BMJ Open Effect of increased water intake on plasma copeptin in patients with chronic kidney disease: results from a pilot randomised controlled trial

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ABSTRACT

Objectives: Increased water intake may have a beneficial effect on the kidney through suppression of plasma vasopressin. We examined the effect of increased water intake on plasma copeptin (a marker of vasopressin) over 6 weeks in patients with chronic kidney disease.

Design: Secondary analysis of a randomised controlled parallel-group pilot trial.

Setting: Canada, 2012–2013.

Participants: 28 patients with stage 3 chronic kidney disease randomised (2:1) to a hydration (n=17) or control group (n=11).

Intervention: The hydration group was coached to increase water intake by up to 1.5 L/day for 6 weeks. The control group was asked to maintain regular water intake.

Measures and outcomes: Participants provided blood and 24 h urine samples at baseline and 6 weeks. Change in plasma copeptin was compared within and between study groups.

Results: Participants were 64% male with a mean age of 62 years and an estimated glomerular filtration rate of 40 mL/min/1.73 m². Between baseline and 6 weeks, 24 h urine volume increased by 0.7 L/day in the hydration group, rising from 2.3 to 3.0 L/day (p=0.01), while decreasing by 0.3 L/day among controls, from 2.0 to 1.7 L/day (p=0.07); between-group difference: 0.9 L/day (95% CI 0.37 to 1.46; p=0.002). In the hydration group, median copeptin decreased by 3.6 pmol/L, from 15.0 to 10.8 pmol/L (p=0.005), while remaining stable among controls at 19 pmol/L (p=0.76; p=0.19 for the between-group difference in median change); the between-group difference in mean change was 5.4 pmol/L (95% CI –1.2 to 12.0; p=0.11).

Conclusions: Adults with stage 3 chronic kidney disease can be successfully randomised to drink approximately 1 L more per day than controls. This increased water intake caused a significant decrease in plasma copeptin concentration. Our larger 12-month trial will examine whether increased water intake can slow renal decline in patients with chronic kidney disease.

Trial registration number: NCT01753466.

Strengths and limitations of this study

- In this randomised controlled pilot trial, 28 patients with stage 3 chronic kidney disease were successfully randomised to drink approximately 1 L more per day than controls for 6 weeks, as verified by 24 h urine collections. This increased water intake caused a significant decrease in plasma copeptin concentration.
- Patients were followed for only 6 weeks.
- Whether the effect of increased water intake on plasma copeptin concentration is clinically significant, beneficial or sustainable over time is unknown.

INTRODUCTION

Vasopressin is an essential antidiuretic hormone in mammals that regulates thirst and urine water.¹ However, chronically elevated levels of vasopressin may have adverse health effects. Until recently, it was not possible to reliably measure vasopressin due to the limited sensitivity of available assays; however, in 2006, Morgenthaler *et al*² developed an immunoassay for copeptin—a glycosylated peptide that is co-released with vasopressin from the hypothalamus. Copeptin can be measured from blood samples and is demonstrated to be a reliable marker of vasopressin.^{2–3} The availability of this assay has renewed scientific interest into the role of vasopressin and copeptin in chronic illness. In longitudinal studies, a higher baseline concentration of plasma copeptin predicts kidney function decline in patients with autosomal dominant polycystic kidney disease,^{4–5} and other studies have linked copeptin to the development of diabetes,⁶ the metabolic syndrome,⁷ and heart failure.^{8–9} In cohort studies, elevated plasma copeptin at baseline is strongly predictive of subsequent myocardial infarction^{10–11} and end-stage kidney disease.¹²

Many factors are known to stimulate vasopressin secretion, including acute stress and illness.¹³ Other stimuli include high plasma osmolality and dehydration—vasopressin is the first hormone released during dehydration.¹ In experimental studies of rats, increased water intake was shown to suppress vasopressin, reduce proteinuria and improve creatinine clearance.^{14 15} In large cohort studies, renal decline was slower in those with greater water intake,^{16–18} but evidence from clinical trials is lacking. It is not known whether copeptin can be adequately suppressed by increased water intake in patients with chronic kidney disease. In 2012, we launched the pilot phase of a randomised controlled trial that will test whether increased water intake can slow renal decline in patients with chronic kidney disease. The results of the pilot trial were published in December 2013;¹⁹ however, data on plasma copeptin did not become available until 2014. Here, we examine the effect of increased water intake on plasma copeptin. We also examine the relationships between copeptin and 24 h urine volume, osmolality, sodium, albuminuria and estimated glomerular filtration rate (eGFR).

