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The primary aim of *Electrolytes & Blood Pressure* is to serve as a distinguished forum for the publication and dissemination of high-quality research and comprehensive review articles that deepen our understanding of the complex physiological and pathological processes underlying renal function and blood pressure regulation. The journal welcomes contributions across a wide range of disciplines, with particular emphasis on the mechanisms and clinical relevance of solute and water transport, acidification, urine concentration, vasoactive mediators, nephrolithiasis, inherited kidney disorders, and aging-related changes in renal physiology. A distinctive focus of the journal lies in translational research—investigations that effectively bridge basic laboratory discoveries with their clinical applications in the diagnosis, treatment, and management of disorders involving fluid and electrolyte balance, acid-base homeostasis, and renal hypertension. By promoting the integration of molecular, physiological, and clinical approaches, the journal seeks to foster interdisciplinary dialogue and innovation in nephrology and cardiovascular research.

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Contents

Review Articles

- 147** Monogenic Kidney Disorders as Hidden Drivers of Electrolyte Imbalance and Hypertension
Yo Han Ahn
- 158** Dietary Salt Intake and Hypertension in Chronic Kidney Disease
Eunjin Bae
- 166** Overcorrection of Hyponatremia: A Complicated Story
Gheun-Ho Kim
- 175** Impact of the Four Pillars on Electrolyte Derangements during State-of-the-Art Therapy for Diabetic Kidney Disease
Mie Jung Yoo, Shina Lee

Original Article

- 189** Unsupervised Clustering of Intradialytic Blood Pressure Patterns and Their Associations With Body Composition in Patients Undergoing Chronic Hemodialysis
Hongtae Kim, Soie Kwon, Jin Ho Hwang, Jungho Shin

Case Report

- 200** Long-Standing Hypokalemia and Hypomagnesemia in a 61 Year-Old Woman: A Delayed Diagnosis of Gitelman Syndrome
Shin Young Lee, Sang-Woong Han, Jiwon Lee, Mi-Yeon Yu

Letter to the Editor

- 205** From Specialty Silos to Integrated Care: A Korean Initiative for Cardiovascular-Kidney-Metabolic Health
Sungjin Chung, Jihyun Yang, