Significance of hypo- and hypernatremia in chronic kidney disease

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Abstract

Both hypo- and hypernatremia are common conditions, especially in hospitalized patients and in patients with various comorbid conditions such as congestive heart failure or liver cirrhosis. Abnormal serum sodium levels have been associated with increased mortality in numerous observational studies. Patients with chronic kidney disease (CKD) represent a group with a high prevalence of comorbid conditions that could predispose to dysnatremias. In addition, the failing kidney is also characterized by a gradual development of hyposthenuria, and even isosthenuria, which results in further predisposition to the development of hypo- and hypernatremia in those with advancing stages of CKD. To date, there has been a paucity of population-wide assessments of the incidence and prevalence of dysnatremias, their clinical characteristics and the outcomes associated with them in patients with various stages of CKD. We review the physiology and pathophysiology of water homeostasis with special emphasis on changes occurring in CKD, the outcomes associated with abnormal serum sodium in patients with normal kidney function and the results of recent studies in patients with various stages of CKD, which indicate a substantial incidence and prevalence and significant adverse outcomes associated with dysnatremias in this patient population.

Keywords: chronic kidney disease; hypernatremia; hyponatremia; mortality; serum sodium

Introduction

Hyponatremia is one of the most common electrolyte abnormalities encountered in clinical practice, occurring in as many as 42% of acutely hospitalized patients [1]. Hyponatremia is associated with many different disease states such as congestive heart failure (CHF), liver cirrhosis, pneumonia and acquired immune deficiency syndrome, and is regarded as an important marker of the severity of these conditions [2, 3]. Other risk factors of hyponatremia are advanced age [1], male gender[1], low body weight [4, 5] and in nursing home populations also hypotonic fluid intake, low-sodium diet and tube feeding [6]. Both hypo- and hypernatremia are associated with significant increases in mortality in hospitalized patients and in patients with various comorbid conditions [7–28]. The development of vasopressin receptor antagonist medications that are able to induce a selective water diuresis without affecting sodium excretion [29] has led to renewed interest in the link between hyponatremia and various adverse outcomes. These medications have been shown to reliably correct hyponatremia [30–33], and hence could represent therapeutic options for patients under a variety of circumstances.

Chronic kidney disease (CKD) is known to affect the ability of the kidneys to regulate water homeostasis [34], and hence the risk of both hypo- and hypernatremia can increase with advancing stages of CKD. In spite of such physiological considerations, the results of earlier small observational studies suggested that frank hypo- or hypernatremia resulting from advancing CKD alone are rare or even non-existent even in patients with very advanced stages of non-dialysis-dependent CKD [35]. However, there has been a lack of population-level surveys of the incidence and/or prevalence of hypo- or hypernatremia in patients with CKD. It has also been unclear to what extent dysnatremias are associated with outcomes in patients with various stages of non-dialysis-dependent CKD. Due to their high numbers and their particular disease characteristics that predispose them to dysnatremias, patients with CKD represent a large and under-studied group in whom the characteristics and the consequences of both hypo- and hypernatremia still need to be clarified. In this review, we discuss briefly the physiology and pathophysiology of water homeostasis, the consequences of hypo- and hypernatremia in patients with normal kidney function and recent findings regarding the characteristics and outcomes associated with dysnatremias in patients with various stages of CKD.

Physiological background and significance of dysnatremias in patients with normal kidney function

Sodium is the most abundant electrolyte in the extracellular fluid, and it is the main contributor to extracellular tonicity.
The physiological regulation of serum sodium level is maintained by balancing water intake and water excretion; the former through control of thirst sensation and the latter through control of antidiuretic hormone (ADH) secretion [36]. The ADH vasopressin (VP) [37] stimulates the plasma membrane accumulation of a water channel, aquaporin 2, which is a member of a family of water channel molecules that is located primarily in the kidney collecting duct principal cells [38]. The accumulation of aquaporin 2 in the collecting duct epithelium increases its water permeability, allowing osmotic equilibration of the luminal fluid with the surrounding interstitium and leading to urinary dilution [39].

