

Fluid Intake and Vasopressin: Connecting the Dots

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Key Words

Vasopressin · Copeptin · Fluid intake · Hydration · Urine osmolality · Biomarkers · Kidney · Chronic kidney disease · Metabolic syndrome · Diabetes

Abstract

In the last decade, cross-sectional and multiple cohort studies have associated total fluid intake or water intake with the risk for chronic kidney disease (CKD) and even the risk of developing hyperglycemia. Urine biomarkers have also been linked to the risk of CKD and lithiasis, and these biomarkers respond quickly to variations in fluid intake. High circulating copeptin levels, a surrogate marker of arginine vasopressin, have been associated with metabolic syndrome, renal dysfunction and increased risk for diabetes mellitus, cardiovascular disease and death. The aim of this paper was to explore how the various findings on water intake, hydration and health are interconnected, to highlight current gaps in our understanding and to propose a model that links water intake, homeostatic mechanisms to maintain water balance and health outcomes. Since plasma copeptin and vasopressin have been demonstrated to be sensitive to changes in water intake, inversely associated with 24-hour urine volume, and associated with urine biomarkers and fluid intake, vasopressin is proposed as the central player in this theoretical physiological model.

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Arginine vasopressin (AVP; also known as the antidiuretic hormone) is a bloodborne molecule identified as a key player in water homeostasis. Osmotically driven release of AVP notably increases water reabsorption in the kidney via action at V2 receptors, increasing the expression of aquaporin-2 channels and thus increasing water reabsorption capacity in the collecting duct. However, the effects of AVP are not limited to water balance; its actions also include inducing vasoconstriction in vascular cells, glycogenolysis in hepatocytes and ACTH release from the anterior pituitary via lower-affinity V1a and V1b receptors. AVP is derived from a pre-pro-hormone, which also includes the carrier protein neurophysin II and the peptide copeptin. Once in circulation, AVP is unstable in plasma and has a half-life ranging between 16 and 20 min [1, 2], which makes direct measurement quite difficult. Because copeptin is synthesized in a one-to-one ratio with AVP, is more stable and is relatively easy to measure, it has gained popularity as a surrogate measure for AVP secretion.

In the literature, AVP has been associated with adverse effects in several conditions such as sepsis, cardiac disease and lower respiratory tract infection [3]. Higher circulating copeptin levels have also been associated with increased risk of developing pathologies (e.g., metabolic syndrome, renal dysfunction), increased risk for diabetes mellitus [4] or cardiovascular disease and death [5]. Interestingly, in separate cohorts, lower total fluid intake [6], lower plain water intake [7] and lower 24-hour urine vol-

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0250-6807/16/0686-0006\$39.50/0

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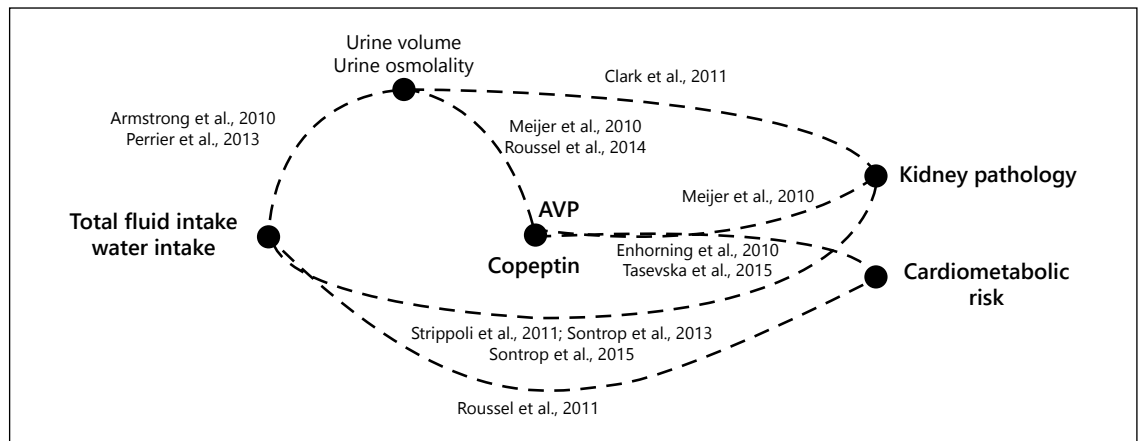


Fig. 1. Theoretical model linking total fluid intake to urine variables, vasopressin and health outcomes.

ume [8] all have been associated with increased risk for chronic kidney disease (CKD); low water intake also has been associated with new-onset hyperglycemia [9]. Moreover, individuals with habitually lower fluid intake have higher circulating AVP, lower 24-hour urine volume and higher urine concentration [10, 11]. Given that higher circulating AVP is an indicator of chronic or habitual anti-diuresis (indicating insufficient water intake), these findings suggest that there may be biologically significant interconnections between AVP, water intake and renal and metabolic health (fig. 1). This paper aims to propose a theoretical working model to link water intake, homeostatic mechanisms to maintain water balance and health outcomes; highlight current gaps in our understanding and provide some of the information needed to answer the following question: is reducing AVP concentration through increased water intake an effective means to reduce the risk of renal or metabolic pathologies and improve health?

