Fluid and Electrolyte Problems in Chronic Kidney Disease

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Before You Start: Facts You Need to Know

- Sodium is the most abundant ion in the extracellular fluid (ECF), and the ECF volume is determined by the total body sodium content.
- Total body water determines ECF osmolality which affects cell volume. Because sodium is the principal ion in the ECF, water balance disorders present as altered plasma sodium concentrations.
- Although potassium is mostly located in the intracellular fluid (ICF), normal plasma potassium is critical for heart, nerves, and skeletal muscle because the ratio between ECF and ICF potassium concentration is a determinant of transmembrane electrochemical gradients and neuromuscular excitability.
- With glomerular filtration rate (GFR) declining, renal excretion of sodium, water, and potassium is progressively reduced.

22.1 Introduction

Kidney handles sodium, water, and potassium excretion. Glomerular filtration and tubular transport harmoniously participate in these processes. With declining of glomerular filtration rate (GFR), less plasma sodium, water, and potassium are eliminated from the glomeruli. Therefore, sodium, water, and potassium balances are altered in chronic kidney disease (CKD). Typically, urinary excretion of sodium and water is regulated by tubular reabsorption, whereas urinary excretion of potassium is regulated by tubular secretion. These tubular transport processes are also modified in CKD to minimize the disturbed balances (Fig. 22.1).

Serum sodium is a function of total body sodium and water, and the kidney can retain its ability to excrete both sodium and water through advanced CKD because of tubular adaptation. Consequently, serum sodium concentration can remain within the normal range until the end stage kidney disease (ESKD). Serum potassium does not increase unless GFR declines below 50% of normal because of tubular secretion and transcellular shift [1].

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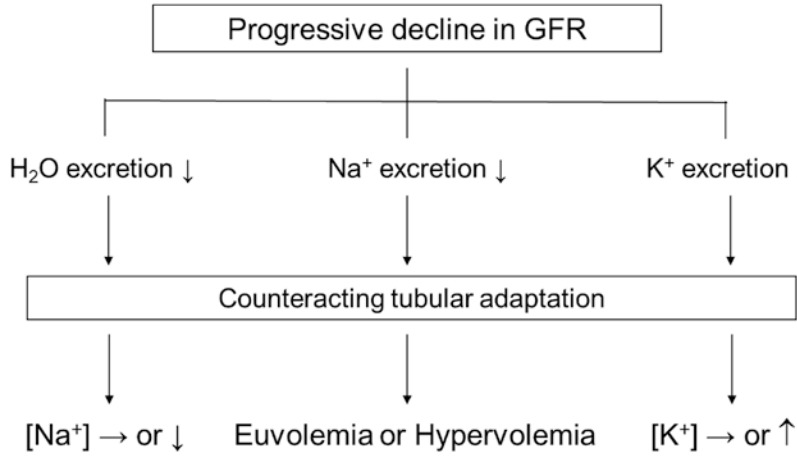

Fig. 22.1 Pathophysiology of fluid and electrolyte disturbances in chronic kidney disease. *GFR* glomerular filtration rate

22.2 Volume or Sodium Balance Disorders

Sodium is the most abundant ion in the extracellular fluid (ECF), which can be divided into plasma and interstitial fluid (ISF). The ECF volume is determined by the total body sodium content because thirst and the kidney's regulated excretion of water work together to maintain serum osmolality within a narrow range. Sodium content is derived from the balance between sodium intake and renal excretion of sodium. With progression of CKD and its accompanying reduction of renal sodium excretion, manifestations of ECF volume overload can occur such as edema and hypertension. Edema is caused by the expansion of ISF, which in turn increases plasma volume and exerts pressure on arterial blood.

22.2.1 Role of the Kidney in Sodium Balance Regulation

The kidney regulates sodium content by adjusting renal sodium excretion. As a result, it also regulates the ECF volume and controls the arterial blood pressure. In normal circumstances, kidneys balance sodium excretion with sodium intake, even though the daily intake of sodium is highly variable, owing to cultural, social, and personal factors [2].

Table 22.1 Regulatory systems for renal sodium excretion

System	Pathways
Sensors	Extrarenal baroreceptors: Arterial circulation, aortic arch, carotid sinuses, cardiac atria
	Renal: Juxtaglomerular apparatus
Effectors	Neurohormones: Sympathetic nervous system, renin, angiotensin II, aldosterone, atrial natriuretic peptide, prostaglandins, nitric oxide
	Direct effects on kidney: Changes in peritubular-capillary Starling forces
Kidney	Glomerular filtration rate
	Tubular sodium reabsorption

For modulation of renal sodium excretion, afferent sensor systems and efferent effector systems should be coordinated (Table 22.1). Baroreceptors located at arterial circulation, aortic arch, carotid sinuses, cardiac atria, and juxtaglomerular apparatus sense changes in intravascular volume and blood pressure caused by alterations in sodium balance. Carotid sinus volume receptors increase sympathetic outflow in response to hypotension. The increased sympathetic tone of the renal vasculature decreases sodium excretion. Renal sympathetic activation and catecholamines released from the adrenal medulla stimulate renin release. The juxtaglomerular apparatus senses renal perfusion and also stimulates renin release when the perfusion pressure is reduced. In addition to increasing circulat-

ing levels of angiotensin II, stimulation of these receptors leads to alterations in the local concentration of angiotensin, which profoundly decreases sodium excretion. Consequently, the renin–angiotensin–aldosterone system is activated by sodium depletion. Conversely, the atria contain secretory granules which, in response to an increase in ECF volume, release atrial natriuretic peptide (ANP), which increases sodium excretion and causes peripheral vasodilation [2]. Renal prostaglandins and nitric oxide can also increase renal sodium excretion in response to volume overload.

In addition, the balance of Starling forces between renal tubules and peritubular capillaries affects tubular sodium reabsorption. The increased arterial pressure raises peritubular hydrostatic pressure, leading to decreased tubular sodium reabsorption. When arterial pressure decreases, the decreased peritubular hydrostatic pressure will enhance tubular sodium reabsorption. This direct effect on the kidney may explain pressure–natriuresis relationship.

Neurohormonal effectors play the major regulatory role in renal sodium excretion. Plasma sodium is freely filtered at glomeruli, and more than 99% of filtered sodium is reabsorbed along the renal tubule. Approximately one-third of glomerular filtered sodium is reabsorbed in the proximal tubule, where Na^+/H^+ exchanger 3 (NHE3) acts as the major transcellular sodium transporter. The NHE3 activity is mainly regulated by angiotensin II in the proximal tubule. The thick ascending limb of Henle's loop is the second major site of sodium reabsorption, where 20–25% of glomerular filtered sodium is reabsorbed mainly via Na^+-K^+-$2Cl^-$ cotransporter 2 (NKCC2). The major effector on NKCC2 is vasopressin, which binds to arginine vasopressin (AVP) receptor 2 and activates the cAMP-protein kinase A pathway. Five to 7% of glomerular filtered sodium is reabsorbed in the distal convoluted tubule through Na^+-Cl^- cotransporter (NCC), and the remaining sodium can be reabsorbed along the collecting duct via epithelial Na^+ channel (ENaC). The distal convoluted tubule, connecting tubule, and cortical collecting duct are collectively called aldosterone-sensitive distal nephron (ASDN), and the final urinary sodium excretion is finely tuned by the action of aldosterone and angiotensin II in the ASDN. The ASDN plays an important role in independent regulation of sodium and potassium balance in response to varying intake of sodium and potassium [3].

