The chronic kidney disease Water Intake Trial (WIT): results from the pilot randomised controlled trial

William F Clark,1 Jessica M Sontrop,1,2 Shih-Han Huang,1 Kerri Gallo,2 Louise Moist,1,2 Andrew A House,1 Matthew A Weir,1 Amit X Garg1,2

ABSTRACT

Background and objectives: Increased water intake may benefit kidney function. Prior to initiating a larger randomised controlled trial (RCT), we examined the safety and feasibility of asking adults with chronic kidney disease (CKD) to increase their water intake.

Design, setting, participants and measurements: Beginning in October 2012, we randomly assigned 29 adults with stage 3 CKD (estimated glomerular filtration rate (eGFR) 30–60 mL/min/1.73 m² and albuminuria) to one of the two groups of water intake: hydration (n=18) or standard (n=11). We asked the hydration group to increase their water intake by 1.0–1.5 L/day (in addition to usual intake, depending on sex and weight) for 6 weeks, while the control group carried on with their usual intake. Participants collected a 24 h urine sample at baseline and at 2 and 6 weeks after randomisation. Our primary outcome was the between-group difference in change in 24 h urine volume from baseline to 6 weeks.

Results: (63%) of participants were men, 81% were Caucasians and the average age was 61 years (SD 14 years). The average baseline eGFR was 40 mL/min/1.73 m² (SD 11 mL/min/1.73 m²); the median albumin to creatinine ratio was 19 mg/mmol (IQR 6–74 mg/mmol). Between baseline and 6-week follow-up, the hydration group’s average 24 h urine volume increased by 0.7 L/day (from 2.3 to 3.0 L/day) and the control group’s 24 h urine decreased by 0.3 L/day (from 2.0 to 1.7 L/day; between-group difference in change: 0.9 L/day (95% CI 0.4 to 1.5; p=0.002)). We found no significant changes in urine, serum osmolality or electrolyte concentrations, or eGFR. No serious adverse events or changes in quality of life were reported.

Conclusions: A pilot RCT indicates adults with stage 3 CKD can successfully and safely increase water intake by up to 0.7 L/day in addition to usual fluid intake.

Trial registration Registered with Clinical Trials—government identifier: NCT01753466.

BACKGROUND

Evidence from animal and human studies suggests a specific beneficial effect of water intake on the kidney.1–10 Increased water intake suppresses plasma vasopressin,6 11 which is an antidiuretic hormone that regulates thirst and water conservation in mammals. While essential for water regulation, vasopressin has vasoconstrictive effects and there is evidence that increased plasma levels can have negative effects on renal haemodynamics, blood pressure and ventricular function.12–18 In animal models, an increased water intake has been shown to reduce proteinuria and slow the progression of chronic kidney disease (CKD).6 8 In humans, several observational studies report positive associations between greater water intake and kidney function.1–4 10 In a recently published prospective cohort study of 2000 Canadian adults without kidney disease, higher urine volume at baseline was associated with slower renal decline over follow-up.1 Similarly, in two cross-sectional analyses of Australian and American cohorts, higher self-reported water intake was associated with better kidney function.2 10 Most recently, researchers identified chronic dehydration from heat stress as the most likely causal factor in a perplexing epidemic of CKD in Central America.5 4
Taken together, these findings support a protective effect of greater water intake on the kidney; however, evidence from a large, well-designed randomised controlled trial is needed to determine if higher water intake can slow the rate of kidney function decline.

We designed a randomised controlled trial to test whether increased water intake can slow renal decline in adults with stage 3 CKD. However, due to the expressed concerns by the clinicians about increasing hydration in patients with CKD and the potential for fluid overload and water intoxication, we conducted a 6-week pilot trial to assess the feasibility, safety and quality of life changes that occur when adults with CKD increase their water intake by 1.0–1.5 L/day (in addition to usual consumed beverages) for 6 weeks. This report describes the results of this pilot trial.

