

The medicinal use of water in renal disease

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Although water is essential for life, its use for medicinal purposes is not universally accepted. We performed a comprehensive review of the literature to determine where the evolving state of knowledge lies regarding the benefits of water as a therapy for renal diseases. In the past two decades, water has emerged as a potential therapeutic agent in nephrolithiasis, chronic kidney disease (CKD), and polycystic kidney disease (PKD) in particular. In nephrolithiasis, the benefit of drinking water beyond that demanded by thirst is a cornerstone of therapy for both primary and secondary disease. In CKD, recent observational studies suggest a strong, direct association between preservation of renal function and fluid intake. In PKD, increased water intake slows renal cyst growth in animals via direct vasopressin suppression, and pharmacologic blockade of renal vasopressin-V2 receptors has recently been shown to be efficacious in retarding cyst growth in PKD patients. Although evidence is lacking to support increased water intake in the general population, available evidence indicates that individuals who are at risk for nephrolithiasis as well as those with CKD and PKD may benefit from 3 to 4 l of urine output each day, a level of excretion that is likely to be safe.

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Water is essential to life itself, and since ancient times has been recognized as such. Thales of Miletus, one of the seven sages of ancient Greece, declared (c. 585 BCE) that water is ‘the principle, or the element, of things’, while Shizhen-Li, a Chinese physician of the Ming Dynasty, wrote in the *Compendium of Materia Medica* (1578) that ‘water is the best medicine’. Thus, in cultural traditions as varied as those of classical Greece and late Imperial China, the therapeutic benefits of water were heralded, even as its mechanism of therapeutic action remained to be determined.

In the modern era, the earliest commonly accepted therapeutic benefit of water was in the treatment of nephrolithiasis, a development which had its roots in the 1930s. Since then, ecologic studies as well as work with large patient databases have suggested benefits in non-renal conditions as disparate as bladder cancer,¹ colorectal cancer² and, potentially, coronary artery disease.³ However, it is in renal disorders, such as nephrolithiasis, chronic kidney disease (CKD) and, most recently, autosomal dominant polycystic kidney disease (ADPKD), that the putative therapeutic effects of water have been particularly well studied. Indeed, recent exciting observations are consistent with the view that higher levels of water intake are associated with slower progression of CKD^{4,5} and with reduced cyst growth rate in ADPKD.^{6,7} In the present review, we evaluate the evidence supporting the medicinal use of water in these three conditions and offer guidance about how much water patients with established renal disease can safely drink.

FUNDAMENTAL RELATIONSHIPS BETWEEN SOLUTE AND WATER EXCRETION

Understanding the linkage between solute and water excretion is important in evaluating potential medicinal uses of water (Figure 1). The water content of the human body is regulated by the kidneys, which adjust excretion according to the variable intakes of water and solute, as well as variable losses of water and solutes by the lungs, the skin, and the gastrointestinal tract. Although the kidneys can normally eliminate more water than any human would care to drink in a 24-h period, the minimum amount of water that must be excreted depends upon the amount of solute that must be eliminated to maintain the body’s solute content a steady state, albeit conditioned by the maximal extent to which the kidneys can concentrate urinary solutes. Most textbooks cite a maximum concentrating capacity of 1200 mosm/kg H₂O in those with normal renal function.

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The obligatory urine volume (V) can be determined for individuals by dividing the daily osmolar excretion (mosm/day) by the maximal urine osmolality ($U_{osm\ max}$):

$$\text{Obligatory } V \text{ (ml)} = \text{daily osmolar excretion (mosm)} \div U_{osm\ max} \text{ (mosm/kg H}_2\text{O)}$$

Table 1 lists the amounts of water that must be excreted to ‘cover’ the osmoles in a hypothetical 24-h sample of urine for individuals who can achieve a maximal osmolality of 1000, 500, or 285 mosm/kg H₂O (thresholds which can be viewed as maximal urine osmolalities in mild, moderate, and severe renal disease, respectively), and clearly shows how the requirements for urinary water are increased as the solute

load is increased. Thus, the failing kidneys lose the capacity to concentrate the urine maximally, meaning 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. This is shown in Figure 1, which illustrates how, as an individual ages and CKD progresses, mean concentrating ability of the kidneys falls. While men, on average, demonstrate higher U_{osm} than women, the relationship between U_{osm} and renal function is evident in both men and women.

WATER THERAPY IN NEPHROLITHIASIS

Among renal disorders, nephrolithiasis is the condition for which water as a therapy is firmly established. For the purpose of this review, primary nephrolithiasis refers to the first episode of a kidney stone, whereas secondary nephrolithiasis refers to disease recurrence.