22.2.2 Volume Overload in CKD

Volume overload is increasingly common in patients with advanced CKD. As GFR falls to less than 30 mL/min, the ability of renal sodium excretion can be compromised, leading to ECF volume overload [4]. However, a study by Hung and colleagues in patients with CKD stages 3–5 demonstrated that 48% were euvolemic according to bioimpedance assessment [5]. When the ECF volume was measured in CKD patients using chromium-labeled red blood cells, exchangeable sodium, bromide, or sulfate, it is usually normal, at least until GFR is profoundly decreased to <10 mL/min [6], because of tubular adaptation (Fig. 22.1). Other comorbidities such as heart failure, hypertension, and arterial stiffness will increase the prevalence of volume overload.

22.2.2.1 Clinical Diagnosis of Volume Overload

Clinical manifestations depend on the amount and relative distribution of accumulated fluid [2]. In severe cases, patients may experience dyspnea, peripheral edema, ascites, and pleural effusion, reduced exercise tolerance often accompanied by concomitant hypertension. On physical examination, left heart failure is associated with pulmonary venous congestion as manifested by pulmonary crackles. Secondary right heart failure is characterized by neck vein engorgement, peripheral edema, hepatic congestion, and ascites. Pleural effusions usually are a manifestation of combined right and left heart failure. Pitting peripheral edema usually requires 3 L of interstitial fluid excess [2].

Kidney disease can be diagnosed through urinalysis, azotemia, and renal imaging. Atrophic kidneys may suggest chronicity of kidney failure. An elevated brain natriuretic peptide (BNP) level

is seen in heart failure, and BNP may be the more appropriate biomarker to screen for cardiac dysfunction than NT-proBNP in CKD or cardiorenal syndrome because plasma BNP level is relatively independent of GFR [7].

22.2.2.2 Treatment of Volume Overload

To restore sodium balance in CKD patients with volume overload, sodium intake should be restricted and/or natriuresis can be enhanced by diuretics. Previous clinical trials have shown the effects of dietary sodium restriction on ECF volume, hypertension, and proteinuria in CKD patients. McMahon et al. conducted a double-blind placebo-controlled randomized crossover trial in 20 adult patients with hypertensive stage 3–4 CKD and found that a two-week sodium restriction (<100 mmol/day) for resulted in reduced blood pressure, ECF volume (assessed by body composition monitor), albuminuria, and proteinuria compared to a high sodium intake (additional 120 mmol sodium tablets) [8]. Saran et al. conducted a similar randomized crossover trial in 58 adults with stage 3–4 CKD to evaluate the effects of dietary sodium restriction (target <2 g sodium/day) over 4 weeks and found a reduction in blood pressure but no change in albuminuria [9]. It remains to be clear whether the blood pressure-lowering effect persists in the long term and whether the reduction in proteinuria is connected to the preservation of GFR. Interestingly, a post-hoc analysis of the HALT Progression of Polycystic Kidney Disease (HALT-PKD) clinical trials reported that dietary sodium restriction was also beneficial in the management of autosomal dominant polycystic kidney disease [10].

Diuretic therapy is the practical approach to correct volume overload because the effect of dietary sodium restriction is slow and adherence to a low-sodium diet is difficult. In CKD patients, diuretics can alleviate edema, control blood pressure, and potentiate the effects of other antihypertensive agents [4]. Three main classes of diuretics may be used in CKD; loop diuretics are the most potent and useful for patients with advanced CKD, thiazides and thiazide-like diuretics may also be used alone or in combination with a loop diuretic in CKD, and potassium-sparing diuretics may be useful for patients without hyperkalemia. In contrast, acetazolamide is a weak diuretic acting as a carbonic anhydrase inhibitor in the proximal tubule and should be avoided in advanced CKD patients.

Loop diuretics, such as furosemide, bumetanide, and torsemide, inhibit the NKCC2 in the thick ascending limb of the loop of Henle. The ceiling or maximally effective doses can lead to an almost complete block of sodium reabsorption in the Henle's loop, and fractional excretion of sodium increases up to 20–25%. Loop diuretics circulate bound to albumin and are secreted into the tubular fluid by organic anion transporter 1 (OAT1) in the proximal tubule. In CKD and nephrotic syndrome, these processes are compromised, and the target site (the thick ascending limb NKCC2) may not be intact. To overcome this diuretic resistance, higher doses of diuretics are required in CKD. For instance, CKD stages 4–5 patients should be started at a dose of 40–80 mg once daily and then titrated upward by 25–50% weekly depending on the desired effects on lowering ECF volume [11]. Torsemide has the advantage of a higher oral bioavailability and a longer half-life compared with furosemide. Intravenous furosemide has a rapid onset of action and is more potent than oral furosemide. The greatest natriuretic response is observed with intravenous doses of 160–200 mg of furosemide or equivalent doses of bumetanide (6–8 mg) and torsemide (80–100 mg) [12]. Because hypertension in CKD is usually volume-dependent, loop diuretics can play a role in the management of hypertension in advanced stages of CKD.

Thiazide diuretics, such as hydrochlorothiazide, inhibit the NCC in the distal convoluted tubule. Typically, the natriuretic effect of hydrochlorothiazide is dampened in patients with GFR <50 mL/min [13], and higher doses are needed if kidney function is compromised [14]. However, long-acting thiazide-like diuretics, such as metolazone, indapamide, and chlorthalidone, are associated with more sustained low-level diuresis and tend to be more effective in advanced stages of CKD than hydrochlorothiazide [15]. Agarwal

et al. recently reported that chlorthalidone (12.5–50 mg/day) improved blood pressure control and reduced albuminuria over 12 weeks in 160 patients with stage 4 CKD [16]. These responses were associated with decreases in ECF volume markers, and chlorthalidone should be used with caution in patients receiving loop diuretics, especially because of the increased risk of azotemia and electrolyte disorders [17].

Potassium-sparing diuretics can be classified into ENaC blockades and mineralocorticoid receptor antagonists (MRAs). The ENaC blockades such as amiloride and triamterene inhibit the ENaC in the collecting duct. The MRAs including spironolactone, eplerenone, and finerenone tend to have small effects on decreasing extracellular volume but may have antiproteinuric effects and cardioprotective benefits. In particular, finerenone was recently reported to reduce the risk of cardiovascular and kidney outcomes in CKD patients with type 2 diabetes [18]. However, these agents must be used cautiously in CKD patients because of the risk of hyperkalemia, and initiation of therapy with low doses is recommended along with slow-dose titration and frequent monitoring of potassium levels [11].

