The CKD Water Intake Trial (WIT)

RESEARCH PROPOSAL

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BACKGROUND

The message "to drink at least eight glasses of water a day to be healthy" is an almost universal exhortation, but remains controversial in the scientific literature.[1-4] Two major medical journals, the *British Medical Journal* and the *Lancet*, described this fluid craze as "a medical myth propagated by the popular press".[1;5] However, as scientists turn their attention to studying this issue, there is now better evidence that increasing fluid intake may have health benefits. Several randomized controlled trials have demonstrated that increased water intake can promote weight loss in overweight adults[6;7]; other observational data show a protective effect of increased water intake on hyperglycemia[8] and cardiovascular mortality.[9] With respect to kidney health, high fluid intake has proven to be the most effective therapeutic measure to prevent kidney stone formation.[10;11] More recently, researchers studying the chronic kidney disease epidemic in Central America have identified chronic dehydration resulting from heat stress as the likely causal factor.[12;13]

Vasopressin in chronic kidney disease

It is increasingly recognized that vasopressin, which is suppressed by increased fluid intake, contributes to chronic kidney disease progression through its effects on renal hemodynamics and blood pressure.[14-19] Plasma vasopressin levels are increased in animal models and also in patients with diabetic and non-diabetic chronic kidney disease.[14;20;21] In several studies of 5/6 nephrectomized rats (the universal model of progressive renal impairment), suppression of vasopressin by increased water intake reduced blood pressure, proteinuria and renal hypertrophy, glomerulosclerosis, and tubular interstitial fibrosis.[16;22;23] Through a similar mechanism, high fluid intake preserved the renal function of rats with polycystic kidney disease.[24-27] Although these findings are provocative, we still require adequate evidence from studies of humans that vasopressin inhibition by increased hydration can protect the kidney.

Observational studies of hydration and kidney health

To date, three observational studies have directly examined the relationship between hydration and kidney function.[28-30]

Renal decline and urine volume in chronic kidney disease patients

In an observational study, Hebert et al. studied 581 patients with chronic kidney disease, of whom 442 had polycystic kidney disease.[28] Participants had a baseline GFR of 25-55 ml/min and advice about fluid intake was left to the discretion of the individual physician. The key outcome measure was a change in annualized GFR slope in relation to mean 24-hour urine volume. In this population, higher urine volume was associated with faster GFR decline; however, this association may be explained by greater diuretic use among those with higher urine volumes. As well, as kidney function decreases, the kidneys are less able to concentrate urine, and because this was observational data, temporality is bidirectional: it is possible that higher urine volume with low osmolality was the result, not the cause, of faster renal decline.

Chronic kidney disease is lower in adults with higher fluid intake: A cross-sectional study

More recently, a study by Strippoli et al. analyzed data from two cross-sectional populations in which fluid intake was assessed by a validated nutrition and food-frequency questionnaire.[29] Participants with the highest quintile of fluid intake (greater than 3.2 L/day) had a significantly lower risk of having chronic kidney disease (estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2): odds ratio 0.5; 95% confidence interval 0.32-0.77; P-for trend of 0.003. These findings were consistent across both study periods, and the authors concluded the higher fluid intake appeared to protect against chronic kidney disease. They did emphasize the need for verification from longitudinal observational studies as well as a well constructed RCT to establish the benefits of hydration.

Renal decline is slower in healthy adults with higher urine volume: A prospective cohort study

