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Acid-Base and Electrolyte Disorders in Patients with and without Chronic Kidney Disease: An Update

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Abstract
Kidneys play a pivotal role in the maintenance and regulation of acid-base and electrolyte homeostasis, which is the prerequisite for numerous metabolic processes and organ functions in the human body. Chronic kidney diseases compromise the regulatory functions, resulting in alterations in electrolyte and acid-base balance that can be life-threatening. In this review, we discuss the renal regulations of electrolyte and acid-base balance and several common disorders including metabolic acidosis, alkalosis, dysnatremia, dyskalemia, and dysmagnesemia. Common disorders in chronic kidney disease are also discussed. The most recent and relevant advances on pathophysiology, clinical characteristics, diagnosis, and management of these conditions have been incorporated.

Introduction

Acid-base and electrolyte homeostasis is vital for proper functioning of numerous metabolic processes and organ functions in the human body. Kidneys play a critical role in the maintenance and regulation of this homeostasis. Kidney diseases and dysfunction (chronic kidney disease, CKD) compromise the regulatory functions, resulting in alterations in electrolyte and acid-base balances that can be life-threatening. We discuss the renal regulation of electrolyte and acid-base balance and several common disorders incorporating the most relevant advances in the field and with a focus on pathophysiology, clinical features, diagnosis and management in patients with and without CKD.

Acid-Base Balance and Disorders

On a typical western diet, an adult generates approximately 0.8–1 mEq/kg body weight of nonvolatile acid [1] and 15,000 mEq of CO_2 (volatile acid) daily. Depending on the pCO_2, a small fraction of CO_2 is dissolved in body fluids as carbonic acid (H_2CO_3), a weak acid, while a large amount of CO_2 is eliminated through respiration. Non-

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volatile acids are buffered in the body to prevent acute systemic pH perturbations. HCO_3^-/H_2CO_3 is the major buffer system which neutralizes nonvolatile acids at the cost of HCO_3^-. Additionally, circulating phosphate, plasma and intracellular proteins, and bone all contribute to the buffering process. Kidneys are responsible for reclamation of all HCO_3^- filtered through glomeruli and generation of new HCO_3^- to replenish and re-balance the acid-base system. Kidneys also regulate phosphate balance and contribute to bone health through multiple mechanisms.

Renal Regulation of Acid-Base Balance

Under physiological conditions, renal net acid excretion (RNAE) is equal to net endogenous acid production. Such a balance is achieved via (1) reclamation of filtered HCO_3^- (approximately 4,500 mEq daily), and (2) urinary buffering, which includes (a) tubular regulation of titratable acids (TAs) and (b) generation and excretion of ammonia/ammonium (NH_3/NH_4^+). Approximately 80% of the filtered bicarbonate is reclaimed back into the circulation by the proximal tubule. The thick ascending limb of Henle (TALH) and distal convoluted tubule (DCT) reclaim an additional 16%, while the remaining 4% is reclaimed by the collecting ducts.

In the collecting ducts, intercalated cells are responsible for proton (H^+) and bicarbonate transport. Acid-secreting (type A) α-intercalated cells contain vacuolar H^+-ATPase, located in the apical membrane. Bicarbonate exits the cells across the basolateral membrane via Cl^--HCO_3^- antiporter (AE-1). Base-secreting (type B) β-intercalated cells are less abundant and have vacuolar H^+-ATPase distributed in the basolateral membrane and a Cl^--HCO_3^- antiporter (pendrin) in the apical membrane. Additional non-A, non-B interacted cells express both pendrin and H^+-ATPase in the apical membrane [2–4]. There is compelling evidence for the existence of phenotypic plasticity amongst intercalated cells [5]. Moreover, β- and non-A, non-B intercalated cells are capable of transporting NaCl through pendrin and Na-dependent Cl^--HCO_3^- exchanger, a NaCl absorptive pathway implicated in the genesis of salt-sensitive hypertension [4, 6–8].

HPO_4^{2-} is the major urinary TA. HPO_4^{2-} is capable of incorporating H^+, forming $H_2PO_4^-$ containing salt and excreted in the urine. For every H^+ incorporated and excreted, a HCO_3^- is gained. Other minor buffers are citrate, creatinine, and uric acid. TA excretion is responsible for approximately one-third of RNAE and is a low-capacity system, limited by dietary phosphate intake and the amount of filtered phosphate (HPO_4^{2-}). Parathyroid hormone and fibroblast growth factor 23 decrease renal proximal tubular phosphate reabsorption and thus can increase H^+ excretion. Approximately two-thirds of RNAE take place via renal generation and excretion of NH_4^+. Renal ammoniagenesis and excretion is a high-capacity system; it can increase many fold in response to increased acid-load, from a baseline of ~30–40 to >250 mEq/day [9]. Ammoniagenesis occurs primarily in the proximal tubules, predominantly from glutamine metabolism. For each glutamine metabolized, 2 NH_4^+ and 2 HCO_3^- are generated. NH_4^+ is secreted into the lumen of the proximal tubule by Na^+/H^+ exchanger (NHE3), during which NH_4^+ substitutes for cytosolic H^+. By substituting for K^+ of Na^+-K^+-$2Cl^-$ cotransporter, NH_4^+ is reabsorbed in the TALH and into the medullary interstitium. There, NH_4^+ equilibrates with NH_3 (deprotonated from NH_4^+, pKa ~9.15). NH_4^+/NH_3 undergoes medullary recycling. In the DCT and connecting tubule, Rhesus glycoproteins, RHBG and RHCG, are involved in NH_4^+/NH_3 transport. In the inner medullary collecting duct, NH_4^+/NH_3 is excreted into the lumen through both diffusion and transporter-mediated mechanisms. The latter involves substituting NH_4^+ for H^+ of H^+-ATPase and for K^+ of Na^+/K^+-ATPase [10–14]. For every NH_4^+ excreted in the urine, equimolar HCO_3^- is gained. Acidemia and hypokalemia promote ammoniagenesis, while alkalemia and hyperkalemia cause an opposite effect.

