Urotensin II is an inverse predictor of incident cardiovascular events in end-stage renal disease

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Urotensin II (UTN) is a vasoactive substance that may induce vasoconstriction or vasodilatation. Although this peptide is seen as a vasculotoxic substance, to date there is no prospective study examining the relationship between UTN and hard end points like cardiovascular (CV) events. UTN is much increased in end-stage renal disease (ESRD) and this disease may represent a useful natural model to explore the relationship between UTN and CV outcomes. In this study, we analysed the relationship between plasma UTN and incident CV events (fatal and non-fatal) in a cohort of 191 haemodialysis patients followed up for an average time of 3.6 years (range 0.07–5.8 years). Plasma UTN in haemodialysis patients (median: 6.5 ng/ml) was twice higher than in healthy subjects (median: 3.3 ng/ml). During the follow-up period, 94 patients died and 88 had incident fatal and non-fatal CV events. UTN was significantly lower in patients with incident CV events (median: 5.3 ng/ml) than in events-free patients (median: 7.1 ng/ml), and in a Kaplan–Meier analysis, high UTN was strongly and inversely associated with incident CV events ($P<0.001$). Multivariate Cox's regression analysis fully confirmed plasma UTN as an inverse predictor of adverse CV outcomes, and in this analysis, UTN resulted to be the third factor in rank, after age and diabetes, explaining the incidence of CV events. UTN is an inverse predictor of CV outcomes in ESRD. Our data suggest that UTN should not be necessarily seen as a vasculotoxic peptide in haemodialysis patients.

Kidney International (2006) **69,** 1253–1258. doi:10.1038/sj.ki.5000114; published online 1 March 2006

KEYWORDS: cardiovascular risk; dialysis; epidemiology; ESRD reverse epidemiology; urotensin

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Received 11 August 2005; revised 20 September 2005; accepted 6 October 2005; published online 1 March 2006

Urotensin II (UTN) is a cyclic undecapeptide with structural homology to somatostatin, which binds to an orphan G-protein receptor (GPR14) in the mouse and in humans.[1–3] Initially found to have potent vasoconstrictive activities in a variety of vessels from diverse species,[4] it is now clear that UTN also possesses endothelium-dependent vasodilatation properties in the rat[5,6] and in humans.[7] The plasma concentration of this peptide is increased in a variety of human diseases such as essential hypertension,[8] heart failure,[9–14] liver cirrhosis,[15] diabetic nephropathy[16,17] and chronic renal insufficiency.[18] The observation that UTN is overexpressed in coronary plaques in humans is of particular interest because it suggests that this peptide may be implicated in atheromatous complications in patients with coronary heart disease.[2] UTN in heart failure increases in parallel with hormones fundamental for cardiovascular (CV) homeostasis such as brain natriuretic peptide (BNP),[14] a phenomenon suggesting that high UTN participates in the counter-regulatory response to systolic failure. The potential relevance of UTN in CV biology is also highlighted by its high concentration in atherosclerotic lesions.[19]

Notwithstanding the growing interest on this peptide, to date there is no study in humans testing the relationship between UTN and solid outcome measures like mortality and incident CV events. This information is of obvious importance for the interpretation of the biological relevance of UTN because it was emphasized that there are arguments for viewing this substance both as a vasculotoxic and as a vasculoprotective one.[4,20]

End-stage renal disease (ESRD) is a condition where circulating UTN is much increased and it was speculated that UTN is implicated in CV complications in uraemic individuals.[18] Therefore, this disease may represent an useful natural model to explore the relationship between UTN and CV outcomes. Somewhat unexpectedly, in a pilot study in a group of 63 well-nourished, uncomplicated, ESRD patients, we found that UTN was inversely related to inflammation markers and pulse pressure (Mallamaci F *et al. XLI Congress ERA-EDTA*, 2004 (abstract); abstract book: 84pp). Likewise, in a recent survey in a large cohort of dialysis patients, we found that UTN was inversely, rather than directly, related with CV stress hormones like norepinephrine (NE) and BNP.[21] These apparently paradoxical associations may

suggest that relatively higher plasma UTN levels may signal a vasculoprotective situation in these patients.

To shed further light on this issue herein, we analyse the relationship between UTN and incident CV events in this cohort over a follow-up extended to 5.8 years.