When edema is refractory to conventional diuretic therapy, the following stepwise strategy is recommended. First of all, dietary sodium restriction should be assessed by measuring 24-h urinary sodium excretion (< 100 mmol/day). When the ceiling dose of a loop diuretic is insufficient to induce a negative sodium balance, the combination of diuretics acting on separate nephron sites (e.g., thiazide-like agents) may be synergistic and lead to significant decreases in ECF volume [19]. In those patients with significant symptomatic volume overload and advanced CKD, continuous intravenous infusion of loop diuretics may confer additional benefits [20]. This can avoid post-diuretic sodium retention, which is accompanied with intermittent bolus loop diuretic injection. Moreover, continuous infusion of loop diuretics may be associated with lower peak plasma concentrations than high-dose intravenous dosing and may lead to fewer dose-related side effects, such as ototoxicity [4]. When these medical treatments are not effective in reducing volume overload, ultrafiltration is indicated with or without dialytic therapy according to the degree of uremia.

22.2.3 Volume Depletion in CKD

In general, ECF volume is depleted by fluid (sodium and water) loss through renal and nonrenal routes. Renal loss includes diuretic overuse, inherited sodium-wasting tubulopathies, tubulointerstitial nephritis, obstructive uropathies, and hypoaldosteronism. In this context, the CKD patients whose underlying disease has remarkable tubulointerstitial pathology are susceptible to becoming volume-depleted. Other CKD patients can also experience volume depletion when they are complicated by bleeding or extrarenal fluid loss due to diarrhea, vomiting, extensive burns, or excessive sweating.

22.2.3.1 Clinical Diagnosis of Volume Depletion

A detailed history will usually reveal the source of volume losses. The clinical manifestations of volume depletion depend on its magnitude, the rate at which it develops, and the type of fluid that was lost [2]. Thirst is common as the volume loss worsens. Whereas hypovolemic shock can occur with a rapid volume loss in severe cases, gradual volume loss with an intravascular volume contraction of less than 5% may be asymptomatic and associated with few physical findings. An intravascular volume contraction of 5–15% typically causes symptoms and signs, often including postural lightheadedness and weakness. Physical findings are not very helpful in diagnosing volume depletion. Findings such as reduced skin or eyeball turgor and dry mucous membranes are not reliable indicators of hypovolemia [2].

The classic urinary indices suggestive of volume depletion may be confounded by the preexisting CKD. Despite hypovolemia, urine osmolality may not increase to >800 mOsm/kg H_2O and urine sodium concentration may not decrease to <20 mmol/L due to accompanying tubular dysfunction. Similarly, the application of fractional excretion of sodium is limited in CKD

as a marker for hypovolemia. Preexisting azotemia is frequently aggravated by volume depletion. The rise of BUN out of proportion to that of serum creatinine may suggest renal hypoperfusion. Anemia of chronic disease is often associated with CKD, but bleeding episodes should be suspected when the hemoglobin level is acutely reduced. Serum sodium, potassium, and bicarbonate may change according to the components of lost fluids.

22.2.3.2 Treatment of Volume Depletion

Patients with CKD are unable to promptly conserve sodium in the face of volume depletion. However, the principles in treatment of volume depletion in CKD are the same as in general subjects. To restore hemodynamic integrity and tissue perfusion, the volume deficit should be replaced with isotonic fluids until the patient's heart rate, blood pressure, consciousness, and urine output are stabilized. Blood transfusions are necessary for hemorrhage, but the administration of colloids generally is no better than crystalloids for fluid resuscitation. At the same time, the underlying factors for fluid loss need to be found and corrected. Additionally, maintenance fluids are administered based on the ongoing losses. Because the patients with advanced CKD have limited capacity to excrete sodium and water, overshoot hypervolemia must be avoided.

22.3 Water Balance Disorders

Total body water determines ECF osmolality which affects cell volume. For normal cell volumes, human body fluid osmolality should be maintained between 280 and 295 mOsm/kg H_2O. This can be achieved by maintaining a water balance between water intake and renal water excretion. With progression of CKD, water may be retained by the kidney with a resultant decrease in ECF osmolality. Rarely, in patients with CKD and water deficit, the ECF osmolality may increase.

Water balance disorders present as altered plasma sodium concentrations (dysnatremia) because sodium is the principal ion in the ECF. Both urine concentrating and diluting mechanisms are impaired with progressive kidney disease. Therefore, CKD patients have limited abilities in water excretion and water conservation (Fig. 22.2) and are susceptible to both hyponatremia and hypernatremia.

22.3.1 Role of the Kidney in Water Balance Regulation

Vasopressin plays a pivotal role in regulation of water balance. Water intake is stimulated by thirst, and the kidney regulates water balance by adjusting renal water excretion, or urine concentration and dilution. When water intake is insuf-

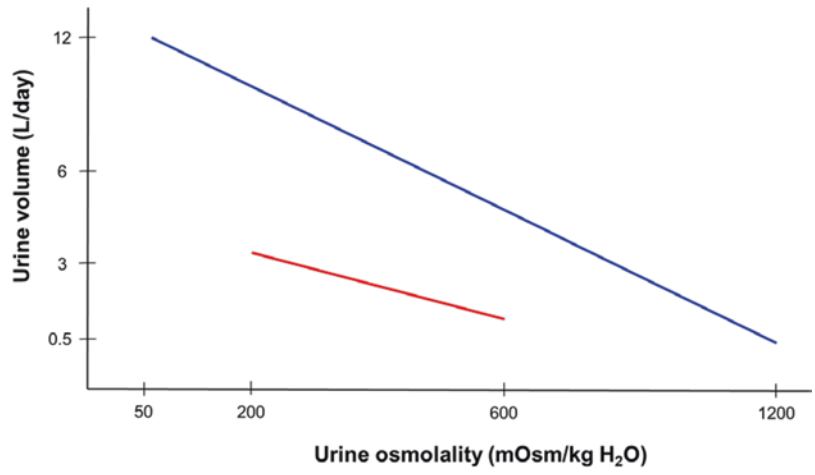

Fig. 22.2 Comparison of different ranges of urine osmolality and urine volume between advanced CKD (red, an assumptive case) and normal kidney function (blue). The range of obtainable osmolalities dwindles with declining GFR. Accordingly, the adaptive range of urine volume is limited in advanced CKD. *CKD* chronic kidney disease, *GFR* glomerular filtration rate

ficient, more water is retained by the kidney through the action of arginine vasopressin (AVP). The AVP produced in hypothalamus is released from posterior pituitary gland and acts on the renal tubules where urine concentration is promoted. First, AVP binds to the AVP receptor 2 in collecting duct principal cells and activates aquaporin-2 (AQP2) water channel to reabsorb water. Second, AVP binds to the AVP receptor 2 in thick ascending limb cells of the Henle's loop and activates NKCC2 to increase outer medullary interstitial hypertonicity. Finally, AVP upregulates urea transporter A2 in the thin descending limb to enhance inner medullary urea cycling. The latter two are critical components of countercurrent multiplication.