Assessment of Urinary NH_4^+ Excretion

Because direct assay for urine NH_4^+ is not widely available, urinary NH_4^+ excretion is often estimated by calculating urine anion gap (UAG).

$$UAG = [Urine\ Na^+] + [Urine\ K^+] - [Urine\ Cl^-]$$

When in balance, the sum of urinary Na^+ and K^+ exceeds urinary Cl^-, resulting in a positive UAG. In the setting of metabolic acidosis, the kidneys respond with increasing urine NH_4^+ excretion. NH_4^+ is coupled predominantly to Cl^-, resulting in an increased urine Cl^- excretion (exceeding the sum of Na^+ and K^+) and a negative UAG. The UAG assumes that the major cations in the urine are Na^+, K^+, and NH_4^+, and the major anion is Cl^- (if urine pH is <6.5, no urinary HCO_3^- should be present). If other unmeasured anions (i.e., β-hydroxybutyrate or lactate) are present, the UAG equation would not accurately estimate urinary NH_4^+.

Metabolic Acidosis and Serum Anion Gap

Metabolic acidosis can be broadly classified into (1) elevated anion gap (AG) acidosis and (2) normal AG acidosis. Symptoms of metabolic acidosis are summarized in

Table 1. Elevated AG acidosis

Causes of acidosis	Clinical scenario and features	Other lab features	Management
Glycols			
(1) Ethylene glycol	Antifreeze poisoning Flank pain, hematuria Renal failure, death	Serum OG >10 Urine CaOx (monohydrate and dihydrate) crystals, AKI	– Fomepizole/ethanol – Dialysis
(2) Propylene glycol	Prolonged IV infusion of benzodiazepines, phenobarbital	Serum OG >10 Increased lactate	– Stop offending agents – Dialysis
5-Oxoproline/ pyroglutamate	Chronic acetaminophen use in malnourished females, glutathione depletion	Urine and serum 5-Oxoproline↑	– Stop acetaminophen – Bicarbonate – N-acetyl cysteine
L-Lactic acidosis	Type A: septic shock, heart failure, hypovolemic shock Type B: cancer, severe inflammation, medications such as metformin, linezolid	Lactate↑	– Treat underlying cause – IV bicarbonate if pH <7.1
D-Lactic acidosis	Short gut syndrome, gut bacterial overgrowth, propylene glycol poisoning	D-Lactate↑	– Avoid large carbohydrate meals – Bicarbonate – Oral antibiotics
Methanol	Adulterated alcohol (moonshine) Accidental poisoning Headache, visual loss Coma, death	Serum OG >10	– Fomepizole/ethanol – Dialysis
Aspirin	Intentional /unintentional overdose	Salicylate level↑ Mixed AG acidosis and respiratory alkalosis	– Urine alkalinization – Dialysis
Renal failure	Advanced stages of renal failure, uremia	BUN↑, Cr↑	– $NaHCO_3$ – Dialysis
Ketoacidosis	Diabetic Starvation	↑ serum β-hydroxybutyrate, acetoacetate, glucose + urine ketones	– Insulin – IV fluids – Nutrition

Serum osmolar gap (OG): Serum OG >10 is considered to be elevated. Serum OG = calculated serum osmolality – measured serum osmolality. Calculated serum osmolality = $2 \times [Na^+] + [glucose]/18 + [BUN]/2.8$. Isopropyl alcohol causes increased OG but does not cause high AG metabolic acidosis as it is metabolized to acetone.

Table 1 (left column). AG calculation helps to determine the presence or absence of unmeasured anions.

The ionic environment of the blood is neutral with the sum of cations always equal to the sum of anions. In practice, however, only several ions (Na^+, K^+, Cl^-, and HCO_3^-) are routinely measured. The cations (Na^+ and K^+) exceed the total anions (Cl^- and HCO_3^-) resulting in an artificial AG. Serum albumin is the major contributor to the gap. AG is calculated by the formula: $AG = [Na^+] - ([Cl^-] + [HCO_3^-])$ (note: serum K^+ concentration is typically omitted from the calculation).

In healthy adults, AG ranges from 8 to 12 mEq/L. AG should be corrected for alterations of serum albumin. For every 1 g/dL drop in serum albumin, expected AG should accordingly drop by 2.5 mEq/L (i.e., if albumin drops from 4.5 to 3.5 g/dL, expected AG should drop to 7.5 from 10 mEq/L). Other factors that may lower AG are the presence of cationic monoclonal gammopathy, polyclonal gammopathy, hypercalcemia, lithium and bromide, or iodide intoxication. Factors that could raise calculated AG, mostly by a small degree (<3 mEq/L), include hemoconcentration, metabolic alkalosis, severe hyperphosphatemia and elevated anionic paraproteins.