METHODS

Study population

We analysed data from the pilot phase of the Water Intake Trial (WIT), a parallel-group randomised controlled trial conducted between October 2012 and March 2013 in London, Ontario, Canada (registered at clinicaltrials.gov NCT01753466).¹⁹ A figure detailing participant selection and follow-up is available in Clark *et al.*¹⁹ The primary aim was to assess the feasibility and safety of asking adults with stage 3 chronic kidney disease to increase their water intake and to test our planned procedures, recruitment and operational strategies for use in our larger trial (NCT01766687). We enrolled 29 patients as recommended by Moore *et al* and Julious for pilot studies assessing feasibility.^{20 21} All patients provided informed consent consistent with the Declaration of Helsinki.

Eligibility criteria included age 30–80 years; chronic kidney disease (stage 3), defined as the presence of reduced kidney function (an eGFR 30–60 mL/min/1.73 m²) determined from a blood sample taken from participants at baseline; proteinuria (albumin/creatinine >2.8 mg/mmol (if female) or >2.0 mg/mmol (if male) from a spot urine sample or trace protein (albustix));²² and 24 h urine volume <3 L/day (all participants provided a 24 h urine sample at baseline). We excluded patients who met any of the following criteria: self-reported fluid intake ≥10 cups/day; had received a dialysis treatment in the past month; kidney transplant recipient (or on waiting list); under fluid restriction; pregnant or breast feeding; symptomatic kidney stones in past 5 years; a life expectancy less than 2 years; serum sodium ≤130 mmol/L; serum calcium >2.6 mmol/L; currently taking lithium (a drug which affects thirst and

urination) or high daily doses of the following diuretics: hydrochlorothiazide >25 mg/day, indapamide >1.25 mg/day, furosemide >40 mg/day or metolazone >2.5 mg/day.

Intervention

We randomised 29 patients by computer-generated randomisation in block sizes of 3 to a hydration or control group (2:1), stratified by gender. This 2:1 randomisation in the pilot phase was chosen to provide experience delivering the hydration intervention to more patients within an overall sample of 29 patients. The hydration group (n=18) was coached to increase their oral water intake by 1.0–1.5 L/day depending on sex, weight and 24 h urine osmolality (in addition to usual consumed beverages) for 6 weeks (see table 1 in Clark *et al.*¹⁹). We advised a gradual increase in water intake over 2 weeks. During week 1, we instructed participants to consume one cup of water at breakfast, lunch and dinner, and during week 2, the full amount according to weight and sex (table 1 in Clark *et al.*¹⁹). We used a variety of techniques to encourage adherence to the fluid regimen. Participants were given reusable drinking containers, and the study dietician provided individual consultations with all participants (in person or by telephone). We also conducted informed hydration coaching (table 2 in Clark *et al.*¹⁹) based on urine colour charts and level of spot urine osmolality, which was measured every 2 weeks after randomisation. At these times, the research coordinator also inquired about regimen tolerance and adherence. The control group (n=11) was asked to continue with their usual water intake or to decrease water intake by 1–2 cups/day depending on their baseline 24 h urine osmolality.

Outcomes, measurements and definitions

In this secondary analysis of the WIT pilot trial, the primary outcome was the between-group change in plasma copeptin. All participants provided 24 h urine samples and blood samples at baseline and 6 weeks after randomisation. Serum creatinine was measured using the isotope dilution/mass spectroscopy-traceable enzymatic method, and eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.²³

We measured the concentration of sodium, osmolality, and urea in blood and 24 h urine samples and the 24 h urine albumin-to-creatinine ratio using standard methods.¹⁹ Copeptin concentration was measured in plasma-EDTA samples. Samples were stored at –20°C and analysed for copeptin in a single batch analysis to eliminate interassay variation. Copeptin concentration was measured using a sandwich immunoassay (Thermo Fisher Scientific B.R.A.H.M.S, Hennigsdorf/ Berlin, Germany).