Stone prevention: primary disease

Four studies drawn from two large prospective cohorts convincingly addressed the utility of medicinal water in primary stone prevention (Table 2).^{8–11} The National Health Professionals cohort, which included >90,000 men aged 44–69 years, and the National Nurse Association cohort, which included >20,000 women aged 33–60 years, originally created to study causes of mortality on a population-wide basis were utilized to assess the relationship between water intake and stone formation. The mean follow-up ranged from 8 (ref. 10,11) to 14 (ref. 8,9) years and demonstrated an association of high urine volumes with a reduced risk of first stone formation. This association was strengthened by finding an inverse relationship between the amount of urine excreted and the risk of developing a renal stone. In two studies using data from the National Health Professionals cohort, men with the highest urine volume (mean, 2.5 l/day), compared with men with the lowest urine volume (1.2 l/day), had a significant reduction in the relative risk of stone formation to 0.58 (95% confidence intervals, 0.42–0.79) at 8 years of follow-up and to 0.71 (95% confidence interval, 0.59–0.85) at 14 years. Similar findings were also demonstrated in two studies of women from the National Nurse Association cohort.

Role of family history

A family history of nephrolithiasis in the National Health Professionals cohort received particular scrutiny by Curhan *et al.*¹¹ A positive family history was an independent risk factor for nephrolithiasis that was not modified by increased fluid intake, suggesting that several different stone-forming phenotypes might exist. One phenotype is typified by patients in whom supersaturation-related spontaneous nucleation is the predominant mechanism of stone formation and is usually associated with low daily urine volumes and increased calcium ingestion;¹² water would be expected to be salutary in this group of patients. Another phenotype is characterized by specific alterations in renal

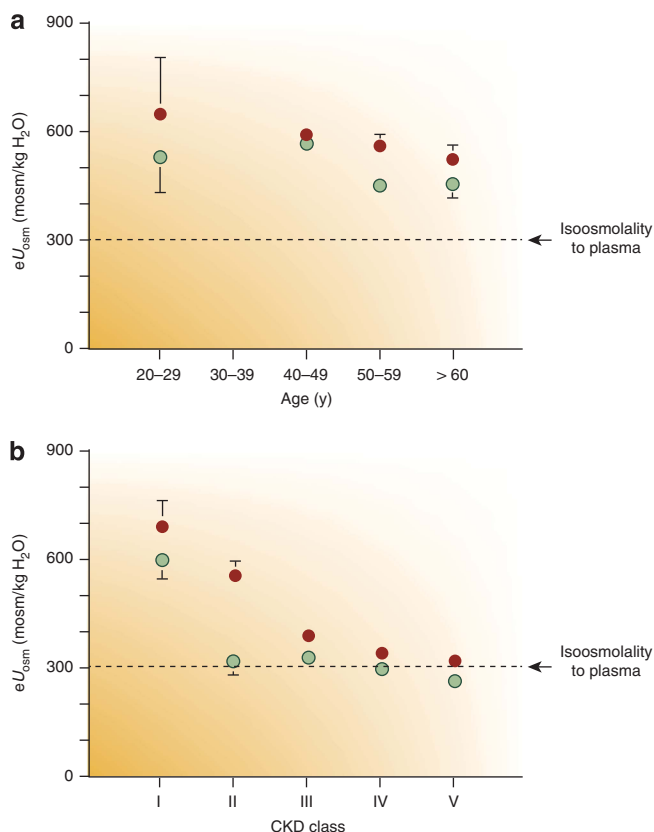


Figure 1 | Mean 24-h urine osmolality in different populations. Difference of mean 24-h urine osmolality in individuals with (a) intact or (b) impaired renal function. Open circles represent females; closed circles represent males. (Reproduced from Perucca *et al.*⁷¹) CKD, chronic kidney disease; eU_{osm} , estimated urine osmolality.

Table 1 | Obligatory urine volume required to achieve different mean osmolalities in 24-h collections

Total daily urine osmolar excretion (mosm/day)	Obligatory urine volume (l/day)		
	$U_{osm\ max}$ 1000 mosm/kg H ₂ O	$U_{osm\ max}$ 500 mosm/kg H ₂ O	$U_{osm\ max}$ 285 mosm/kg H ₂ O
200	0.2	0.4	0.7
400	0.4	0.8	1.4
600	0.6	1.2	2.1
800	0.8	1.6	2.8
1100	1.1	2.2	3.7

Abbreviations: max, maximum; U_{osm} , urinary osmolality.

Table 2 | Primary prevention studies of nephrolithiasis

Reference	Study design	Number of participants	Age at baseline	Years of follow-up	Urine volume, lowest quintile (l/day)	Urine volume, highest quintile (l/day)	Relative risk (95% CI)
Curhan ¹¹	Prospective	37,999	55 ^a	8	<1.3	>2.5	0.58 (0.42–0.79)
Taylor ⁹	Prospective	45,619	40–75 ^b	14	<1.3	>2.5	0.71 (0.59–0.85)
Curhan ¹⁰	Prospective	96,245	36 ^a	8	<1.4	>2.8	0.68 (0.56–0.83)
Curhan ⁸	Prospective	91,731	30–55 ^b	12	<1.4	>2.6	0.61 (0.48–0.78)

Abbreviation: CI, confidence interval.

