Sodium and Volume Disorders in Advanced Chronic Kidney Disease

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The kidney has a remarkable ability to modulate sodium and water excretion to maintain homeostasis despite a widely varying dietary intake. However, as glomerular filtration rate falls to less than 30 mL/min, this ability can be compromised leading to an increased risk for disorders of serum sodium and extracellular volume. In all cases, these disorders are associated with an increased rate of morbidity and mortality. Management strategies to both prevent and treat these conditions are available but requiring special attention to the unique circumstance of advanced CKD to maximize therapeutic response and prevent complications.

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The kidney is the major regulator of both plasma sodium/osmolality and volume control. The former is controlled through variable water excretion and the latter through modulation of sodium excretion. As glomerular filtration rate (GFR) decreases and patients progress to worsening stages of CKD (stages 4 and 5), the ability to regulate these processes and retain tight control over both plasma sodium/osmolality and volume may become impaired. This inability to maintain homeostasis is most marked under stress conditions such as when comorbid conditions, such as heart failure, liver disease, or wide variations in dietary intake of sodium and water, interact to increase the risk for volume overload and either hyponatremia or hypernatremia. In all cases, the presence of volume overload, hyponatremia, or hypernatremia significantly increases the risk for mortality and poor outcomes.[1-3] This highlights the importance of maintaining euvolemia and normal plasma sodium levels.

SODIUM DISORDERS IN CKD

Epidemiology of Sodium Disorders in CKD

Hyponatremia (defined as a serum sodium $<$ 135 meq/L) is one of the most common electrolyte disorders encountered in clinical practice, estimated to be present in 10% to 30% of acutely hospitalized patients.[4,5] In the elderly population, hyponatremia is especially common and surveys of nursing home residents indicate a prevalence of hyponatremia as high as 30%.[6] The presence of hyponatremia, no matter what the etiology may be, is associated with increased morbidity and mortality in ambulatory and hospitalized patients and may be regarded as an important marker of severe disease.[7] It is likely that the major mortality effect attributed to hyponatremia derives more from the underlying etiology leading to the electrolyte disorder rather than hyponatremia itself.[5,8] The majority of these epidemiologic studies do not include data on the kidney function of these patients, so specific data on the association with or without CKD are not available except for a single study discussed below.

Hypernatremia (defined as serum sodium $>$ 145 meq/L) is much less common than hyponatremia, estimated to be 2% to 5% in acutely ill patients.[9,10] This is likely because the fact that in the presence of a normal thirst sensation, most people are able to maintain serum sodium levels $<$ 145 meq/L. It is only when thirst sensation is impaired (for instance, in patients who have serious disorders of cognition) or when water access is limited that hypernatremia occurs.[11] This can be exacerbated by excessive urinary or other body water losses.[12] As an example, patients with significant cognitive impairment who are hospitalized often have inadequate thirst sensation cannot easily ask for water and may not have ready access to fluids. Thus, these patients are prone to the development of hypernatremia.

Although CKD is known to affect the ability of the kidneys to regulate water homeostasis, because of impaired diluting and concentrating mechanisms with progressive kidney disease, studies have indicated that dysnatremias resulting from worsening CKD alone are rare, even in patients with advanced CKD.[2,13,14] A large observational study evaluated the prevalence of dysnatremias in 655,493 US veterans with non-dialysis-dependent CKD.[15] At baseline, 13.5% of patients had hyponatremia (serum sodium $<$ 136 mEq/L) and 2% had hypernatremia (serum sodium $>$ 145 mEq/L). However, over a mean 5-year period of observation, 26% of all patients developed at least 1 episode of hyponatremia and 7% developed hypernatremia. The prevalence of hyponatremia did not have a strong correlation with CKD stage and was essentially similar in patients with Stage 3, Stage 4, and Stage 5 CKD (11%-12%).[15] However, the prevalence of hypernatremia showed a significant increase with advancing CKD (up to maximum of 3.1% in stages 4 and 5). Attributing the dysnatremia solely to advancing CKD is difficult in these observational studies as patients had serum sodium levels measured in both the inpatient and

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outpatient setting, and the circumstances regarding the measurement of the serum sodium were not known (ie, the laboratory values may have been obtained during an acute illness, such as pneumonia).