**METHODS**

**Design, setting and participants**

We conducted a parallel-group randomised controlled pilot trial (London, Ontario, Canada 2012–2013). Adult patients (age 30–80 years) attending a CKD Clinic at the London Health Sciences Centre (Victoria Hospital), who met the study’s eligibility criteria, were invited to participate. We defined CKD (stage 3) as the presence of reduced kidney function (at least one estimated glomerular filtration rate (eGFR) 30–60 mL/min/1.73 m²) and 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). We used the CKD Epidemiology Collaboration (CKD-EPI) equation to calculate eGFR from serum creatinine. We excluded those who met any of the following criteria: required fluid restriction (<1.5 L/day) for kidney disease, heart failure or liver disease; lived too far from the clinic to reliably participate in follow-up visits; self-reported fluid intake ≥10 cups/day or 24 h urine volume ≥3 L; enrolled in another trial that could influence the intervention, outcomes or data collection of this trial; received a dialysis treatment in the past month; kidney transplant recipient (or on waiting list); pregnant or breastfeeding; a history of symptomatic kidney stones in the past 5 years; less than 2 years life expectancy; serum sodium ≤130 mmol/L; serum calcium >2.6 mmol/L and currently taking lithium (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.

**Enrolment**

The patient’s nephrologist invited interested patients to speak with a research assistant who explained the study, confirmed eligibility and obtained consent. To confirm that urine volume was less than 3 L/day at baseline, the participants were asked to provide a 24 h urine sample within 2 weeks of enrolment. A research assistant arranged to meet the participants the same day the 24 h collection was completed, and a blood sample for baseline laboratory measures was obtained. Once eligibility was confirmed, the participants were randomised to the hydration group or the control group and those in the hydration group were instructed on the intervention.

**Randomisation and intervention**

Participants were randomised in block sizes of three by computer-generated randomisation to the hydration group or the control group (2:1), stratified by gender. An unequal randomisation of 2:1 vs 1:1 was chosen to provide experience delivering the hydration intervention to more patients. The random allocation was concealed to patients, their healthcare providers and research staff. The hydration group was asked to drink 1–1.5 L water per day for 6 weeks, in addition to usual consumed beverages, depending on sex, weight and 24 h urine osmolality (tables 1 and 2). To encourage adherence to the allocated water intake, the participants in both groups were given reusable drinking containers and research personnel maintained regular contact with the participants and inquired about regimen tolerance and adherence. Participants randomised to the control group were advised to continue usual fluid intake or to decrease fluid intake by 1–2 cups/day depending on their baseline 24 h urine osmolality (table 2). Continued hydration coaching based on 24 h urine osmolality was conducted after the second 24 h urine sample (2 weeks after randomisation) was obtained (table 2).

**Objectives and outcomes**

The primary aim of this pilot trial was to assess the feasibility and safety of asking adults with stage 3 CKD to follow the above hydration intervention. Our primary assessment of feasibility was to compare the between-group change in

<table>
<thead>
<tr>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Recommended increase in water intake</th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Dinner</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Daily total (L/day)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>&lt;70</td>
<td>1.0</td>
<td>250 mL (1 cup)</td>
<td>500 mL (2 cups)</td>
<td>250 mL (1 cup)</td>
</tr>
<tr>
<td></td>
<td>≥70</td>
<td>1.25</td>
<td>250 mL (1 cup)</td>
<td>500 mL (2 cups)</td>
<td>500 mL (2 cups)</td>
</tr>
<tr>
<td>Men</td>
<td>&lt;70</td>
<td>1.25</td>
<td>250 mL (1 cup)</td>
<td>500 mL (2 cups)</td>
<td>500 mL (2 cups)</td>
</tr>
<tr>
<td></td>
<td>≥70</td>
<td>1.5</td>
<td>500 mL (2 cups)</td>
<td>500 mL (2 cups)</td>
<td>500 mL (2 cups)</td>
</tr>
</tbody>
</table>
24 h urine volume from baseline to 6-week follow-up. Our primary safety endpoints were the proportion of participants with a serum sodium <130 mmol/L at any point during study follow-up and the between-group change in serum sodium values. Finally, we compared between-group changes in kidney function, physical health and health-related quality of life (HRQL).

### Data collection and measures

Baseline data included the most recent list of medications, height, weight and blood pressure. Seated blood pressure was measured with a Welch Allyn Sphygmomanometer using a standardised protocol. Weight was measured at baseline and again at the final follow-up using a gravity-weighted scale. At baseline and 6 weeks after randomisation, participants completed a survey on their medical history and answered questions about their HRQL from the Kidney Disease Health Related Quality of Life (KDQOL-SF) questionnaire.\(^{22,23}\) Two weeks after randomisation, all participants completed a 3-day diet record and had a 45 min consultation with a renal dietician. Diet records were analysed for daily protein, sodium and fluid intake. Blood samples were obtained at baseline and every 2 weeks after randomisation. The participants collected a 24 h urine sample at baseline and again between 2 and 6 weeks after randomisation.

