Review

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High Water Intake and Progression of Chronic Kidney Diseases

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Impact of water intake on the courses of chronic kidney and urinary tract diseases, such as urolithiasis, urinary tract infections, chronic kidney diseases (CKD), autosomal dominant polycystic kidney diseases and bladder cancer, has recently been studied. It still remains controversial whether increased water intake slows the progression of CKD or not. However, high water intake suppresses plasma levels of arginine vasopressin (AVP), which is expected to be beneficial for the preservation of the kidney function. Previous studies suggest that water intake suppresses plasma levels of AVP, and high levels of AVP have been suggested to play deleterious roles in animal models of kidney disease. Moreover, recent epidemic of CKD of unknown origin, which was supposed to be related to the insufficient water intake and chronic volume depletion, has been reported in Central America, further suggesting that the suppression of AVP by sustained water intake might be beneficial in this CKD population. Indeed, the data from recent studies were consistent with the view that high water intake is associated with slower progression of CKD. However, contradictory findings also exist. The intriguing effects of increased urine volume in preserving the glomerular filtration rate in human patients with CKD require more large and well-designed randomized prospective clinical trials.

Key Words: Water, Intake, Hydration, Dehydration, Progression, Chronic kidney disease

Introduction

Water is the most abundant compound on Earth's surface, covering 70 percent of the planet. In nature, water exists in liquid, solid, and gaseous states. It is in dynamic equilibrium between the liquid and gas states at standard temperature and pressure. At room temperature, it is a tasteless and odorless liquid, nearly colorless with a tint of blue. Many substances dissolve in water and it is commonly referred to as the universal solvent. Water is essential for all life on earth and makes up for more than 60% of our bodies. It plays an important roles in physiological and biochemical functions. The therapeutic benefits of water were heralded in those of Classical Greece and late Imperial China, even as its mechanism of therapeutic action remained to be determined. Impact of water intake in the prevention of urinary system diseases such as uroli- thiasis, urinary tract infections, chronic kidney disease (CKD), autosomal dominant polycystic kidney diseases (ADPKD) and bladder cancer were studied recently[1]. In this review, we focus on the water intake and progression of CKD.

Water balance and the kidney

Under normal conditions, the kidneys are the primary organ of water balance. The weight of the kidneys are less than 0.5% of the total body weight (about 150 g/kidney), but usual blood flow to the kidneys at rest is approx-

imately 25% of cardiac output. Although the kidneys filter more than 150 L body fluid on a daily basis depending on glomerular filtration rate (GFR), less than 1% of filtered fluid is actually passed into the urine. Renal water excretion is primarily under the control of arginine vasopressin (AVP; an antidiuretic hormone) and the renin-angiotensin system. Under normal circumstances, water ingestion in human is driven by thirst. When plasma osmolality increases or plasma volume decreases, perception of thirst rises[2]. Thirst, as a homeostatic mechanism for the maintenance of fluid balance and, is controlled by plasma osmolality and plasma volume[3]. Of those two signals, the former is the main regulator because just a 2-3% increase in plasma osmolality induces a strong perception of thirst[4], whereas plasma volume must decrease by approximately 10% to stimulate thirst[5]. AVP levels increase rapidly with small increases in plasma osmolality, and changes in plasma volume appear to modulate this osmotic stimulation[6]. The relatively short half-life of water excretion (about 100 minutes), which is dependent upon a high renal dilution capacity, prevents water intoxication effectively[7]. The kidneys adjust excretion according to the variable intakes of water and solute, as well as variable losses of water and solutes by the lungs, skin, and gastrointestinal tract. In addition to hormonally mediated water balance, the kidneys require water for solute excretion[8]. The kidneys can concentrate and dilute urinary solutes from a maximum concentrating capacity of 1,400 mosm/kg H_2O to a minimum diluting capacity of 40 mOsm/kg H_2O in those with normal renal function[9].

The obligatory urine volume (V) can be determined for individuals by dividing the daily osmolar solute excretion (mosm/day) by the maximal urine osmolality (Uosm max):

Obligatory urine Volume (mL)=daily osmolar solute excretion (mosm)/Uosm max (mosm/kg H_2O).