^aMean.^bRange.**Table 3 | Secondary prevention studies of nephrolithiasis**

Reference	Study design	Number of participants	Age at baseline (years)	Years of follow-up	Water prescription (l)	Urine volume at baseline	Urine volume at follow-up	Stone recurrence rate (%)
Strauss ¹⁵	Retrospective	256	43	4.3	Drink 1	Recurrence: 1.7 No recurrence: 1.5	1.7 1.8	23.2
Hosking ¹⁶	Retrospective	108	Men: 49 Women: 43	5.2	V>2.5	Recurrence: 1.6 No recurrence: 1.6	1.7 2.1	42.2
Daudon ¹⁸	Retrospective	181	Recurrence: 28 No recurrence: 32	3.0	V>2	Recurrence: 1.4 No recurrence: 1.6	1.7 2.1	39.8
Embon ¹⁷	Retrospective	98	43	4.9	V>3	Recurrence: 1.4 Overall: 1.7	2.0 2.4	7.1
Borghi ¹⁹	Prospective	199	Water therapy: 40 Control: 42	5.0	V>2	Fluid therapy: 1.1 Control: 1.0	2.6 1.0	Fluid therapy: 12.1 Control: 27.0
Sarica ²⁰	Prospective	70	Water therapy: 31 Control: 35	2.5	V>2.5	NA	NA	Fluid therapy: 8.3 Control: 55.0

Abbreviations: NA, not available; V, urine volume.

tubule function, leading to increased calcium and oxalate excretion and may be less responsive to increased water intake.

Stone prevention: secondary disease

In the 1960s, it was recognized that living in a tropical climate¹³ or lacking access to water were associated with an increased risk of stone formation.¹⁴ Four key retrospective studies have addressed the use of water in the treatment of secondary nephrolithiasis (Table 3).^{15–18} Study sample sizes ranged from 108 to 256 patients and follow-up time ranged from 3.0 to 5.2 years. In each study, first-time stone formers were encouraged to drink more fluid, ranging from 1.9 to 3.0 l/day. Upon follow-up, urine volumes were compared between those with and without stone recurrence. Baseline urine volumes were similar, but recurrent stone formers tended to have less daily increase in their urine output than individuals who had no recurrence (+0.25 l vs. +0.50 l, respectively), emphasizing the potential role of increased water intake in the prevention of stone recurrence.

In prospective studies, Borghi *et al.* randomized 199 patients with idiopathic calcium stones to either no intervention or to increased water intake sufficient to produce urine volumes of >2 l/day. Significantly greater daily urine volumes were achieved in the treatment arm (2.6 l vs. 1.0 l in the controls, $P<0.0001$), accompanied by a significant lowering of the stone recurrence rate (12 vs. 27%, $P=0.008$).¹⁹ In 70 stone formers, Sarica *et al.*²⁰ found that increasing fluid intake to a level sufficient to achieve daily

urine volumes of >2.5 l was associated with a lower recurrence rate compared with the group that did not increase water intake (increased water, 8.7%; placebo, 55.0%, $P<0.05$). Taken together four of the studies in which data are available show that the average follow-up urine volume in those with recurrent stones (1.8 l/day) was consistently less than in those who passed no stones (2.1 l/day).

Adherence to fluid intake

The real-world effectiveness of increased water intake outside of study environments remains uncertain. The retrospective studies^{16–18} showed that those who do not develop more stones drank ~500 ml more fluid than repeat stone formers. This suggests that at least some patients are able to maintain substantially increased water intake. However, only one study has specifically examined the issue of adherence utilizing pre- and post-study questionnaires.²¹ Episodes of 'dehydration' (e.g., exposure to high ambient temperature or barriers at work to water drinking or to urination) were reported by nearly 50% of first-time stone formers. After the patients were counseled to increase water intake, the investigators found that 11% of patients were still unable to increase water intake; 35% of patients had daily urine volumes not greater than 2 l; and 30% could drink sufficient water only during non-working hours. Consequently, adherence to an increased fluid intake prescription remains a problem. More fundamentally, this suggests the possibility that individuals who can adhere to therapy might differ in important ways from those who cannot (such as in adherence to other health-promoting

behaviors), and, consequently, that the ability to adhere to therapy in such studies might confound the effects attributed solely to increased water intake.

In summary, increased fluid intake has been shown to be effective in primary and secondary prevention in stone formation, but adherence to prescribed regimens has been suboptimal as many barriers are present. Insights into specific therapeutic recommendations are probably best derived from prospective studies. The prospective observational work of Curhan *et al.*^{9,11} demonstrated that intake of >2.5 l/day was associated with an ~29% risk reduction in first stone occurrence, while Borghi *et al.*¹⁹ showed that fluid intake exceeding 2 l/day reduced stone recurrence by ~15%, providing a rational basis for a water 'prescription' in these settings. While pollakiuria and nocturia are nontrivial complications of increased water intake, there is no evidence so far suggesting that doing so would risk serious urological or other complications.