### Laboratory analysis

Serum creatinine was measured using the isotope dilution/mass spectroscopy-traceable enzymatic method. Blood sodium concentrations were measured with indirect ion-selective electrodes and urea concentrations were measured with enzymatic photometric methods. Serum osmolality was measured by freezing point depression using an advanced instrument MicroOsmometer. The serum cystatin C was measured by nephelometry. Twenty-four-hour urine creatinine was measured using enzymatic methods and the 24 h albumin:creatinine ratio was analysed using an immunoturbimetric assay. Twenty-four-hour urine sodium and potassium were measured with indirect ion-selective electrodes. Urine specific gravity was measured using a digital urine-specific gravity PEN Refractometer (PEN-Urine S.G.).

### Statistical analysis

Normally distributed data were summarised using means and SD; non-normally distributed data were summarised using medians and IQR. We followed an intent-to-treat analysis: all randomised participants were included in the analysis and analysed according to group assignment. We compared the between-group change in urine volume, kidney function, electrolytes and other variables using the independent t test or Mann-Whitney U, as appropriate. Bivariate correlations were estimated using the Pearson product-moment correlation coefficient (r). No subgroup analyses were performed. Data were analysed using IBM SPSS Statistics V.19.

### RESULTS

Enrolment occurred between 16 October 2012 and 29 January 2013. During this time, 74 patients met the initial eligibility criteria and were approached for trial participation. A flow diagram of patient selection and follow-up is presented in figure 1. In total, 29 participants were randomised. One participant withdrew from the study after randomisation due to a flare-up of Crohn’s disease.

Sixty-three per cent of the participants were men, 81% were Caucasian; and the average age was 61 years (SD 14); 54% of the participants had diabetes and 86% had hypertension. The average eGFR at baseline was 40 mL/min/1.73 m\(^2\) (SD 11). Characteristics of participants randomised to the hydration (n=18) and control groups (n=11) are shown in table 3. Although randomisation protects against baseline differences between the groups, baseline differences may occur in smaller samples such as this. Participants randomised to the control group were older, had more comorbidities and had more diuretic use compared with those in the hydration group.

#### A 24 h urine volume

Change in 24 h urine volume is shown in figure 2 and table 4. Between baseline and 6-week follow-up, the hydration group’s 24 h urine volume increased by 0.7 L/day (from 2.3 L to 3.0 L/day) and the control group’s 24 h urine volume decreased by 0.3 L/day (from 2.0 L to 1.7 L/day; between-group difference in change: 0.9 L/day; 95% CI 0.4 to 1.5; p=0.002). The difference between groups at the last follow-up was 1.3 L/day (p=0.005).

#### Serum sodium

Serum sodium concentration remained above 130 mmol/L for all participants at all follow-up points and was similar between the groups at all comparison points (table 4). Change from baseline did not differ...
between the groups (p=0.37). At the final follow-up, the average sodium concentration was 138 mmol/L in both groups.

**Kidney function, electrolytes and osmolality**

Measures of kidney function, electrolytes and osmolality remained within expected ranges for patients with CKD (table 4). Urine osmolality decreased by 76 mOsm/kg in the hydration group and by 19 mOsm/kg in the control group; p=0.27 for between-group change. The 24 h urine osmolality did not vary significantly with eGFR at baseline or follow-up. 24 h urine creatinine remained within 10% of baseline values.

**HRQL and diet**

No appreciable differences in HRQL were evident (table 5). Although the hydration group reported a higher frequency of night-time urination at final follow-up (2.6 vs 1.8), HRQL sleep scores were similar between the groups at final follow-up (82 in both groups; p=0.46). Average intakes of sodium and protein (measured from a 3-day diet record 2 weeks after randomisation) were similar between the hydration and control groups (average sodium intake was 259 (SD 275) and 201 mmol/day (SD 161), respectively (p=0.56); average protein intake was 1.1 (SD 0.2) and 1.1 g/kg/day (SD 0.3), respectively (p=0.52)). Body mass index was similar between the hydration and control groups at baseline (table 1) and was 30 kg/m² in each group at the 6-week follow-up (p=0.28 for between-group change). As shown in figure 3, the average self-reported fluid intake (2 weeks after randomisation) was strongly correlated with 24 h urine volume (r=0.84; p<0.001). As well, mean fluid intake was significantly higher in the hydration group than in the control.
2.8 L/day (SD 0.8) vs 1.9 L/day (SD 0.5), respectively; p=0.002.

