Natriuretic peptide and adrenomedullin levels in chronic renal failure and effects of peritoneal dialysis

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Plasma levels of B-type natriuretic peptide (BNP) and its N-terminal propeptide (NT-BNP) are elevated in renal impairment and provide a robust prognostic index. The effect of peritoneal dialysis on plasma NT-BNP, however, is unknown. Furthermore, no information exists regarding levels of the N-terminal propeptide for C-type natriuretic peptide (NT-CNP) in renal failure and the effects of peritoneal dialysis. Accordingly, we documented venous levels of these peptides, and adrenomedullin, across peritoneal dialysis. We measured venous BNP, NT-BNP, NT-CNP, adrenomedullin, blood urea nitrogen (BUN) and creatinine before, during and after completion of overnight peritoneal dialysis in 11 patients, and identical sampling was carried out in eight patients (controls) but between peritoneal dialysis treatments. Peptide levels were measured using well-validated, published methods. Baseline levels of NT-CNP (212, 150–303 pmol/l, median and 25th and 75th percentiles) were much higher than recorded previously in healthy volunteers or in heart failure, and correlated with plasma creatinine ($r_s = 0.53$, $P < 0.05$). Peritoneal dialysis had no effect on plasma NT-CNP, nor on NT-BNP, BNP or adrenomedullin (all elevated above normal), whereas both BUN and creatinine levels, as expected, declined ($P < 0.001$). We conclude that plasma levels of NT-CNP are grossly elevated in chronic renal failure and correlated with plasma creatinine, but are not altered by peritoneal dialysis. Likewise, BNP, NT-BNP and adrenomedullin are elevated but are not altered by peritoneal dialysis. This information is needed if levels of these hormones are to be used as prognostic indicators or as a guide to the management of patients with chronic renal failure.

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It is known that circulating concentrations of the bioactive cardiac natriuretic peptides, atrial and B-type natriuretic peptide (A-type peptide (ANP) and B-type peptide (BNP), respectively), are elevated in patients with impaired renal function.[1,2] Most reports are that plasma levels of these peptides relate not only to the severity of renal dysfunction but also to indices of cardiac structure and function such as left ventricular ejection fraction (inverse correlation) and left ventricular diameters, left ventricular mass index, and pulmonary artery or wedge pressure (positive correlations).[2,3] Furthermore, the CREED investigators, who studied a large cohort of patients requiring chronic dialysis, showed that plasma BNP and ANP levels were robust predictors of total and cardiovascular mortality.[4] Accordingly, it is possible that circulating concentrations of these peptides will provide an objective guide for the management of such patients in regard to their dietary habits, dialysis requirements and pharmacological treatment.[5]

Interpretation of plasma cardiac natriuretic peptide levels in patients with chronic renal failure, however, requires an understanding of the effects of dialysis on their circulating concentrations. Hemodialysis- and peritoneal dialysis-induced effects on plasma ANP and BNP have been reported, but it is not known whether levels of the 1–76 amino-acid N-terminal fragment (NT-BNP) of proBNP are altered by peritoneal dialysis. This is of potential importance as there has been speculation that NT-BNP might provide a better index of cardiac function or dysfunction than BNP itself.[6]

The first aim in the present study, therefore, was to document NT-BNP levels across peritoneal dialysis. The second aim was to record plasma levels of peptides that are likely to afford cardiovascular protection in patients with chronic renal failure and the effects on them of peritoneal dialysis. One is the recently discovered N-terminal fragment (NT-C-type natriuretic peptide (CNP)) of the propeptide of the third natriuretic peptide, CNP,[7] which circulates at higher concentrations than CNP itself. The other peptide is adrenomedullin, which is secreted largely by the vascular endothelium and whose levels are known to be elevated in renal failure.[8]

RESULTS

Characteristics of patients in the active and control groups are shown in Table 1. Body weight declined across dialysis by an average of 2.2 kg in the active group (range 0–5 kg). Plasma levels of BNP, NT-BNP, NT-CNP and adrenomedullin were elevated well above the normal range as determined in healthy volunteers using the same radioimmunoassays (Table 1). In the case of NT-CNP, the levels (212, 150–303 pmol/l, median and 25th and 75th percentiles) were also very much higher ($P<0.001$) than documented previously in 77 patients aged 74 ± 1.8 years (mean $\pm$ s.e.m.) with heart failure (32.4, 25.4–39.4 pmol/l)[9] and 101 healthy volunteers aged 66.5 ± 0.8 years (18.5, 15.8–28.9 pmol/l), again using the same assay (Figure 1). Baseline indices were similar in the two groups of patients with chronic renal failure except for plasma levels of NT-CNP, which were significantly higher in the active group than in controls ($P<0.01$).

