RESULTS

Patient characteristics

Table 1 presents the demographic and the baseline characteristics of the study cohort. At enrollment, the study population had an average age of 71 ± 11 years, 64% of the patients were male, 24% had diabetes, and 58% had background cardiovascular complications. Baseline glomerular filtration rate (GFR) was $31 \pm 15\,ml\,min^{-1}$ per $1.73\,m^2$, and serum creatinine was $2.4 \pm 1.2\,mg\,dl^{-1}$. In this cohort, plasma UTN (median $4.4\,ng\,ml^{-1}$, interquartile range: 2.0–7.4 $ng\,ml^{-1}$) was significantly higher ($P<0.01$) than that in healthy subjects (median $2.8\,ng\,ml^{-1}$, interquartile range: 1.9–4.6 $ng\,ml^{-1}$), but did not differ significantly by diabetic status ($P=0.255$).

Correlates of UTN and multiple linear regression model

At univariate analysis, plasma UTN was related inversely to age ($r=-0.18$, $P=0.04$), history of coronary artery disease ($r=-0.28$, $P=0.002$) and serum C-reactive protein (CRP; $r=-0.21$, $P=0.02$) and directly to serum albumin ($r=0.37$, $P<0.001$), male sex ($r=0.22$, $P=0.02$), and serum creatinine ($r=0.18$, $P=0.04$). No association was found between plasma UTN and GFR ($r=-0.01$, $P=0.87$), as well as between UTN and the remaining risk factors listed in Table 1. After adjustment for all univariate correlates of plasma UTN, only serum albumin ($\beta=0.26$, $P=0.004$) and history of coronary artery disease ($\beta=-0.22$, $P=0.01$) maintained an independent association with plasma UTN (Table 2). In this multiple regression model, due to the collinearity between history of coronary artery disease and serum albumin with serum CRP ($r=0.30$, $P=0.001$ and $r=-0.24$, $P=0.006$, respectively), this latter variable failed to correlate significantly with plasma UTN. Serum CRP becomes a significant correlate of plasma UTN ($\beta=-0.18$, $P=0.05$) only when history of coronary artery disease and serum albumin were excluded from the model.

Survival data

During the study period (mean follow-up 41 months; median 48, range 3.4–60), 43 patients died (29 for cardiovascular events, 8 for malignancies or cachexia, and 6 for infectious diseases); 29 subjects started dialysis and 13 had a reduction of GFR to values lower than half of their baseline measures. Table 3 summarizes the unadjusted hazard ratios for death from all causes associated with UTN and other considered risk factors. In this crude analysis, UTN, acute phase reactive proteins (serum albumin, CRP, and fibrinogen), baseline GFR and proteinuria, update values of GFR over time or progression to ESRD, and complications of CKD such as anemia as well as previous history of coronary artery disease were associated with adverse outcomes, whereas remaining variables in Table 1 were not. Other comorbid conditions, including diabetes and neoplasm, and current specific and multiple treatments were not found to be significantly associated with death.

An initial model was built on age, baseline GFR and proteinuria, UTN, and CRP. The use of updated rather than baseline GFR values improved the model fit, whereas history of coronary artery disease replaced age (those with

Table 1 | Main demographic, somato-metric, clinical, and biochemical parameters of the study population

Age (year)	71.0±11.0
BMI ($kg\,m^{-2}$)	26.6±4.7 (>25 in 74 patients (61%))
Male sex no. (%)	78 (64%)
Diabetics no. (%)	29 (24%)
Presence of any cardiovascular disease (%)	75 (61%)
Patients with coronary artery disease no. (%)	44 (36%)
Patients with peripheral vascular disease no. (%)	34 (28%)
Patients with cerebro-vascular disease no. (%)	31 (25%)
Patients with heart failure no. (%)	34 (28%)
Systolic pressure (mm Hg)	139.8±14.0 (>140 in 37 patients (30%))
Diastolic pressure (mm Hg)	81.1±7.6 (>90 in 7 patients (6%))
Albumin ($g\,dl^{-1}$)	3.9±0.6 (<4 in 72 patients (59%))
Calcium ($mg\,dl^{-1}$)	9.4±0.7 (<8.8 in 13 patients (11%)) (>10.2 in 6 patients (5%))
Phosphate ($mg\,dl^{-1}$)	3.4±0.8 (<2.5 in 8 patients (7%)) (>5.0 in 5 patients (4%))
Hemoglobin ($g\,dl^{-1}$)	12.8±1.5 (Females: <12.0 in 20 patients (45%)) (Males: <13.6 in 46 patients (59%))
Cholesterol ($mg\,dl^{-1}$)	209±49 (>265 in 16 patients (13%))
HDL ($mg\,dl^{-1}$)	53±13 (<30 in 0 patient)
Triglycerides ($mg\,dl^{-1}$)	134 (105–190) (>160 in 45 patients (37%))
CRP ($mg\,l^{-1}$)	4.7 (1.4–10.1) (>3 in 79 patients (65%))
Homocysteine ($\mu mol\,l^{-1}$)	23.7 (17.8–31.4) (>15 in 102 patients (84%))
Uric acid ($mg\,dl^{-1}$)	6.9±2.2 (>7 in 47 patients (38%))
UTN ($ng\,ml^{-1}$)	5.0±3.6
Urinary protein (mg per 24 h)	20 (absolute range 2–724)

BMI, body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; UTN, urotensin II.