Just Add Water

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"Just add water" is the modern chime turning various prepared foods into family dinner; however, is it good advice for people at the table as well? In this issue of *JASN*, Berl[1] describes how solute intake affects the kidney's handling of water. What of the converse: How does intake of water affect kidney function and other physiologic variables? A brief search of the Internet will find multiple web sites warning health-conscious readers they must drink eight glasses of 8 oz/d to remove dangerous "poisons."[2,3] Is there evidence behind these recommendations? Furthermore, if targeted amounts of water consumption are therapeutic, then what are the improved outcomes?

It is widely known that humans cannot survive for more than a few days without ingesting water in excess of solutes.[4] The dangers of severe hypertonicity and volume depletion are not up for debate. It is also obvious that individuals in hot, dry climates have increased need for water, as do people who engage in strenuous physical exertion.[5] There are certainly well-recognized disease states, such as nephrolithiasis, for which increased fluid intake is therapeutic,[6] but do average, healthy individuals living in a temperate climate need to drink extra fluid—even when not thirsty—to maintain health? The classic recommendation is known as "8 × 8": Eight glasses of 8 oz of liquid per day—not including caffeinated and alcoholic beverages. Where did this recommendation come from? In his exceedingly thorough review of this subject, Valtin[7] reached the following conclusion: Nobody really knows. There is no single study—and therefore no single outcome—that has led to these recommendations. Different authors make different claims regarding the potential benefits of water drinking, and it is instructive to examine some of these in turn.

First is the notion that increased water intake improves kidney function and clearance of toxins. The kidney manifests several mechanisms to rid the body of toxins, including glomerular filtration, tubular secretion, and various degradative metabolic pathways. If excess water intake were to have an impact on toxin removal, then it would be through one of these mechanisms.

Water ingestion can acutely affect GFR, although not necessarily in the direction one might expect. Using 12 young, healthy individuals as their own controls, Anastasio *et al.*[8] found increased water intake actually *decreases* GFR. It might therefore seem that any "toxin" removed purely by glomerular filtration is cleared *less* efficiently in the setting of increased water intake; however, it is not certain such changes in GFR persist over time. Indeed, GFR was unchanged during a 6-mo randomized trial of increased water intake in older men who had benign prostatic hypertrophy.[9] Of course, the populations in the two studies are different, and the main goal of the randomized trial was to evaluate bladder function rather than kidney function; as an aside, the study did show some improvement in bladder function, although the clinical significance of the findings is unclear.[10]

Of course, most endogenous substances are not cleared purely by glomerular filtration alone. Anastasio *et al.*[8] found the total clearance of osmoles increased as water intake increased, probably as a result of reduced reabsorption. If there are "dangerous" substances among these osmoles, then increased water intake might indeed help in their clearance. Interestingly, one of the osmoles whose clearance was increased was sodium. Given the suspected role of long-term sodium retention in the development of hypertension,[11] one could speculate that increased clearance of sodium is beneficial. Urea clearance also increases with high water intake, but urea is not a toxin. It is unclear whether any of these changes persist in the long term. In short, increased water intake does have some impact on renal clearance of various substances, but current data are insufficient to assess the clinical significance of these observations. In fact, given how little is known about the identity of toxic substances cleared by the kidney, it is unlikely this type of data can conclusively demonstrate a benefit from excess water drinking.

Another popular idea found on Internet sites is that ingested water is retained in various organs and improves their function. For this hypothesis to be plausible, one must first show that "normal" individuals who are not thirsty will nevertheless retain ingested water in their body rather than excrete it in the urine. One study of 14 individuals in "good health" suggested that water retention is quite variable and depends significantly on the speed with which water is ingested. A water load ingested over 15 min is largely excreted, whereas a water load ingested over 2.5 h is largely retained.[12] In addition, water mixed with a poorly absorbed sugar, thereby slowing absorption of water from the gut, is largely retained, whereas water mixed with an easily absorbed sugar is largely excreted. This pattern is similar in both men and

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women, although a separate study suggested water retention in women is greater than in men.[13] Such studies examine relatively short-term changes, usually over 24 h. We are not aware of data regarding what type of steady state develops over longer periods of increased water intake. Even if such data were available, it is difficult to know how to interpret their clinical importance; therefore, it may be more fruitful to focus on outcomes that have more established clinical relevance.

