Increasing Water Intake in Chronic Kidney Disease: Why? Safe? Possible?

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Key Words

Water · Chronic kidney disease · Pilot study · Randomized controlled trial · Antidiuretic hormone · Water intake

Abstract

Increased water intake may slow the progression of chronic kidney disease by lowering vasopressin levels. Prior to initiating a large randomized controlled trial on the effect of increased water intake on renal decline, we conducted a six-week pilot study to examine the safety and feasibility of asking adults with chronic kidney disease to increase their water intake. We randomly assigned 29 patients to either a hydration or a control group. The hydration group was asked to increase water intake by 1 to 1.5 l/day relative to their weight, gender, and 24 h urine osmolality, in addition to usual consumed beverages; the control group was asked to continue with usual fluid intake. After six weeks, the change in urine volume was significantly different between groups (0.9 l/day; $p = 0.002$) with no change in serum sodium and no serious adverse effects. Similarly, preliminary results of our large clinical trial of the same intervention (489 patients enrolled to date) demonstrated a significant separation be-

tween groups on 24 h urine volume (at 12 months the mean difference between groups was 1.2 l/day; $p < 0.001$) with no serious adverse effects. Serum sodium has remained stable in both groups over follow-up. To our knowledge, this trial is currently the largest of its kind to date; the significant separation between groups with respect to urine volume indicates that we will have scientifically reliable data on the effect of increased fluid intake on renal decline. The analysis of primary and secondary outcomes will be conducted at the conclusion of follow-up in July 2016. © 2015 S. Karger AG, Basel

Since life forms emerged from water to land, antidiuretic hormones have played an important role in ensuring water homeostasis. The antidiuretic response appears to be an adaptation related to terrestrial habitat [1]. While essential for water regulation, antidiuretic hormones have vasoconstrictive effects that in the short term ensure a necessary intravascular volume for such vital issues as the flight and fight reaction, but in the long term have negative effects on renal hemodynamics, blood pressure, and ventricular function [2–4]. The antidiuretic

hormone (vasopressin) infusion increases proteinuria, renal plasma flow, and hyper filtration, while the administration of vasopressin antagonists reduces proteinuria and lowers blood pressure [2, 4]. Humans are normally antidiuretic, excreting urine with osmolality greater than plasma throughout most of the day and night. Ingestion of supplemental water to cause a water diuresis lowers the plasma level of vasopressin.

In the animal experimental model of chronic progressive kidney disease (5/6 nephrectomy), Professors Bouby and Bankir have demonstrated that increasing water intake suppresses vasopressin and reduces blood pressure, proteinuria, renal hypertrophy, glomerulosclerosis, and interstitial fibrosis [5]. A more recent study in this model of chronic progressive kidney injury has shown that the introduction of an antidiuretic hormone inhibitor was additive to renin angiotensin system blockade in providing increased kidney protection [4]. At present, there is conflicting evidence in human studies about the role of increased hydration on kidney function. An early retrospective analysis reported that higher urine volumes were associated with a faster decline in estimated glomerular filtration rate (eGFR); however, 75% of the patients had polycystic kidney disease and the association disappeared after controlling for diuretic and anti-hypertensive use [6].

Results from three additional studies (two cross-sectional and one longitudinal) suggest a potentially protective effect of greater water intake on kidney function. In a seven-year longitudinal study of 2,144 participants, we demonstrated that 24 h urine volume at baseline was associated with a slower decline in eGFR after adjusting for many potential confounders [7]. In two cross-sectional studies (one conducted in Australia and the other in the United States), low fluid intake and water intake, respectively, correlated with a higher prevalence of chronic kidney disease [8, 9]. These studies offer support for the hypothesis that increased water intake slows progression of chronic kidney disease by lowering vasopressin levels and provide the biologic rationale for conducting a clinical trial. Prior to launching a randomized control trial on the effect of increased water intake on renal decline, we conducted a six-week pilot study to examine the safety and feasibility of asking adults with chronic kidney disease to increase their water intake by 1 to 1.5 l/day [10]. We wished to address the issue of safety in view of clinician concerns about water intoxication in patients with chronic kidney disease [10]; also, with respect to feasibility, only one study with a pre- and post-study questionnaire showed that 11% of participants were unable to increase

hydration, 35% produce daily urine volumes of less than 2 l/day, and 30% reported that they were able to increase their water intake only during non-working hours [11]. For these reasons, as well as concerns about regression to the mean, we needed to test the feasibility of whether subjects coached to increase water intake versus those who were coached to maintain normal fluid intake, would have different urine volumes at the end of the pilot study [10]. Because increased hydration can decrease appetite and increase urination, particularly at night, which could negatively affect sleep patterns, we also compared groups on these measures and on their quality of life.

