



Is high fluid intake good for the kidney?

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The article by Min et al [1], in the current issue of *Kidney Research and Clinical Practice* discusses the role of sub-morbid dehydration in initiating glomerular hyperfiltration as a potential harbinger and cause of progressive chronic kidney injury. They conducted a cross-sectional analysis of over 28,342 ambulatory, community-dwelling, civilian, non-institutionalized Korean adults as part of the Korea National Health and Nutrition Examination Surveys, which measure urine specific gravity (SGU) as the primary variable indicating hydration status. The estimated glomerular filtration rate (eGFR) was considered as the primary outcome. In their study, sub-morbid dehydration measured by increased SGU was associated with higher eGFR, and they concluded that the clinical significance of sub-morbid dehydration-associated glomerular hyperfiltration requires further investigation.

Though the initial interpretation of their observational study was plausible, critical evaluation of these results is still necessary. SGU is a crude measure of the kidney's ability to concentrate urine, relying both on kidney function and the state of hydration. The subjects' SGU and eGFR values were estimated after 8 hours of fasting. The confounder between eGFR and specific gravity is that those with higher eGFRs (i.e., better kidney function)

would be expected to concentrate their urine to a higher specific gravity after 8 hours of fasting. This interpretation is consistent with the fact that the quartile with the highest specific gravity consists of those who are significantly younger, as noted in Table 1 of their study; in particular, age is associated with progressive decline in kidney function [2]. Additionally, they noted higher eGFR is negatively associated with diabetes mellitus and proteinuria, which agrees with the well-known associated risk of lower eGFR due to decreased kidney function, as noted in Table 2 of their study [2]. However, in defense of their hypothesis, they note a highly significant correlation between eGFR and SGU after multivariate adjustment in their study, which is one of the largest observational studies of postulated sub-morbid dehydration associated hyperfiltration. Dehydration is known to induce vasopressin release. There is ample human and animal experimental evidence supporting a causative role of vasopressin in renal hyperfiltration induction and the development of proteinuria with associated progressive renal injury [3]. However, the coining of the term “sub-morbid dehydration associated glomerular hyperfiltration” adds a subtle new wrinkle to the dialogue regarding hydration and its potential role in the pathogenesis of kidney disease.

While the cross-sectional nature of their study precludes causal associations, longitudinal studies of their patient cohort may yield stronger associations, particularly if copeptin (a vasopressin analogue) measurements are performed to understand vasopressin's relationship with sub-morbid dehydration [4,5]. We note that in a population of 2,148 community dwelling adults with eGFR > 60 mL/min/1.73 m², a 6-year longitudinal follow-up study demonstrated that declined kidney function was significantly slower in those with higher versus lower urine volume, demonstrating a dose response effect

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[6] (Fig. 1). In other words, people with normal kidney function and increased hydration (i.e., increased urine output) had better preservation of eGFR over 6 years relative to those with lower urine output and presumed sub-optimal hydration (Fig. 2). These findings and the work of several others have prompted us to conduct a randomized control trial of the effect of increasing water intake on kidney function decline in 631 adults with chronic kidney disease [7]. In this study, no association was detected after 1 year. We looked at all water drinkers (aver-

age intake, 2.6 L/day) with only mildly elevated copeptin, and attempts to increase their average intake by 1.5 L of water failed (with their actual average increase being 0.6 L), even with active coaching; this result is in contrast to studies on low water intake [8,9]. It may be short-sighted to look at all chronic kidney disease patients rather than those who are low-water drinkers (i.e., those with low water intake) or individuals suffering from sub-morbid dehydration, who are at greater risk of progressive loss of kidney function, as evidenced by our original longitudinal observations of normal subjects with decreased urine output [6].

The current article on the role of sub-morbid dehydration induced hyperfiltration warrants further investigation to determine its significance over time regarding the pathophysiology of kidney injury. The potential action of sub-morbid dehydration induced renal hyperfiltration becomes more important when considering the rising awareness of heat-stress dehydration and subsequent renal injury in this era of global warming [10]. Thus, sub-morbid dehydration may be an emerging reality that needs serious consideration.

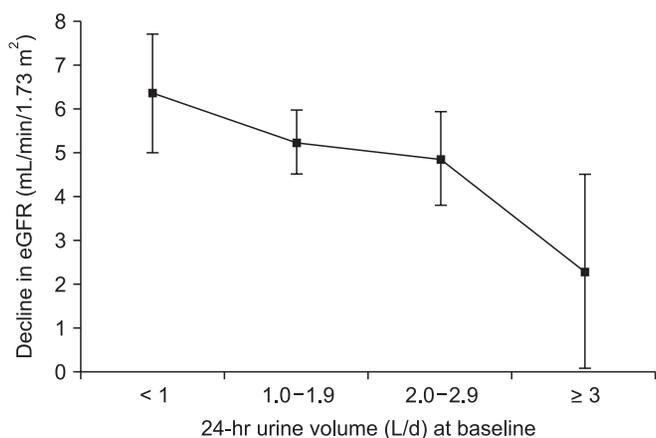


Figure 1. Decline in kidney function between the first and last assessments over 5.7 years (n = 2,148). Reproduced from the article of Clark et al [6] with original copyright holder’s permission. eGFR, estimated glomerular filtration rate.

Conflicts of interest

The author’s last completed randomized controlled trial was funded by Danone Research.

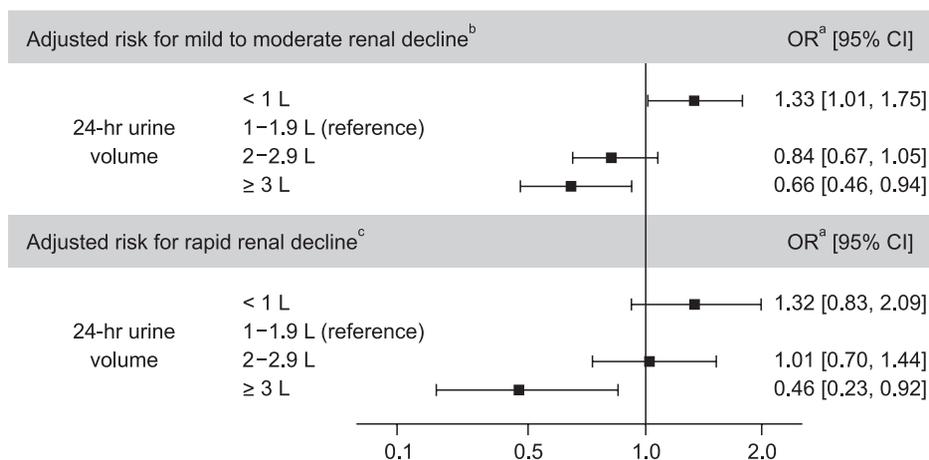


Figure 2. Urine volume and risk for renal decline in the general population (n = 2,148). Reproduced from the article of Clark et al [6] with original copyright holder’s permission.

OR, odds ratio; CI, confidence interval.

^aMultinomial logistic regression adjusted for age, sex, baseline estimated glomerular filtration rate (eGFR), dipstick protein ≥ 1 g/L, medication use for hypertension (including diuretics), diabetes and cardiovascular disease.

^beGFR decline from baseline between 1% and 4.9%, ^ceGFR decline from baseline ≥ 5%.

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