In a longitudinal community-based cohort study by Clark et al., 2141 participants free of chronic kidney disease at baseline provided 24-hour urine samples and had their kidney function measured annually for six years.[30] Decline in kidney function was significantly slower in those with higher vs. lower baseline urine volume. The age and sex-adjusted average annual decline in eGFR was 0.6 ml/min/1.73m^2/yr slower for those with urine volume ≥3 L/day compared to those with smaller urine volumes. For each increasing category of 24-hour urine volume (<1 L/day, 1-1.9 L/day, 2-2.9 L/day, ≥3 L/day), percentage annual eGFR decline was progressively slower (1.3%, 1.0%, 0.8%, and 0.5%, respectively; p=0.02). As well, after adjusting for age, gender, baseline eGFR, medication used for hypertension (including diuretics), proteinuria, diabetes, and cardiovascular disease; those with the largest urine volumes (≥3 L/day) were least likely to demonstrate mild-to-moderate renal decline (odds ratio 0.66; 95% confidence interval: 0.46-0.94) or rapid renal decline (odds ratio 0.46; 95% confidence interval: 0.23-0.92).

Next Steps

We have designed a randomized controlled trial to test whether increased fluid intake slows renal decline in patients with chronic kidney disease [eGFR 30 to 60 ml/min/1.73m^2 and microalbuminuria (albumin to creatinine ratio >2.8 mg/mmol (if female); >2.0 mg/mmol (if male) or trace proteinuria].

Study Overview: All participants will receive coaching on how to follow a healthy lifestyle for chronic kidney disease; however, participants randomized to the hydration-intervention group will be asked to drink 1.0 to 1.5 L of water per day (depending on age and sex – see Table 1), in addition to usual fluid intake, for one year. We will estimate the change in estimated glomerular filtration rate, measured every three months for 12 months, and compare the rate of renal decline between the intervention and control groups.

Hypothesis: We hypothesize that increased fluid intake will slow renal decline.

METHODS

Overview: We will conduct a parallel-group randomized controlled trial. The Trial will be conducted out of the London Kidney Clinical Research Unit, a 4,000 square foot facility located at the London Health Sciences Centre's Victoria Hospital in London, Ontario.[31] Enrollment will occur over 18 months and participants will be followed for one year after study entry. The schedule of study visits and measures collected is summarized in **Table 3** (page 8).

Participants

All patients attending the Chronic Kidney Disease Clinic at the London Health Sciences Centre (University Hospital and Victoria Hospital) who meet the study's eligibility criteria will be invited to participate in the trial.

Inclusion criteria

- Age 18-75 years
- Able to provide informed consent and willing to complete follow-up visits.
- Estimated glomerular filtration rate between 30 and 60 ml/min/1.73m^2
- Trace protein or urine albumin/creatinine ratio $\geq$2.8 mg/mmol (if female) or $\geq$2.0 mg/mmol (if male)

Exclusion criteria

- Self-reported fluid intake $\geq$10 cups/day or 24-hr urine volume $\geq$2L.
- Enrolled in another randomized controlled trial that could influence the intervention, outcomes or data collection of this trial (or previously enrolled in this trial)
- Received one or more dialysis treatments in the past month
- Kidney transplant recipient (or on waiting list)
- Pregnant or breastfeeding
- History of kidney stones in past 5 years
- Less than two years life expectancy
- Serum sodium <130 mEq/L without suitable explanation
- Serum calcium >2.6 mmol/L without suitable explanation
- Currently taking hydrochlorothiazide >25 mg/d, indapamide >1.25 mg/d, furosemide >40 mg, or metolazone >2.5 mg/d
- Currently taking lithium
- Patient is under fluid restriction (<1.5 L a day) for kidney disease, heart failure, or liver disease, AND meets any of the following criteria: *i*) end stage of the disease (heart left ventricular ejection fraction <40%, NYHA class 3 or 4, or end stage cirrhosis) *or ii*) hospitalization secondary to heart failure, ascites and/or anasarca

Enrollment and Baseline Data Collection

The patient's healthcare provider will invite interested patients to speak with the study's research coordinator who will explain the study, provide a letter of information, confirm eligibility, and obtain written informed consent. Patients will be randomized to one of two groups by a computer-generated algorithm. More details about randomization and the intervention are described in the Intervention section.