Statistical analyses

Normally distributed data were summarised using means and SDs, and non-normally distributed data were

Table 1 Baseline characteristics by treatment assignment

	Treatment group	
	Control n=11	Hydration n=17
Mean age, years (SD)	67 (11)	60 (14)
Males, n (%)	7 (64)	11 (65)
Caucasian, n (%)	10 (91)	13 (77)
Body mass index, kg/m ² (SD)	30 (6)	31 (6)
Waist circumference, cm (SD)	110 (11)	101 (18)
Smoking status, n (%)		
Current	0	1 (6)
Former	8 (73)	9 (53)
Cause of chronic kidney disease, n (%)		
Diabetes	5 (46)	3 (18)
Hypertension	3 (27)	3 (18)
Polycystic kidney disease	0	3 (18)
Unknown/other	4 (36)	8 (47)
Comorbidities, n (%)		
Hypertension	11 (100)	12 (71)
Hyperlipidaemia	8 (73)	8 (47)
Diabetes	7 (64)	7 (41)
Peripheral vascular disease	3 (27)	1 (6)
Gastric bleeding	2 (18)	0
Malignancy	0	2 (12)
Cerebrovascular/TIA	1 (9)	1 (6)
Coronary artery disease	1 (9)	1 (6)
COPD	1 (9)	1 (6)
Mean blood pressure, mm Hg (SD)		
Systolic	143 (17)	139 (22)
Diastolic	73 (11)	79 (11)
eGFR, mL/min/1.73 m ² (SD)	39 (11)	41 (10)
Hematocrit, L/L (SD)	0.39 (0.05)	0.39 (0.06)
HbA1c, % (SD)	0.07 (0.02)	0.07 (0.01)
Medications, n (%)		
ACE/ARB inhibitors	7 (64)	11 (65)
Statin	7 (64)	8 (47)
Diuretics	9 (82)	5 (29)
Calcium channel blockers	5 (46)	4 (24)
Aspirin	5 (46)	3 (18)
Angiotensin II receptor blockers	5 (46)	3 (18)
β-blockers	3 (27)	3 (18)
Vasopressor	0	1 (6)
First degree relative with hypertension or kidney failure, n (%)	5 (46)	10 (59)

ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disorder; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; TIA, transient ischaemic attack.

summarised using medians and IQR. All randomised participants were included in the analysis and analysed according to group assignment. Within-group changes in the amount of urine volume and the concentration of plasma copeptin were compared using the paired t test and the related-samples Wilcoxon signed-rank test, respectively; the between-group change was compared using the independent t test and Mann-Whitney U, as appropriate. Correlations between copeptin and measures of kidney function, urine volume, sodium, osmolality, and albumin were analysed using the Spearman's

rank correlation coefficient (r) for non-normally distributed data. Correlations are presented for the overall sample at baseline and 6 weeks follow-up. Data were analysed using SPSS V.21.

RESULTS

Of 74 participants who met the initial eligibility criteria and were invited to participate, 33 were consented and 29 were randomised (4 patients withdrew before randomisation). One participant in the hydration group withdrew after randomisation due to a flare up of Crohn's disease.

Participants were 64% male and 82% Caucasian with an average age of 62 years (SD 14) and an average eGFR of 40 mL/min/1.73 m² (SD 11 mL/min/1.73 m²); 50% had diabetes and 82% had hypertension. Median copeptin at baseline was 17 pmol/L (IQR 9–31), and was higher in males (17 (IQR 11–35) vs 12 (IQR 6–30) in females). Participant characteristics by treatment group are shown in table 1 (as per CONSORT guidelines,²⁴ p values were not calculated). Although randomisation protects against baseline differences between groups, differences can arise in smaller samples,²⁵ for example, participants in the control group were older, had more comorbidities and had more diuretic use compared with those in the hydration group. As well, there were three participants with polycystic kidney disease in the hydration group (and none in the control group); however, study results remained unchanged when these patients were excluded in sensitivity analysis (the copeptin levels of these three participants were 16.3, 12.0 and 7.5; slightly below the group average).