WATER THERAPY IN CKD

It is not an uncommon practice for physicians to recommend a high fluid intake (3–4.5 l/day) to individuals with kidney diseases^{22,23} based on the following lines of evidence. Older studies in humans noted that urea clearance was significantly increased as urine flow doubled from 1–2 ml/min (ref. 24) and that blood urea nitrogen levels were lower in patients who, on average, drank more fluid.²⁵ Moreover, glomerular filtration rate (GFR) measured by inulin clearance declined in humans experiencing severe dehydration.²⁶ Recent studies on vasopressin have rekindled interest in the possibility that increased water intake may ameliorate the progressive decline in GFR that occurs regularly with aging and at a more rapid pace in those with chronic, progressive renal diseases.

Arginine vasopressin (AVP), a crucial peptide hormone that regulates water homeostasis, is recently suggested to contribute to CKD progression. In the rat model of 5/6 nephrectomy, increasing water intake, which decreases AVP, slowed the decline in GFR and reduced histological damage and protein excretion.^{27,28} Conversely, fluid restriction (which results in sustained high levels of AVP) accelerated CKD progression in the same animal model, an effect duplicated by AVP infusion.²⁹ Several mechanisms of the deleterious effect of AVP on kidney were suggested (Figure 2). First, AVP induces glomerular hyperfiltration and hypertension via V2 receptor-mediated, enhanced urea recycling^{30–32} and/or tubular sodium reabsorption,^{33,34} as well as partial V1a receptor-mediated vasoconstriction.³³ Second, AVP stimulates renin synthesis by the activation of V2 receptor,³⁵ which is the first step in a well-characterized cascade of events leading to scar formation in the kidney.³⁶ Third, AVP exerts a direct effect on mesangial cell contraction and proliferation.^{37,38} Although the benefits of vasopressin receptor blockade have been well demonstrated in animal models,³⁹ similar findings in humans are yet to be demonstrated.

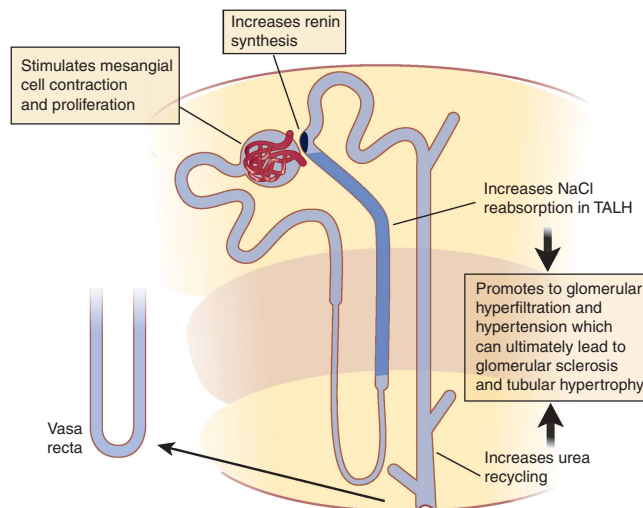


Figure 2 | Possible mechanisms by which vasopressin may adversely affect the progression of established renal diseases. NaCl, sodium chloride; TALH, thick ascending limb of Henle's loop.

Epidemiologic evidence also suggests that the balance of water intake and output may have implications for the development of CKD. Insufficient water intake, particularly in settings of arduous physical labor and/or high ambient temperature, may be associated with CKD prevalence.^{40,41} Peraza *et al.*⁴¹ postulated that chronic volume depletion may cause subclinical acute kidney injury, with repeated insults eventually predisposing to CKD. In their study, the effects of temperature and intense physical activity were examined in 638 healthy participants from Central America. In general, CKD was more commonly observed in individuals who worked in hotter environments or who engaged in more strenuous physical activities (e.g, laboring in sugarcane or cotton fields). For example, the odds ratio of having an elevated serum creatinine concentration was 3.1 for men and 2.3 for women who worked for ≥ 10 years at a coastal sugarcane or cotton production facility compared with those who never worked in these settings.

While these findings provide tantalizing hints that the suppression of AVP by sustained increases of water intake might be beneficial in CKD, a contrarian view has emerged. Hebert *et al.*⁴² performed a retrospective analysis of 581 CKD patients with estimated GFR 25–55 ml/min in the Modification of Diet in Renal Disease cohort A. Estimated GFR was repeatedly determined in 442 ADPKD patients and 139 patients with CKD from other causes over an average interval of 2.3 years. Antithetical 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 an estimated GFR decline of 5.5 ml/min/year, while individuals in the lowest quartile (<2 l/day) had an average declines that were significantly lower (3.5 ml/min/year). However, statistical modeling for potentially confounding factors such as proteinuria, blood pressure, ACE inhibitors (which reduce estimated GFR (eGFR) via hemodynamic mechanisms), and diuretic use appeared to

abolish the association between urine volume and eGFR decline, suggesting that high urine volume, in and of itself, was not an independent risk factor for eGFR decline. Similarly, in a study validating a new eGFR equation using the AASK (African American Study of Kidney Disease and Hypertension) study population, whose baseline GFR ranges between 20–65 ml/min per 1.73 m², Wang *et al.*⁴³ found a weak association between higher baseline urine volume and GFR decline. Although this finding reached statistical significance, the actual decline in GFR was clinically trivial (0.5–2.0 ml/min/decade for each 900 cc increase in daily urine output).