The coordinator will ask participants to complete a survey and diet questionnaire, which can be completed in person, mailed to the study centre or completed over the telephone. The study coordinator will request that a 24-hr urine sample be collected within one week. Participants can deliver the 24-hour urine sample to a local laboratory, study centre, or arrange pick-up by hospital courier. Participants will be randomized to the fluid-intervention group or control group only after all baseline measures are completed.

Once the 24-hour urine sample is received and analyzed, the coordinator will contact the participant to *i)* randomize to the hydration or control group, *ii)* review the intervention, and *iii)* arrange a schedule of follow-up visits (**Table 3, page 8**).

Intervention

Randomization: Participants will be randomized to the fluid-intervention and control groups (1:1) by computer-generated randomization.

Hydration intervention: Participants who are randomized to the hydration-intervention group will be asked to consume 1.0 to 1.5 L of water per day (depending on age and sex) in addition to usual consumed beverages for 12 months. We will advise a gradual increase in water intake over a two-week period: during week one, we will ask participants to consume 250 ml water at breakfast, lunch, and dinner; during week two, the full amount according to age and sex as outlined in **Table 1, below**.

Table 1. Hydration intervention by age and sex

		Fluid Intervention			
Sex	**Weight**	**Daily total (L/day)**	**Breakfast**	**Lunch**	**Dinner**
Female	< 70 kg	1.0	250 ml (1 cup)	500 ml (2 cups)	250 ml (1 cup)
	≥ 70 kg	1.25	250 ml (1 cup)	500 ml (2 cups)	500 ml (2 cups)
Male	< 70 kg	1.25	250 ml (1 cup)	500 ml (2 cups)	500 ml (2 cups)
	≥ 70 kg	1.5	500 ml (2 cups)	500 ml (2 cups)	500 ml (2 cups)

To encourage adherence to the fluid regimen, the research coordinator will maintain regular contact with participants and inquire about regimen tolerance and adherence. We will provide participants with reusable drinking containers, and the study dietician will provide individual consultations with all participants (in person or by telephone) throughout the study. We will also conduct informed hydration coaching (**Table 2, page 6**) based on level of spot urine osmolality,[32] which will be measured at 3 weeks after randomization and again at 3, 6, and 9 months after randomization.

Table 2. Informed hydration coaching based on osmolality measured in spot urine samples taken at three weeks after randomization, and again at 3, 6, and 9 months after randomization.

Trial Group	Urine osmolality	Hydration coaching
Hydration	< 300 mosmol/kg	Maintain current fluid intake
	300-500 mosmol/kg	Increase fluid intake by 1-2 cups/day
	>500 mosmol/kg	Increase fluid intake by 2 cups/day
Control	< 300 mosmol/kg	Reduce fluid intake by 1-2 cups/day
	300-500 mosmol/kg	Reduce fluid intake by 1 cup/day
	>500 mosmol/kg	Maintain current fluid intake

Measures

The schedule of study visits and measures is summarized in **Table 3 (page 8)**. At the baseline (pre-randomization) visit, participants will complete a short survey and a research assistant will measure each person's height, weight, waist circumference, and blood pressure.

Participants will also be asked to provide a 10-ml blood sample at baseline, at 3-weeks after starting the intervention and at 3, 6, 9 and 12-months follow-up; 24-hour urine collections will be requested at baseline and at 6-months and 12-months follow-up. These measures may be collected at the study research unit or by laboratory requisition at a local laboratory. After the final 12-month study visit, information on renal function will be obtained from participants' medical charts at two additional time-points: 18-months and 24-months post-randomization.

Key measures collected during the study include:

Fluid Intake and Urine Samples

24-hr urine volume: To assess fluid intake and adherence to the fluid regimen, we will ask participants to provide 24-hour urine samples at baseline and again at 6-months and 12-months after randomization. Self-reported fluid intake will be measured as part of the diet questionnaire at baseline and we will ask participants to complete urine colour charts throughout the study.

24-hour urine osmolality and urine specific gravity will be measured at baseline and again at 6 and 12 months after randomization by 1) freezing point depression using an advanced instrument micro osmometer and 2) dipstick analysis, respectively.

