

Electrolyte and Acid–Base Disorders in Chronic Kidney Disease and End-Stage Kidney Failure

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Key Words

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Abstract

The kidneys play a pivotal role in the regulation of electrolyte and acid–base balance. With progressive loss of kidney function, derangements in electrolytes and acid–base inevitably occur and contribute to poor patient outcomes. As chronic kidney disease (CKD) has become a worldwide epidemic, medical providers are increasingly confronted with such problems. Adequate diagnosis and treatment will minimize complications and can potentially be lifesaving. In this review, we discuss the current understanding of the disease process, clinical presentation, diagnosis and treatment strategies, integrating up-to-date knowledge in the field. Although electrolyte and acid–base derangements are significant causes of morbidity and mortality in CKD and end-stage renal disease patients, they can be effectively managed through a timely institution of combined preventive measures and pharmacological therapy. Exciting ad-

vances and several upcoming outcome trials will provide further information to guide treatment and improve patient outcomes.

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Introduction

Chronic kidney disease (CKD) has become a global epidemic with an estimated prevalence of 14% in the United States and 5–15% throughout the world [1, 2]. It is associated with an increased risk of adverse cardiovascular outcomes, progression to end-stage renal disease (ESRD), and decreased survival. As the kidneys play a central role in the regulation of body fluids, electrolytes and acid–base balance, CKD and ESRD predictably result in multiple derangements including hyperkalemia, metabolic acidosis and hyperphosphatemia which, in turn, lead to serious complications including muscle wasting, bone-mineral disorder, vascular calcification and mortality. Although, in patients with ESRD, some derangements can be corrected by the renal replacement therapy, existing dialysis modalities are far from ideal. In this review,

we discuss the current understanding of disease process, diagnosis, and treatment strategies in the areas of electrolyte and acid–base regulation relevant to CKD and ESRD, with specific emphasis on dyskalemia, acidosis and mineral bone disorder (MBD).

Potassium Derangements

Potassium (K) is the most abundant intracellular cation with >98% of total body K located intracellularly and <2% extracellularly. The steep trans-cellular K gradient, generated in an energy-dependent (Na-K-ATPase) manner, is vital to the maintenance of cell membrane potential and multiple cellular functions. Kidneys, in response to increased serum K, aldosterone, distal renal tubular sodium (Na) delivery and tubular fluid flow, excrete 98% of daily K intake and are the organs that play a major role in the maintenance of K homeostasis. CKD and ESRD inevitably lead to K derangements and increased risk of adverse cardiovascular events and mortality [3].

Hyperkalemia

Hyperkalemia is one of the most common and life-threatening electrolyte disorders in CKD and ESRD [4]. It becomes increasingly prevalent as CKD advances [5, 6]. Hyperkalemia has been classified somewhat arbitrarily into mild (5.1–<6 mmol/l), moderate (6–<7 mmol/l) and severe (≥ 7 mmol/l) [7]. Diagnosis of hyperkalemia should be confirmed to rule out pseudo-hyperkalemia, which can be caused by poor phlebotomy technique, hemolysis in the test tube, thrombocytosis, and leukocytosis [8]. Although primarily caused by reduced kidney function, hyperkalemia can also be caused or exacerbated by (1) trans-cellular shift due to insulin deficiency, mineral metabolic acidosis and tissue breakdown (hemolysis, rhabdomyolysis, tumor lysis, and tissue ischemia), (2) high K intake (usually in patients with underlying CKD) and (3) medication-induced defects in renal K excretion, most commonly angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists, K sparing diuretics, and calcineurin inhibitors. Diabetic CKD patients are also at risk for developing hyperkalemia due to hyporeninemic hypoaldosteronism (type 4 renal tubular acidosis).

Clinical manifestations of hyperkalemia vary widely from nonspecific muscle weakness to paresthesia, paralysis, cardiac arrhythmias and cardiac arrest. Cardiac manifestations of hyperkalemia are of critical importance. Hyperkalemia reduces the transmembrane K gradient

and can cause multiple electrocardiographic changes including peaked T waves, prolonged PR interval, loss of P waves and widening of QRS complex [9]. It should, however, be noted that ECG itself is insensitive in detecting hyperkalemia. CKD patients can have severe hyperkalemia without any ECG manifestation [10]. In patients with implanted cardioverter/defibrillator, severe hyperkalemia could alter the device-triggering threshold, leading to under- or over-sensing, and triggering of inappropriate shock [11].