However, two large studies recently reported that higher urine volumes⁴ and fluid intakes⁵ were associated with preservation of renal function. In the first study, a prospective cohort of 2148 apparently normal participants from a Canadian community (mean baseline eGFR 87 ml/min) was followed for 6 years.⁴ The principal finding was that individuals with the highest rates of daily urine excretion had the lowest rates of decline in eGFR (based on serum creatinine concentration). For each liter increase in 24-h urine volume from <1 to >31 (stratified by quartile), the annual percentage decline in eGFR decreased by 1.3, 1.0, 0.8, and 0.5%, respectively, a finding that remained significant after multivariable adjustment (including diuretic use). In the second study, 2744 individuals were surveyed in cross-sectional manner and 2476 were surveyed ~5 years later (some individuals in the initial survey cohort were included in the latter).⁵ CKD prevalence (defined as creatinine clearance of <50 ml/min by the Cockcroft-Gault equation) was assessed in association with self-reported fluid intake. Compared with the referent group, which had a mean of daily fluid intake of 1.81, the groups averaging 2.4 and 3.21 had, respectively, 30% and 50% reductions in CKD prevalence. Overall, there was a significant inverse linear association between self-reported daily fluid intake volume and CKD prevalence.

Irrespective of whether urine volume⁴ or fluid intake⁵ was measured, several factors strengthen the salutary association between water ingestion and preservation of GFR. First, compared with the populations studied by Clark *et al.*⁴ and Strippoli *et al.*,⁵ those of Hebert *et al.*⁴² and the AASK investigators⁴³ had substantially lower mean GFR at baseline. The paradoxical findings of Hebert *et al.* and AASK investigators might be explained by alterations in water metabolism associated with declining GFR. In patients with falling GFRs who maintain the same intake of total solutes, water intake and concomitant urine output increase to maintain osmotic balance as the ability to concentrate urine to osmolalities greater than that of plasma is progressively lost. A point is eventually reached at which maximal urine concentrating capacity becomes equal to plasma osmolality (isothermia) and a fixed urine specific gravity of 1.010. Excretion of osmoles equal to the oral intake each day obligates the excretion of more urine, and therefore more water intake, than when the kidney function was normal (refer to Table 1, column labeled '285 mosm/kg H₂O'). Thus, the observed high urine volumes in the study by Hebert *et al.*

are more than likely the result of, rather than the cause of, GFR decline. Second, it has been demonstrated in animal models that AVP-mediated renal damage can be allayed only in the early phase of the disease,⁴⁴ so studies of water intake in populations with advanced CKD⁴² may be futile. Third, the prospective designs of Clark *et al.*⁴ and Strippoli *et al.*⁵ were not at risk of ascertainment bias unlike the retrospective analysis of Hebert *et al.*⁴² and AASK investigators.⁴³ Finally, the much larger sample sizes and observation windows of the Clark and Strippoli studies make it more likely that a true association has been uncovered.

The effect of urine output on renal function has also been examined in a small, prospective study of transplant patients with a solitary functioning kidney. Magpantay *et al.*⁴⁵ 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 41 compared with patients who were prescribed 21 daily. There are several possible reasons for the failure to detect any difference related to water intake in this study. First, a power calculation appears to show that the study is underpowered, as 250 subjects on each arm are needed for adequacy while the study included only 30 subjects in each group. Second, 12-month duration may not be sufficient to detect clinically significant changes of GFR. Third, adherence to prescribed fluid regimen seems to have been poor as the U_{osm} at month 12 was lower in the high fluid intake group. Fourth, the highest targeted urine flow rate may be above than that is needed to demonstrate benefit in preserving GFR. As previously discussed,^{4,5} in patients with two kidneys, the most effective intake rate for slowing disease progression was ~3 l/day, or ~1.5 l/day/kidney. Additional fluid intake—for example, that required to generate a urine flow rate in the range of >2 l/day/kidney—might not confer any additional benefit. The high-intake arm in this study prescribed 41 l/day to be excreted by a single functioning (transplanted) kidney, which may exceed the maximal effective rate associated with preservation of renal function. Thus, given previous data, it may be unrealistic to expect urine flow rates reaching 41 l/day to demonstrate benefits beyond that resulting from an intake equivalent to 2 l/day/kidney. Parenthetically, the stabilization of function in individuals with fluid intakes of 41 l/day (equivalent to 8 l/day of output in two kidneys) indicates that kidneys can tolerate relatively extreme rates of urine flow relatively well for at least a year.