Table 2. Renal tubular acidosis

	Type 1: distal tubular acidosis	Type II: proximal tubular acidosis	Type IV: hyporeninemic hypoaldosteronism
Defects	↓ H^+ excretion in distal tubule	↓ HCO_3^- reabsorption in proximal tubule	↓ renin and ↓ aldosterone
Etiology and clinical setting	*Acquired:* Chronic autoimmune connective tissue diseases (i.e., Sjögren, lupus, rheumatoid arthritis)	*Acquired:* Dysproteinemia (MM), interstitial renal diseases (less frequently), lead or mercury toxicity	*Acquired:* Mild-to-moderate CKD (not severe enough to explain the hyperkalemia and acidosis, often in diabetic patients) Adrenal insufficiency due to autoimmune or infectious etiology Bilateral urinary tract obstruction (voltage-dependent distal RTA)
	Drugs: – Amphotericin – Lithium	*Drugs:* – CA inhibitors (topiramate, acetazolamide) – Ifosfamide – Antiretroviral (tenofovir) – Valproic acid – Expired tetracycline	*Drugs:* – ACE inhibitors – Renin inhibitors – ARBs – Aldosterone antagonists – K^+-sparing diuretics – Calcineurin inhibitors – NSAIDs – Heparin infusion
	Hereditary: Loss-of-function mutations of *SLC4A1*, encoding the AE1 anion exchanger or *ATP6V1B1ATP* and *6V0A4*, encoding the β_1- and α_4-subunits of the H^+ATPase	*Hereditary:* – Loss-of-function mutations of *NBCe1* encoding $Na^+/3HCO_3^-$ cotransporter – Glycogen storage disease – Mitochondrial diseases – Cystinosis – Wilson disease	*Hereditary:* PHA1 (inactivating mutations of the *ENaC* and *NR3C2*) PHAII, aka Gordon Syndrome (pathogenic mutations in *WNK1, WNK4, CUL3*, or *KLHL3*)
Acidemia Serum K	Severe if untreated ↓	Self-limiting (HCO_3^- at ~14–18 mEq/L) ↓	Mild ↑
Urine pH Urine NH_4^+ excretion UAG Urine citrate	↑ (>5.3) ↓ Positive ↓	Variable, ↓ (when HCO_3 <Tm) Lack of ↑ in acidosis Variable Normal or ↑	Variable ↓ Positive Normal
Urinary loss of nutrients (glucose, amino acids, and phosphate)	No	Yes	No
Nephrocalcinosis $CaPO_4$ stones Osteomalacia	Yes Yes Yes	No No Yes	No No No
FE-HCO_3	<5%	Can be ↑ with alkali intake	Variable
Treatment	Alkali $NaHCO_3$ or citrate (approximately 1–2 mEq/kg/day)	Treat underlying causes Alkali (ineffective, not routinely used)	Treat underlying causes if possible Thiazide and/or loop diuretics (except for using salt supplementation for PHA1) Alkali (small requirement)

CKD, chronic kidney disease; DM, diabetes mellitus; FE, fractional excretion; H^+, hydrogen ion; HCO_3, bicarbonate; MM, multiple myeloma; Tm, tubular transport maximum; Ca^{2+} PO_4^-, calcium phosphate; NH_4^+, ammonium; AE1, anion exchanger 1 (Cl^--HCO_3^- exchanger); PHA, pseudohypoaldosteronism.

Elevated AG Acidosis

Elevated AG acidosis occurs when there is an overproduction and/or under-excretion of nonvolatile acids or the presence of exogenous organic anions. Major etiology, key clinical and lab features and management principles are summarized in Table 1.

Normal AG Acidosis

Normal AG acidosis develops when there is (1) excessive loss of renal or gastrointestinal HCO_3^- (or HCO_3^- equivalent) or (2) decrease in renal acid excretion, or (3) large volume (>2 L) high-Cl^- fluid infusion. Common causes of gastrointestinal HCO_3^- loss include diarrhea,

Table 3. Symptoms of metabolic acidosis and alkalosis

Symptoms of metabolic acidosis	Symptoms of metabolic alkalosis
Central nervous system	*Central nervous system*
(1) Headache	(1) Confusion
(2) Sleepiness	(2) Light-headedness
(3) Confusion	(3) Stupor
(4) Loss of consciousness	(4) Coma
(5) Coma	*Peripheral nervous system*
Respiratory	(1) Hand tremor
(1) Shortness of breath	(2) Numbness and tingling in the face and extremities
(2) Dry cough	*Cardiovascular*
Cardiovascular	(1) Arrhythmias (especially when associated with low K^+ or low Ca^{2+})
(1) Tachycardia	(2) Decreased contractility
(2) Arrhythmia	*Musculoskeletal system*
(3) Hypotension	(1) Muscle spasm
Musculoskeletal	(2) Twitching
(1) Weakness	*Gastrointestinal*
(2) Spasms/seizure	(1) Nausea and vomiting
Gastrointestinal	
(1) Nausea and vomiting	
(2) Diarrhea	

pancreatic or intestinal fistula, and ureteroileostomy, while renal loss of HCO_3^- or defect in H^+ excretion occurs in renal tubular acidosis (RTA). Type IV RTA is the most common form of RTA. Table 2 summarizes the characteristics of RTAs and their management. Another distinct entity, linked to the distal RTA, is incomplete distal RTA. Affected individuals develop hypocitraturia, nephrocalcinosis, and nephrolithiasis (calcium phosphate stones typically), but show a normal baseline acid-base status. They are typically unable to acidify urine in response to acid loading (typically oral NH_4Cl). The underlying mechanism of this entity is unclear. Incomplete RTA is relatively common in patients with Sjögren syndrome, up to 25% in one study [15]. It is treated with potassium citrate.

Acidosis in CKD

The prevalence of metabolic acidosis increases with progression of CKD. In a cross-sectional analysis of the baseline data from the Chronic Renal Insufficiency Cohort (CRIC) study involving 3,900 patients in CKD stages 2–4, the prevalence of metabolic acidosis (serum $HCO3^-$ <22 mEq/L) was 7% for CKD stage 2, 13% for CKD stage 3 and 33% for CKD 4 with an overall acidosis occurrence of 17.3% [16]. Normal AG acidosis is predominant in early stages of CKD; AG acidosis occurs in late stages (GFR <30 mL/min/1.73 m^2) due to retention of anions such as sulfate, phosphate, and urate. It should be noted that net endogenous acid production is relatively unchanged in CKD [17]. Intrarenal ammonia and acid retention, consequences of acidosis, can cause complement activation and chronic tubule-interstitial inflammation [18] and increased generation of endothelin-1, angiotensin II and aldosterone production [19], potentially promoting CKD progression. Indeed, metabolic acidosis in CKD is associated with more rapid progression of CKD [17] and increased mortality [20]. In addition to the symptoms summarized in Table 3 (left column), acidosis in CKD is associated with the development of sarcopenia, bone demineralization, impaired function of growth hormone and insulin, and growth retardation in children.