Thus, the requirements for urinary water loss are increased as the solute load is increased. In cases of CKD, the failing kidneys lose the capacity to concentrate the urine maximally, which means that they must excrete more water to eliminate the solutes acquired in the diet. As a consequence, patients are forced by thirst to drink more water to cover the loss linked to solute excretion. However, in cases where the volume of water ingested cannot be excreted fully with urine output due to a defect in maximal urine dilutional capacity, an individual can enter a hyponatremic state. AVP acts at the collecting duct of the kidney to decrease urine volume and promote water retention[10]. On the contrary, AVP release is inhibited and the kidney increases hypotonic urinary output to maintain plasma osmolality and volume. AVP is a nanopeptide hormone that is derived from a precursor form synthesized in the hypothalamus. After being synthesized in the hypothalamus, it is transported to the neurohypophysis where it is secreted in reaction to an increase in plasma osmolality and a decrease in effective blood volume[3,11,12]. Vasopressin can bind three receptor subtypes known as, the V1a, V1b and V2 receptors. In the kidneys, the V1a receptor is mainly localized in the interlobular arteries, the descending vasa recta, the macular densa and the collecting duct[13-15]. The V2 receptor is predominantly localized in the collecting duct, the macular densa and the thick ascending limb of Henle. Stimulations of the V1a receptor and the V2 receptor result in an increase in blood pressure by vasoconstriction and in increase of water reabsorption by inserting aquaporin-2 of the collecting duct[3,10,14,16-19]. In the rats with CKD, V2 receptor mRNA levels have been shown to be significantly decreased that indicated AVP resistance in CKD[18,20].

Although vasopressin has a pivotal role in normal water metabolism, in certain situations, it may have deleterious effects on the kidney by causing increased glomerular pressure, renin release, hypertension and mesangial cell proliferation. Bouby and Fernandes[21] in 2003 reported that low hydration with sustained high levels of vasopressin induces morphological and functional changes in the kidney. In this experiment, mild dehydration with sustained high levels of vasopressin impaired renal sodium excretion. Bouby et al.[22] in 1990 showed the effect of high water intake on the progression of chronic renal failure in the experimental model of a 5/6 nephrectomized rat. In this experiment, they studied renal function for

10 weeks and kidney morphology assessed thereafter. Increased water intake in high water intake (HWI) rat reduced solute-free water reabsorption and urine osmolality. The progressive increases in urinary protein excretion and in systolic blood pressure observed in this model of CKD were significantly slowed in HWI rat compared with normal water intake (NWI) rat. Incidence of glomerulosclerosis was also reduced in HWI rat ($p<0.01$). Inhibition of AVP by high water intake may have slow the progression of chronic renal failure in this experimental rat model. In another study in rats with 5/6 nephrectomy, Sugiura et al.[23] showed that high water intake ameliorates tubulointerstitial injury in rats with subtotal nephrectomy. Urinary volume increased and urinary osmolarity decreased after the nephrectomy, suggesting impaired renal urinary concentrating capacity. Northern blot analysis demonstrated that transforming growth factor-beta (TGF-beta) mRNA expression was significantly suppressed in HWI rats. In situ hybridization revealed that HWI suppressed TGF-beta mRNA expression mainly in the outer medulla. Vasopressin levels were found to be elevated compared to control rats. When rats were into a high water intake, vasopressin levels decreased, and blood pressure, proteinuria and plasma creatinine were reduced.

To show the importance of vasopressin inhibition in the progression of CKD rat model, Bouby et al.[24] made 5/6 nephrectomized rat in genetically vasopressin-deficient Brattleboro rats and compared it to rats with normal vasopressin. In Brattleboro rats, compensatory renal hypertrophy and CKD progression were attenuated when compared to rats with normal vasopressin. In an experimental SIADH (syndrome of inappropriate antidiuretic hormone secretion) model induced by continuous administration of desmopressin to rats, Naito et al.[25] also observed the same renal histopathologic abnormalities, such as dilatation of tubules, and inflammatory cell infiltration, accompanied by significant increases in the relative weight of the kidney.

Water intake and progression of chronic kidney disease

Whether increased water intake slows the progression of CKD or not, still remains a controversial topic among the nephrology community. HWI suppresses plasma levels of AVP and suppression of AVP is expected to be beneficial to kidney function. Previous animal experiments suggest that water intake suppresses plasma levels of AVP, high levels of which have been suggested to play deleterious roles in animal models of kidney disease[21-25]. Recent epidemics of CKD of unknown origin in Central America, which is probably related to insufficient water intake and chronic volume depletion, were reported and named "Mesoamerican nephropathy"[26]. It occured primarily in young male agricultural workers in sugar cane fields. The cause of the disease thus far was unknown.