Although urine volumes exceeding 3 l/day appear to be tolerated in the studies examined thus far, in individuals with comorbidities that limit the renal generation or the increased reabsorption of 'free' water in large quantities could lead to weight gain, hypertension, and hyponatremia. Use of thiazide diuretics, ultra-low sodium diets, and impaired diluting capacity could prompt unintended consequences. Furthermore, a risk could arise from sudden cessation of high water intake. High water intake can result in diminished medullary hypertonicity; a reduction of urinary maximal concentrating ability by as much as 30% was observed immediately

following a period of sustained high fluid intake.⁴⁶ Hence, a large and sudden drop in fluid intake could lead to free water loss over several days until the maximal medullary concentration gradient is reconstituted.

Conversely, fluid intake of 3 l daily seems likely to be well tolerated in patients with preserved GFR. For example, Spitz *et al.*⁴⁷ demonstrated that, in older males with normal renal function, an additional 1.5 l of daily water resulted in an expected total daily urine output of 3.6 l without weight gain, hypertension, hyponatremia, or decreased quality of life. Similar findings were observed in a small group of patients with eGFR between 10 and 15 ml/min (CKD stage 5).⁴⁸ After being challenged with an extra 2 l of water daily for 3 weeks, no patients experienced adverse events such as increase in body weight or blood pressure or decrease in serum sodium and eGFR; these findings are not unexpected as diluting capacity is generally preserved as long as GFR exceeds 10 ml/min.

Nevertheless, one might ask whether, as an alternative to increased water intake, salt intake (which stimulates AVP release through increasing serum osmolality) might be reduced. Unfortunately, such a strategy seems unlikely to yield major clinical benefits. First, many, and perhaps most, CKD patients already restrict their salt intake due to the presence of hypertension, leaving little potential for further AVP reduction. Second, the degree of salt restriction required to achieve the AVP-lowering goal would be draconian. Isosthenuria (285 mosm/kg H₂O) at a daily urine volume of 2 l (rather than 3–4 l) requires a daily urinary solute excretion of only 570 mosm (a substantial reduction from the mean intake of a typical Western diet), and is complicated by the fact that protein, sodium, and potassium would all have to be reduced concomitantly.

Despite the encouraging association between high urine volume and preserved eGFR in the two large observational studies, causal relationships between exposures and outcomes cannot be proven, merely inferred. The intriguing effects of increased urine volume flow rates in preserving glomerular filtration in both humans and animals with acquired renal disease call for future prospective clinical trials. In the meantime, the available evidence indicates that water in excess of that needed to cover the osmolar load may help to preserve renal function. A total daily urine output of 3 l for a moderate-sized person seems reasonable.

WATER THERAPY IN ADPKD

ADPKD is the fourth leading cause of renal insufficiency and leads to ESRD in most patients by the 6th decade. It accounts for about one-tenth of kidney-related health-care expenditures, so any therapy that could significantly ameliorate the natural history of the disease would likely have a major cost benefit.⁴⁹ Prolific research advances in this group of renal disorders have been recounted in several recent reviews.^{50–54}

Understanding the central role that cyclic 3'-5'-adenosine monophosphate (cAMP) has in cyst growth has shed considerable light on potential therapeutic mechanisms that

could alter the course of the disease. In both *in vivo* and *in vitro* studies, cAMP has been shown to promote cellular proliferation and transepithelial fluid secretion, key processes in cyst formation and expansion.^{55–58} Vasopressin (AVP) enhances cyst expansion by increasing the cAMP levels in the epithelial cells comprising cysts. It is not generally recognized that terrestrial animals, including normal humans, persistently excrete urine with osmolalities greater than plasma, meaning that cAMP-generating levels of vasopressin are constantly stimulating cyst growth in those with renal cystic disorders. The administration of an AVP-V₂ receptor inhibitor to rats and mice with renal cystic disorders strikingly reduced the rate of kidney enlargement and reduced the decline in renal function.^{59–62}

Tolvaptan, a highly specific AVP-V₂ receptor inhibitor, blocks the action of vasopressin to increase the rates of proliferation and of anion-dependent fluid secretion by cyst epithelial cells.⁶³ In an open-label pilot study of 63 subjects with ADPKD lasting 3 years, administration of tolvaptan reduced the rate of cyst growth and slightly slowed the rate of eGFR decline compared with historical controls.⁶ The dose of tolvaptan was titrated to give a trough U_{osm} of <300 mosm/kg H₂O thereby producing urine volumes of ~3–4 l/day. However, the most definitive evidence to date of the potential benefits of this treatment strategy has recently been published. The long-awaited double-blinded, placebo-controlled TEMPO 3:4 clinical trial⁶⁴ enrolled 1445 ADPKD patients with preserved eGFR and followed them for 3 years. Torres *et al.* found that tolvaptan-induced aquaresis can alter the natural history of the disorder, demonstrating a significant reduction in the primary endpoint of annual kidney volume growth (2.8% in the tolvaptan group vs. 5.5% in the placebo group, $P < 0.001$). In addition to the profound anatomical implications reported, there was also a significantly slower rate of kidney function decline in the tolvaptan-treated patients (a 1/serum creatinine annualized rate of -2.61 (mg/ml)⁻¹/year vs. -3.81 (mg/ml)⁻¹/year, $P < 0.001$). While the authors were careful not to endorse universal use of tolvaptan in ADPKD patients at this juncture, TEMPO 3:4 provides the clearest evidence to date that therapies inducing aquaresis via V₂ receptor blockade could fundamentally alter the progression of the disorder.