Correcting metabolic acidosis with alkali administration [21–23] or dietary intake of alkali precursors [21, 24] slows CKD progression and improves nutritional status. KDIGO 2012 guidelines recommend correction of metabolic acidosis [25]. Oral $NaHCO_3$ is a commonly used alkali and may be initiated at a dosage of 650 mg (7.7 mEq of bicarbonate) 2–3 times daily. Dosage should be adjusted to keep serum HCO_3^- in the range of 22–26 mEq/L. The treatment is well tolerated and has not been shown to cause or worsen fluid retention and hypertension [26]. The most common adverse effects are bloating and abdominal fullness. Sodium citrate is an alternative agent but should be avoided in patients on aluminum-based phosphate binders due to the risk of aluminum intoxication.

Metabolic Alkalosis

Metabolic alkalosis can result from a net loss of acid or a net gain of bicarbonate (generation phase). The alkalosis is then perpetuated by hypokalemia, chloride depletion, hypovolemia or excessive mineralocorticoid stimulation. These conditions prevent the kidney from unloading the accumulated HCO_3^- (maintenance phase). Clinical manifestations are summarized in Table 3 (right panel). The major causes, pathophysiology, diagnostic features, and therapy in the general population are summarized in Table 4.

Although less common than metabolic acidosis, metabolic alkalosis can occur in patients with CKD. CKD patients are commonly on diuretics as well as calcium carbonate or citrate which can cause hypokalemia and alkalosis. Diagnosis is based on elevations of serum HCO_3^- and pH (>7.45). Measurement of urine Cl^- may not be helpful as renal Cl^- regulation is likely impaired in CKD.

Table 4. Metabolic alkalosis

Causes	Pathophysiology	Diagnostic features	Treatment
Vomiting and gastric suction	Loss of gastric acid	↓urine Cl (<10 mEq/L)	Saline administration
Thiazide or loop diuretics	↑urine loss of Cl^-	Hypovolemia or euvolemia, ↑urine Cl	Discontinue offending agents
Hypokalemia	↑urine NH_4^+ excretion ↑renal Rhbg expression	Refractory alkalosis until serum K^+ is restored	KCl
$NaHCO_3$ administration	Exceeding the capacity of renal HCO_3^- excretion	Euvolemia or hypervolemia	Discontinue $NaHCO_3$
Chloride diarrhea (chloridorrhea)	GI loss of HCO_3^- poor fluid	Hypovolemia	Treat diarrhea Saline administration
Primary hyperaldosteronism	↑renal H^+ excretion	Hypervolemia (urine Cl >20 mmol/L)	Correcting hyperaldosteronism

Electrolyte Disorders

Electrolyte disorders are common in CKD. Hyperkalemia is among the most common electrolyte disorders. Dysnatremia occurs more often in CKD due to compromised renal water regulation. The prevalence of dysmagnesemia in the CKD population is unclear but is likely underdiagnosed.

Potassium Regulation and Dyskalemia

Potassium (K^+) is the most abundant intracellular cation, with >98% of total body K^+ (3,500 mEq) being intracellular and <2% (70 mEq) extracellular. The steep intracellular and extracellular K^+ gradient is the major determinant of the plasma membrane potential. K^+ also participates in the regulation of cell volume, pH and multiple cellular functions. In excitable tissues, such as heart, nerves, and skeletal muscle, K^+ is critical for the dynamic action potentials and electrical excitability. In a steady state, kidneys excrete approximately 95% of dietary K^+, and the remainder is excreted through the gastrointestinal system.

Renal Potassium Regulation

Potassium is freely filtered through glomeruli. The proximal tubules reabsorb approximately 65% of the filtered K^+, while the TALH reabsorbs approximately 25%. Distal nephron (the DCT and collecting duct) is the major site of renal K^+ regulation. Depending on physiological needs, distal nephron can excrete or absorb K^+. Combined presence and synchronizing activities of apical Na^+-Cl^- cotransporter, renal outer medullary K^+ (ROMK) channel, epithelial sodium channel (ENaC), and BK channels, powered by the basolateral Na^+/K^+-ATPase and regulated by aldosterone, allow distal nephron to extrude K^+ efficiently. When appropriate, K^+ absorption occurs in the medullary collecting duct, where H^+-K^+-ATPase in the apical membrane of the α-intercalated cells pumps K^+ into the cells in exchange for H^+.

On a typical Western diet, K^+ intake is higher (~90–120 mEq/day) than the total extracellular K^+ (70 mEq). By and large, distal nephron excretes K^+ to achieve balance. Key factors that determine the distal nephron K^+ secretion are (1) serum K^+ concentration, (2) distal tubular Na^+ delivery, (3) tubular fluid flow, and (4) serum aldosterone level. Aldosterone binds intracellular mineralocorticoid receptor, stimulates glucocorticoid-inducible kinase 1 (GSK1) activity, leading to inhibition of ubiquitin-protein ligase Nedd4-2, reducing Nedd4-2-mediated ENaC degradation, thus promoting ENaC-mediated Na^+ absorption. The enhanced Na^+ absorption generates a favorable electrochemical gradient for K^+ secretion, primarily via the apical membrane ROMK channels. Aldosterone also increases the basolateral Na^+/K^+-ATPase activity and promotes apical membrane expression and activity of thiazide-sensitive Na^+-Cl^- cotransporters. In addition, serine protease tissue kallikrein, produced in the connecting duct, can augment kaliuresis by enhancing ENaC activity and suppressing K^+ absorption via H^+-K^+-ATPase. Acid-base perturbations also affect renal K^+ excretion, primarily through influencing the activity of H^+-K^+-ATPase. Acidosis reduces and alkalosis enhances K^+ secretion. Renal K^+ excretion has also shown rhythmicity as well as anticipatory K^+ excretion; both are influenced by brain (clock gene) [27] and intestinal K^+ exposure [28], independent of aldosterone and serum K^+ concentrations.