Water balance can be disturbed by pathological states causing either abnormal water intake (through disordered thirst sensation or impeded access to water), changes in ADH secretion that override the primary osmotic stimulus for this hormone or abnormalities involving the VP receptor or aquaporin 2 in the collecting duct [40]. The resulting water excess or deficit leads to abnormal dilution or concentration of the extracellular fluid, most readily measured through concentration changes of serum sodium and hence resulting in hyper- or hypotremia. As a result of such alterations in extracellular tonicity, a concentration gradient may occur between the intra- and extracellular space especially after rapidly developing hypo- or hypernatremia with water shifts leading to cellular swelling or shrinking. The physiological consequences of this are most acutely recognized in the central nervous system, where they could lead to potentially fatal brain edema or osmotic demyelination syndrome, respectively [41–43]. The impact of transtelular water shifts on the structure and function of organs whose cells are not limited to a closed space such as the cranium is less clear, but there have been suggestions that hyponatremia could be implicated in bone fractures [44–46], rhabdomyolysis [47], CHF and/or pulmonary edema [48, 49].

Based on these physiological considerations, it is plausible to postulate that both hypo- and hypernatremia can lead to adverse clinical consequences and potentially result in increased deaths, especially if they occur acutely. Outcomes associated with abnormal serum sodium levels have been explored by a substantial number of observational studies [7–28], mostly in the setting of acute hospitalization, or in patient populations known to be at risk for the development of abnormal serum sodium levels (such as patients with CHF or liver cirrhosis) (Table 1). The majority of these observational studies focused on the association of hyponatremia with outcomes such as mortality. Lower serum sodium levels have been associated with adverse clinical outcomes in most of the studies, independent of the presence of various confounders (Table 1). Hyponatremia has been generally under-emphasized, but it has also been found to be associated with a significant increase in mortality (Table 1) [7, 14].

In spite of the robust association of hypo- and hypernatremia with outcomes such as mortality, one cannot determine with certainty to what extent these associations may be biased by unmeasured confounders, especially since abnormal ADH secretion and consequently hyponatremia can occur as a result of various stress stimuli that can be difficult to quantify in observational studies. The emergence of specific pharmacologic inhibitors of the vasopressin receptor [29] has allowed the testing in clinical trials of the hypothesis that hyponatremia is causally involved in excess mortality, and hence its correction results in improved clinical outcomes. The short-term administration of vasopressin receptor antagonists was shown to result in a predictable correction of hyponatremia [30–33] and improvement in peripheral edema and various other clinical features of CHF [50, 51]. Based on such results, the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) trial was designed to test the hypothesis that correction of hyponatremia using tolvaptan (an oral selective V2 receptor antagonist [30]) versus placebo therapy on top of routine medical management of patients hospitalized with CHF resulted in improved all-cause mortality, cardiovascular mortality or CHF-related hospital admissions [52]. This study included 4133 patients treated with tolvaptan versus placebo for a minimum of 60 days and showed that none of the primary end points of the study were affected significantly by such treatment. While the results of the EVEREST study appear to refute the hypothesis invoking hyponatremia as a cause of increased mortality in CHF, it is unclear how the correction of hyponatremia would impact outcomes under different circumstances; patients with more severe hyponatremia or patients with hyponatremia unrelated to CHF may respond differently to the same treatment, and the longer duration of therapy with the same drug or effect of other interventions to correct hyponatremia may also result in different outcomes. At the present time, medical interventions including vasopressin receptor antagonists are indicated only for the correction of a biochemical abnormality (hyponatremia) but without a clear understanding of their impact on longer-term outcomes.

