Hydration for Health: So What? Ten Advances in Recent Hydration History

Erica T. Perrier

Hydration and Health Department, Danone Research, Palaiseau, France

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We have long understood that water is essential to life. From early experiments on water's importance for survival in extreme environments [1] to a thorough understanding of how hydration affects sports performance and safety [2–6], the importance of replacing body water losses is well-known and markers of water loss dehydration are well-understood. However, outside of sport and occupational health, water has remained to a large extent an essential but also an invisible nutrient [7–10]. The past decade marks a turning point in considering the importance of water and hydration for the general population, with significant ad-

vances in our understanding of water, hydration, and health. On this tenth anniversary of the Hydration for Health Scientific Conference, we offer the following “top ten list” describing key advances in the hydration and health sciences and present perspectives for the next decade.

The Concept of the *Low Drinker*

This concerns the physiological characterization of otherwise healthy adults who, despite free access to water and other beverages during their daily activities, routinely consume far less than the Adequate Intake for water as defined by European [11] or American [12] public health authorities. These *low drinkers* maintain a normal total body water volume and plasma osmolality and are thus not dehydrated. Yet, they remain in a state of near-

constant water saving, as evidenced by consecutive days of low urine volume, high or approaching maximal urine concentration, with normal but elevated circulating arginine vasopressin (AVP) and cortisol [13–18], and, curiously, no evidence of increased thirst drive [17, 19] to stimulate increased drinking. This suggests that at least a segment of the general population is relatively insensitive to physiological cues to drink adequately, with possible implications to kidney or metabolic health (see below).

The First Acknowledgement of “Desirable” Urine Concentration in Setting a Dietary Reference Value for Water

The EFSA Scientific Opinion on Dietary Reference Values for water [11], published in 2010, considered for the first time that an adequate intake of water should provide a margin or buffer between “desirable” and maximal urine concentrating capacity. The committee concluded that it would be prudent to provide for a safe margin of “free water reserve” [8, 20]. The water requirement was thus targeted to achieve a urine osmolality around 500 mosm/L, well below the maximum concentrating capacity of the kidneys.

A Heightened Interest in Accurately Recording Fluid Intake

A key aspect to understanding the relationships between water intake, hydration, and health begins with widespread and accurate recording of fluid intake in population surveys and clinical trials. As recently as 2014, a systematic review of fluid intake across age groups found that while most publications describing fluid intake in adults recorded water intake, more than half the publications involving teenagers or children did not record plain water consumption [21]. Recent work has highlighted that water and fluid intake are underestimated in combined food and beverage recording instruments [22, 23], suggesting the need for a fluid-specific tool. Recently a prospective, 7-day fluid-specific diary was validated against a gold-standard method of water turnover [24]. This validated tool, along with increasing publications describing fluid intake patterns worldwide [25–34], allows for a growing, global worldwide picture of what people drink, essential to understand the impact of fluid intake on health.

The Widespread Availability of an Ultrasensitive Copeptin Assay

AVP, or the antidiuretic hormone, is a key regulator of total body water. It acts via V2 receptors to modulate water reabsorption in renal collecting ducts and thus adjust urinary water losses to maintain body water homeostasis in response to changes in daily water intake. Beyond its role in body water homeostasis, AVP also has widespread central and peripheral effects that make it an interesting candidate in the study of many diseases [35]; however, its instability and rapid clearance have historically made reliable measurement difficult [36]. Copeptin, the C-terminal portion of the AVP prohormone, is released in equimolar concentration to AVP, and therefore would provide a quantitative measure of AVP release. The development and commercialization of an ultrasensitive sandwich immunoassay (B.R.A.H.M.S Copeptin pro-AVP, Thermo Scientific, Hennigsdorf, Germany) made possible an explosion of new research on AVP through its surrogate, copeptin. The research impact of this assay has already been profound: a full 3 quarters of scientific papers including copeptin have been published in just the past six years.¹ This includes explorations of the role AVP may play in the development of kidney and cardiometabolic disease (see below).