From these regulatory actions, urine concentration varies over a wide range. In normal humans, urine osmolality can increase up to 1200 mOsm/kg H_2O with increased circulating AVP (maximally concentrated urine). It also can decrease down to 30–50 mOsm/kg H_2O in the absence of circulating AVP (maximally diluted urine). These wide ranges of urine osmolality progressively dwindle in CKD, suggestive of impairment of both concentrating and diluting mechanisms [21]. The French NephroTest Cohort Study showed that baseline fasting urinary osmolality was strongly associated with measured GFR in 2084 adult patients with CKD stages 1–4 [22]. In a Korean CKD cohort, the urine osmolality obtained from the first voided urine in the fasting status was 400–500 mOsm/kg H_2O in CKD stage 3 and decreased below 400 mOsm/kg H_2O in CKD stage 4 [23]. Isosthenuria is defined as the specific gravity of urine becoming relatively fixed at 1.010, which is approximately the same as that of blood (~300 mOsm/kg H_2O). It is typically one of the constant signs of kidney failure [24].

22.3.2 Hyponatremia in CKD

Hyponatremia, which is defined as a plasma sodium concentration <135 mmol/L, can occur in CKD when renal water excretion is less than water intake. Rarely, depletional (hypovolemic) hyponatremia is induced in CKD patients when they are complicated with sodium (volume) losses and maintaining water intake. Typically, dilutional hyponatremia occurs in CKD patients because of impaired urinary diluting ability. As patients reach CKD stage 5, the urine osmolality hardly goes down to ~100 mOsm/kg H_2O in response to water load.

When hyponatremia was defined as a serum sodium concentration <136 mmol/L, its baseline prevalence was 13.5% in 655,493 US veterans with non-dialysis-dependent CKD [25]. However, over a mean 5-year period of observation, 26% of all patients developed at least 1 episode of hyponatremia. In this cohort, mortality increased with the severity of hyponatremia although it was not influenced by CKD stage.

Kidney failure is one of the major causes of hyponatremia because the reduced GFR accompanies a decrease in solute-free water clearance. Although both urine concentration and dilution are impaired in kidney failure, hyponatremia is more frequent than hypernatremia in CKD patients because glomerular filtration is the initial prerequisite for urine dilution. Three components are required for the production of dilute urine [4]: (1) there must be enough glomerular filtrate delivered to the distal nephron for dilution and excretion, (2) the diluting segments of the distal nephron must selectively reabsorb sodium and lead to a fall in urine osmolality, and finally, and (3) AVP levels must fall and the collecting duct must decrease its permeability to water reabsorption and allow water to be excreted (dilute urine). In addition to the decline in GFR, defects in the diluting segment should be additionally associated with CKD for development of hyponatremia [26]. In renal cortex, the distal convoluted tubule acts as the diluting segment because of the presence of NCC and ENaC and the absence of AQP2. Consistent with this, the risk of hyponatremia is increased by using thiazides and amiloride. The clinical phenotype of hyponatremia in CKD may be similar to that in syndrome of inappropriate ADH secretion (SIADH). Plasma AVP levels are elevated in patients with CKD because of reduction of its metabolic clearance rate [27].

22.3.2.1 Differential Diagnosis of Hyponatremia

Many CKD patients with hyponatremia are asymptomatic because the onset of hyponatremia is usually gradual. Mild to moderate symptoms include dizziness, headache, nausea, and vomiting. Severe neurologic manifestations are confusion, lethargy, seizures, and coma caused by brainstem herniation. Since most of the CKD patients are free of edema, hyponatremia in CKD can be classified as euvolemic. However, CKD patients may be edematous or hypervolemic when they are nephrotic or markedly uremic. Rarely, they can also be hypovolemic when they are complicated by fluid or blood loss.

Hyponatremia in CKD is hypotonic, but measured osmolality can vary from hypoosmolar to hyperosmolar according to the level of blood urea nitrogen (BUN). A high level of BUN will increase the measured osmolality, whereas tonicity or effective osmolality is not affected by blood urea. Urine sodium is also not very helpful in laboratory diagnosis because its concentration is typically >20 mmol/L in CKD. If tubular function is intact, urine sodium could be <20 mmol/L when remarkable volume depletion or edematous disorders such as nephrotic syndrome, liver cirrhosis, and congestive heart failure are coexistent.

22.3.2.2 Treatment of Hyponatremia

The treatment of hyponatremia in CKD patients follows the same principles as the treatment of hyponatremia in patients without CKD. Water restriction is the first measure to restore water balance although it is a slow acting approach to correct hyponatremia. When the patients are symptomatic and acute hyponatremia is suspected, 3% hypertonic saline can be infused to elevate the serum sodium level. Like cases without CKD, frequent monitoring of serum sodium levels is required to prevent overcorrection. Normal saline solution is the treatment of choice for hypovolemic hyponatremic conditions [26]. In cases with volume overload or hypertension, loop diuretics such as furosemide and torsemide are effective not only in relieving edema but also in elevating serum sodium levels. Tolvaptan, an oral AVP receptor 2 antagonist, may be added to furosemide in hyponatremic CKD patients when a greater diuretic effect is necessary [28]. Ultrafiltration therapy should be considered for patients with refractory edema that is not responsive to intensive diuretic treatment.

Results of a large epidemiologic study revealed the lowest mortality in patients with sodium levels of 140 mmol/L and adjusted hazard ratios for the group <130 and 130 to 135 mmol/L to be 1.93 and 1.28, respectively [25]. Therefore, gradual correction of plasma sodium levels to 135 mmol/L appears to be a reasonable target.

22.3.3 Hypernatremia in CKD

Hypernatremia, which is defined as a plasma sodium concentration >145 mmol/L, is infrequently noted in CKD patients when sodium or water balance is disturbed. If sodium intake exceeds the capacity of the kidneys to excrete sodium, it can result in sodium overload, leading to edema and hypernatremia. This usually derives from inadvertent salt overuse or iatrogenic causes such as intravenous hypertonic NaCl or $NaHCO_3$ infusion. The other more common etiology is water deficit caused by either insufficient water intake or enhanced water loss via renal and extrarenal routes. In any case, CKD patients are susceptible to hypernatremia because of impaired urinary concentration. To excrete the dietary solute load of 600 mOsm/day, as little as 0.5 L/day of highly concentrated urine (1200 mOsm/kg H_2O) would suffice. However, 2 L/day of urine output is necessary to excrete the dietary solute load of 600 mOsm/day when the urinary concentration is reduced to 300 mOsm/kg H_2O (Fig. 22.2). Thus, water deficit occurs if water intake is less than 2 L/day.

Hypernatremia increases osmolality of the ECF, causing an efflux of intracellular water and cellular shrinkage. As with hyponatremia, the symptoms of hypernatremia vary from asymptomatic to neurologically serious depending on the severity and rate of onset of hypernatremia. Altered consciousness is the typical manifestation, ranging from mild confusion and lethargy to deep coma [29].

On physical examination, edema can be found if sodium is primarily retained. In contrast with hyponatremia, measurement of serum osmolality is unnecessary for differential diagnosis of hypernatremia because hyperosmolality is naturally produced by hypernatremia and azotemia. In general, measurement of urine osmolality is useful in differentiating renal water loss from extrarenal water loss. However, its significance is limited in CKD because urine concentration is already disturbed by the associated tubular injury.