A closely related question is whether a reduction of plasma AVP levels, without the use of pharmacological blockade of AVP, can decrease disease progression. Nagao *et al.*⁷ tested the effect of increased water intake sufficient to lower U_{osm} in rats with the homolog of autosomal recessive PKD. The resultant polyuria and U_{osm} below that of plasma was associated with a reduction in renal weight (volume), reduced renal cyst area, and a decrease in the blood urea nitrogen levels below the controls, consistent with a positive therapeutic effect. Increased amounts of ordinary water would seem, therefore, to be a rational prescription for ADPKD patients in lieu of AVP-V₂ receptor inhibitors, but this hypothesis has not yet been tested in humans.

As the amount of water required to achieve the same degree of urinary dilution varies considerably between

individuals, a quantitative method was developed to determine the amount of water to prescribe to achieve a U_{osm} goal in a particular patient.⁶⁵ The total amount of fluid needed to achieve a mean daily U_{osm} of 285 mosm/kg H_2O was computed based on the day-to-day 24-h urine osmolar excretion rate. Using this individually tailored method, extra water, prescribed in addition to eight ADPKD patients' usual intake, caused a 50% increase of urine volume and a 35% decrease of mean U_{osm} without altering weight, blood pressure, serum sodium, or eGFR. The regimen was generally well tolerated by the patients: 62.5% ($n=5$) of participants were highly adherent (defined as being able to drink water sufficient to lower U_{osm} to the target of 285 mosm/kg), 12.5% ($n=1$) were somewhat adherent (defined as drinking enough to lower U_{osm} to 50% of the baseline value), and 25% ($n=2$) were able to drink sufficiently to lower U_{osm} by a more modest 20%. However, this small group of participants was highly selected, and their results may not be representative of the effects achievable in an undifferentiated group of patients. Complementing this work, Barash *et al.*⁶⁶ confirmed in ADPKD patients that the acute ingestion of water reduced U_{osm} below that of plasma, and that the low U_{osm} could be maintained by drinking supplemental water for at least 7 days.

If the lowering of AVP effect by pharmacologic inhibition is eventually shown to be effective in slowing cyst growth, the potential benefits of water as a therapy in ADPKD lie not only with its wide availability and trivial cost, but also with its tonic effect on AVP. Tonic inhibition has considerable appeal because, as a potent vasoconstrictor, AVP has been shown to have a role in animal models of hypertension.^{67,68} Although it is the case that there have been no reports that tolvaptan use aggravates hypertension when used in the treatment of hyponatremia⁶⁹ or ADPKD,⁶ elevation of plasma AVP levels might nevertheless be expected in response to extracellular fluid (ECF) volume contraction that may accompany the use of tolvaptan (or, indeed, any diuretic), making water an attractive alternative to pharmacotherapy as AVP levels may be continuously suppressed when surplus water is drunk throughout the waking hours (Figure 3).

How much water is safe and appropriate in ADPKD?

Lacking specific studies that directly tested the long-term impact of high urine flow rates on renal structure and function, we have attempted to define a safe upper limit that is experience based. The average daily U_{osm} is 1.7–2.5 times greater than plasma osmolality in non-diseased women and men, respectively.⁵⁰ Assuming (1) that plasma AVP is effectively suppressed to a nominal amount (2.5 pg/ml) when U_{osm} is diluted to 285 mosm/kg H_2O ,⁷⁰ and (2) that the daily osmolar excretion is assumed to be 800 mosm for women and 1100 mosm for men, urine volume would have to be increased to 2.8 and 3.7 l/day, respectively. Thus, daily water intakes of ~3 l for women and ~4 l for men in temperate climates would be sufficient to lower plasma AVP, levels which in nephrolithiasis and CKD progression have been shown to