Another increasingly common and difficult scenario is the inability to use many potentially lifesaving therapies for CKD patients due to hyperkalemia. A compelling example is the use of renin-angiotensin-aldosterone (RAAS) inhibitors. There is definitive evidence supporting the benefit of RAAS inhibitors in heart failure, acute coronary syndrome, CKD, and diabetic nephropathy; yet, hyperkalemia often limits their use. A database study (n = 205,108) of patients on RAAS inhibitors has shown that RAAS inhibitors were discontinued in 16–18% of the patients due to medication-associated hyperkalemia. Among those who discontinued RAAS inhibitors, the mortality rate was threefold higher than in those who continued with the treatment [12].

Until recently, therapeutic options for hyperkalemia have been limited to a low K diet, discontinuation of RAAS inhibitors, and initiation of loop or thiazide diuretics and oral Na polystyrene sulfonate (a polymer that exchanges Na for K, calcium, ammonium and magnesium (Mg) [13]). Although approved by the US Food and Drug Administration (FDA) to treat hyperkalemia in 1958, Na polystyrene sulfonate has not been shown to increase fecal K loss in human or animal study. A recent randomized controlled study showed K reduction in a cohort of CKD patients (n = 33) with mild hyperkalemia [14]. Fatal colonic necrosis and perforation have been reported with its use [15].

Patiromer is a newer K-lowering agent, a non-absorbable, sorbitol-containing, calcium-K exchange polymer, which binds K primarily in the colon [16]. In healthy individuals, patiromer exhibits a dose-dependent lowering of urine K, Na, phosphate and Mg, consistent with an increased intestinal binding of these ions. It, on the contrary, increases urine calcium excretion, reflecting its calcium-releasing capacity [22]. It has an onset of action of 7 h. The OPAL-HK study [17] demonstrated the achievement of normokalemia after 4 weeks of patiromer treatment in 76% of hyperkalemic CKD stages 3 and 4 patients (n = 237) on RAAS inhibitors. In AMETHYST-DN trial [18] involving CKD stages 3 and 4 patients (n = 306) on RAAS inhibitors with diabetes and hyperkalemia, signifi-

cant K reduction was achieved with patiromer at week 4 and the effect sustained for 52 weeks while on treatment. The main adverse effects were mild-to-moderate constipation (11%) and mild hypomagnesaemia (3%). In addition to lowering K, patiromer treatment was associated with significant reduction in serum aldosterone and blood pressure [19]. Thus, patiromer may exert a long-term organ protective effect by reducing aldosterone level [20, 21]. Patiromer obtained FDA approval in the latter half of 2015 for the treatment of hyperkalemia in non-dialysis CKD patients in a non-acute setting. It comes as a powder (in 3 strengths of 8.4, 16.2 and 25.2 g) with a maximal recommended dose of 25.2 g daily. Concerning the risk of drug interaction, its intake should be spaced >6 h apart from other medications.

ZS-9, a sodium zirconium cyclocilate, is another novel K-lowering agent. It is a Na-K exchanger that traps K throughout the gastrointestinal tract. It has an onset of action in 2 h [23, 24]. HARMONIZE trial, hyperkalemic patients (n = 258) were placed on 10 g of ZS-9 (3× daily). Ninety percent of them achieved normokalemia with median time to normalization of 2.2 h [24]. In the randomized phase of the same study, 5, 10 and 15 g daily or placebo for a total of 28 days, K level was significantly lowered with all three dosages compared to placebo. Six percent of the patients on 10 g and 14% on 15 g developed peripheral edema. ZS-9 has not received FDA approval yet. Given the relative fast onset of its hypokalemic action, it has the potential to have a positive impact on the acute management of hyperkalemia.

Both patiromer and ZS-9 hold promise in controlling inter-dialytic hyperkalemia. In a recent proof-of-concept study, patiromer, used in six hemodialysis patients, was found to be effective in reducing inter-dialytic hyperkalemia [25]. For severe hyperkalemia, refractory to medication, dialysis remains the most effective therapy.