Change in copeptin between baseline and 6 weeks is shown in table 2 and figure 1. During this time, 24 h urine volume increased by 0.7 L/day in the hydration group (p=0.01) and decreased by 0.3 L/day in the control group (p=0.07); the between-group difference in change was 0.9 L/day (95% CI 0.37 to 1.46; p=0.002). In the hydration group, the median plasma copeptin concentration decreased significantly between baseline and follow-up, from 15.0 to 10.8 pmol/L (p=0.005), while remaining relatively stable among controls, at 19 pmol/L (p=0.76); p=0.19 for the between-group difference in median change. The between-group difference in the mean change was 5.4 pmol/L (95% CI –1.2 to 12.0; p=0.11).

Correlations between the concentration of plasma copeptin and urine volume, eGFR, and other urine and serum measures are shown in table 3 (scatter plots of these correlations are provided in online supplementary figures S1–S8). At baseline, copeptin was inversely correlated with eGFR (r=–0.53; p=0.003) and positively correlated with serum osmolality (r=0.58; p=0.001) and serum urea (r=0.51; p=0.001). At 6 weeks follow-up, copeptin was inversely correlated with 24 h urine volume (r=–0.48; p=0.01) and eGFR (r=–0.56; p=0.002), and positively correlated with the albumin-to-creatinine ratio

Table 2 Effect of increased water intake on the plasma concentration of copeptin

	Baseline	6 weeks	Change*	p Value†
Mean urine volume, L/day (SD)				
Control (n=11)	2.0 (0.7)	1.7 (0.6)	−0.2 (p=0.07)	0.002
Hydration (n=17)	2.3 (0.6)	3.0 (1.2)	0.7 (p=0.01)	
Median copeptin, pmol/L (IQR)				
Control (n=11)	19.3 (12–36)	19.4 (14–33)	−1.1 (p=0.76)	0.19
Hydration (n=17)	15.0 (8–29)	10.8 (6–26)	−3.6 (p=0.005)	

*Follow-up—baseline; p value for within-group change calculated using the paired-samples t test (urine volume) and the related-samples Wilcoxon signed-rank test (copeptin).

†The between-group difference in change from baseline to week 6 was compared using the independent t test (urine volume) and the Mann-Whitney U test (copeptin).

($r=0.44$; $p=0.02$), serum urea ($r=0.49$; $p=0.008$) and urine and serum osmolality ($r=0.53$; $p=0.004$ and $r=0.47$; $p=0.01$, respectively). No correlation was seen with urine sodium or serum sodium at either time point.

DISCUSSION

In this randomised controlled pilot trial of 28 patients with stage 3 chronic kidney disease, patients were successfully randomised to drink approximately 1 L more per day than controls for 6 weeks. In the hydration group, 24 h urine volume increased significantly and the between-group difference was 1.3 L/day at 6 weeks. This increased water intake caused a significant decrease in plasma copeptin concentration among patients in the hydration group, although the between-group difference was not statistically significant. No adverse effects were reported nor observed.¹⁹

The median baseline copeptin concentration in our study was 17 pmol/L, which is approximately four times higher than values reported in healthy volunteers.¹³ Other studies have shown that copeptin is elevated in patients with chronic kidney disease,³ diabetes,⁶

myocardial infarction^{10 11} and heart failure.^{8 9} In kidney transplant recipients, higher levels of copeptin at baseline predicted a significantly faster decline in kidney graft function over a median follow-up of 3.6 years, independent of baseline eGFR, proteinuria and other risk factors.²⁶

In our study, copeptin was inversely correlated with both 24 h urine volume and eGFR, and positively correlated with urine protein, urine osmolality, serum osmolality and serum urea. If copeptin is cleared by the kidneys, then it will necessarily increase as kidney function declines, and this could explain the inverse relationship between copeptin and eGFR. However, in a study by Zittema *et al*,²⁷ copeptin was not associated with GFR in healthy living kidney donors—and copeptin levels did not change after donation despite a significant drop in kidney function after nephrectomy. These data suggest that GFR alone is not a principal determinant of copeptin.

