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 cancer[2] 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 H_2O in those with normal renal function.

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):

Obligatory V (ml) = daily osmolar excretion (mosm) ÷ U_{osm} max (mosm/kg H_2O)

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 H_2O (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.

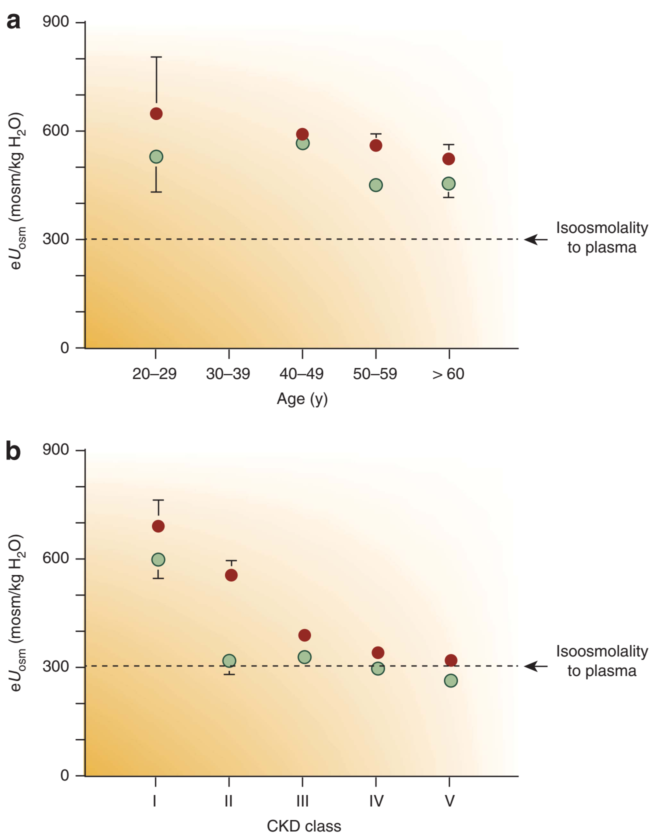

Figure 1 | Mean 24-h urine osmolality in different populations. Difference of mean 24-h urine osmolality in individuals with (**a**) intact or (**b**) impaired renal function. Open circles represent females; closed circles represent males. (Reproduced from Perucca *et al.*[71]) CKD, chronic kidney disease;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

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

	Obligatory urine volume (l/day)		
Total daily urine osmolar excretion (mosm/day)	U_{osm} max 1000 mosm/kg H_2O	U_{osm} max 500 mosm/kg H_2O	U_{osm} max 285 mosm/kg H_2O
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.

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