Hypokalemia

Although equally dangerous, hypokalemia is less common in CKD patients, as impaired renal K excretion usually leads to hyperkalemia. CKD patients can, however, still develop hypokalemia due to gastrointestinal K loss from diarrhea or vomiting or renal K loss from non-K-sparing diuretics. K deficiency augments the detrimental impact of Na excess (seen in patients on a regular Western diet). Converging evidence indicates a pathogenic role of combined high body Na and low K in the development of hypertension and hypertension-associated cardiovascular complications [26]. Moreover, K is capable of exerting vascular protective effects independent of its antihyper-

tensive effect [27]. Acutely, severe hypokalemia can cause paralysis, ileus, and cardiac arrhythmias. Management involves K repletion and close monitoring.

Hypokalemia can also occur in dialysis patients mainly due to the exposure to low K (≤ 2 K) dialysate. Post-dialysis hypokalemia has been associated with life-threatening cardiac arrhythmias and sudden cardiac deaths. The latter is the leading cause of death in the dialysis population, accounting for 25% of the all-cause mortality and 67% of all cardiac deaths [28, 29]. The susceptibility to hypokalemia-triggered cardiovascular events could be related to the underlying cardiovascular diseases, occurring in a majority of ESRD patients [28, 30].

Dialysis, especially with low K dialysate, predictably causes a large transmembrane K shift, which is thought to be a major contributor to the occurrence cardiac events. Low dialysate K and larger volume removal have been associated with higher rates of atrial fibrillation and higher rate of premature ventricular beats [31]. In a case-control study of dialysis patients (n = 43,000), exposure to dialysate K of <2 mEq/l doubled the risk of sudden cardiac arrest irrespective of pre-dialysis K level [32]. Similarly, in the Dialysis Outcomes and Practice Patterns Study (DOPPS) analysis of hemodialysis patients (n = 37,765) in 12 different countries, the use of low K dialysate (1 or 2–2.5 K) was independently associated with higher risk of sudden cardiac death and all-cause mortality compared to use of higher K (≥ 3 K mEq/l) dialysate [33]. Other contributory factors include a long (2-day) inter-dialytic interval [34, 35], rapid and large amounts of fluid removal, low dialysate calcium and Mg [33, 36]. Current recommendations are to use ≥ 3 K dialysate for patients with pre-dialysis serum K of <5 mmol/l [33]. In patients with pre-dialysis hyperkalemia (K >5.5 mEq/l), however, lower K dialysate continues to be used. The challenge lies in balancing the need to treat pre-dialysis hyperkalemia and avoid post-dialysis hypokalemia. Various strategies such as K profiling [37], longer and more frequent dialysis, and control of inter-dialytic hyperkalemia with patiromer/ZS-9 can all be explored as potential ways to minimize dialysis-related hypokalemia and its complications.

Metabolic Acidosis

Under physiological conditions, renal tubules reabsorb ~4,500 mmol of filtered bicarbonate daily. In addition, renal tubules generate ~80 mEq to neutralize the daily net acid generation in a normal-sized adult. The kidney is also endowed with a large capacity to unload excess

acid via ammonia (NH_3) genesis and (NH_4^+) excretion. With declining kidney function, the capacity of bicarbonate conservation and generation decreases, while the net endogenous acid production in CKD remains unchanged, leading to the genesis of acidosis [38]. A reduced number of functioning nephrons in CKD also compromises the kidney's capacity to excrete excess acid (in the form of NH_4^+ via ammonia genesis [38, 39]). Notably, each residual-functioning nephron, however, undergoes hypertrophy and compensatorily generates a large amount of NH_3 [40, 41]. Studies have shown an enhanced expression of $\text{NH}_3/\text{NH}_4^+$ transporters RHCG and RHDG on the apical and basolateral membranes of renal tubules [40]. The consequent increase in the intra-renal $\text{NH}_3/\text{NH}_4^+$ can activate the complement pathway leading to tubulo-interstitial inflammation and injury [42]. Excess acid also increases endothelin-1 and aldosterone production [43, 44], accelerating CKD progression [38, 45–47].

Clinically, metabolic acidosis is considered to be present when serum bicarbonate levels falls below the level 22 mmol/l. In a cross-sectional analysis of the baseline data in the Chronic Renal Insufficiency Cohort study of patients with CKD stages 2–4 ($n = 3,900$), prevalence of serum bicarbonate <22 mmol/l was 17.3% for overall, 7, 13 and 33% for CKD stages 2, 3 and 4, respectively [48].