What is the link between copeptin and kidney function?

An inverse relationship between copeptin and kidney function is consistently demonstrated in experimental

Figure 1 Intraindividual change in copeptin between baseline and 6 weeks after randomisation.

Table 3 Correlations with copeptin in 28 patients with stage 3 chronic kidney disease

	Baseline		6 weeks	
	r†	p Value	r†	p Value
Urine volume, L/day	−0.17	0.38	−0.48*	0.01
eGFR, mL/min/1.73 m ²	−0.53**	0.003	−0.56**	0.002
Urine osmolality, mOsm/kg	0.26	0.17	0.53**	0.004
Serum osmolality, mOsm/kg	0.58**	0.001	0.47*	0.01
Serum urea, mmol/L	0.51*	0.006	0.49**	0.008
Albumin/creatinine, mg/mmol	0.35	0.07	0.44*	0.02
Urine sodium, mmol/day	0.15	0.44	0.13	0.50
Serum sodium, mmol/L	−0.04	0.83	0.01	0.94

*p<0.05; **p<0.01.

†Spearman's correlation coefficient.

eGFR, estimated glomerular filtration rate.

and observational studies, in diverse patient groups, and appears to be independent of age, sex, blood pressure and other risk factors.^{3 26 28} Nonetheless, it remains unknown whether copeptin itself has a direct causal effect on kidney function. In the unique case of autosomal dominant polycystic kidney disease (ADPKD), a rise in vasopressin (and copeptin) stimulates the formation of cAMP (3',5'-cyclic AMP), which promotes cell proliferation and cyst growth leading to kidney enlargement and a subsequent decline in kidney function.^{29 30} Accordingly, in several animal studies, researchers showed that blocking the cAMP-mediated pathway with V2-receptor antagonists resulted in significantly reduced cyst growth,^{31 32} and in a 3-year double-blind randomised placebo-controlled trial, patients treated with tolvaptan (a V2-receptor antagonist) experienced a significantly slower increase in total kidney volume and a significantly slower decline in kidney function.³³ Interestingly, increased oral water intake in rats has been demonstrated to have a similar suppressing effect on vasopressin secretion.³¹

Vasopressin has potent vasoconstrictive effects, and some hypothesise that the associations observed between copeptin and renal/cardiovascular outcomes may be partly explained by vasopressin's effect on blood pressure;^{12 34 35} however, there is no convincing evidence that vasopressin increases blood pressure. In patients treated with selective V2-receptor antagonists, the plasma level of vasopressin increases by about three times with no concomitant change in blood pressure.^{36–38} In human cohort studies, the relationship between copeptin and blood pressure is inconsistent and weak, and associations between copeptin and other outcomes remain significant after controlling for blood pressure or hypertension.^{28 35 39} In our study, correlations between copeptin and blood pressure were below 0.1 (data not shown). Many other mechanisms have been proposed to explain the link between vasopressin/copeptin, GFR and albuminuria; these include vasopressin's effect on urinary concentrating activity,^{40 41} hyperosmolality,⁴² activation of the renin-angiotensin system,⁴³ glomerular hyperfiltration and hypertrophy,^{1 26 30} high salt intake and

V2-receptor-dependent tubular effects on sodium reabsorption.^{12 44} As described in Bolignano and Zoccali,⁴⁵ these pathways are not mutually exclusive and may act together to affect renal outcomes.