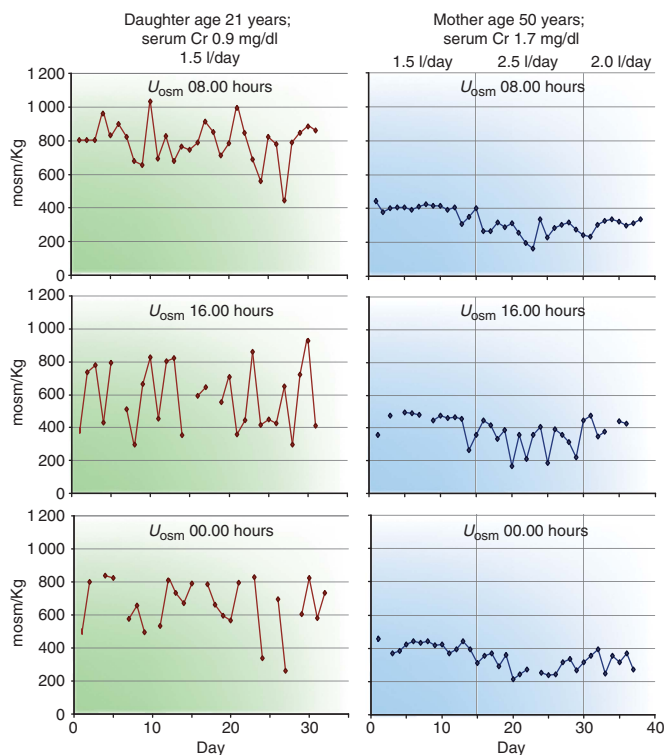


Figure 3 | Cases of autosomal dominant polycystic kidney disease (ADPKD) illustrating the pattern of daily urine osmolality on a fixed or changing fluid intake. A 50-year-old woman (creatinine (Cr) 1.7 mg/dl) and her 20-year-old daughter (Cr 0.9 mg/dl) maintained a fixed water prescription for several weeks. Urine osmolality was recorded at 0800, 1600, and 0000 hours daily. (a) The urine osmolality (U_{osm}) of a young woman with relatively normal serum Cr fell below 285 mosm/kg H_2O on only one occasion while drinking 1.5 l of fluid daily. Morning (first void) U_{osm} values exceed 800 mosm/kg H_2O , indicating preserved medullary function. (b) By contrast the older person had elevated serum Cr levels and the morning U_{osm} was about 400 mosm/kg H_2O reflecting decreased renal function. Nonetheless, she established a new steady state when the fluid intake increased to 2.5 l/day by excreting urine with an osmolality between 200 and 400 mosm/kg H_2O . Body weight did not change appreciably in either person.

be beneficial and relatively safe. Indeed, based on the U_{osm} troughs of 228–310 mosm/kg H_2O in the open-label tolvaptan study,⁶ we estimate that daily urine volume would have ranged from 2.6 to 4.8 l, an amount of urine output that was associated with better preservation of renal function relative to individuals who did not receive tolvaptan. We think it is therefore reasonable to suggest that 3–4 l of water daily can be safely prescribed for individuals with ADPKD at stage 4 CKD or better. Admittedly, meeting water intake goals by volitional drinking alone has been shown to be difficult in the setting of stone prevention²¹ and is likely to be proven difficult when medicinal water is recommended for ADPKD patients.

WATER INTAKE AND ITS EFFECT ON OTHER DIETARY CONSTITUENTS

It is reasonable to inquire whether increased water intake might alter the consumption of other dietary constituents,

Table 4 | Changes in other dietary constituents in studies of increased water intake

Author	Participant characteristics	Number of participants	Follow-up duration	Intervention	Total urinary solute (mosm/day)	Urea excretion (mmol/day)	Non-urea solute excretion (mmol/day)	Sodium excretion (mmol/day)
Borghini ¹⁹	Nephrolithiasis with normal GFR	99	5 Years	UOP to 2l		383 vs. 378		158 vs. 156.7
Daudon ¹⁸	Nephrolithiasis with normal GFR	109	6.9 Years	UOP to 2l		388 vs. 403		
Vaanmonde ⁴⁶	Healthy volunteers with normal GFR	8	48h	0.1 l/kg/day	1129 vs. 1136	480 vs. 512	649 vs. 625	
Wang ⁶⁵	ADPKD with normal GFR	8	5 Days	U_{osm} 285	673 vs. 689	132 vs. 138	302 vs. 304	132 vs. 136

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; GFR, glomerular filtration rate; UOP, urinary output; U_{osm} , urine osmolality.

such as protein and sodium, as such alterations could impact renal function, independent of water intake, over the long term. Although clinical trials designed to answer this specific question are lacking, a few studies,^{18,19,46,65} summarized in Table 4, provide insights into this issue. All four studies examined urea excretion (a proxy for protein intake), whereas two (one in non-diseased individuals and one in ADPKD patients) examined total urinary solute excretion and non-urea solute excretion and two (one in nephrolithiasis patients and one in ADPKD patients) examined sodium excretion. In all cases, measured analytes were virtually unchanged despite increased water intake, suggesting that the effects attributable to water were not confounded by changes in other dietary constituents.

CONCLUSION

Water has promising therapeutic roles in nephrology. Vasopressin suppression, a target for allaying nephrolithiasis, slowing CKD progression, and reducing the rate of renal cyst growth, can be achieved when sufficient extra water is given to increase urine volume above baseline levels without producing a gain in body weight or a reduction in the plasma sodium concentration. Until future clinical trials suggest differently, the available evidence leads us to conclude that daily urine volumes of ~3–4 l/day for an average-sized individuals can be safely recommended for those at risk for nephrolithiasis and those with CKD and, more specifically, ADPKD.

DISCLOSURE

JJG is a consultant to Otsuka.

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