Hyperkalemia

Hyperkalemia is the most common electrolyte disorder in patients with CKD. Its prevalence increases as CKD

progresses. In a retrospective study (n = 240,000), CKD patients were more prone to hyperkalemic events (K^+ ≥5.5 mEq/L) than patients without CKD, with odds ratios of 2.2 for CKD stage 3, 5.9 for CKD stage 4, and 11 for CKD stage 5 [29]. Decreased glomerular filtration and ability of tubular K^+ secretion, often in combination with a diet generous in K^+, are the major cause of hyperkalemia. Other causes of hyperkalemia pertinent to CKD patients are (1) medications that further reduce the already limited capacity of distal nephron K^+ excretion such as renin angiotensin aldosterone system inhibitors, K^+-sparing diuretics and calcineurin inhibitors, (2) transcellular K^+ shift due to insulin deficiency, mineral metabolic acidosis, and tissue breakdown (hemolysis, rhabdomyolysis, tumor lysis syndrome), and (3) hyporeninemic hypoaldosteronism (type IV) RTA.

Hyperkalemia is defined as serum K^+ concentration >5.3 mEq/L and is often arbitrarily classified as mild (5.4 to <6 mEq/L), moderate (6 to <7 mEq/L), and severe (≥7 mEq/L) [30]. Symptoms and signs of hyperkalemia vary widely from nonspecific muscle weakness to paresthesia, muscle paralysis, cardiac arrhythmias, and cardiac arrest. Electrocardiogram may show arrhythmias, peaked T waves, prolonged PR interval, loss of P waves, widening of QRS complex and sine waves. It is important to note that ECG changes are not sensitive in detecting hyperkalemia. CKD patients can develop life-threatening hyperkalemia without appreciable EKG changes [31].

Treatment for hyperkalemia should be multipronged. Dietary modification with initiation of a low K^+ diet (<75 mEq/day) is an important part of intervention. Medication regimen must be reviewed to minimize the exposure of drugs that may induce hyperkalemia. Loop and thiazide diuretics can be used to promote kaliuresis. Patiromer is a newer K^+-lowering oral agent and can be tried when appropriate. Patiromer is a nonabsorbable, sorbitol containing Ca^{2+}-K^+ exchange polymer that selectively binds K^+ mainly in the colon. Its onset of action is 7 h. Placebo-controlled clinical trials [32, 33] have demonstrated its efficacy and safety. It is FDA approved for treatment of chronic hyperkalemia in non-dialysis CKD patients in a nonacute setting. Patiromer comes as a powder (in 3 strengths of 8.4, 16.2, and 25.2 g) with a recommended starting dose of 8.4 g daily. Its dosage may be titrated up in increments of 8.4 g weekly to a maximum daily dose of 25.2 g. Its intake should be spaced at least 3 h apart from other medications due to a potential risk of drug-drug interaction. The most common known side effects are constipation and mild hypomagnesemia.

Management of acute and symptomatic hyperkalemia requires monitoring in an inpatient setting. In the presence of ECG changes, intravenous calcium should be administered to stabilize myocardium. Temporizing measures that shift K^+ into the cells such as albuterol (10 mg) inhalation and intravenous regular insulin (10 units) combined with dextrose are indicated. Sodium bicarbonate can be considered if there is coexistent metabolic acidosis. Definitive measures aim to excrete K^+ out of the body. These include loop diuretics and/or thiazide to promote renal K^+ excretion, Kayexalate (sodium polystyrene sulfonate) to promote bowel excretion when appropriate, and hemodialysis if indicated. Hemodialysis is the most effective and definitive treatment for hyperkalemia.

Hypokalemia

Hypokalemia (serum [K^+] <3.5 mEq/L) is less common in CKD than hyperkalemia. It can, however, occur due to a multitude of reasons including non-K^+-sparing diuretic use, alkalosis, hypomagnesemia, vomiting, and diarrhea.

Clinical symptoms and signs of hypokalemia depend on the rate of onset and severity. These include muscle weakness, cramps, muscle paralysis and respiratory failure, cardiac arrhythmias, paralytic ileus and rhabdomyolysis. Cardiac arrhythmias could include sinus bradycardia, A-V block, paroxysmal atrial or junctional tachycardia, ventricular tachycardia and fibrillation. EKG changes include loss of T wave, emergence of U wave, prolonged QTc and torsade's pointes. Hypokalemia increases renal proximal tubular ammoniagenesis and is associated with metabolic alkalosis. Prolonged hypokalemia is associated with renal cyst formation, parenchymal fibrosis, and CKD progression. In a study of patients (n = 2,500) with CKD stages 1–4 (mean eGFR of 40.6 mL/min/1.73m$^{2)}$, those with hypokalemia (serum K^+ <3.5 mEq/L) had a significantly higher risk of developing ESRD than the risk in patients with serum K^+ of 4.5–5 mEq/L, (HR of 1.82, 95% CI: 1.03–3.22) [34].

Management of hypokalemia in CKD patients involves correcting the underlying causes and cautious K^+ replacement. Hypokalemia can precipitate digoxin toxicity. Withholding digoxin when appropriate may be necessary. Close follow-up is required.