Several recent observational studies have examined the role of water intake in CKD progression. Two large studies recently reported that higher urine volumes[27] and fluid intakes[28] were associated with the preservation of renal function. Clark et al.[27] found in a prospective Canadian cohort of 2,148 apparently normal participants followed up for 6 years that the rate of estimated glomerular filtration rate (eGFR) decline was inversely related to increased 24-hour urine volume. For each liter increase in 24-h urine volume from <1 L to >3 L (stratified by quartile), the annual percentage decline in eGFR decreased by 1.3, 1.0, 0.8, and 0.5 %, respectively. The adjusted odds ratio of developing rapid renal decline, defined as eGFR loss >5%/year, was 0.46 for individuals with urine volume >3 L/day compared with the reference group (urine volume 1-1.9 L/day). They concluded that in this community-based cohort, the decline in kidney function was significantly slower in those with higher urine volume compared to lower urine volume. In another study, Strippoli et al.[28] in 2011 performed two Australian cross-sectional population based studies. The proportion of participants who completed the food frequency questionnaires (FFQ) and had GFR measures was 2,744/3,654 (75.0%) for the first and 2,476/3,508 (70.6%) for the second survey. CKD was present in 12.4-23.5% men and 14.9-28.7% women (mean ages 66.4-65.4 years), respectively. Participants who had the highest quintile of fluid intake (3.2 L/day) had a significantly lower risk of CKD

(odds ratio 0.5; 95% CI 0.32 to 0.77, p for trend=0.003). There was a significant inverse linear association between self-reported daily fluid intake volume and CKD prevalence. They concluded that higher intakes of fluid appear to protect against CKD. CKD may be preventable at a population level with low-cost increased fluid intake. Most recently, Sontrop et al.[29] conducted a cross-sectional analysis of the 2005-2006 U.S. National Health and Nutrition Examination Survey. They categorized total water intake from foods and beverages as low (<2.0 L/day), moderate (2.0-4.3 L/day) and high (>4.3 L/day) and found higher CKD prevalence among those with the lowest fluid intake (<2 L/day) versus highest total fluid intake (>4.3 L/day) (adjusted odds ratio 2.52; 95% CI 0.91-6.96). Interestingly, when stratified by intake of (1) plain water and (2) other beverages, CKD was associated with low intake of plain water: adjusted OR 2.36 (95% CI 1.10-5.06), but not other beverages: adjusted OR 0.87 (95% CI 0.30-2.50). Their results provide additional evidence suggesting a potentially protective effect of higher total water intake, particularly plain water, on the kidney. In 2013, Clark et al.[30] also conducted a six-week pilot study to examine the safety and feasibility of asking adults with CKD to increase their water intake. They 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. This study provided clear evidence of safety feasibility and the absence of a negative impact on the quality of life of the hydration intervention relative to the control CKD population.

However, contradictory findings were also reported previously. Hebert et al.[31] performed a retrospective analysis of 581 CKD patients with eGFR 25-55 mL/min in the Modification of Diet in Renal Disease cohort A. eGFR was repeatedly determined in 442 ADPKD patients and 139 patients with CKD from other causes over an average interval of 2.3 years. They tested the hypothesis that urine volume, urine osmolality (Uosm), or both are significantly associated with GFR decline in patients with chronic renal insufficiency. Contrary to the prevailing view that water is beneficial in CKD, the authors reported that individuals in the highest quartile of urine volume (>2.85 L/day) showed a faster eGFR decline than individuals in the lowest quartile of urine volume (<2 L/day). The authors concluded that sustained high urine volume and low Uosm are independent risk factors for faster GFR decline in patients with chronic renal insufficiency. Thus, high fluid intake does not appear to slow renal disease progression in humans. They suggest that until better evidence becomes available, patients with chronic renal insufficiency should generally let their thirst guide fluid intake. In general, kidney transplant recipients are instructed to increase their daily fluid intake so as to preserve kidney function. However, studies supporting this hypothesis are lacking. Magpantay et al.[32] examined the effect of urine output on renal function. They observed in renal transplant patients with baseline eGFR of 46 mL/min that renal function decline was not different between patients who were prescribed a daily fluid intake of 4 L compared with patients who were prescribed 2 L daily. The authors of this study concluded that recommendation of higher fluid intake does not seem to improve chronic kidney transplant failure. Very recently, Sontrop et al.[33] performed a randomized controlled pilot trial with 28 patients with stage 3 CKD. HWI group drink approximately upto 1.5 L more per day than controls for 6 weeks and the control group was asked to maintain regular water intake. This increased water intake caused a significant decrease in plasma copeptin concentration among patients in the hydration group. Whether the effect of increased water intake on plasma copeptin concentration is clinically significant, beneficial or sustainable over time is unknown at present.

Conclusion

In conclusion, despite the encouraging association be-

tween HWI and preserved eGFR in the two large observational studies[27,28], causal relationships between increased water intake and reduced GFR loss among individuals with CKD remain speculative. The intriguing effects of increased urine volume in preserving the glomerular filtration rate in humans with chronic renal disease need for large well-designed randomized prospective clinical trials.

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