The treatment of hypernatremia in CKD patients follows the same principles as the treatment of hypernatremia in patients without CKD [30]. Simultaneously, efforts to seek and eliminate the underlying cause of water deficiency or sodium overload are mandatory. If hypernatremia is symptomatic, hypotonic fluids should be infused to lower serum sodium levels. Dextrose water is appropriate for treating pure water loss, and half-saline may be required for treating water and sodium loss. The rate and amount of daily water replacement should be based not on the calculated water deficit, but on the repeated measurements of serum [Na^+] to prevent under- or overcorrection. If hypernatremia is chronic (≥48 h) or of unknown duration, serum sodium correction should be gradual, not exceeding 8–10 mmol/L in the first 24 h to prevent cerebral edema [29]. More rapid serum Na^+ correction (up to 1 mmol/L per hour) may be appropriate if onset of hypernatremia is acute (<48 h).

According to the observational study from 655,493 US veterans with non-dialysis-dependent CKD, the prevalence of hypernatremia defined as a serum sodium concentration >145 mmol/L were 2% at baseline and 7% over a mean 5-year period of observation [25]. Thus, the prevalence of hypernatremia was much lower than that of hyponatremia but showed a significant increase with advancing stages of CKD, supporting the observation that the kidney's concentrating ability is affected to a greater extent by advancing CKD than its diluting ability [31]. Interestingly, the association between hypernatremia and mortality appeared to diminish linearly with more advanced stages of CKD [32]. This apparent "protective" effect of advanced CKD on hypernatremia-related mortality may be because of adaptation to increased extracellular (uremic) osmolality in patients with more advanced CKD [4].

22.4 Potassium Balance Disorders

Potassium is mostly (>98%) located in the intracellular fluid (ICF) and is required for normal cell function. In particular, the ratio between ECF and ICF potassium concentration is a determinant of transmembrane electrochemical gradient and neuromuscular excitability. Therefore, potassium balance is critical for the excitable tissues such as heart, nerves, and skeletal muscle, and the ECF potassium level should be maintained within a narrow normal range (3.5–5.0 mmo/L). Potassium also has a strong relationship with sodium, affecting plasma volume and blood pressure.

The potassium balance can be divided into internal and external. The internal potassium balance is determined by transcellular shift of K^+ across the cell membrane, which is mainly exerted by Na^+/K^+-ATPase. Insulin and catecholamines are the most important determinants of cell membrane potential and govern K^+ distribution into and out of cells. The external balance is resultant from dietary intake and fecal and urinary excretion. On a typical Western diet, daily potassium intake ranges from 90 to 120 mmol/day [30]. At steady state, the kidneys excrete 90–95% of dietary potassium, with the small remainder excreted in stool through the colonic secretion. With progression of CKD, renal potassium excretion may decrease, leading to an elevation in plasma potassium levels. Altered potassium secretion in the ASDN is the major component of dysregulated potassium homeostasis.

22.4.1 Role of the Kidney in Potassium Balance Regulation

The kidney is the major organ that regulates potassium balance. Although small amounts of potassium are excreted in stool and sweat, this

amount is essentially constant and is not regulated. Plasma potassium is freely filtered at glomeruli, but urinary potassium excretion can vary according to the status of total body potassium. Approximately 65% of glomerular filtered potassium is reabsorbed in the proximal tubule, where paracellular solvent drag and diffusion act as the major driving forces for potassium reabsorption [33]. In the thick ascending limb of Henle's loop, approximately 25% of the glomerular filtered potassium is reabsorbed mainly through the paracellular pathway. This is driven by the lumen-positive voltage promoted by apical K^+ recycling, which is resultant from the coupled action of NKCC2 and renal outer medullary potassium channel (ROMK).

Like sodium, the final urinary potassium excretion is finely tuned by regulation of potassium secretion in the ASDN. The major K^+ channels in the ASDN are Kir4.1 and Kir5.1 in the basolateral membrane and Kir1.1 (ROMK) and Ca^{2+}-activated big conductance K^+ channel (BK) in the apical membrane. Among these, the ROMK plays a major role by regulating potassium secretion in the later part of the ASDN. Usual fractional excretions of potassium range 15–20%. When potassium intake increases, fractional excretion of potassium can rise up to 80% [34] mainly caused by the increased potassium section in the principal cells. In cases of potassium depletion, H^+/K^+-ATPase in the α-intercalated cells activates to reabsorb potassium, and fractional excretion of potassium can be reduced down to 1.5% [35]. Because of the enhanced action of H^+/K^+-ATPase, urine ammonium excretion is increased and metabolic alkalosis may be associated [36].

In the ASDN, both sodium reabsorption through the ENaC and potassium secretion through the ROMK are regulated by aldosterone. However, the renal effects of aldosterone action are different between hypovolemia and hyperkalemia (aldosterone paradox) [37]. When aldosterone is stimulated by volume depletion or hyperreninemia, the aldosterone-regulated sodium transporters NCC and ENaC are activated to conserve sodium. Importantly, undesired potassium loss is prevented by the activated angiotensin II because of its inhibitory action on ROMK. When aldosterone is stimulated by hyperkalemia, the ROMK is activated to enhance potassium secretion and potassium balance can be restored. However, undesired sodium retention is prevented by downregulation of NCC because the NCC is dephosphorylated by hyperkalemia or dietary potassium loading [38]. Thus, aldosterone acts in the kidney to independently regulate sodium and potassium balance.

Kidneys can retain the ability to maintain potassium balance and normal serum potassium levels until very late stages of CKD. In response to oral potassium load, however, the increase in urinary potassium excretion is blunted in CKD patients compared with normal subjects [39]. Urinary potassium excretion gradually decreases with declining of GFR, but the fractional excretion of potassium increases (Fig. 22.3) because potassium secretion per nephron increases with progression of CKD [40]. In advanced CKD, potassium secretion increases in principal cells of the cortical collecting duct in association with increased activity of Na^+-K^+-ATPase [41]. In addition, as CKD progresses, intestinal potassium excretion also increases in concert with increased colonic Na^+-K^+-ATPase activity [42] and BK channel-mediated potassium permeability [43, 44].

22.4.2 Hyperkalemia in CKD

Hyperkalemia, defined as a plasma potassium concentration >5.0 mmol/L, is the most common electrolyte disorder in patients with advanced CKD. Decreased GFR and impaired sodium delivery to the distal nephron both hinder renal potassium excretion in patients with CKD [45]. The risk of hyperkalemia may increase when estimated GFR drops below 40 mL/min/1.73 m^2 [46], and the incidence of hyperkalemia increases as the CKD advances from stage 1 to 5.