Mortality associated with dysnatremias in patients with non-dialysis CKD was also studied in the large Veteran's cohort described earlier.[15] In this study, mortality was lowest in patients with a serum sodium between 140 and 144 meq/L and then showed a linear increase with the severity of both hyponatremia and hypernatremia that was present in all subgroups (including those with and without heart failure and liver disease). Patients with serum sodium levels < 130, 130 to 135, 145 to 149, and > 150 mEq/L compared with the reference level of 136 to 145 mEq/L had a statistically significant hazard ratio for all-cause mortality. The mortality association with hyponatremia was not influenced by CKD stage. However, the association of hypernatremia and mortality was actually lower in more advanced stages of CKD. The explanation for this apparent "protective" effect of advanced CKD on hypernatremia-related mortality is not clear, but the authors have speculated that this may be because of adaptation to increased extracellular osmolality in patients with more advanced CKD who experience a gradual accumulation of uremic solutes.[15] This more gradual change in extracellular osmolality allows for cellular adaptation that can occur over a longer time frame.

CLINICAL SUMMARY

1. As kidney function decreases, the ability to maintain plasma osmolality and volume within normal limits can be impaired and this is especially true during states of stress such as heart or liver failure.
2. In patients with CKD, hyponatremia is far more common than hypernatremia.
3. Treatment of hyponatremia and hypernatremia in the patient with CKD follows the same principles as for patients with normal kidney function.
4. In patients with advanced CKD and volume overload, loop diuretics are the agents of choice to increase sodium excretion.

Pathophysiology of Sodium Disorders: The Role of CKD

Under normal circumstances, sodium levels are maintained because of a balance between net water intake and excretion. Impaired concentrating and diluting abilities occur with CKD that stress the ability of the body to maintain normonatremia.[2] Typically with CKD, the capacity to dilute the urine is maintained longer than the capacity to concentrate the urine, but as patients reach ESRD, the urine osmolality reaches a constant level at approximately 300 mOsm/L (isosthenuria).[16] At this late stage, factors other than the urine-concentrating/diluting mechanism must take precedence to maintain normal serum osmolality. These include the amount of water intake and the solute load and residual GFR.[17]

Urine Concentration Ability in CKD. The ability to concentrate urine is dependent on the presence of a hypertonic medullary interstitium and collecting tubule permeability that varies substantially under the influence of arginine vasopressin (AVP). Several factors have been thought to contribute to impaired concentrating ability and subsequent isosthenuria that is characteristic of CKD.[18] These include an osmotic diuresis from excess solute excretion in remaining functional nephrons that are now carrying a greater load of solute filtration, decreased tubular responsiveness to AVP, and an impaired countercurrent mechanism in disorders affecting the renal medulla.[19-21] Animal models have additionally demonstrated decreased urea recycling in the loop of Henle in CKD models, which contributes to decreased medullary tonicity.[22] Additionally, concentrating defects are more pronounced in those interstitial-prominent diseases affecting the renal medulla.[22,23] Furthermore, many patients with CKD are taking loop diuretics that impair the development of a hypertonic medullary gradient. Impaired ability to concentrate the urine typically leads to excessive urine output (polyuria) and nocturia and in the face of impaired thirst sensation or limited water access predisposes individuals to the development of hypernatremia. The fact that urine-concentrating ability is affected to a greater extent than diluting ability is supported by the fact that the rate of hypernatremia increases with advancing CKD, whereas the rate of hyponatremia does not.[15]

Impaired Urinary Diluting Ability. Additionally, impaired urinary dilution, as manifested by an inability to lower urine osmolality appropriately, has been observed in advanced kidney dysfunction.[19,24] The mechanisms for this disorder are less clear than those of impaired urinary concentrating ability in CKD. In order for dilute urine to be made, several mechanisms must be operative: (a) there must be enough filtrate delivered to the distal nephron for dilution and excretion, (b) the diluting segments of the distal nephron must selectively reabsorb sodium and lead to a fall in urine osmolality and finally, and (c) AVP levels must fall and the collecting tubule must decrease its permeability to water reabsorption and allow water to be excreted (dilute urine). It is unlikely that limitations in filtrate amount affect this process until very late CKD (with GFRs <5 mL/min), and it is most likely that CKD may be associated with defects in the diluting segment.[2] This may be further exacerbated using thiazide diuretics, with resulting natriuresis, and vasopressin release.[25] The net result of these impairments in urine dilution is that the risk of hyponatremia may be increased. However, based on observational studies, this risk of hyponatremia with advancing CKD is likely small.[15]

Integrated Physiology of Impairments in Dilution/Concentration in CKD

As an example of how these derangements in kidney function may lead to dysnatremias, it is instructive to look at typical urine osmolalities and water intakes. Under normal circumstances, with intact countercurrent

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