Table 1 | Baseline indices (mean $\pm$ s.e.m., or median and interquartile range) in patients with chronic renal failure

	Active group (n=11)	Control group (n=8)	Normal range
Age (years)	44.7 $\pm$ 8	45.1 $\pm$ 5	—
Weight (kg)	67.5 $\pm$ 6	67.4 $\pm$ 4	—
Plasma BUN (mg/dl)	80 (59, 115)	92 (77, 114)	5–25
Plasma creatinine (mg/dl)	10.0 (6.6, 15.3)	7.4 (4.9, 11.3)	0.5–1.5
Plasma BNP (pmol/l	13.5 (8.0, 49.7)	14.1 (5.5, 149.6)	3–12
Plasma NT-BNP (pmol/l)	54 (41, 678)	81 (27, 1500)	2–50
Plasma NT-CNP (pmol/l)	269 (212, 321)**	148 (93, 167)	13–29
Plasma adrenomedullin (pmol/l)	9.5 (7.9, 18.7)	9.6 (7.6, 32.7)	4–28

**$P<0.01$ compared to the control group.

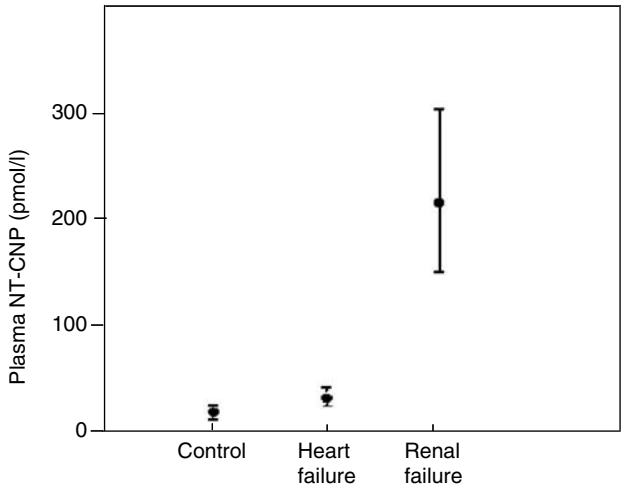

Figure 1 | Plasma levels of NT-CNP in healthy volunteers ($n=101$), patients with heart failure ($n=77$) and patients with chronic renal failure ($n=19$). Data are shown as median and 25th and 75th percentiles.

A statistically significant association was noted between baseline plasma levels of NT-CNP and creatinine ($r_s=0.53$, $P<0.05$, $n=19$, Figure 2). Patient age was not significantly related to any of the peptide hormones but correlated inversely with baseline levels of plasma creatinine ($r_s=-0.46$, $P<0.05$).

Plasma blood urea nitrogen (BUN) and creatinine levels fell significantly ($P<0.001$) across dialysis compared to those of controls (−25 (−36, −4) versus 2 (0.4, 4) mg/dl and −1.2 (−2.7, −0.5) versus 0.0 (−0.2, 0.4) mg/dl). By contrast, plasma levels of BNP, NT-BNP, NT-CNP and adrenomedullin did not change in either active or control patients (Table 2).

DISCUSSION

It is clear from previous reports that plasma levels of cardiac natriuretic peptides are elevated in patients with chronic renal failure.[1,2] In that their levels in the plasma correlate with haemodynamic indices and left ventricular mass and also predict cardiovascular and total mortality,[2–4] there is every possibility that they might prove to be clinically useful as one index of cardiac dysfunction and fluid status, and as a guide to the complex management of patients requiring long-term dialysis.[5] Interpretation of natriuretic peptide levels, however, requires an understanding of what factors can alter their circulating concentrations. In this regard, it is known that plasma levels of ANP fall substantially across both haemodialysis and peritoneal dialysis.[1,10] Compared with ANP, plasma BNP levels exhibit no change or a lesser percentage decline,[1,11] and Wahl *et al.*[12] reported that NT-BNP levels were altered little by haemodialysis, falling slightly (by 2.3%) when a high-flux membrane was used and