Link No. 1: Water and/or Fluid Intake and Kidney Disease

Evidence from multiple cohort studies has linked water intake volume to kidney disease risk. A cross-sectional investigation has shown that a total fluid intake of 3.3 liters/day was associated with a 30–50% reduction in the likelihood of developing CKD compared with an intake of 1.7 liters/day [6]. Similarly, results from the 2005–2006 National Health and Nutrition Examination Survey have shown that high intake of plain water (>2.6 liters/day) was inversely related to CKD prevalence [7]. This association was not seen for beverages other than plain

water. A third confirmation comes from a prospective 6 years observation showing an inverse, graded relationship between urine volume and estimated glomerular filtration rate (eGFR) decline. The authors found that, for each increasing category of 24-hour urine volume, annual eGFR decline was progressively slower, even after adjusting for potential confounders. In the highest (≥ 3 liters/day) urine volume categories, the risk for mild to moderate or severe renal decline was reduced by roughly 50% [8].

Despite the increasing amount of data demonstrating positive associations between increased water intake and kidney health, there exist conflicting reports. A recent prospective study failed to find a link between fluid intake and GFR, demonstrating that fluid intake from food and beverages, excluding water, were not associated with improved kidney function or reduced mortality [12]. However, a major shortcoming of this study involves the fact that the intake of plain water was not included in the final analysis; the questionnaire used to collect fluid intake data did not include a specific question about plain water consumption. Because plain water consumption is one of the key drivers of high total fluid consumption the omission of plain water from the analysis limited the ability to evaluate associations between water intake and disease [13].

Link No. 2: Vasopressin as a Prognostic Biomarker of Chronic Diseases

Higher circulating copeptin levels have been associated with metabolic syndrome, renal dysfunction, increased risk for diabetes mellitus [4] or cardiovascular

disease and death [5]. A large cohort study of healthy adults demonstrated an increased incidence of components of the metabolic syndrome as quartiles of median copeptin concentration increased from 3.41 pmol/l in women and 5.56 pmol/l in men [14]. In another community-based study (n = 1,197), quartiles of men and women with a plasma copeptin concentration >5 pmol/l were significantly associated with the presence of metabolic syndrome [15]. In another study (n = 3,702), subjects (men and women) who developed new-onset diabetes mellitus after 12.6 years of follow-up had a median plasma copeptin level that was 40% higher than control subjects at baseline (6.74 vs. 4.9 pmol/l) [4]. Similarly, plasma copeptin concentration has been associated with declining GFR [16] and cardiovascular disease [5] in diabetic patients, and disease progression in patients with CKD [17]. These findings are striking considering that the concentration of copeptin associated with increased disease risk is, today, considered to be physiologically normal, and can be observed in habitual low-volume drinkers with ad libitum access to fluids, and in the absence of excessive water losses. Taken together, these findings suggest that (a) plasma copeptin above approximately 5.5 pmol/l, while physiologically normal, may increase the risk of disease and (b) reducing copeptin to <5 pmol/l, which is likely attainable in most individuals simply by increasing water intake, may be beneficial to long-term health. While increasing fluid consumption seems to be an easy strategy to modulate AVP, the nature of fluid consumed may also influence plasma copeptin. In a cohort study, Roussel et al. [18], demonstrated that plasma copeptin was higher in participants with greater sugar sweetened beverage intake, and lower in participants with greater plain water intake. Unfortunately, the studies described above did not report plain water or total fluid consumption of subjects. Including a specific questionnaire about water consumption in future prospective studies would strengthen the possibility to evaluate the impact of increased fluid intake and the quantitative relationship between fluid intake and copeptin.