**Water homeostasis, hyponatremia and hypernatremia in CKD**

With advancing CKD, the kidney has a remarkable ability to maintain homeostasis, including the regulation of water balance [34]. In a study of 70 patients with advanced CKD (serum creatinine levels >10 mg/dL), serum sodium levels remained normal even until the point of the patients requiring initiation of renal replacement therapy [35]. The ability of the kidneys to adapt to changes in water intake does, however, diminish as both the maximum dilution and concentration of the urine gradually decline during the course of CKD (hyposthenuria), with the capacity to dilute typically being maintained longer than the capacity to concentrate [53]. Ultimately, as the patients reach end-stage kidney failure, the urine osmolality remains constant at ~300 mOsm/L (isosthenuria) irrespective of the actual volume of water intake. As a result, physiological factors other than the amount of water intake and urinary dilution and concentration will determine the amount of excreted water, and hence the development of hypo- and hypernatremia in patients with CKD. These include the amount of water delivered from the proximal tubule (which is typically decreased as a result of low glomerular filtration rate) and the amount of excreted solute, which can facilitate the development of both hypo- and hypernatremia in patients with...
<table>
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<td>Wald et al. [7]</td>
<td>N = 53,236 patients hospitalized at a single medical center</td>
<td>Hyponatremia associated with increased mortality and length of stay and increased risk of discharge to a long-term facility. Hypernatremia also associated with higher mortality</td>
<td>Equal incidence of community and hospital-acquired hyponatremia (37.9 and 38.2%)</td>
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<td>Waikar et al. [8]</td>
<td>N = 98,411 patients admitted to two hospitals</td>
<td>Higher 1- and 5-year mortality risk associated with hyponatremia</td>
<td>Incidence of hyponatremia of 14.5%</td>
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<td>Zilberberg et al. [9]</td>
<td>N = 198,281 hospitalizations from 39 US hospitals</td>
<td>Hyponatremia associated with increased mortality, ICU admissions, mechanical ventilation, hospital length of stay and cost of care</td>
<td>Incidence of hyponatremia was 5.5%</td>
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<td>Tierney et al. [10]</td>
<td>N = 13,979 patients admitted over 46 months</td>
<td>Hyponatremia associated with increased in-hospital and long-term mortality</td>
<td>Incidence of hyponatremia at admission was 4%</td>
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<td>Gill et al. [11]</td>
<td>N = 104 hyponatremic hospitalized patients compared to N = 104 randomly chosen normonatremic patients</td>
<td>Mortality and length of stay higher in the hyponatremic group</td>
<td>Mortality was higher if serum sodium fell during hospitalization</td>
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<td>Clayton et al. [12]</td>
<td>N = 108 hospitalized patients with serum sodium &lt; 125 mEq/L compared to normonatremic patients</td>
<td>Mortality was higher in the hyponatremic group</td>
<td>Mortality depended on the etiology and not the severity of the hyponatremia</td>
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<td>Lee et al. [13]</td>
<td>N = 3784 patients admitted to en emergency department</td>
<td>Lower serum sodium was associated with higher mortality</td>
<td>3.8% of patients had serum sodium &lt; 134 mEq/L. Most hyponatremic patients had hypovolemia</td>
</tr>
<tr>
<td>Mohammed et al. [14]</td>
<td>N = 628 patients presenting to an emergency department with decompensated CHF</td>
<td>Both hyponatremia and hypernatremia were associated with higher 1-year mortality rates</td>
<td>24% of patients had serum sodium &lt; 135 mEq/L. Lower serum sodium was associated with higher NT-proBNP levels</td>
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<td>Gheorghiade et al. [15]</td>
<td>N = 48,612 patients hospitalized with CHF from 259 hospitals</td>
<td>Hyponatremia associated with higher in-hospital and follow-up mortality and longer hospital stay</td>
<td>19.7% of patients had serum sodium &lt; 135 mEq/L.</td>
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<td>Gheorghiade et al. [16]</td>
<td>Post hoc analysis of N = 433 patients hospitalized with Stage 4 CHF and enrolled in a clinical trial</td>
<td>Persistent hyponatremia independently associated with increased mortality and re-hospitalization</td>
<td>23.8% of patients had hyponatremia; of these 68.9% had persistent hyponatremia</td>
</tr>
<tr>
<td>Rossi et al. [17]</td>
<td>Post hoc analysis in N = 319 hospitalized CHF patients treated with tolvaptan versus placebo</td>
<td>Significantly lower mortality of patients who had improvement in serum sodium levels</td>
<td>21.6% of patients had hyponatremia</td>
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<td>Klein et al. [18]</td>
<td>Post hoc analysis in N = 942 hospitalized CHF patients treated with milrinone versus placebo</td>
<td>Lower sodium associated with increased in-hospital and 60-day mortality</td>
<td>Patients with lower serum sodium had more severe CHF</td>
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<td>Lee et al. [19]</td>
<td>N = 203 patients with severe CHF</td>
<td>Hyponatremia was associated with increased CV mortality</td>
<td>Hyponatremic patients treated with ACEI had better outcomes</td>
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<td>Goldberg et al. [20]</td>
<td>N = 978 patients with ST-elevation MI and no CHF</td>
<td>Hyponatremia associated with increased mortality and hospital readmission rates</td>
<td>11% of patients had serum sodium &lt; 136 mEq/L.</td>
</tr>
<tr>
<td>Goldberg et al. [21]</td>
<td>N = 1047 patients with acute ST-elevation MI</td>
<td>Hyponatremia associated with increased 30-day mortality</td>
<td>12.5% of patients had serum sodium &lt; 136 mEq/L on admission and developed in 19.9% within 72 h</td>
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Table 1. Continued