Water Regulation and Dysnatremia

Serum [Na^+] represents water balance and is the primary determinant of serum osmolality. Changes in serum osmolality drive fluid in and out of cells and affect

cell volume and function. Serum [Na^+] is tightly regulated by arginine vasopressin (AVP) and thirst in a narrow range of 135–145 mEq/L. AVP is produced in the supraoptic and paraventricular nuclei of the hypothalamus and released from the posterior pituitary in response to increased serum osmolality (sensed by osmoreceptors in the hypothalamus) and reduced intravascular volume (sensed by baroreceptors in the carotids and aortic arch). In the kidneys, AVP binds to V2 receptors in the basolateral membrane of collecting ducts, activates adenylyl cyclase-mediated cAMP production and PKA signaling, leading to increased production and phosphorylation/apical membrane insertion of aquaporin 2 channels. This, in turn, leads to free water absorption in the presence of tubulomedullary osmotic gradient.

In a retrospective study involving a cohort of veterans (n = 655,000) with non-dialysis-dependent CKD, Kovesdy et al. [35] found a U-shaped association between serum [Na^+] and mortality with both hypernatremia (Na^+ >145 mEq/L) and hyponatremia (Na^+ <136 mEq/L) associated with increased mortality.

Hyponatremia

Hyponatremia, defined as the serum [Na^+] <135 mEq/L, is the most common electrolyte disorder in both the community-dwelling population [36] and in hospitalized patients [37] with occurrence rates of 7.7–15 and 44%, respectively [38]. Patients with CKD are at higher risk of hyponatremia than the general population due to diminished GFR and tubular regulation. In the same study noted above, veterans with CKD (mean eGFR of 52 mL/min/1.73 m^2) were followed for a median period of 5.5 years, and 26% of the subjects developed at least 1 episode of hyponatremia [35].

Clinical signs and symptoms of hyponatremia are relatively nonspecific and dependent on the severity and rate of hyponatremia onset. Patients with mild-to-moderate hyponatremia may be asymptomatic or present with malaise, nausea, lethargy and fatigue. The more overt neurological symptoms often manifest when hyponatremia is severe (<120 mEq/L) and has developed rapidly. Patients can present with headache, slowing of mentation, confusion, ataxia, seizures, and coma. Measurement of serum osmolality (normal serum osmolality = 280–290 mosm/kg) is necessary to rule out pseudohyponatremia, isotonic hyponatremia in the setting of hyperlipidemia and paraproteinemias, and hyperosmolar (>290 mosm/kg) hyponatremia in the setting of hyperglycemia or mannitol administration. Low serum osmolality (<280 mosm/kg) along with hyponatremia indicates true hypotonic hyponatremia. After confirming the presence of hypotonic hyponatremia, the patient's volume status should be determined to guide treatment decisions. Volume replacement with isotonic fluids is the treatment of choice in patients with volume depletion. Restoration of volume will turn off the stimulus for vasopressin release, leading to renal water excretion and correction of hyponatremia. Causes, clinical features, and treatment for euvolemic hyponatremia are summarized in Table 5. Hypervolemic hyponatremia due to liver or heart failure should be treated with loop diuretics combined with free water restriction (≤1L/day). Vasopressin V_2 receptor blockers (vaptans) are not used routinely due to prohibitive cost and concerns of hepatotoxicity. The FDA has approved the use of tolvaptan, a selective V_2 receptor blocker, for less than 30 days for hyponatremia due to congestive heart failure but not for patients with cirrhosis. Several clinical trials have failed to show a reduction in long-term mortality and morbidity in heart failure patients treated with V2 receptor blocker despite increasing serum [Na^+] [39, 40]. Similarly, in a recently published TACTICS-HF study involving patients hospitalized for acute heart failure (n = 257), randomization to 3 days of daily tolvaptan compared to placebo failed to show any difference in length of hospital stay, 30-day mortality, and 30-day re-hospitalization rates [41]. Similar results were found in the SECRET of CHF trial [42]. Patients with late-stage CKD often develop euvolemic or hypervolemic hyponatremia due to limited kidney function. Management involves free water restriction, use of loop diuretics and, if necessary, dialysis.

Regardless of the etiology, the rate of serum [Na^+] correction depends on 2 key factors: (1) whether the patient is symptomatic, and (2) the rate of hyponatremia onset (<48 h or ≥48 h). For symptomatic hyponatremia, 3% saline should be administered intravenously with the goal of raising serum [Na^+] by 4–5 mEq/L. If asymptomatic and the onset of hyponatremia is ≥48 h, serum [Na^+] should be corrected slowly (not exceeding 6–8 mEq/L in the 1st 24 h and 18 mEq/L within 48 h) to prevent neurological damage such as central-pontine demyelination syndrome. Inadvertent over correction should be reversed with hypotonic fluids. Serial serum [Na^+] measurements (every 2–6 h) may be necessary to evaluate treatment adequacy, especially during the initial 24 h.

Hypernatremia

Hypernatremia (serum [Na^+] >145 mEq/L) is relatively common with a reported incidence of 1–3.4% in hos-

Table 5. Euvolemic hyponatremia

Cause	Clinical and lab features	Treatment
Severe hypothyroidism	↑TSH ↓T4 Myxedema, stigmata of hypothyroidism	Levothyroxine Free water restriction
Secondary adrenal insufficiency	↓ACTH ↓cortisol	Hydrocortisone
Low solute intake	Elderly/malnourished (tea and toast diet) Beer potomania	Protein nutrition supplement Stop beer intake
Psychogenic polydipsia	Large water intake Dilute urine (osmolality <100 mosm/kg)	Free water restriction
SIADH Idiopathic/aging related Nausea/vomiting Pain Cancer (small cell lung cancer) *Lung*: abscess/empyema/COPD *CNS*: meningitis/encephalitis brain abscess/stroke *Medications*: SSRIs, TCAs antiepileptics, barbiturates	 – Urine osmolality >150 mEq/L – Urine Na^+ high or low based on Na^+ intake – ↓serum uric acid	 Fluid restriction (<1 L/day) Salt tablets Loop diuretics V_2 (AVP) receptor blockers[a] Treat the underlying cause Stop the offending medication (if possible)

SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants. [a] V_2 blockers should be initiated in hospital setting and should not be used beyond 30 days.

pitalized patients [36, 43]. In CKD, as cited above [35], there is a reported 2% (n = 13,289) prevalence of hypernatremia and 7% (n = 45,666) occurrence of at least 1 episode of hypernatremia in non-dialysis CKD veterans with 5.5 years follow-up.