Link No. 3: Modulating Vasopressin via Increased Fluid Intake

Considering that AVP regulates total body water balance, it is unsurprising that AVP differs as a function of fluid intake: subjects drinking <1.2 liters/day had a significantly higher plasma AVP concentration compared to

those drinking >2 liters/day (2.4 vs. 1.5 pmol/l) [10]. This suggests that small differences in plasma AVP concentration, while remaining in the physiologically normal range, may have utility as a surrogate marker of fluid intake. As well as AVP, plasma copeptin was statistically correlated with changes in water intake and to be inversely associated with 24-hour urine volume [19–21]. In the absence of kidney pathology or infection, plasma copeptin is generally <10 pmol/l with median values varying from 3.8 to 6.0 pmol/l [22]. This suggests that a substantial proportion of the population has a circulating copeptin >5.5, the concentration associated with increased risk of metabolic disease. Moreover, increasing water intake among low drinkers can measurably reduce circulating copeptin: in 54 young healthy adults, an increased water intake during 6 weeks significantly reduced circulating copeptin from 5.18 to 3.90 pmol/l [Lemetais, 2016. unpublished data]. Unfortunately, the biological significance of such differences is still unknown. Currently, no specific copeptin threshold has been associated with an increased risk of developing pathologies. However, even if these variations of plasma copeptin remain small in magnitude, the relative decrease (–24.7%) is substantial. These results corroborate findings by Sontrop et al. [20], who observed a similar relative decrease of plasma copeptin concentration (from 15.0 to 10.8 pmol/l; –24.8%, p = 0.005), in 17 patients with stage 3 CKD who increased their water intake during 6 weeks.

Today, insufficient evidence exists to confirm any specific value for plasma copeptin as ‘desirable’ from the perspective of long-term health. However, 24-hour urine concentration represents the end result of all of the concentrating and diluting mechanisms to maintain total body water homeostasis, and thus is a reflection of AVP secretion; increased circulating AVP or copeptin has been associated with increasing urine osmolality (U_{Osm}) in a number of studies [18, 23–25]. Recently, we proposed a 24 h U_{Osm} threshold of 500 mOsm/kg as a target for ‘optimal’ hydration [26]. Taking into account the intake reference values, risk for lithiasis and CKD, and circulating AVP, a target 24 h U_{Osm} of 500 mOsm/kg ensures a total fluid intake that is sufficient to replace losses, maintain a high urine volume and reduce circulating AVP. Taking these 3 links together, copeptin represents a promising candidate to fill the gap in the literature and demonstrate a link between water intake and certain health outcomes. However, additional evidence (i.e., controlled, randomized clinical trials) is needed to complete this theoretical model.