The prevalence of hyperkalemia varies depending on the patient population studied and how it is defined. Overall, the prevalence of hyperkalemia in CKD is 14–20% [47], and Fig. 22.4 presents data from a Korean CKD

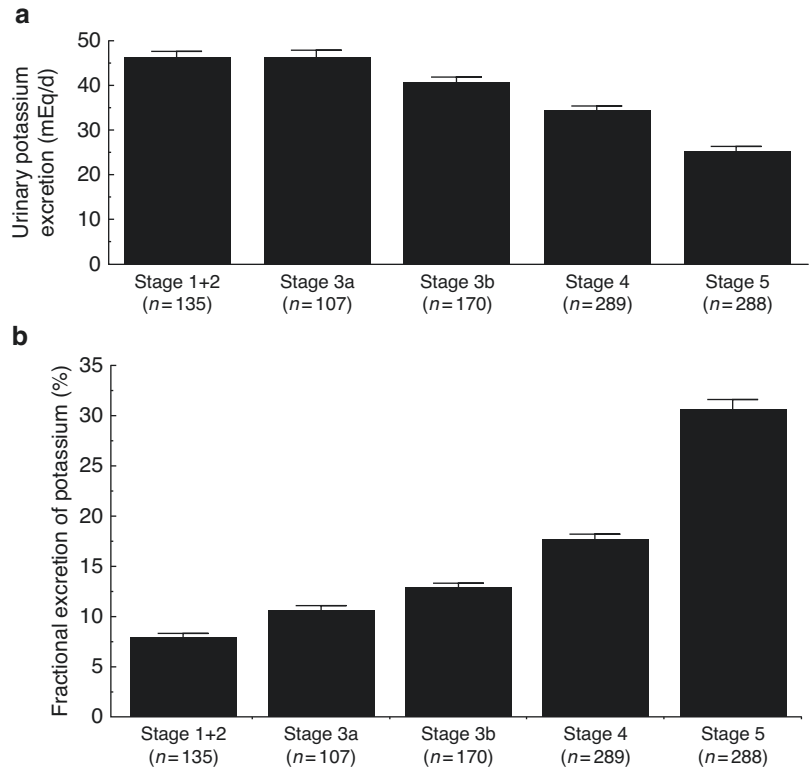

Fig. 22.3 Changes in urinary potassium excretion (**a**) and fractional excretion of potassium (**b**) according to different stages of CKD. *CKD* chronic kidney disease. (Reproduced with permission from the Korean Society of Nephrology: Ueda et al. [38])

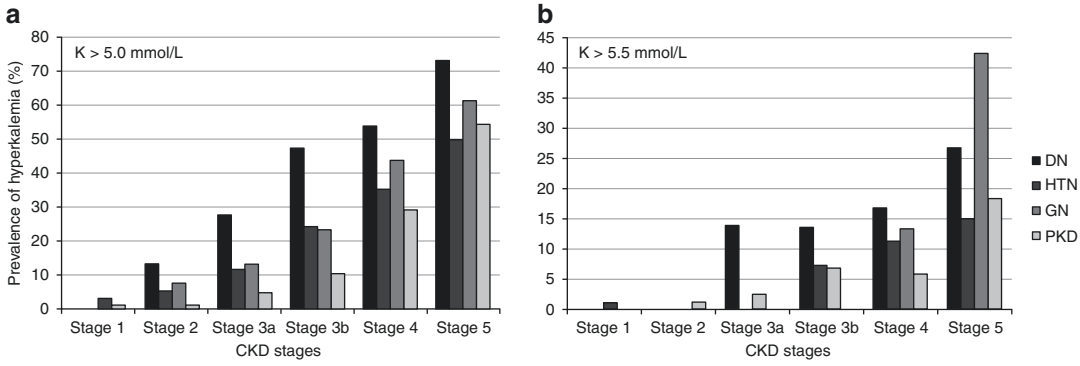

Fig. 22.4 Prevalence of hyperkalemia according to etiology of CKD in each CKD stage when hyperkalemia was defined as >5.0 mmol/L (**a**) and as >5.5 mmol/L (**b**). CKD, chronic kidney disease. (Adapted from the article of Kim et al. [48], according to the Creative Commons Attribution 4.0 International License)

cohort (n = 1788) with respect to different underlying diseases of CKD [48].

Even moderate levels of hyperkalemia are associated with unfavorable outcomes. Hyperkalemia is independently associated with significantly higher all-cause and cardiovascular mortality and with higher risk of ESKD [49]. Interestingly, the mortality associated with hyperkalemia is lower in patients with CKD compared with those with normal kidney function, probably due to the chronicity of hyperkalemia [50].

22.4.2.1 Differential Diagnosis of Hyperkalemia

The typical causes of hyperkalemia are similar in patients with and without CKD [51]. Excessive

dietary potassium intake can cause hyperkalemia in individuals with advanced CKD. When insulin deficiency, mineral acidosis, or hyperosmolality (e.g., hyperglycemia or contrast media) are associated, hyperkalemia is induced by the redistribution of potassium out of cells. The reduction of GFR < 15 mL/min/1.73 m^2 (or CKD stage 5) may be the major cause of decreased renal excretion of potassium [51], but hypoaldosteronism to impair potassium secretion in the ASDN may be a more important cause of hyperkalemia in earlier stages of CKD. The combination of hyperkalemia and hyperchloremic metabolic acidosis, or type 4 renal tubular acidosis is common in CKD and is most often attributable to either hyporeninemic hypoaldosteronism or obstructive uropathy. Hyporeninemic hypoaldosteronism can occur in patients with diabetic nephropathy and hypertensive nephrosclerosis, and many medications inhibiting the renin-angiotensin-aldosterone system (RAAS) in the kidney may result in hypoaldosteronism and hyperkalemia (Table 22.2). The RAAS inhibitors typically include angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockades (ARBs), and MRAs, and the combined use of more than one drug in this category increases the risk for hyperkalemia. Because RAAS inhibitors are commonly used in CKD patients who have diabetes mellitus and/or heart failure, these comorbidities put CKD patients at risk of hyperkalemia.

Table 22.2 Medications associated with hyperkalemia resulting from RAAS inhibition

Mechanism	Drug
Impaired release of renin	NSAIDs, beta-blockers, calcineurin inhibitors
Direct renin inhibitor	Aliskiren
ACE inhibitors	Captopril, enalapril, ramipril, perindopril
Angiotensin receptor blockers	Losartan, irbesartan, telmisartan, olmesartan
Impaired release of aldosterone	Heparin, ketoconazole
Mineralocorticoid receptor antagonists	Spironolactone, eplerenone, finerenone
ENaC blockers	Amiloride, triamterene, trimethoprim, pentamidine

ACE angiotensin converting enzyme, *ENaC* epithelial sodium channel, *NSAIDs* nonsteroidal anti-inflammatory drugs, *RAAS* renin–angiotensin–aldosterone system

Pseudohyperaldosteronism type II, also known as familial hyperkalemic hypertension or Gordon's syndrome is an inherited syndrome of hypertension and hyperkalemia. Other associated findings include hyperchloremia, metabolic acidosis, hypercalciuria, and suppressed plasma renin levels. These clinical features can be explained by the NCC hyperactivity in the distal convoluted tubule, caused by mutations of NCC regulator genes including *WNK1*, *WNK4*, *CUL3*, or *KLHL3*. A similar but more common acquired phenotype may occur when calcineurin inhibitors are administered to kidney transplant patients. Calcineurin inhibitors were reported to upregulate NCC, leading to a syndrome of hypertension and hyperkalemia [52].

Clinical manifestations of hyperkalemia vary widely from nonspecific muscle weakness to paresthesia, muscle paralysis, cardiac arrhythmias, and cardiac arrest. As hyperkalemia progresses, a series of abnormal electrocardiographic findings may occur: peaked T waves, prolonged PR interval, loss of P waves, widening of the QRS complex, and sine waves. However, these changes are not sensitive in detecting hyperkalemia, particularly in patients with advanced CKD. The reasons why the electrocardiographic changes are attenuated in hyperkalemic CKD patients are unclear, but variations in serum calcium concentration and the slow rate of rise in serum potassium have been proposed as possible explanations [53].