Hypernatremia signifies total body water deficiency relative to total body sodium. It can result from either (1) loss of water or hypotonic fluid (loss of water > loss of Na^+) or (2) gain of Na^+ (and K^+), such as incidental hypertonic fluid ingestion or infusion. Diabetes insipidus, chronic hypokalemia, hypercalcemia, hyperglycemia, and medications such as loop and osmotic diuretics, lithium, and vasopressin V_2 receptor blockers can cause hypernatremia due to renal hypotonic fluid loss. Nonrenal causes of hypernatremia include osmotic diarrhea, vomiting, excessive sweating, and burns. Sustained hypernatremia typically occurs when thirst mechanism is impaired (thirst stimulates AVP secretion leading to renal water preservation) and or there is lack of access to water. Hence, intubated patients, patients with altered mental status or under sedation, elderly nursing home residents, and infants are more susceptible to hypernatremia.

Clinical symptoms and signs of hypernatremia are nonspecific and vary from asymptomatic to comatose depending on the severity and rate of onset of hypernatremia. Common manifestations include intense thirst (if thirst mechanism is intact), fatigue, and lethargy, muscle weakness, slowing of mentation, confusion, and coma.

Hypernatremia is a hypertonic state. Thus, measurement of serum osmolality is, in general, unnecessary. Measurement of urine osmolality is useful in differentiating renal water loss such as diabetes insipidus (inappropriately dilute urine) from extrarenal water loss (concentrated urine). In patients on diuretics, urine osmolality may vary depending on the timing of diuretic intake. Patients with severe hyperglycemia can be in a hyperosmolar state, but their serum [Na^+] may be falsely normal or even reduced. Typically, serum [Na^+] is reduced by ~1.6 mEq/L for each 100 mg/dL elevation of glucose above normal range.

Management of hypernatremia should focus on (1) correction of the underlying cause and (2) treatment of hypernatremia. If hypernatremia is chronic (≥48 h) or of unknown duration, serum [Na^+] correction should be

Table 6. Dysmagnesemia

Causes	Pathophysiology and gene mutations	Special features
Hypomagnesemia		
Hereditary		
– FHHNC (AR)	*CLDN16* and *CLDN19*	CKD by 2nd decade in most patients, nephrocalcinosis, ocular changes (Claudin 19 mutations) severe hypomagnesemia
– HSH (AR)	*TRPM6*	Severe hypomagnesemia, hypocalcemia
– IRH (AR)	*EGF* (decreased EGFR-mediated TRPM6 expression)	Isolated severe Mg^{2+} deficiency Seizure, mental retardation
– IDH (AD)	*FXYD2* (γ-subunit of Na^+/K^+ ATPase)	Hypomagnesemia , hypocalcemia
– ADH (AD)	*KCNA1* (some mutations cause episodic ataxia without Mg^{2+} alteration)	Severe hypomagnesemia, myokymia, tetany
EAST syndrome	*KCNJ10* (coding for inward rectifying K^+ channel KCNJ10/Kir4.1)	Epilepsy, ataxia, sensorineural deafness, tubulopathy, hypokalemia, metabolic alkalosis
Hypomagnesemia with maturity onset diabetes of young (MODY)	*HNF1B* or *PCBD*	MODY, urogenital malformations, cystic renal disease, AD inheritance
Bartter syndrome type V (AR)	*CASR* (activating mutations)	Hypokalemia, metabolic alkalosis, hypercalciuria
Gitelman syndrome (AR)	*SLC12A3*	Hypokalemia, metabolic alkalosis, hypomagnesemia and hypocalciuria
Acquired		
– Alcoholism	↓ oral intake, GI loss	
– Malabsorption/chronic diarrhea	↓ intestinal Mg^{2+} absorption, GI loss	
– Recovery phase of obstructive uropathy and ATN	↓ renal tubular Mg^{2+} reabsorption	
Hormonal deficiency – PTH – AVP – Insulin – Estrogen – Vitamin D	Defects in Mg^{2+} absorption in the TALH and distal tubules	
Medications		
– Loop/thiazide diuretic	↓ renal Mg^{2+} reabsorption in TALH/ DCT	
– PPIs	↓ intestinal Mg^{2+} absorption	
– Calcineurin inhibitors	Downregulation of TRPM6, Claudin 16, ↑ Claudin 14 (↓Mg^{2+} reabsorption [37])	
– Cetuximab/panitumumab	EGFR blockade	
– Cisplatin/carboplatin	TRPM6 downregulation	
– Aminoglycosides	Activation of CaSR	
– Amphotericin	↓ Mg^{2+} reabsorption	
Hypercalcemia	CaSR activation	
Hypophosphatemia	↓ Mg^{2+} uptake in DCT	
Metabolic acidosis (chronic)	TRPM6 downregulation	
Hypermagnesemia		
Hereditary		
FHH (AD)	*CASR* (inactivating mutations)	Mild ↑Mg^{2+}, Ca^{2+}
NSHPT (AR)		Severe ↑ Ca^{2+}, lethal
Acquired		
Advanced renal failure + Mg^{2+} containing agents: – Laxatives/enema – Antacids – Phosphate binders – Mg^{2+} infusion	↓ renal excretion + Mg^{2+} load	