Adverse events
No serious adverse events were reported. One patient in the hydration group reported transient nausea; however, serum sodium was 140 mmol/L, eGFR was 44 mL/min/1.73 m² and no other symptoms were noted. One patient in the control group had low urine potassium 2 weeks after randomisation; however, this was due to severe diarrhoea unrelated to study participation. Participants’ primary care physicians and treating nephrologists were notified and patients were followed up with no further concerns. No other adverse events were reported.

DISCUSSION
In this randomised controlled pilot trial, patients with CKD were able to successfully and safely follow being allocated either to a higher or usual oral water intake over a 6-week period. Participants randomised to the hydration group increased their 24 h urine volumes from 2.3 L to 3.0 L/day; in contrast, among controls, 24 h urine volume decreased by 0.2 L/day. There was consistent between-group separation of the 24 h urine volumes in the follow-up. Electrolytes, osmolality and parameters of kidney function remained within the expected ranges for patients with CKD. Importantly, the serum sodium was similar between the groups at all comparison points and all values remained above 130 mmol/L. As well, HRQL, social functioning, sleep and appetite quality remained similar between groups.

No serious adverse events were observed. We are using these pilot data to inform elements of a larger randomised controlled trial to understand the outcomes of an increased water intake in CKD.
knowledge, there are no previous clinical trials of increased water intake in adults with CKD. The clinical trials of increased fluid intake in other patient groups (eg, overweight adults, elderly men and patients with polycystic kidney disease or kidney stones) demonstrate no adverse effects. These studies instructed participants to increase water intake by 1–3 L/day. In particular, Spigt et al25–27 conducted several studies of healthy elderly men, and showed that an increased fluid intake of 1 L/day, on an average, was safe in terms of serum sodium, eGFR and quality of life (n=142), and can be sustained over a 6-month period. Furthermore, in a subset of 44 elderly men, a 2 L increase in fluid intake for up to 2 months was associated with improvement in lower bladder function.25 Similar to the Spigt’s study,27 the participants in the hydration group experienced a significant increase in nocturia; however, this was not associated with any measurable changes in HRQL. Although increased water intake is known to be the most effective therapeutic measure to prevent kidney stones, surveys of patients with recurrent kidney stones show poor compliance with prescriptions for increased water intake.28 Wang et al recently reported results of a water prescription study in eight patients with autosomal dominant polycystic kidney disease who were asked to drink 0.4–1.4 L/day of water for 5 days, in addition to usual fluid intake. Three 24 h urine samples were collected in the week preceding the intervention and again during the week of the intervention and participants were able to achieve their targets (mean 24 h urine volume increased by about 0.8 L/day), albeit for a brief period of study. In contrast, our pilot study of patients with CKD (eGFR 30–60 mL/min/1.73 m²) was 6 weeks in duration. The hydration group increased

### Table 4 Change in clinical variables between prerandomisation and 6-week postrandomisation*

<table>
<thead>
<tr>
<th></th>
<th>Prerandomisation</th>
<th>Postrandomisation</th>
<th>Change from baseline†</th>
<th>p Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Hydration</td>
<td>Control</td>
<td>Hydration</td>
</tr>
<tr>
<td>24 h urine volume, L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.0 (0.7)</td>
<td>2.3 (0.6)</td>
<td>1.7 (0.6)</td>
<td>3.0 (1.2)</td>
</tr>
<tr>
<td>24 h urine creatinine, mmol/day</td>
<td>10.9 (4.3)</td>
<td>13.0 (4.0)</td>
<td>10.2 (3.6)</td>
<td>13.5 (4.7)</td>
</tr>
<tr>
<td>24 h urine sodium, mmol/day</td>
<td>155 (68)</td>
<td>163 (68)</td>
<td>114 (66)</td>
<td>148 (55)</td>
</tr>
<tr>
<td>24 h urine potassium, mmol/day</td>
<td>58 (30)</td>
<td>69 (32)</td>
<td>56 (25)</td>
<td>71 (34)</td>
</tr>
<tr>
<td>24 h urine osmolality, mOsm/kg</td>
<td>344 (136)</td>
<td>388 (136)</td>
<td>304 (116)</td>
<td>407 (116)</td>
</tr>
<tr>
<td>24 h urine urea, mmol/day</td>
<td>430 (123)</td>
<td>393 (161)</td>
<td>410 (75)</td>
<td>317 (110)</td>
</tr>
<tr>
<td>24 h urine ACR, mg/mmol, median (IQR)</td>
<td>20 (7, 77)</td>
<td>16 (6, 60)</td>
<td>17 (6, 86)</td>
<td>16 (5, 78)</td>
</tr>
</tbody>
</table>