22.4.2.2 Treatment of Hyperkalemia

Acute treatment for severe hyperkalemia includes intravenous calcium, insulin, sodium bicarbonate, and inhaled β2-adrenergic agonists. Hyperkalemia may be classified as severe when the plasma potassium level is 6.5 mmol/L or higher, regardless of any associated ECG changes [54]. If no arrhythmia is associated, pseudohyperkalemia or spuriously high measurement of potassium must be ruled out. In vitro hemolysis is the major cause of pseudohyperkalemia and can be suspected by inspection of the serum. Clinicians may be advised to compare the serum and plasma potassium level because pseudohy-

perkalemia is a rise in serum potassium with concurrently normal plasma potassium concentration.

If ECG abnormalities are found, 1 g calcium gluconate (10 mL of 10% solution) or calcium chloride (3–4 mL of 10% solution) should be infused intravenously over 2–3 min with cardiac monitoring. Calcium reverses the depolarization blockade due to hyperkalemia by raising the action potential threshold and reducing excitability, without changing the resting membrane potential [29]. The infusion may be repeated because the electrical effect on cardiac excitation lasts for 30–60 min. To rapidly reduce the plasma potassium level, measures to translocate potassium from the extracellular space to the intracellular space are simultaneously necessary. Intravenous regular insulin 5 units plus 25 g glucose (50 mL of 50%) can be given with close monitoring of plasma glucose concentration. The effect begins in 10–20 min, peaks at 30–60 min, and lasts for 4–6 h. β2-Adrenergic agonists are also effective, and albuterol (salbutamol) 10 mg nebulized in 4 mL of normal saline is inhaled over 10 min. The effect starts at about 30 min, reaches its peak at about 90 min, and lasts for 2–6 h. Because tachycardia is a side effect, β2-adrenergic agonists should be used with caution in patients with cardiac disease [29]. Insulin and albuterol may have an additive effect on plasma potassium concentration. Conversely, intravenous bicarbonate has no role in the acute treatment of hyperkalemia because of its slow onset of action and low efficacy. It may be considered in hyperkalemic patients with metabolic acidosis but without volume overload. Intravenous bicarbonate (50 mL of 8.4% solution, containing 50 mmol each of Na^+ and HCO_3^-) can be given over 15 min [54]. If these medical treatments are unsuccessful, acute hemodialysis is indicated. For this, a vascular access is required, either a central venous catheter or a preexisting arteriovenous access.

Chronic treatment for mild to moderate hyperkalemia includes restriction of dietary potassium intake, avoidance of drugs that may induce hyperkalemia, augmentation of urinary potassium excretion, and enhanced fecal potassium elimination using cation exchange resins or potassium binders. If the CKD patients are hyperkalemic, dietary potassium needs to be limited to less than 75 mmol/day. Thus, plasma potassium levels should be monitored while restricting intake of potassium-rich foods such as vegetables, fruits, and nuts. Medications that may induce hyperkalemia (e.g., nonsteroidal anti-inflammatory drugs, nonselective beta-blockers, calcineurin inhibitors, and heparin) should be reviewed. They mostly interfere with potassium secretion from ASDN, and RAAS inhibitors including ACE inhibitors, ARBs, and MRAs are frequently used in patients with CKD and cardiorenal syndrome because of their cardiorenal protection. In cases of severe hyperkalemia, all agents that cause hyperkalemia should be discontinued. However, the benefit of RAAS inhibition may be considered in cases of mild hyperkalemia because potassium-lowering agents are available. Whether to stop or reduce RAAS inhibitors is an important issue, as it involves comparing the risk of hyperkalemia with the benefits of RAAS inhibition. The ongoing DIAMOND trial will show whether the use of novel potassium binders such as patiromer provides the long-term benefits for patients with heart failure and hyperkalemia who are taking RAAS inhibitors [55].

Loop diuretics, potassium binders, and dialysis are interventions used to remove potassium from the body. Loop diuretics with or without thiazides can be used to promote kaliuresis. These are beneficial for edematous patients, but caution needs to be paid to the risk of plasma volume depletion caused by overuse of diuretics. Fludrocortisone acetate may be prescribed to increase urinary potassium excretion in patients with aldosterone deficiency. However, larger doses (up to 0.4–1.0 mg/day) are required to effectively lower potassium level, and sodium retention, edema, and hypertension may be complicated [56]. Old potassium binders are cation exchange resins and include sodium polystyrene sulfonate (SPS) and calcium polystyrene sulfonate (CPS). Novel potassium binders are patiromer and sodium zirconium cyclosilicate (ZS-9) and lack the intestinal toxicity. These agents have revolutionized the management of hyperkalemia

in users of RAAS inhibitors in CKD. The availability of safe, well-tolerated potassium binders allows for the continued use of RAAS inhibitors for cardiorenal protection [29]. However, the high cost currently limits the global use of novel potassium binders.

Sodium polystyrene sulfonate (SPS) is a cation exchange resin, which exchanges sodium for calcium, ammonium, and magnesium in addition to potassium. Thus, it is not very selective for serum potassium lowering and may lead to hypocalcemia and hypomagnesemia. Kayexalate was the commercial name given to the powdered form of SPS, first introduced in the 1950s [57]. Cation exchange resins seem to act on crypt enterocytes in the distal colon, which have the secretory pathway of potassium from basolateral NKCC1 cotransporter and Na/K-ATPase to apical BK channel [58]. Oral administration of SPS 15–60 g per day can be given in divided doses but without sorbitol because of the risk of intestinal necrosis [54]. The efficacy and safety of SPS were previously concerned, but the use of SPS may continue due to its clinical familiarity and lower cost [59].

Calcium polystyrene sulfonate (CPS) is another cation exchange resin, which exchanges calcium for potassium. Compared with SPS, CPS may have a higher potassium-selectivity at cation exchange [60]. Although CPS has been widely used for patients with advanced CKD in many countries, few studies have reported on its efficacy and adverse effects. Yu et al. conducted a retrospective analysis from 247 adult patients who were prescribed CPS for weeks to years [61]. They found that long-term use of small doses (5–15 g/day) of oral CPS was effective and safe for controlling mild hyperkalemia. Considering the similar action mechanisms, CPS could be used as an alternative to patiromer in countries where novel potassium binders are unavailable [62]. In a comparative study between CPS and SPS, serum potassium lowering was similar [60]. Unlike CPS, however, SPS significantly increased serum sodium and decreased serum calcium and magnesium concentrations.

Patiromer is a non-absorbable polymer consisting of smooth spherical beads approximately 100 μm in diameter. The active moiety of the polymer is composed of α-fluorocarboxylic acid that contains a calcium ion which dissociates in favor of a potassium ion to promote fecal potassium excretion in the distal colon [57]. Oral administration of patiromer can increase fecal potassium in a dose-related fashion, and doses of 15–30 g/day increased daily fecal potassium by approximately 15–20 mmol [63]. Randomized, controlled trials have evaluated the efficacy and safety of patiromer in hyperkalemic CKD patients already treated with RAAS blockers. Serum potassium lowering was demonstrated by daily doses between 8.4 and 30 g up to 52 weeks. Major adverse events were constipation and hypomagnesemia [64]. Based on these results, patiromer was approved by the Food and Drug Administration in 2015.