Study | Patient population | Results | Other findings
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Zilberberg et al. [22] | N = 76 patients hospitalized with pneumonia | Hyponatremia associated with increased mortality, ICU admissions, mechanical ventilation, hospital length of stay and cost of care | Persistent azotemia and MELD score also predictive of mortality
Borroni et al. [23] | N = 156 hospitalized patients with liver cirrhosis | Hyponatremia was associated with increased short-term mortality | Serum sodium level was not an independent predictor of mortality once adjusted for effect of GFR
Lim et al. [24] | N = 837 patients listed for liver transplantation | Hyponatremia was associated with higher mortality | Serum sodium level was not an independent predictor of mortality once adjusted for effect of GFR
Londono et al. [25] | N = 241 patients who received a liver transplant | Hyponatremia at the time of transplantation predicted 90-day post-transplant mortality | Hyponatremia was independently associated with 90-day post-transplant mortality
Terzian et al. [26] | N = 419 hospitalized elderly patients | Hyponatremia was independently associated with 90-day post-transplant mortality | Hyponatremia was independently associated with 90-day post-transplant mortality
Heuman et al. [27] | N = 507 patients referred for liver transplantation | Hyponatremia was associated with higher mortality | GFR was measured by iothalamate clearance
Bennani et al. [28] | N = 2188 patients admitted to an intensive care unit | Sodium < 125 mEq/L was an independent predictor of mortality | Prevalence of hyponatremia was 3.5% and the point prevalence of hypernatremia (serum sodium > 145 mEq/L) was 2% [55]. During a mean duration of follow-up of ~5 years, however, 26% of all patients developed at least one episode of hyponatremia and 7% had at least one episode of hypernatremia, suggesting that these conditions and especially mild hyponatremia are common occurrences in patients with CKD.