In addition to promoting CKD progression, metabolic acidosis is known to cause protein catabolism, muscle wasting, bone demineralization, insulin resistance, impaired thyroid hormone and growth hormone secretion, exacerbation of β_2 microglobulin accumulation [49, 50] and increased mortality [46, 51]. A recent study of CKD patients ($n = 1,065$) with median glomerular filtration rate (GFR) of 37.6 ml/min/1.73 m² followed for 4.3 years, showed that lower urinary ammonia excretion (net positive acid balance) was associated with faster decline of GFR and CKD progression to ESRD (HR 1.82 with 95% CI 1.06–3.13) [38]. In the Multi-Ethnic Study of Atherosclerosis involving participants with estimated GFR (eGFR) (>60 ml/min/1.73 m²) lower bicarbonate <21 mmol/l compared to bicarbonate of 23–24 mmol/l, was associated with an accelerated renal function decline ($>5\%$ eGFR decline/year) [52]. Taken together, metabolic acidosis is associated with accelerated CKD progression and elevated all-cause mortality.

The beneficial effects of correcting acidosis have been noted in multiple studies [42, 53–55]. Phisitkul et al. [55] also demonstrated reductions in urine endothelin-1 and N-acetyl-beta-D-glucosaminidase (marker of tubulo-interstitial injury) excretion and slowing the CKD progression with oral alkali (Na citrate) in CKD patients. In a

single-blinded study of 20 CKD patients (eGFR 15–45 ml/min/1.73 m²) with serum bicarbonate of 20–24 mmol/l, oral NaHCO_3 improved lower extremity muscle strength [56]. The 2012 KDIGO guidelines recommended oral NaHCO_3 for CKD patients with $\text{NaHCO}_3 <22$ mmol/l [57]. Interestingly, Goraya et al. [58] showed a beneficial effect of oral NaHCO_3 or dietary alkali (fruits and vegetables) in preserving renal function in a cohort of stage 3 CKD patients with preserved NaHCO_3 level (22–24 mmol/l), suggesting a potential benefit in early dietary optimization.

The upper target of the serum bicarbonate for CKD patients has not been established. Different studies have used varying target serum bicarbonate levels. An appropriate upper target is important as studies have shown a U-shaped association between mortality and serum bicarbonate, with elevated serum bicarbonate (>26 mmol/l) being associated with increased mortality risk [51, 59]. There are several ongoing randomized clinical trials evaluating the effect of NaHCO_3 on renal function, rate of CKD, mortality, bone turnover markers, muscle strength and quality of life [60–62]. The results from these trials will clarify the effects of oral bicarbonate as well as an appropriate upper serum bicarbonate target.

Most clinical data associated with acidosis are generated from CKD patients and not specifically from dialysis patients. Given the known pathobiology of acidosis, we expect a similar negative impact on morbidity and mortality in dialysis patients. A unique aspect of patients on hemodialysis is the exposure to a large fluctuation of the acid–base status with each dialysis episode, from varying degrees of pre-dialysis acidosis to alkalosis rapidly corrected by the dialysis. The large pH swing in a short period of 3–4 h could lead to a multitude of adverse effects. The acute rise of blood pH (from 37 mmol/l bicarbonate in dialysate) can cause hypoventilation due to the depression of central respiratory center, acute reduction in tissue O_2 delivery due to vasoconstriction and left shifting of the hemoglobin- O_2 dissociation curve, and acute reduction in ionized calcium leading to diaphragmatic muscle weakness. Moreover, bicarbonate binding of endogenous acid can cause rapid CO_2 accumulation and paradoxical intracellular acidosis, resulting in multiple cellular function defects. In the DOPPS study of in-center hemodialysis patients ($n = 17,031$), the use of higher bicarbonate dialysate was associated with higher mortality with a calculated HR of 1.08/4 mEq/l higher dialysate bicarbonate (95% CI 1.01–1.15) [63]. Taken together, the pre-dialysis acidosis and rapid correction of acidosis to the range of alkalosis by dialysis can negatively impact

patient outcome. Bicarbonate profiling during hemodialysis or graded bicarbonate dialysate might minimize the large acid–base swing. Further studies are needed to explore these potential strategies.

Derangements of Bone Mineral Metabolism

Bone mineral metabolism and calcium-phosphorus homeostasis involve a complex interplay among kidneys, gut, bone and parathyroid glands. The metabolism involves parathyroid hormone (PTH), vitamin D and vitamin D receptors, fibroblast growth factor-23 (FGF23), Klotho and calcium-sensing receptors. As regulated excretion of calcium and phosphate is carried out primarily by the kidney, kidney failure inevitably causes abnormalities in bone turnover and, in most cases, soft tissue and vascular calcification, leading to increased mortality. This triad of laboratory abnormalities, bone disorder and soft tissue calcification is collectively termed MBD [64].