RESULTS

The prevalence of diabetes mellitus in the study cohort was 15% (i.e. 28 patients out of 191). Ninety-four patients had had one or more CV events (electrocardiogram documented angina or myocardial infarction, peripheral artery diseases, arrhythmia, transient ischaemic attacks and stroke). Plasma UTN in haemodialysis patients (median: 6.5 ng/ml, inter-quartile range 2.9–11.5 ng/ml) was twice higher than in healthy subjects (median: 3.3, 2.4–4.6 ng/ml) (Figure 1); it exceeded the upper limit of the normal range (90th percentile in healthy subjects: 6.8 ng/ml) in 92 out of 191 cases (48%) and it was higher than the median value in healthy subjects (3.3 ng/ml) in 136 cases (71%).

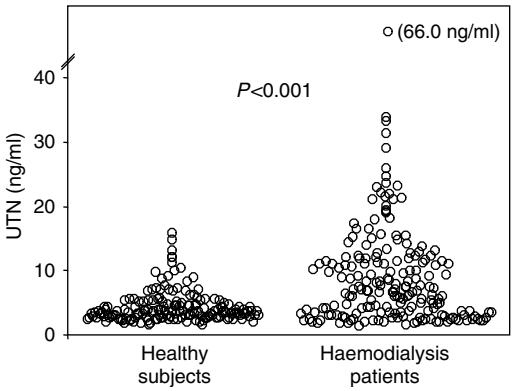

Figure 1 | Plasma levels of UTN in healthy subjects and in haemodialysis patients.

In Table 1, patients are grouped according to whether or not they developed incident CV events during the 5.8 years follow-up. Patients with incident CV events were older, with a higher prevalence of smokers and diabetics, with a higher burden of background CV complications and more likely to be on antihypertensive treatment. Furthermore, serum C-reactive protein (CRP) and plasma total homocysteine concentrations in these patients tended to be higher than in those who did not develop such events. NE and BNP were both raised in patients with incident CV events, but only BNP significantly so.

In this analysis, plasma UTN was significantly lower in patients with incident CV events (median: 5.3, 2.4–11.0 ng/ml) than in events-free patients (median: 7.1, 3.8–11.8 ng/ml) (Table 1) and inversely related both with plasma NE ($r=-0.28$, $P<0.001$) and BNP ($r=-0.41$, $P<0.001$).

Plasma urotensin and incident CV events

During the follow-up period, 94 patients died and 88 had incident CV events (fatal in 63 patients and non-fatal in the remaining 25 patients). Plasma UTN was lower in patients who died (median: 5.6, 2.4–11.5 ng/ml) than in those who survived (median: 6.8, 3.6–11.3 ng/ml), but the difference was not significant ($P=0.20$). Likewise, plasma UTN expressed as a dichotomous variable (on the basis of the median value in healthy subjects: cutoff 3.3 ng/ml) was weakly related to death at univariate Cox's analysis ($P=0.05$), but this association become weaker on multivariate analysis ($P=0.09$). However, in a Kaplan–Meier analysis, high UTN was strongly ($P<0.001$) and inversely associated with incident CV events (Figure 2). Multivariate Cox's regression analysis fully

Table 1 | Main demographic, somatometric, clinical and biochemical data of patients

	Without CV events (*n*=103)	With CV events (*n*=88)	*P*-value
Age (years)	54±16	64±11	<0.001
Duration of maintenance hemodialysis (months)	41 (18–110)	46 (22–103)	0.25
Male sex, *n* (%)	56 (54)	50 (57)	0.73
Smokers, *n* (%)	32 (31)	42 (48)	0.02
Diabetics, *n* (%)	7 (7)	21 (24)	0.001
With background CV complications, *n* (%)	36 (35)	58 (66)	<0.001
On antihypertensive therapy, *n* (%)	30 (29)	42 (48)	0.008
Haemoglobin (g/l)	108±17	106±20	0.34
Albumin (g/l)	42±5	41±5	0.14
Cholesterol (mg/dl)	207±57	207±55	0.99
Calcium phosphate ($mmol^2/l^2$)	4.6±1.3	4.5±1.0	0.71
Systolic pressure (mmHg)	138±22	144±27	0.15
Diastolic pressure (mmHg)	78±11	75±15	0.10
Heart rate (beats/min)	78±10	79±11	0.55
Urotensin (ng/ml)	7.1 (3.8–11.8)	5.3 (2.4–11.0)	0.04
CRP (mg/l)	4.7 (3.4–15.3)	9.6 (3.5–18.3)	0.06
Homocysteine (μmol/l)	25.7 (18.2–38.5)	28.7 (21.9–47.1)	0.08
NE (nmol/l)	2.78 (1.74–4.38)	3.31(1.64–6.33)	0.40
Brain natriuretic peptide (pmol/l)	15.9 (4.9–29.2)	28.9(13.9–48.9)	<0.001

Data are expressed mean±s.d., median and inter-quartile range or as percent frequency, as appropriate.