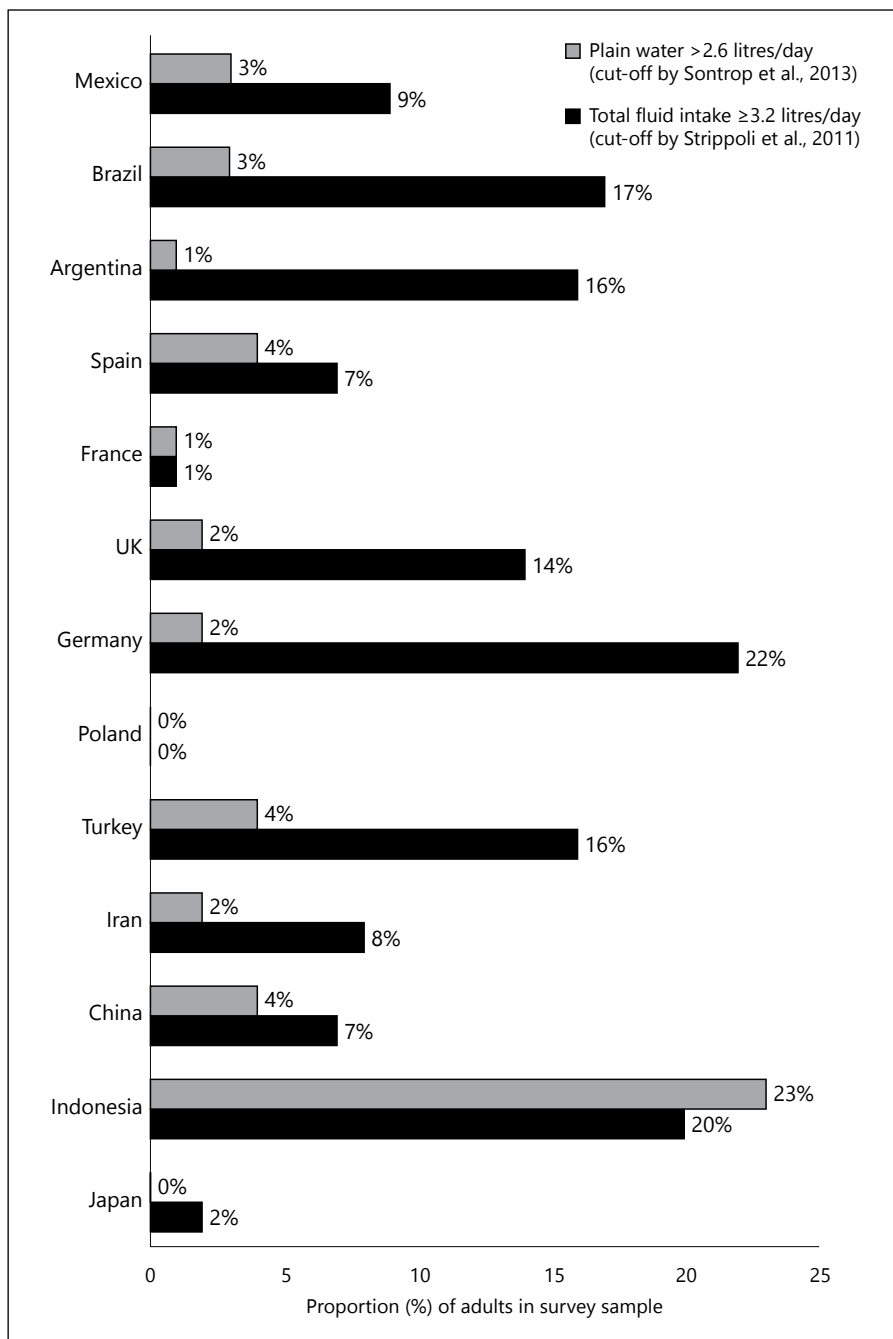


Fig. 2. Proportion of adult subjects participating in the Liq.In⁷ surveys [29, 30] who have a mean daily water intake >2.6 liters/day or mean daily total fluid intake ≥3.2 liters/day.

Missing Links: A Need for Valid Fluid Intake Data and Consistent Copeptin Measurement

Determining whether increasing fluid intake can reduce circulating AVP and impact upon health is only possible with valid data. In general, the quality of the data specific to plain water and total fluid intake gleaned from nutrition surveys is highly variable, subject to self-report

bias and under-reporting of fluid intake between meals [27]. Until recently, many major surveys omitted questions regarding plain water intake [12, 28], limiting our ability to draw conclusions about associations between plain water intake and health. Two things are required to firmly establish links between fluid intake and health outcome, investigate dose–response relationships and develop meaningful reference intake values: (1) an assessment

method validated for total water intake or total fluid intake and (2) studies to determine relative validation and potential measurement errors when assessing total fluid intake.

Thorough, population-based fluid intake surveys also would allow public health officials to estimate the proportion of the population at risk for a given water-related pathology. For instance, to determine the proportion of adults consuming enough plain water or total fluid to reduce CKD risk, thresholds of 2.6 liters/day for plain water [7] or 3.2 liters/day total fluid [6, 8] could be applied to the participants of the Liq.In⁷ surveys. The latter are cross-sectional surveys in large national samples with the primary aim to assess fluid intake with a 7-day fluid-specific record [29, 30]. As shown in figure 2, once additional evidence becomes available, this model could potentially carry a relevant public health message because many people are concerned by a low intake of plain water.

The measurement of plasma copeptin in population surveys is becoming more commonplace. The recent availability of ultra-sensitive kits has opened the door to measuring small differences in copeptin in healthy individuals. However, circulating copeptin in healthy people and, consequently, differences between low drinkers and high drinkers are very low. Many kits with different sensitivity are used in the literature and there is a need for consensus on analytical process. Thus, for quantification of copeptin in physiologically normal individuals, we suggest using copeptin ultrasensitive kits with high sensitivity.

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In summary, plasma copeptin is proposed as a prognostic biomarker of renal and metabolic pathologies and is more and more often being associated with hydration biomarkers such as U_{Osm} . However the number of publications on the topic is limited and the level of evidence supporting the interrelationships between water, AVP and health outcomes is weak. Currently, only a few prospective cohort studies have evaluated the link between copeptin and pathology; no information is available on fluid consumption. To date, no randomized, controlled clinical trial has focused on the health impact of a chronic low water intake stress or the relationship between fluid intake, U_{Osm} , plasma copeptin and pathology. Complementary studies are necessary to understand if the manipulation of plasma AVP, through increased water consumption, decreases risk of pathologies. Future epidemiological studies that collect both fluid intake data and urine measurements will allow better understanding of these relationships. Our theory proposes that consuming a few additional glasses of water each day, may someday be recognized as a simple means to reduce the risk of metabolic syndrome, renal dysfunction, diabetes mellitus [4] and/or cardiovascular disease [5].

Disclosure Statement

I.G., M.V., E.T.P. and G.L. are full-time employees of Danone Research.

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