Serum phosphorus may remain normal in most CKD patients with eGFR >40 ml/min/1.73 m² due to the upregulation of PTH and FGF23 and attendant inhibition of proximal tubular phosphate reabsorption [65, 66]. As CKD progresses, renal phosphate excretory capacity becomes exhausted, and hyperphosphatemia ensues [65–67].

Hyperphosphatemia, through PTH, causes an increased bone turnover and contributes to the development of osteitis fibrosa cystica and osteomalacia. More importantly, hyperphosphatemia promotes osteo-chondrogenic transformation and apoptosis of vascular smooth muscle cells and vessel wall collagen matrix accumulation and mineralization [68–70]. Large cohort studies have consistently shown that hyperphosphatemia is associated with vascular calcification [71], CKD progression [72] and increased risk of cardiovascular events and mortality [73–75]. In a 2015 meta-analysis of 12 cohort studies of non-dialysis CKD patients (n = 25,500), an independent association of hyperphosphatemia and risk of CKD progression and mortality was observed [76]. Collectively, the association of serum phosphorus with cardiovascular events and mortality begins at a high normal range of phosphorus [77–79] and occurs in patients at all stages of CKD [80, 81], as well as in critically ill patients with dialysis-requiring acute kidney injury [75]. Causal relationship between hyperphosphatemia and CKD progression and mortality, however, remains to be established.

Secondary hyperparathyroidism develops in CKD and ESRD patients due to hyperphosphatemia, hypocalcemia, 1,25(OH)₂ vitamin D deficiency, skeletal resistance to vitamin D, and reduced expression of calcium sensing receptors [82]. In addition to decreasing proximal tubular phosphorus reabsorption and increasing distal calcium reabsorption, PTH increases the renal expression of 1 α -hydroxylase and suppresses inactivating enzyme 24 α -hydroxylase, leading to a net increase in the formation of 1,25(OH)₂ vitamin D [83–85]. PTH increases bone turnover via the activation of both osteoclast and osteoblasts, and the effects are mediated through RANK ligand and the decoy protein osteoprotegerin [82]. Bone disorder in CKD-MBD varies widely from a high bone turnover state (osteitis fibrosa cystica) due to excessive PTH elevation to a low turnover, adynamic state, due often to PTH over-suppression. The combined elevations of PTH, calcium and phosphorus in a uremic milieu create a pre-condition for the development of a highly fatal calcific uremic arteriopathy (calciphylaxis) [86].

1,25(OH)₂ vitamin D increases the intestinal absorption of calcium and phosphorus and promotes bone mineralization. In addition, vitamin D has multiple pleiotropic effects including regulating cell growth, differentiation and immunity, anti-inflammatory response, neuron health, insulin secretion and lipid metabolism [87, 88]. Vitamin D deficiency in patients with and without CKD is associated with increased mortality [89, 90]. Vitamin D deficiency has also been associated with cardiovascular disease, decreased muscle strength, and decreased cognitive function. CKD patients are more prone to develop vitamin D deficiency [91]. In the NHANES III cohort (n = 15,828), CKD was associated with 32% more vitamin D deficiency than in non-CKD patients [92].

FGF23, secreted by osteocytes in response to hyperphosphatemia, is a key phosphaturic and a vitamin D counter-regulatory hormone. It binds to FGF receptor-Klotho complex and decreases proximal tubular phosphate reabsorption by down-regulating Na-phosphate co-transporters (Na-Pi 2a and 2c) [93]. FGF23 also inhibits renal 1 α -hydroxylase, and stimulates inactivating enzyme 24 α -hydroxylase resulting in decreased 1,25(OH)₂ vitamin D and 25(OH) vitamin D respectively [94]. In the parathyroid gland, FGF23 binds to the FGF receptor-Klotho complex and inhibits PTH expression and secretion [95]. These effects, however, dissipate in CKD and ESRD due to a decreased expression of FGF receptor-Klotho complex [96]. FGF23 elevation is one of the earli-

est markers of BMD in CKD, much before the elevations PTH and phosphate [97] and an independent risk factor for left ventricular hypertrophy [98, 99], cardiovascular events, CKD progression [100] and mortality [101]. In a nested case-control study of dialysis patients (n = 400), a strong association between FGF23 elevation and mortality was also observed [80].