24-hr urine sodium and potassium will be measured at baseline and again at 6 and 12 months after randomization using indirect potentiometry with sodium and potassium electrodes.

Measures from Blood Samples

Serum creatinine and estimated glomerular filtration rate: We will estimate kidney function from serum creatinine (measured every three months for one year) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[35]

Copeptin, a reliable surrogate of arginine vasopressin, will be measured from 150 ul serum samples. Samples will be stored at -80C and analyzed in batches using the sandwich

immunoluminometric assay (B.R.A.H.M.S. AG, Hennigsdorf/Berlin, Germany), as described by Morgenthaler et al.[18;19;33;34]

Serum sodium and urea will be measured using 1) indirect ion-selective electrodes and 2) enzymatic photometric methods, respectively.

Serum osmolality will be measured by freezing point depression using an advanced instrument micro osmometer.

Serum hematocrit cystatin C will be measured using using 1) Beckman Coulter automated cell counters and 2) nephelometry, respectively.

Glycated hemoglobin (HbA1c) provides an index of the integrated plasma glucose values over the past 6-8 weeks and is not subject to the fluctuations observed in blood glucose concentrations. Given the potential inverse association between water intake and hyperglycemia[11], we will measure HbA1c from blood samples collected. HbA1c will be measured using non-porous ion exchange high-performance liquid chromatography.

Physical Examination

Blood pressure: We will measure blood pressure at each study visit (baseline, 6-months and 12-months). Both sitting and standing pressures will be measured with a sphygmomanometer using a standardized protocol.

Body mass index and waist circumference: Because increasing water intake may promote weight loss[6;7], we will measure body mass index and waist circumference at baseline and again at 6 and 12 months after randomization. Weight will be measured using a gravity weighted scale.

Self-report Measures and Medical History

Kidney Disease Health Related Quality of Life (KDQOL-SF): The KDQOL-SF is a self-report instrument developed and validated to measure health-related quality of life in patients with kidney disease.[36;37] We will ask participants five questions from this instrument that relate to general health and sleep (items 1, 10, 17, 18, and 22). In addition, we will ask participants about their appetite and frequency of urination (during the day and evening). These questions will be asked at baseline and again at 6 and 12 months after randomization.

We will also collect data on other known risk factors for renal decline including age, sex, self-reported race, diet (with an emphasis on daily protein and fluid intake), smoking status; history of hypertension, diabetes, or cardiovascular disease; and prescriptions for medications that could influence the outcome, such as agents that block the rennin-angiotensin system. We will obtain this information from patient interview and medical chart review at baseline and at 6-months and 12-months follow-up.

Table 3. Schedule of study visits and measures

	Baseline[a]	Follow-up[b,c]				
		3 weeks	3 months	6 months	9 months	12 months
SURVEY						
Demographics	+					
Diet (3-day diet record)	+					
Health history	+			+		+
Health-related quality of life	+			+		+
CLINICAL						
Height (cm)	+					
Weight (Kg)	+			+		+
Waist circumference (cm)	+			+		+
Blood pressure (mm Hg)	+			+		+
Medications	+			+		+
BLOOD						
Blood sample	+	+	+	+	+	+
Serum creatinine (umol/L)	+	+	+	+	+	+
Serum sodium (mmol/L)	+	+	+	+	+	+
Urea (mmol/L)	+			+		+
Osmolality (mosm/kg)	+			+		+
Copeptin (pmol/L)	+			+		+
Hematocrit (L/L)	+			+		+
Cystatin C (mg/L)	+			+		+
HbA1c (%)	+			+		+
URINE						
24-hour urine sample (L)	+			+		+
Urine creatinine (mmol/L)	+			+		+
Urine sodium (mmol/d)	+			+		+
Urine potassium (mmol/d)	+			+		+
Urea (mmol/d)	+			+		+
Osmolality (mosm/kg)	+			+		+
Albumin/creatinine (mg/mmol)	+			+		+
Random spot urine sample	+			+		+
Specific gravity (g)	+			+		+
Osmolality (mosm/kg)	+			+		+

[a]Pre-randomization.
[b] Time after randomization.
[c]After the final 12-month study visit, information on renal function will be obtained from participants' medical charts at two additional time-points: 18-months and 24-months post-randomization.