Twenty-nine adults with chronic kidney disease (an eGFR between 30 and 60 ml/min/1.73 m² and albuminuria [albumin:creatinine ratio >2.8 mg/mmol for females and >2.0 mg/mmol for males]) were placed in block sizes of 3 by computer-generated randomization to a hydration or control group in a 2:1 ratio. The hydration group (n = 18) was asked to increase their water intake by 1 to 1.5 l/day, relative to their weight, gender, and 24 h urine osmolality in addition to usual beverage intake for 6 weeks. The control group (n = 11) was asked to maintain normal fluid intake. To encourage adherence, research personnel made regular contact with participants and inquired about regimen tolerance and adherence to their prescribed water intake. Between baseline and six weeks, the 24 h urine volume of the hydration group increased by 0.7 l/day (from 2.3 to 3.0 l/day) and the 24 h urine volume of the control group decreased by 0.3 l/day (from 2.0 to 1.7 l/day). The change in urine volume was significantly different between groups (0.9 l/day; p = 0.002). We found no significant change in serum osmolality, sodium concentration, eGFR, or quality of life, and no serious events were reported nor observed. This pilot study demonstrated that patients with chronic kidney disease can successfully and safely increase their water intake by 1 to 1.5 l/day over and above the usual fluid intake with no serious adverse effects [10]. Further, to validate the biologic plausibility of our hypothesis, we examined correlations with copeptin (a surrogate marker of vasopressin): at 6 weeks follow-up, copeptin was inversely correlated with both 24 h urine volume and eGFR [12]. These results prepared the way for our large randomized control trial of 700 participants with stage 3 chronic disease (the Water Intake Trial, WIT), which will determine whether increased water intake can slow the progression of chronic kidney disease (registered at ClinicalTrials.gov NCT01766687).

Since recruitment began in April 2013, we have enrolled 489 participants with chronic kidney disease from

Fig. 1. Average 24 h urine volume (l/day) at baseline (black squares), 6 months (open circles), and 12 months (black circles).

Fig. 2. Average daily fluid intake (ml/day) at baseline (black squares), 3 months (open squares), 6 months (black circles) and 9 months (open circles).

clinics in London and Windsor (Ontario, Canada). Recruitment is expected to continue until July 2015. Data collection is going well with less than 2% missing data on key variables such as 24 h urine volume and eGFR. Study withdrawals presently are less than 10%. The results of an interim analysis for safety and monitoring suggest excellent separation between groups; between baseline and 12 months follow-up, 24 h urine increased by 0.9 l/day in the hydration group but remained stable among controls. The difference between groups at 6 months was 1.0 l/day ($p < 0.001$) and the difference between groups at 12 months was 1.2 l/day ($p < 0.001$) (fig. 1). Similarly, between baseline and 9 months, the daily total fluid intake increased from 2.1 l/day to 2.8 l/day in the hydration group and remained stable in the control group at 2.0 l/day (fig. 2). Serum sodium was similar between groups at all comparison points. These results indicate that (1) our coaching system is working, (2) participants in the hydration group are able to maintain an increased fluid intake over time with minimal regression to the mean, and (3) cross-group contamination in the control group is minimal. To our knowledge, this is now the largest randomized controlled trial of increased water intake in patients with chronic kidney disease. The successful separation between groups with respect to fluid intake and 24 h urine volume means that we will have scientifically reliable data

on the effect of increased fluid intake on kidney function, when we examine the primary and secondary outcome data at the conclusion of follow-up in July 2016.

Disclosure Statement

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