The Copeptin Explosion and the Rise of the Cohorts

The availability of the ultrasensitive copeptin assay has facilitated a surge of publications identifying copeptin, a surrogate marker of AVP, as an independent risk factor in kidney and cardiometabolic disease. More specifically, higher plasma copeptin (usually defined as the top quintile or quartile measured in population studies) has been independently associated with increased likelihood for incident impaired fasting glucose or type 2 diabetes mellitus (T2DM) as well as components of the metabolic syndrome including hypertension, high C-reactive protein, or abdominal obesity [37–40]. Moreover, in patients with existing T2DM, higher copeptin appears to be linked to higher risk for the onset of kidney pathology including a more rapid eGFR decline [41] or doubling of serum creatinine in addition to increasing risk for cardiovascular events [42]. This evidence, pooled with associations be-

¹ PubMed search on January 24, 2019 for “copeptin” in Title and/or Abstract. Of a total of 869 records returned in the search, 650 (75%) were published in 2013 or later.

tween low urine volume or low water intake and kidney or cardiometabolic disease [43–46], suggests that a combination of habitual low drinking, highly concentrated urine, and a higher circulating AVP may contribute to increased risk of metabolic disease in healthy individuals and may worsen comorbidities in those with existing T2DM.

New Statistical Approaches Help to Establish a Probable Causal Role of Vasopressin in Metabolic Disease

While large, prospective cohorts have documented associations between AVP and disease risk, these studies cannot establish whether higher circulating AVP plays a causal role in the development of metabolic dysfunction. A recent publication by Roussel et al. [39] attempts to shed light on the directionality of the relationship by exploring patterns of mendelian randomization. Briefly, the authors documented that participants (men and women) in the upper quartiles of copeptin had higher incidence of hyperglycemia and lower insulin sensitivity than those with lower plasma copeptin. They also found that specific variants of the AVP gene were also associated with increased risk for hyperglycemia, and that men expressing these variants also had higher plasma copeptin (no association was found in women, who, on average, tend to have lower plasma copeptin than men). This finding is consistent with previous preclinical evidence that AVP contributes to metabolic dysfunction via V1a and V1b receptors expressed in hepatocytes and pancreatic islets, respectively [47–50].

First Findings that Increasing Water Intake Lowers High AVP, a Risk Factor for Disease

If higher AVP (copeptin) is an independent risk factor for disease, might increasing daily water intake meaningfully lower circulating AVP? And would this reduction subsequently improve long-term health outcomes? Four recent, independent studies provide a convincing proof of concept that among low drinkers, and particularly in those with high baseline AVP, increasing water intake lowers AVP (or copeptin) over hours [51], days [17], or weeks [52, 53]. Promisingly, the copeptin-lowering effect appears to be most pronounced in individuals with higher baseline copeptin as well as other baseline signs of low drinking (such as low urine volume or high urine osmo-

lality), suggesting a potential subpopulation of “water responders” for whom increased water intake may represent an attainable lifestyle intervention with real potential for health benefit. Important gaps still exist as to whether increasing water intake and subsequently lowering AVP would result in a reduction in disease incidence. A recent study by Enhörning et al. [53] found that in addition to reducing copeptin, 6 weeks of increased water intake resulted in a modest but significant lowering of fasting plasma glucose; furthermore, the reduction in glucose was predominantly driven by those with the highest baseline copeptin and the greatest reduction in response to the water intervention. Longer-term, larger-scale interventions are needed to verify whether increasing water intake to lower AVP reduces or slows the onset of disease.

Water Intake as a Potential Therapeutic Target for Renal Disease

Water intake has generated interest as a potential therapeutic agent for multiple kidney diseases including urolithiasis, chronic kidney disease (CKD), autosomal dominant polycystic kidney disease (ADPKD), and the mesoamerican nephropathy epidemic [54, 55]. In urolithiasis, low water intake and low urine volume are known risk factors for stone formation [56–60], and increasing water intake to promote the excretion of a large volume of dilute urine is recognized in secondary stone prevention [56, 61, 62]. Less is known about the potential therapeutic role of water intake and hydration in CKD and ADPKD. While a pilot study involving stage 3 CKD patients documented that increasing water intake increased urine volume and lowered plasma copeptin [63], a larger-scale randomized controlled trial failed to show that an increase in water intake slowed the progression of the disease [64]. However, the increase in urine volume was quite modest (+0.6 L/d) and the follow-up time relatively short. In ADPKD, the suppression of AVP by increased water intake may slow renal cyst growth; however, the limited human data available are conflicting. A large RCT is currently assessing the safety and efficacy of prescribed water intake to slow disease progression [65]. Finally, recurrent exposure to heat stress and dehydration has been identified as a key risk factor in the mesoamerican nephropathy [55], an epidemic of CKD of unknown etiology affecting young men working in Central American agricultural fields in the lower altitudes along the Pacific coast. Further investigation into these pathologies, the mechanisms by which wa-

ter intake may alter the course of the disease, and the efficacy of water intake as a therapeutic agent, all represent exciting future research opportunities with the potential to impact public health.