The management of CKD-MBD is complex and consists of efforts to maintain serum phosphate and calcium levels within or near the normal range, supplement vitamin D or active vitamin D when appropriate, and treat secondary hyperparathyroidism. The management of hyperphosphatemia requires reduction in dietary phosphate (<1,000 mg/day) and the use of phosphate binders, which can be broadly classified into calcium-based and non-calcium-based binders. Multiple studies have shown benefits of using non-calcium-based phosphate binders (sevelamer, lanthanum, ferric citrate and sucroferric oxyhydroxide) over calcium-based binders (calcium acetate, calcium carbonate and calcium citrate) in terms of lower mortality [102–104]. A recent meta-analysis of 28 randomized controlled trials involving CKD-MBD patients (n = 8,335) demonstrated a higher all-cause mortality with calcium-based than with non-calcium-based binders, RR of 1.76 (95% CI 1.21–2.56) [103]. Other phosphate binders that have been explored are a combination of calcium acetate and magnesium carbonate (CaMg). CALMAG randomized controlled trial using CaMg versus sevelamer-HCl in a population of dialysis patients has demonstrated the effectiveness of CaMg complex in lowering serum phosphorus [105]. In rodent CKD models, CaMg reduced arterial calcification, comparable to the effects of sevelamer-HCL, without over-suppression of bone turnover or skeletal Mg accumulation [106–108]. CaMg could potentially be an effective alternative to treat hyperphosphatemia. Further studies, however, are necessary.

KDIGO 2009 CKD-MBD guidelines recommend avoiding an absolute PTH value-based target for non-dialysis CKD patients but to monitor the PTH trend and initiate therapy in the setting of prominent PTH rise. For dialysis patients, a target PTH range of 2–9 times the upper limit of normal is recommended [109]. Cholecalciferol and ergocalciferol can be used to treat suboptimal vitamin D status; they may not suppress PTH secretion [110]. 1,25(OH)₂ vitamin D and synthetic analogue such as paricalcitol have been used to treat secondary hyperparathyroidism. Cinacalcet, a calcimimetic agent, has been approved by the FDA to treat secondary hyperparathyroidism in dialysis patients. A recent observational

study has shown beneficial effects of cinacalcet in lowering PTH, calcium and phosphate in non-dialysis CKD patients [111]. For patients with tertiary hyperparathyroidism (autonomous PTH production), therapeutic options are limited to cinacalcet or subtotal parathyroidectomy [112]. Recent findings regarding the role of Wnt/beta catenin pathway inhibition in the development of CKD-MBD [113, 114] is exciting, offering another potential for future therapeutic targeting.

Other Electrolyte Derangements

Dysnatremia and dysmagnesemia are the other 2 major electrolyte alterations seen in CKD and ESRD. Etiology, clinical features and management strategies for the 2 derangements are largely similar to those in the general population. Below, we focus on the unique aspects relevant to CKD and ESRD patients.

Dysnatremia

Dysnatremia usually indicates a condition where body water becomes excess or deficient. Hyponatremia (Na <135 mmol/l) is the most common electrolyte disorder in community and in hospital patients, ranging from 5 to up to >30% [115–120]. Hypernatremia (Na >145 mmol/l) is much less common, occurring in ~1–4% of hospital patients [117, 121], except for neuro-intensive care unit patients [122]. CKD patients follow a similar pattern of dysnatremia distribution. In a large cohort of 655,000 veterans with a mean eGFR of 50 ml/min/1.73 m², hyponatremia was seen in 13.5%, and hypernatremia in 2% [123]. During a median follow-up of 5.5 years, 26 and 7% of patients developed at least one episode of hypo- or hypernatremia, respectively. A recent meta-analysis of 15 studies has shown a mortality benefit with improving hyponatremia [124].

In addition to the causes of hyponatremia seen in the general population, CKD patients are at additional risk of hyponatremia due to compromised capacity to dilute or concentrate urine. Furthermore, polypharmacy and limited nutritional solute intake [125] are common and can contribute to the Na derangements. In dialysis patients, hyponatremia is mostly dilutional, due to excess water or hypotonic fluid intake. Hypernatremia, when sustained, is mainly seen in those with impaired thirst mechanism and/or lack of access to water, similar to that in the general population [126]. Dysnatremia in CKD and ESRD has mortality significance. A U-shaped association between serum Na and mortal-

ity was found in both non-dialysis CKD [123, 127] and dialysis patients [128, 129]. The management of dysnatremia in CKD patients is similar to that for the general patients and should start with identifying and, if possible, correcting the underlying cause. For dialysis patients, extra sessions of dialysis may be considered. Rapid correction for chronic dysnatremia should be avoided.