Sodium zirconium cyclosilicate (ZS-9) is a crystal that is highly selective for potassium ion trapping. Thus, it may act throughout the gastrointestinal tract and explain the rapid onset of action. ZS-9 was also tested for treating hyperkalemia in CKD, heart failure, or diabetic outpatients. Daily doses between 1.25 and 15 g up to four weeks were used in randomized, controlled trials and showed effective serum potassium lowering. Major adverse events were edema and diarrhea [64]. Based on these results, ZS-9 was approved by the Food and Drug Administration in 2018.

22.4.3 Hypokalemia in CKD

Hypokalemia, defined as a plasma potassium concentration <3.5 mmol/L, uncommonly occurs in CKD patients with inadequate potassium intake, increased intracellular potassium shift, and renal or gastrointestinal potassium loss. Overall, the prevalence of hypokalemia is 1–3% [47]. For hypertensive patients with CKD stage 1 and 2, a daily intake of 4 g of potassium per day (or 102 mmol) is generally recommended and dietary potassium restriction is not recommended until kidney disease is more advanced [49]. Frequent causes of potassium loss are diuretic overuse, metabolic alkalosis, vomiting, diarrhea, and hypomagnesemia.

Clinical symptoms and signs of hypokalemia vary depending on the rate of onset and severity [30]. These include muscle weakness, cramps, muscle paralysis and respiratory failure, cardiac arrhythmias, paralytic ileus, and rhabdomyolysis. In particular, hypokalemia is a major risk factor for both ventricular and atrial arrhythmias [29], including sinus bradycardia, atrioventricular block, paroxysmal atrial or junctional tachycardia, ventricular tachycardia, and fibrillation. ECG changes include broad flat T waves, emergence of U waves, ST depression, and QT prolongation. Hypokalemia also involves skeletal muscles, leading to weakness and even paralysis. Paralytic ileus may result from intestinal smooth muscle involvement. Hypokalemia is frequently associated with metabolic alkalosis because of enhanced renal proximal tubular ammoniagenesis.

22.4.3.1 Differential Diagnosis of Hypokalemia

Clinical settings are important clues for differential diagnosis. The history should focus on diet and dietary habits, medications including diuretics, laxatives, and antibiotics, and gastrointestinal problems such as vomiting and diarrhea [29]. On physical examination, it is important to differentiate whether the patient is hypertensive or hypovolemic. If hypokalemia is accompanied by hypertension, diuretic use should be sought first. When this possibility is excluded, following causes of mineralocorticoid excess need to be differentiated by measuring plasma renin activity and serum aldosterone: primary aldosteronism, renovascular hypertension, Liddle syndrome, and syndrome of apparent mineralocorticoid excess.

Urine potassium excretion or potassium-to-creatinine ratio is the mainstay for the differential diagnosis of hypokalemia. In CKD, however, the cut-off value suggestive of renal potassium wasting is unclear because of the associated tubular injury and dysfunction. Acid–base equilibrium can also be disturbed by impaired urinary acidification in CKD. In cases with normotensive hypokalemic metabolic alkalosis, measurement of urine chloride and urine calcium-to-creatinine ratio is useful for diagnosing vomiting, diuretic abuse, Gitelman syndrome, and Bartter syndrome. The chronic state of hypovolemia, hypotension, and hypokalemia in salt-losing nephropathy can lead to progressive declines in GFR.

22.4.3.2 Treatment of Hypokalemia

Management of hypokalemia in CKD patients involves correcting the underlying causes and cautious potassium replacement. Restriction of dietary potassium should be avoided in patients with hypokalemia. Adequate intake of fruits and vegetables is encouraged unless plasma potassium levels are increased. However, dietary salt intake needs to be restricted because increased distal sodium delivery would result in increased potassium excretion. Foods with a relatively high potassium content (>6.2 mmol/100 g) include spinach, broccoli, carrots, potatoes, kiwis, oranges, and mangos [49]. When potassium supplementation is indicated, small doses of potassium chloride are orally administered. If metabolic acidosis is coexistent, potassium citrate is preferred to elevate plasma bicarbonate. With severe and symptomatic hypokalemia, intravenous potassium chloride can be administered at a rate <10 mmol/h in half-saline. It should be diluted to <40 mmol/L for the peripheral venous route and <100 mmol/L for the central venous route [65]. The plasma potassium levels should be monitored more frequently than in patients without CKD to avoid excessive administration. Daily parenteral doses are typically limited to <60 to 80 mmol/day [66].

Hypokalemia is associated with poor outcomes including mortality and kidney function decline in CKD. Most studies have observed a U-shaped relationship between serum potassium and mortality, with the lowest risk observed in those with a serum potassium of 4–5 mmol/L [47]. Interestingly, prolonged hypokalemia is associated with CKD progression. When 820 patients with CKD were prospectively followed at four US centers for an average of 2.6 years, those with a serum potassium <4 mmol/L had a 69% higher ESKD risk compared to those with normokalemia, whereas ESKD risk was not higher for those with potassium ≥5.5 mmol/L [67]. In a separate

study from 1227 males with CKD, those with a serum potassium <3.6 mmol/L had greater annual loss of GFR (−0.23 mL/min per 1.73 m^2 per year) than those with a serum potassium of 3.6–5.5 mmol/L. In contrast, there was no significant difference in annual GFR loss for those with a serum potassium >5.5 mmol/L [68]. The association of hypokalemia with accelerated progression of CKD was postulated, at least in part, to be due to impaired renal angiogenesis and enhanced renal ammonia production with consequent intrarenal complement activation [69, 70].

Before You Finish: Practice Pearls for the Clinician

- CKD patients are susceptible to ECF overload when their GFRs are reduced to <10 mL/min or when tubular sodium reabsorption is enhanced by the activation of RAAS (e.g., congestive heart failure or nephrotic syndrome).
- Loop diuretics with or without thiazide-like agents are the mainstay for correcting volume overload in CKD. Dietary sodium restriction is a prerequisite for the maintenance of euvolemia.
- Dilutional hyponatremia may be caused by reduced free water clearance and impaired diluting segments in CKD patients and can be treated by restriction of water intake and administration of loop diuretics.
- Saline infusion is indicated when CKD patients are complicated by volume depletion caused by renal and extrarenal fluid losses.
- Hypernatremia is an infrequent electrolyte disorder in CKD, caused by the same etiologies in patients without CKD. Thus, the same treatment principles can be applied.
- Hyperkalemia is the most common electrolyte disorder in CKD patients taking RAAS inhibitors. The risk of hyperkalemia can be reduced by concomitant use of potassium binders.
- Hypokalemia uncommonly occurs in CKD patients with inadequate potassium intake, increased intracellular potassium shift, and renal or gastrointestinal potassium loss. Hypokalemia was known to be associated with accelerated progression of CKD.

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