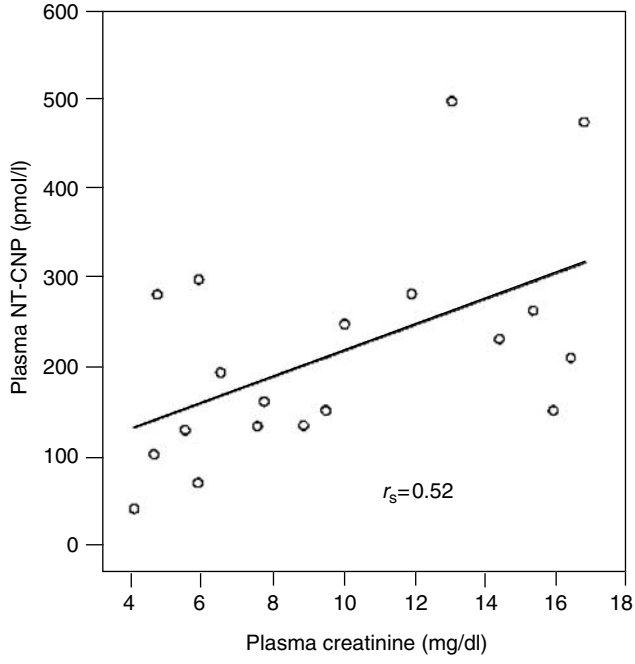

Figure 2 | Plasma levels of creatinine and NT-CNP in 19 patients with chronic renal failure.

Table 2 | Peptide hormone levels (median and interquartile range) before, during and after peritoneal dialysis (active group) and between dialyses (control group)

	Active group (*n*=11)			Control group (*n*=8)		
	Baseline	During dialysis	After dialysis	Baseline	During dialysis	After dialysis
Plasma BNP (pmol/l)	13.5 (8.0, 49.7)	11.3 (9.9, 52.1)	24.7 (7.6, 62.5)	14.1 (5.5, 149.6)	13.1 (6.3, 146.5)	13.7 (5.5, 139.9)
Plasma NT-BNP (pmol/l)	54 (41, 678)	63 (42, 652)	148 (41, 767)	81 (27, 1500)	87 (26, 1531)	79 (30, 1372)
Plasma NT-CNP (pmol/l)	269 (212, 321)	260 (177, 360)	286 (214, 369)	148 (93, 167)	135 (99, 216)	135 (99, 234)
Plasma adrenomedullin (pmol/l)	9.5 (7.9, 18.7)	13.7 (7.8, 15.1)	11.2 (9.3, 13.3)	9.6 (7.6, 32.7)	7.7 (6.7, 37.0)	8.1 (5.2, 28.8)

For the control group, the baseline, during dialysis and after dialysis samples were all drawn between regular peritoneal dialyses.

increasing minimally (by 4.9%) with a low-flux membrane. MacGregor *et al.*[11] reported a statistically significant though minor rise in NT-BNP with haemodialysis. The effect of peritoneal dialysis on circulating NT-BNP has not, to our knowledge, been reported.

In the present study, we have confirmed earlier reports that plasma levels of BNP and NT-BNP are elevated in patients with chronic renal failure. In addition, we demonstrate that peritoneal dialysis had no major effect on circulating levels of either BNP or NT-BNP. We presume, therefore, that the dialysis-induced fall in volume of distribution for these peptides balanced any reduction in their cardiac secretion (resulting from a probable decrease in cardiac preload and afterload) and clearance by dialysis.

Our data do not allow us to comment on circulating levels of the cardiac natriuretic peptides in patients receiving different types of dialysis. In this regard, Nagatani *et al.*[13] noted that plasma levels of BNP were significantly (61%) lower in 32 patients on chronic ambulatory peritoneal dialysis than in 63 patients receiving maintenance haemodialysis, thereby raising the possibility that ventricular load was lower and volume control was superior in the former group of patients.

We were interested to document plasma levels of NT-CNP and adrenomedullin in chronic renal failure and the effects of peritoneal dialysis, as it seems likely that these peptides (or CNP in the case of NT-CNP) are protective of cardiovascular and renal structure and function.[14–18] Such information, therefore, may be of pathophysiological and therapeutic interest. It has been shown previously that plasma levels of immunoreactive CNP are elevated in patients with renal impairment.[19,20] We now show that circulating NT-CNP, which may prove to be a superior index of CNP production than CNP levels (which are extremely low or undetectable in normal subjects[9,15]), are also greatly elevated in patients with longstanding renal failure. Indeed, the levels were much higher than reported earlier in healthy volunteers and in patients with cardiac failure.[9] One caveat here is that our patients with chronic renal failure were considerably younger than control subjects or patients with heart failure, although this is unlikely to account for the sizeable differences in NT-CNP levels between the groups since Wright *et al.*[9] noted only modest, and positive relationships between NT-CNP levels and age in healthy volunteers and in patients with cardiac failure. As in the study of Wright *et al.*[9] in patients with heart failure, we observed a significant, if modest, positive association between plasma creatinine and NT-CNP. Whether this represents heightened secretion of the peptide, a reduction in its clearance from the circulation or a combination of both remains to be determined. Likewise, the source of the CNP peptides in patients with renal impairment is uncertain. Whereas the vascular endothelium is one obvious possibility,[14] increased chondrocyte secretion[21,22] in patients with renal osteodystrophy is another.