Dysmagnesemia

Although etiology and manifestations of dysmagnesemia have been studied mostly in the general population, both hypo- and hypermagnesemia are common in hospitalized patients with reduced eGFR [130]. Sustained hypermagnesemia is seen mostly in patients with advanced CKD and ESRD. Mg-containing medications may contribute to or exacerbate hypermagnesemia in the setting of kidney dysfunction. In dialysis patients, serum Mg is often affected by dialysate Mg content. Sakaguchi et al. [131] investigated a large cohort of dialysis patients (n = 142,000) and found hypomagnesemia, due to lower Mg dialysate, to be a significant predictor of cardiovascular and non-cardiovascular mortality. Similar results are shown in patients on peritoneal dialysis [132]. Taken together, dysmagnesemia exerts morbidity and mortality significance in CKD and ESRD patients; care should be taken to correct Mg derangements.

Conclusion

A variety of electrolyte and acid–base derangements predictably occur with progressive loss of kidney function. Most of the derangements are intricately linked to morbidity and mortality. Prominently, hyperkalemia is linked to acute cardiac death in CKD and ESRD patients. Newer and more effective agents, patiromer and ZS-9, have the potential to mitigate hyperkalemia and improve patient outcomes, especially in those who benefit from RAAS inhibition. Likewise, acidosis in renal failure patients should be carefully followed and corrected. Newer randomized controlled trials will further clarify our management strategy. MBD in CKD and ESRD remains a morbid condition. Existing data suggest that non-calcium-containing phosphorus binders are associated with better cardiovascular outcomes. Newer pathogenic signaling pathways continue to be uncovered, and novel treatment targets will likely emerge in the near future. Na and Mg derangements are reviewed in brief, given the space limitation. Both condi-

tions, however, can be life threatening and should be carefully diagnosed and treated. Taken together, electrolyte and acid–base alterations form a major part of the pathological disease processes in patients with renal failure. Appropriate diagnosis and management should be an integral part of CKD/ESRD care to improve patient outcomes.

Key Messages

- Electrolyte and acid–base derangements in CKD and ESRD are common and are associated with increased morbidity and mortality.
- Patiromer, a calcium-K exchange polymer, is a newer K-lowering oral agent with the onset of action at 7 h. FDA has approved its use for non-dialysis CKD patients.
- ZS-9, a Na-K exchanger, is a novel K-lowering oral agent with a faster onset of action in 2 h. It is not yet approved by the FDA.
- Large fluctuation of serum K levels during and shortly following hemodialysis has been associated with mortality, cardiac arrhythmia, and sudden cardiac death. The current recommendation is to avoid the use of low K dialysate (≤ 2 K dialysate) for patients with predialysis K < 5 mmol/l.
- Metabolic acidosis ($\text{NaHCO}_3 < 22$ mmol/l) in CKD and ESRD should be corrected. Oral NaHCO_3 can be used with a goal to increase NaHCO_3 to ~ 25 mmol/l.
- For patients who develop hyperkalemia on ACE inhibitor and ARB, newer K-lowering agents and correction of acidosis, in conjunction with the existing modalities would be beneficial. It can be lifesaving if ACE inhibitors and ARBs are given continuously for most of the CKD and ESRD patients.
- Serum phosphorus elevation, even in the high-normal range, has been associated with cardiovascular complications and mortality.
- Non-calcium-based phosphate binders may be associated with a decreased risk of all-cause mortality compared with calcium-based phosphate binders.
- Vitamin D insufficiency and deficiency should be corrected in patients with CKD and ESRD.
- The serum PTH level for non-dialysis CKD patients is a matter of controversy. For ESRD dialysis patients, serum PTH should be within 2–9 times the upper limit of the normal value.

- Serum Mg concentration can be affected by the dialysate Mg content. Adjusting the dialysate Mg content may, thus, be necessary when appropriate.
- Hypermagnesemia in CKD patients likely results from a combination of kidney dysfunction and intake of Mg-containing medications. Careful evaluation of the patient's medications, both over-the-counter and prescribed agents, is necessary.

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