*Means and SDs are reported unless otherwise reported.
†Last follow-up—baseline.
‡Change from baseline compared between groups using the independent t test.

### Table 5 Change in health-related quality of life between prerandomisation and 6-week postrandomisation*

<table>
<thead>
<tr>
<th></th>
<th>Prerandomisation</th>
<th>Postrandomisation</th>
<th>Change from baseline†</th>
<th>p Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Hydration</td>
<td>Control</td>
<td>Hydration</td>
</tr>
<tr>
<td>Overall health§</td>
<td>68 (11)</td>
<td>74 (18)</td>
<td>74 (18)</td>
<td>78 (10)</td>
</tr>
<tr>
<td>Affect of physical health on social functioning§</td>
<td>68 (41)</td>
<td>79 (19)</td>
<td>80 (42)</td>
<td>97 (12)</td>
</tr>
<tr>
<td>Sleep quality§</td>
<td>75 (22)</td>
<td>79 (19)</td>
<td>82 (18)</td>
<td>82 (20)</td>
</tr>
<tr>
<td>Appetite quality§</td>
<td>83 (15)</td>
<td>82 (18)</td>
<td>88 (14)</td>
<td>88 (14)</td>
</tr>
<tr>
<td>Urinary frequency Daytime (average per day)</td>
<td>7.8 (1.9)</td>
<td>8.4 (3.0)</td>
<td>7.2 (2.2)</td>
<td>9.4 (4.0)</td>
</tr>
<tr>
<td>Night-time (average per day)</td>
<td>2.3 (1.7)</td>
<td>1.8 (0.8)</td>
<td>1.8 (0.7)</td>
<td>2.6 (1.2)</td>
</tr>
</tbody>
</table>

*Means and SDs are reported unless otherwise reported.
†Last follow-up—baseline.
‡Change from baseline compared between groups using the independent t test.
§Higher scores indicate better functioning (scaled from 0 to 100).
their 24 h urine volume by 0.7 L/day, and the between-group difference at the final follow-up was 1.3 L/day, which we attribute to the coaching skills and frequency of telephone follow-up with participants.29–31 Urine osmolality decreased to a greater extent in the hydration group compared with the control group (by 19% vs 5%, respectively); however, this difference was not statistically significant. Although other studies have demonstrated that acute water loading can significantly reduce urine osmolality,11 32 these studies evaluated hydration regimens that were much greater (eg, ≥3 L/day compared with 1–1.5 L/day in our study).

Our trial has some limitations that merit discussion. Because it was not possible to blind the participants in this pilot trial (nor in the main trial), both groups were fully informed of the main trial’s hypothesis/research question: Does increased hydration reduce progression of CKD? To counteract any potential contamination of our control group being informed about the trial’s objectives and potential benefit, we coached controls to not increase their hydration beyond normal intake or thirst. One explanation for the high refusal rate in this pilot phase is that the participants were asked to collect a total of three 24 h urine samples: one every 2 weeks. However, despite this onerous task, only one patient withdrew from the study after a flare-up of Crohn’s disease. Although neither participants nor assessors were blinded, our primary outcome of change in 24 h urine volume by up to 0.7 L/day (in addition to usual consumed beverages, depending on sex and weight) with no safety concerns.

CONCLUSION

The results of this 6-week pilot study demonstrate that patients with CKD are willing and able to increase water intake by up to 0.7 L/day (in addition to usual consumed beverages, depending on sex and weight) with no safety concerns.

REFERENCES


28. Bankir L, Daudon M. Recurrent (as opposed to non-recurrent) stone formers failed to increase urine volume significantly over a 3-y period in spite of recommendations to drink more, and still showed a higher Tiselius index in morning urine. J Am Geriatr Soc 2008;56:1924–9.