Outcomes associated with hypo- and hypernatremia in CKD

Both hypo- and hypernatremia are associated with increased mortality in patients with normal kidney function (vide supra). These results should not be extrapolated to patients with various degrees of severity of CKD as it is unclear how the hypo- and isosthenuria developing with advancing CKD affect these outcomes when combined with various comorbid conditions that can impact water metabolism and outcomes. It is possible that hypo- and hypernatremia are more severe in CKD and hence they could be more deleterious; one could, however, also hypothesize that the chronic nature of the abnormalities affecting water metabolism in CKD allows the body to adapt...
to these consequences and hence their effects on outcomes could be diminished. We have recently examined the association of serum sodium levels with all-cause mortality in 655,493 US veterans with non-dialysis-dependent CKD Stages 1–5 (mean ± SD age was 73.9 ± 9.8 years, 87 and 9% of patients were white and black, respectively, and mean eGFR was 50.2 ± 14.1 mL/min/1.73 m²) [55]. Both lower and higher time-varying serum sodium levels were associated with a significant increase in mortality, even after adjustment for various potential confounders (Figure 2). Mortality was lowest in patients with serum sodium levels in the 140–144 mEq/L range and showed a linear increase with increasing degree of severity of hypo- and hypernatremia. The association of hypo- and hypernatremia with mortality was present in all examined subgroups, including patients with and without CHF or liver cirrhosis [55], and also in patients with various stages of CKD (Figure 3). The magnitude of the association between hyponatremia and mortality did not appear to vary according to the severity of CKD (Figure 3). Interestingly, the association between hypernatremia and mortality appeared to diminish linearly with more advanced stages of CKD (Figure 3) [55]. The significance of this latter observation is unclear but suggests that perhaps there is indeed an element of adaptation to increased extracellular osmolality in patients with more advanced stages of CKD. As we mentioned previously, our study did not record the circumstances of serum sodium measurement (inpatient hospitalization versus outpatient), hence it is unclear to what extent the observed associations occurred in the context of acute illnesses. When comparing in parallel the associations of baseline serum sodium on longer term outcomes with the associations of time-varying serum sodium on short-term outcomes, the latter clearly showed much more robust associations [55], indicating that abnormalities in serum sodium are indeed either causing acute complications leading to higher short-term mortality or are simply potent surrogate markers of acute illness. Due to the observational nature of our study, we cannot establish causality in spite of the extensive adjustment for various potentially confounding comorbid conditions; such causality can only be proven if interventions of correcting serum sodium levels are shown to result in improved outcomes in CKD patients. Arguing in favor of a potential causal effect of dysnatremias on mortality was a recent study of maintenance hemodialysis patients enrolled in the Hemodialysis (HEMO) study, which reported a significant association of hyponatremia with mortality, even though in anuric dialysis patients the development of hyponatremia is unrelated to the pathological stimulation of ADH by underlying comorbidities [57]. Nevertheless, since in the anuric population, pre-dialysis hyponatremia could be a surrogate

Fig. 1. Prevalence of hyponatremia (A) and hypernatremia (B) in patients with different stages of CKD in 655,493 US veterans with non-dialysis-dependent CKD. Results are based on data obtained from [55]. Note the different scales in the two panels.
marker of increased inter-dialytic volume gain and consequently of a certain lifestyle of non-adherence with medical instructions, the need for interventional trials remains present for proof of a causal effect of hypo- and hypernatremia on mortality in CKD and end-stage renal disease. Conclusions

Abnormalities in water homeostasis, manifested as hypo- and/or hypernatremia, are common clinical occurrences and are associated with adverse clinical outcomes. Patients with CKD can be affected by dysnatremias both because of the high prevalence of comorbidities that can result in dysnatremias in them and by the diminished ability of the failing kidneys to maintain an intact water homeostasis. Recent studies have suggested that the incidence and prevalence of dysnatremias, and especially those of hyponatremia, are substantial in patients with non-dialysis-dependent CKD and that they are associated with a significant increase in all-cause mortality. Hyponatremia appears to affect outcomes equally in patients with different stages of CKD, but hypernatremia appears to be associated with less severe outcomes in those with more advanced stages of CKD. Interventional trials are needed to establish if normalization of serum sodium levels can result in improving mortality rates in patients with CKD.

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