Outcomes

Primary Outcome**:** rate of change in eGFR between baseline and final follow-up. We will fit a linear regression line to all eGFR measures such that the slope of the regression line describes the rate of change in kidney function over time for each individual.

Justification of the primary outcome: An ongoing, accelerated loss of kidney function is a stronger indicator of risk than reduced, but stable kidney function.[38-43] Even in adults with mildly reduced kidney function (eGFR 45 to 90 ml/min/1.73 m^2), an annual renal decline >5% (or >4 ml/min/1.73m^2) significantly associates with cardiovascular disease and mortality.[39;41] Small differences in short-term renal decline translate to large long-term differences and a shortened time to kidney failure and dialysis.

Secondary outcomes**:** between-group differences in the urine albumin to creatinine ratio, rapid renal decline, and health-related quality of life (**Table 4, below**)**.** We will also examine between-group differences in the change in body mass index, waist circumference, blood pressure, albumin to creatinine ratio, HbA1c, and copeptin. Finally, we will examine the relationship between copeptin and renal decline. Differences in renal decline at 24-months post-randomization will also be examined as a secondary outcome.

Table 4. Summary of study outcomes

Primary outcome	**Comparison between groups**
Change in kidney function	Rate of change in eGFR between baseline and 12 months[30;39;41]
Secondary outcomes	
Urine albumin/creatinine ratio (ACR)	Change in ACR
Rapid renal decline	eGFR decline >5% [30;39;44]
Health-related quality of life	Change in health-related quality of life
Body mass index (BMI)	Change in BMI; proportion >30 m/kg^2 at 12 months
Waist circumference	Change in BMI between baseline and 12 months
Blood pressure	Change in blood pressure between baseline and 12 months
HbA1c	Change in HbA1c between baseline and 12 months
Copeptin	Change in copeptin between baseline and 12 months
Relationship between copeptin and kidney function	Correlation

Methods to Minimize Bias

We will use several approaches to minimize bias in this trial.

Concealment of allocation: The study biostatistician will generate a randomization table (with random block sizes) which will allocate patients in a 1:1 ratio to the two groups.

Minimize group contamination: To reduce the potential for communication between study groups, we will work with CKD clinic staff to ensure that participants in the intervention group do not share appointment times with participants in the control group (e.g. to limit the opportunity to discuss the study in the clinic waiting room.

Objective assessment of outcomes: We will use objective measures, such as laboratory values, to assess the primary outcome and key secondary outcomes.

Avoid information biases: All patients, irrespective of the group to which they are randomized, will have the same measurement schedule, including laboratory testing. Laboratory tests will be outlined in pre-printed orders and recorded on case-report forms.

Avoid data analysis biases: For practical reasons we cannot blind the participants or research staff to intervention allocation. However, the biostatistician will be blinded to patient allocation for the analysis of the primary outcome.

Quality assurance: The major components of quality assurance will be staff training, the standardization of data collection, entry and processing, and ongoing monitoring to ensure timeliness and accuracy of the study data. We will compile all study protocols and forms into two operation manuals (one for the clinical site and one for data management).

Sample Retention: We will employ numerous retention strategies to minimize loss to follow-up. The research coordinator will maintain continual contact with participants via telephone, email, and post) to *i)* review the study protocol, *ii)* inquire about regimen tolerance and adherence, and *iii)* schedule follow-up visits.

As well, the study dietician will provide individual consultations with all participants (in person or by telephone) throughout the study. Transportation assistance will be offered and home visits can be scheduled for participants who are unable to complete the study requirements independently. To minimize missing data, a research assistant will follow up all missing survey responses and discrepant data by telephone.