AD, autosomal dominant; AR, autosomal recessive; FHHNC, familial hypomagnesemia with hypercalciuria and nephrocalcinosis; HSH, hypomagnesemia with secondary hypocalcemia; IRH, isolated recessive hypomagnesemia; IDH, isolated dominant hypomagnesemia; EGF, epidermal growth factor; TRPM6, transient receptor potential cation channel subfamily M member 6; CaSR, calcium-sensing receptor; FHH, familial hypocalciuric hypercalcemia; NSHPT, neonatal severe hyperparathyroidism; PPI, proton pump inhibitors; ROMK, renal outer medullary potassium.

gradual, not exceeding 8–10 mEq/L in the first 24 h to prevent cerebral edema [44]. More rapid serum Na^+ correction (up to 1 mEq/L per hour) may be appropriate if onset of hypernatremia is acute (<48 h).

Total body free water deficit in hypernatremia can be estimated with the following formula:

$$\text{Free water deficit} = \text{total body water} \times [(\text{serum } [Na^+]/140) - 1]$$

Where total body water = body weight × (0.6 for men; 0.5 for women)

The calculation provides an initial estimate of total body water deficit. 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.

Magnesium Regulation and Dysmagnesemia

Magnesium (Mg^{2+}) is the second most abundant intracellular cation with more than 99% located intracellularly (53% in bones, 46.5% in soft tissues) and less than 0.5% located extracellularly. About 20–30% of circulating Mg^{2+} is protein bound (mainly to albumin), while 70–80% is freely filtered by kidneys. The unbound Mg^{2+} equilibrates with bone and intracellular Mg^{2+}. Mg^{2+} is a cofactor for numerous intracellular enzymes and has multiple functions in oxidative phosphorylation, DNA synthesis, repair and replication, RNA and protein synthesis and signaling pathways.

Daily Mg^{2+} intake in an adult should be in the range of 350–450 mg. It is absorbed predominantly in the distal small intestine through a paracellular process and in the cecum and colon by a transcellular process involving TRPM6. Intestinal Mg^{2+} absorption can vary significantly from 25 to 75% depending on the amount of Mg^{2+} intake. The kidneys filter approximately 2,400 mg of Mg^{2+} daily, of which ~100 mg is excreted in the urine. Unlike Na^+, K^+, and Ca^{2+}, bulk of filtered Mg^{2+} (about 70%) is reabsorbed in the TALH and only about 20% reabsorbed in the proximal tubule. The remaining 5–10% of filtered Mg^{2+} is reabsorbed in the distal tubule. In the TALH, Mg^{2+} is absorbed paracellularly facilitated by tight junctional proteins, claudins 16 and 19. The major driving force is the lumen-positive transepithelial voltage, generated primarily by the reabsorption of Na^+, K^+, and Cl^- through Na^+-K^+-$2Cl^-$ cotransporter and efflux of K^+ through ROMK channels, which are, in turn, powered by the basolateral Na^+/K^+-ATPase. In the DCT, Mg^{2+} reabsorption is transcellular via TRPM6, driven by the transapical membrane potential. As this is the last part of the renal tubular Mg^{2+} absorption and there is a steep transepithelial Mg^{2+} concentration gradient, the transapical membrane potential is tightly regulated through multitudes of channels and transporter proteins, detailed in a recent review [45].

Both hypermagnesemia (>2.3 mg/dL) and hypomagnesemia (<1.7 mg/dL) are relatively common with reported prevalence of 31 and 20%, respectively, in hospitalized patients [46]. Both hypo- and hypermagnesemia adversely impact patient outcomes, including increased mortality and longer duration of hospital stay. Causes, pathophysiology, and special features of different conditions causing hypomagnesemia and hypermagnesemia are summarized in Table 6.

Symptoms of dysmagnesemia vary significantly. Mild hypo- or hypermagnesemia may be asymptomatic. Severe and chronic hypomagnesemia can present with muscle weakness, paresthesia, tetany, and seizures. It can potentiate cardiac arrhythmias. Severe hypermagnesemia can cause loss of deep tendon reflexes and paralysis.

In early stages of CKD, decreased filtration of Mg^{2+} is balanced by reduced renal tubular reabsorption; hence, dysmagnesemia is uncommon. In advanced CKD, hypermagnesemia can be triggered by Mg^{2+}-rich diet and Mg^{2+}-containing medications. Hypomagnesemia in CKD patients can occur due to inadequate intake, poor intestinal absorption (due to malabsorption syndromes or use of proton pump inhibitors) and renal or extrarenal loss such as chronic diarrhea.

Treatment of dysmagnesemia involves correcting the underlying causes if possible and normalizing Mg^{2+}. For severe symptomatic hypomagnesemia, parenteral magnesium administration is indicated. Oral administration of Mg^{2+} in daily divided doses, however, is the only effective method for total body Mg^{2+} repletion. In patients with adequate renal function, hypermagnesemia would mostly self-correct with urine Mg^{2+} excretion. If necessary, loop diuretics can be used to enhance renal Mg^{2+} excretion. In patients with advanced renal failure and symptomatic hypermagnesemia, intravenous calcium should be considered to stabilize myocardium. Dialysis is the most effective and definitive treatment of hypermagnesemia in patients with renal failure.

Conclusion

We summarize acid-base and electrolyte regulations with updated knowledge. Recent advances on key pathological, clinical and diagnostic features, as well as treatment modalities of several important and common disor-

ders are presented. Essential pathophysiological characteristics of the disorders in patients with reduced kidney function are emphasized. With a growing population of patients with kidney diseases, this update will provide a useful reference and update for researchers and clinicians in the field of general medicine and nephrology.

Conflict of Interest Statement

The authors have no competing interests.

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