The First RCT on Water Intake for the Prevention of Urinary Tract Infection

The recent publication of the first RCT on increased water intake to prevent urinary tract infection (UTI) recurrence demonstrated that water intake can play a powerful role in secondary prevention [66]. This 12-month study demonstrated that increasing water intake by 1.2 L/day cut UTI recurrence in half in women who suffered from recurrent UTI and who, at baseline, consumed <1.5 L of water and other beverages daily. This is especially relevant given the high prevalence of UTI (more than 60% of women worldwide); the widespread use of antibiotics to treat each recurrence or as prophylaxis; and the health-care costs associated with diagnosis and treatment. Moreover, this subject struck a chord with a decidedly nonscientific audience, generating mainstream media attention, a surge of activity on social media, in addition to becoming one of the most attended-to articles on the journal website,² suggesting widespread interest in the fact that something as simple as increasing water intake can measurably impact health.

Growing Academic Interest and Debate around What It Means to Be Well-Hydrated

The study of hydration is expanding, from its origins in dehydration, sports performance, and safety toward an increased understanding of how hydration plays a role in health. Until quite recently, however, the models, terminology, and biomarkers used to describe hydration remained rooted in the concept of body water gains and losses [67]. To be euhydrated was, for all intents and purposes, defined by the absence of dehydration (hypohydration) or measurable body water loss. Little attention was paid to the process by which euhydration was maintained, that is, by modulating urinary water losses

as a function of water intake. Today, we see a growing interest and healthy debate over what it means to be well-hydrated that extends beyond simply replacing body water losses. Recent publications have weighed in on the distinction between the hydration state and the hydration process [18, 68–71]; have proposed cutoffs and criteria for defining underhydration, optimal hydration, and the question of daily water requirements [72–76]; have debated the validity of various hydration biomarkers in different circumstances [77–82]; and have introduced concepts for various beverage indices [83, 84]. Evidently, as in any academic field, there are differences of opinion, discrepancies that require clarification, conflicting evidence, and many subjects that have not been adequately addressed. However, the fact that the subject of hydration for health is now on the table and being vigorously debated is a positive development, which will encourage further scientific advances in the years to come.

Perspectives for the Next Ten Years

Today, we have a solid foundation upon which to build the next generation of hydration and health research. We have valid tools to measure fluid intake and easier access to measuring copeptin, a reliable surrogate for AVP and antidiuretic activity. We have a large body of epidemiological evidence that suggests that low water intake, low urine output, and high AVP are associated with kidney and metabolic disease risk. We have plausible mechanisms and supporting preclinical evidence for how low water intake or suboptimal hydration may contribute to disease. We have proof of concept studies which demonstrate that increasing water intake can lower high plasma copeptin, a key risk factor in disease, and a first large-scale randomized, controlled trial demonstrating that water is effective in secondary prevention of UTI. After ten years of developing the framework for research around hydration for health, where are the critical gaps? What still needs to be done? The following is a nonexhaustive list of opportunities to contribute to this growing field of research:

- Dig further into defining thresholds for copeptin that are predictive of disease risk and deepen our understanding of the apparent sex differences in the relationships between water intake, AVP, and disease.
- Need for large-scale, appropriate-length RCTs to determine under which conditions increased water intake may play a role in disease prevention or health maintenance.

² At the time of writing, the article has been viewed more than 42,000 times at the journal website, is ranked within the top 2% of all research reviewed by Altmetric for quality and quantity of online attention received, including news media, blogs, and social media.

- Support or improve thresholds or criteria for optimal hydration.
- Increase our knowledge of water intake, hydration, and health in underresearched populations, such as young children, pregnant and breastfeeding women, and the elderly.
- Understand the role water intake and hydration may play in modulating comorbidities (for instance, reducing the risk for diabetic nephropathy in T2DM).
- Dig deeper into water and fluid intake patterns of selected demographic groups and develop strategies to encourage healthier drinking habits.

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