Safety and Adverse Events

Hyponatremia: Symptomatic hyponatremia usually occurs when serum sodium falls below130 mEq/L. In the majority of cases, hyponatremia occurs as a result of excess water intake relative to excretion, including renal excretion. Symptoms range from mild to severe and include nausea and vomiting, headache, confusion, tiredness, appetite loss, restlessness and irritability, muscle weakness, spasms, or cramps, seizures, and decreased consciousness or coma.

Although hyponatremia has not occurred in previous intervention studies of high fluid intake among elderly patients, nor those with chronic renal failure,[12;13] we will closely monitor serum sodium throughout the study. Blood samples will be collected at baseline, 3-weeks after beginning the intervention and every three months thereafter; samples will be analyzed for sodium, osmolality, and creatinine. Samples will be analyzed for sodium, osmolality, and creatinine. A study nephrologist will review each participant's data for evidence of hyponatremia. Participants with serum sodium levels below 130 mEq/L will be contacted immediately and instructed to reduce fluid consumption and increase salt/solute intakes, and will receive a nephrologist consult. As well, the research coordinator will maintain regular contact with participants and inquire about symptoms of hyponatremia.

Participants will be educated about the risk for hyponatremia. For example, under temperate, sedentary conditions, participants will be advised to avoid consuming more than four glasses of water within one hour and to avoid consuming more than 14 glasses per day. During strenuous exercise or warm temperatures, participants will be advised to drink extra fluid with an adequate amount of salt (such as a handful of salted peanuts) or to drink an electrolyte-fortified beverage.

Data Safety and Monitoring Board (DSMB)

For purposes of safety, the study statistician will provide the DSMB with a descriptive summary of adverse and clinically important events at three-month intervals throughout the study. If any safety concerns arise, the DSMB chair will assemble a formal meeting with the study investigators to discuss stopping the trial. The DSMB will make their recommendations to the study investigators after considering all available data and any external data from relevant studies.

Statistical Analysis

We will use SAS version 9.2 (SAS Institute Inc., Cary, NC) for all statistical analysis. We will summarize normally distributed data by the mean and standard deviation (SD), and skewed distributions by the median and interquartile range (IQR). The primary analysis will follow an intention-to-treat approach (i.e., all randomized patients in the study will be included in the analysis). As recommended, missing data will be handled using model-based multiple imputation methods and sensitivity analyses will be performed to investigate whether conclusions are sensitive to assumptions about the missing-data mechanism.[101]The primary analysis will compare intervention groups on their mean change in eGFR between baseline and 12 months using analysis of covariance. For this analysis, participants will be considered as random effects, treatment group and visit number as fixed effects, and baseline eGFR will be included as a covariate. Log-binomial models will be used to estimate the relative risk of categorical outcomes.[45;46]

Sample Size and Statistical Power

In previous studies of patients with CKD, the average annual decline in eGFR ranges from 1.5 ml/min/1.73m^2 (SD 4.2) to 3.5 ml/min/1.73m^2 (SD 5.4).[47;48] Enrolling 700 patients (350 per group) over 18 months (to be followed for 12 months), will provide sufficient power to detect a clinically important difference in renal decline between study groups. Depending on the rate and variability of renal decline, we will be powered to detect a difference of at least 0.7 ml/min/1.73m^2 between groups (Table 4). Over 10 years, a difference of this magnitude in annualized renal decline would translate into a sizeable difference of 7 ml/min per 1.73 m^2.

Table 4. Number of participants needed *per arm* at alpha=0.05; power=0.8.[49]

		Standard deviation		
		3	**4**	**5**
Minimum detectable difference in renal decline between groups (ml/min/1.73m^2)	**0.3**	1571	2792	4361
	0.7	289	514	802
	1.0	142	252	393
	1.3	85	150	233

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