It is not known whether NT-CNP has biological effects, but the demonstrated actions of CNP (such as inhibition of cardiac myocyte hypertrophy,[23] prevention of vascular responses to experimental injury[24,25] and inhibition of atherosclerosis in animals[26]) might provide some protection against the widespread cardiovascular damage that typifies and complicates chronic renal failure.[27]

Whether NT-CNP levels will prove useful in the clinical assessment of patients on maintenance dialysis remains to be determined. One theoretical possibility in this regard is that it might provide an index of pathology within the vasculature, thereby complementing the BNPs, which may well find clinical usage in reflecting cardiac impairment and prognosis,[4] and providing guidance to overall management in patients receiving chronic dialysis.[5]

Adrenomedullin, a 52-amino-acid peptide derived largely from vascular tissues, has numerous effects within the kidneys and on the cardiovascular and renin–angiotensin systems.[28] These protean actions of adrenomedullin are generally seen as protective against injury due to hypertension, cardiovascular trophic and toxic factors, and infection.[28,29] The hormone circulates in higher than normal concentrations in patients with renal impairment and is altered variably by haemodialysis.[11,30–34] We confirm here that immunoreactive adrenomedullin levels are elevated indeed in patients with chronic renal impairment. Also, we show that circulating levels of adrenomedullin are not altered significantly across peritoneal dialysis.

In summary, we have demonstrated that plasma levels of BNP, NT-BNP, NT-CNP and adrenomedullin are elevated in patients with chronic renal failure requiring regular peritoneal dialysis. Levels of these peptides, which in the case of NT-CNP correlated with indices of renal function, were not altered by peritoneal dialysis.

MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee of the Faculty of Medicine and Health Sciences at the UAE University. We studied 19 patients, 17 males, aged 28–72 years, with chronic renal failure resulting from diabetes mellitus in 12 patients but of uncertain aetiology in the other patients (presumed glomerulonephritis and/or hypertension). All had been on long-term (at least 4 months) intermittent peritoneal dialysis and all patients had residual renal function. A total of 13 were from the Indian subcontinent, two were of African origin and four were from Arab countries, but all were treated and studied in one of three hospitals within the United Arab Emirates. No patient had clinical evidence of heart failure at the time of study, although most had exhibited fluid overload before the initiation of peritoneal dialysis.

In 11 of the 19 patients (active group), blood samples were drawn from a forearm vein 15 min before and again immediately before a session of regular peritoneal dialysis (baseline), after 2 and 4 h of dialysis, and finally 1 h after completion of dialysis. The number of dialysis cycles in individuals varied between 5 and 30. We did not collect peritoneal dialysate for peptide measurements. The remaining eight patients (control group) had venous samples drawn as above but in the absence of peritoneal dialysis. Blood was taken into chilled tubes containing ethylenediaminetetraacetic acid and centrifuged at $+4^{\circ}$C, and the plasma was stored at -80°C. Plasma samples were couriered on dry ice as a single batch to Christchurch, New Zealand for peptide measurements by the staff who were blinded as to the grouping of patients. Established radioimmunoassay methods were used to measure BNP,[35] the NT-BNP,[36] the NT-CNP[7] and adrenomedullin.[37] The interassay coefficient of variation was between 5.8% for NT-CNP at 15.9 pmol/l and 28.8% for adrenomedullin at 3.8 pmol/l. The intra-assay coefficient of variation was between 3.7% for NT-BNP at 200 pmol/l and 14.5% for adrenomedullin at 3.1 pmol/l. Plasma BUN and creatinine were measured in a single batch using a Synchron CX9 ALX autoanalyser (Beckman-Coulter).

Differences between indices at baseline in the active and control groups were compared using the Mann–Whitney *U*-test and relationships between indices were assessed using Spearman's correlation coefficient. For the purposes of assessing changes across dialysis in the active group and for comparison over time in the control group, results from the two predialysis data points and the two intradialysis data points were each taken as a single mean. Changes between the two groups were calculated and compared also using the non-parametric Mann–Whitney *U*-test. Unless otherwise stated, results are shown as median and interquartile range.

NOTE ADDED IN PROOF

Since submission of this manuscript, a comprehensive review of the natriuretic peptides in end-stage renal disease has been published.[38]

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