One frequent rationale for increasing water intake is to increase satiety as part of the self-management of obesity. There is surprisingly little evidence regarding this issue. One study of women found water drinking before a meal increased satiety during a meal—but not after it.[14] Caloric intake was not measured. Another study—this time of men—found total caloric intake decreased by increasing the volume of a calorie-containing drink given before the start of a meal.[15] Another study by the same group—of women only—showed increasing the water content of foods themselves decreased caloric intake, but offering water in parallel with food did not.[16] None of these studies makes clear whether drinking a large volume of fluid over the course of a day will decrease the number of ingested calories. As an interesting corollary, ingesting water could also affect caloric balance by increasing energy use. Two studies by Boschmann *et al.*[17,18] found consumption of water increased thermogenesis—boosting the number of calories used by the body. This effect is not seen with ingestion of salt-containing fluids. Another group found increased body temperature in athletes who rehydrated with pure water when compared with athletes given a carbohydrate/saline solution[19]; however, other authors have disputed Boschmann's findings.[20] It is unclear why water ingestion would increase energy consumption, although it is relatively well documented that ingestion of pure water increases sympathetic tone whereas consumption of salt-containing solutions does not.[21] In fact, ingestion of 16 fl. oz. of water to activate the gastropressor response is recommended as a treatment for orthostatic hypotension.[22]

Although the data regarding satiety and thermogenesis are intriguing, they are insufficient to clarify the role of water intake in mitigating the obesity epidemic. Although it may be cliché to suggest further research is required, the impact of water on obesity seems the most compelling choice among multiple issues to test regarding the benefits of supplemental water intake. Not only is it highly relevant to public health, but also changes in obesity-related outcomes such as caloric intake and body weight are readily quantifiable and therefore lend themselves to study.

There certainly are other public health concerns invoked in the debate over water intake. Retrospective case-control and cross-sectional studies showed associations between decreased fluid intake and the incidence of such disparate conditions as coronary disease, bladder cancer, and colon cancer.[23,24] Of course, these studies suffered from weaknesses typical of epidemiologic and retrospective case-control data: Are people sick because they drink less, or are they drinking less because they are sick? Only large and expensive randomized trials could settle these questions definitively. Given that water cannot be patented, such trials seem unlikely.

Not all conditions worthy of study need be life threatening. Headache is frequently attributed by the lay public to water deprivation, but there is little study of this phenomenon.[25] To our knowledge, only one trial has examined headache prevention by increasing water intake.[26] Fifteen patients with migraine headaches were randomly assigned to increased water intake or placebo for 12 wk. The number of hours of headache was quantified over 14-d intervals at the beginning and at the end of the trial. Although the treatment group had 21 fewer hours of headache compared with the control group, this difference did not reach statistical significance (the number of patients was obviously quite small). Given the economic impact of migraine on time lost from work, this area would seem to be ripe for further study.

A frequently cited cosmetic benefit of water drinking is improved skin tone. Although frank dehydration can obviously decrease skin turgor, it is not clear what benefit drinking extra water has for skin. One study suggested ingestion of 500 ml of water increases indices of capillary blood flow in the skin.[27] It is unclear whether these changes are clinically significant or how to interpret them in light of water's potential impact on sympathetic tone. We were unable to find any other data regarding the impact of water intake on skin in otherwise healthy people.

To summarize the conclusions of other, more exhaustive reviews: There is no clear evidence of benefit from drinking increased amounts of water.[7] Although we wish we could demolish all of the urban myths found on the Internet regarding the benefits of supplemental water ingestion, we concede there is also no clear evidence of *lack* of benefit. In fact, there is simply a lack of evidence in general. Given the central role of water not only in our bodies but also in our profession, it seems a deficit worthy of repletion.

DISCLOSURES

None.

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See related article, "Impact of Solute Intake on Urine Flow and Water Excretion," on pages 1076–1078.

Integrins, Extracellular Matrix, and Terminal Differentiation of Renal Epithelial Cells

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The mechanism whereby epithelial cells terminally differentiate is an active area of investigation. One potential interface is the spatial and temporal expression of the transmembrane receptors known as integrins and the extracellular matrix (ECM) proteins to which they bind. In this issue of *JASN*, Vijayakumar *et al.*[1] propose that activation of integrin $\alpha v\beta 1$ causes synthesis and deposition of hensin, an ECM protein that forms 50- to 100-nm-long fibers composed of several fibrils. Upon polymerization and deposition into the ECM, hensin binds to $\alpha 6$-containing integrins, a key step in mediating the conversion of epithelial cells to a cuboid-like phenotype capable of apical endocytosis. These novel studies suggest that integrin–hensin interactions play an important role in the terminal differentiation of intercalated cells of the collecting duct.

The collecting system of the kidney is derived from the ureteric bud, which undergoes multiple iterations of branching morphogenesis followed by a phase of growth, maturation, and differentiation.[2] Many mechanisms regulate this branching and tubular expansion. Multiple transcription factors, growth factors, ECM proteins, and various cognate receptors play a critical role in these processes. Less information is available on the moieties that halt collecting duct growth and induce terminal differentiation. A number of transcription factors modulate the terminal differentiation of epithelial cells in

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