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 between 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.

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 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].

Safety of Increased Water Intake in CKD

DOI: 10.1159/000381241

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

William Clark has received consulting fees or honorarium and support to travel to meetings from Danone Research. The Water Intake Trial (WIT) is funded by Danone Research. The study sponsors had no direct role in the data collection, statistical analysis, interpretation of the results, or drafting of the manuscript.

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