Copeptin is also a marker of the body's endocrine stress response, which is mediated through the hypothalamus-pituitary-adrenal system, and is activated in acute illness.^{7 9} For example, copeptin levels spike in concert with cortisol and corticotropin-releasing hormone within hours of acute myocardial infarction onset.⁴⁶ It is unclear, however, whether copeptin is simply a marker of stress or illness, or if it plays a direct causative role in the pathophysiology of cardiovascular and chronic kidney disease.⁴⁷ In studies of animals and humans, stimulating vasopressin causes an increase in proteinuria, while suppressing vasopressin through V2 antagonism or water intake reduces proteinuria.^{14 15 43} Further, in studies that controlled for inflammatory biomarkers (C reactive protein and N-terminal pro brain natriuretic peptide), copeptin remained significantly associated with renal decline and proteinuria.^{26 28} These data have sparked interest in the use of vasopressin receptor antagonists to improve renal and cardiovascular outcomes, and several are currently being investigated for clinical use.^{30 48} If proved effective, copeptin may serve as a useful biomarker to identify patients who may most benefit from treatment.⁴⁶

The main limitations of this study are its small sample size (28 patients) and short follow-up. As the primary aim of this pilot study was to assess the feasibility and safety of increasing hydration among adults with chronic kidney disease,¹⁹ our study was not powered to detect changes in secondary outcome variables. However, few studies have examined short-term changes in copeptin in the same participants. While we were not able to determine the precise time lag between change in water intake and change in plasma copeptin, copeptin decreased in nearly all of the participants in the hydration group between baseline and 6 weeks while showing a more variable pattern in the control group (figure 1). Participants in the hydration group were instructed to increase water intake by up to 1.5 L/day, and 24 h urine

volume was significantly higher in the hydration group compared with controls at the end of 6 weeks. This increase in water intake was associated with a significant decrease in the concentration of plasma copeptin. However, it is not known if decreasing plasma copeptin actually leads to any health benefits for patients, or if any such effects would be sustained over time. Another limitation of this study is that we were not able to determine how much participants increased their intake of plain water versus other fluids (and if different types of fluid affect copeptin differently). In other studies that examined intake of plain water versus other fluids in relation to renal outcomes, a beneficial effect was seen with greater intakes of plain water, but not other beverages, with negative effects seen for increased intake of sweetened beverages.^{3 17 49} Many of these limitations will be addressed in our larger 12-month trial (expected completion date: December 2016; NCT01766687), which will examine the effect of increased water intake and 24 h urine volume on change in renal function in patients with chronic kidney disease (primary outcome); the effect of increased water intake on change in copeptin over 12 months will be examined as a secondary outcome. As well, participants will complete a 3-day food-and-fluid intake record and a water survey at three times during the trial, which will provide additional information on types of fluid consumed.

Our study and others have clearly demonstrated that copeptin is sensitive to changes in water intake and is inversely associated with 24 h urine volume.^{28 50} Copeptin is also inversely related to eGFR, is positively associated with urine protein, and is a prognostic biomarker for future events of diabetes and heart disease.^{6 8–11 27 28 51} Does it follow that hydration is a unifying factor linking copeptin to kidney function and other diseases, as some suggest?⁵² Possibly, however, evidence from a large randomised controlled trial is needed to determine if increased water intake has a direct protective effect on kidney function, and if so, to what extent and by what mechanism. The possibility that hydration may play a protective role in chronic kidney disease is biologically plausible and is supported by a diverse and growing body of research⁵³; however, whether this relationship is causal, clinically significant, and sustained over time is unknown. We anticipate that the results from larger trials (including our own 12-month trial, currently in progress), with repeated measures of copeptin, 24 h urine volume, osmolality and eGFR over time will provide key insight into the causality, direction and magnitude of the relationships between water intake, copeptin and kidney function.

Contributors Each author contributed to the conception and design of the study and interpretation of the data. JMS analysed the data. JMS and WFC drafted the article, and all authors revised it critically for important intellectual content. All authors had full access to all of the data in the study (including statistical reports and tables) and can take responsibility for the integrity of the data and the accuracy of the data analysis. WFC, JMS, S-HH, AXG, LM, AAH and KG were involved in study concept and design. WFC, S-HH, LM, AAH and KG were involved in acquisition of data. JMS was involved in data

analysis. WFC, JMS, S-HH, AXG, LM, AAH and KG were involved in interpretation of the data. JMS and WFC were involved in drafting of the manuscript. JMS, WFC, S-HH, AXG, LM, AAH and KG were involved in critical revision of the manuscript for important intellectual content. WFC is the guarantor.

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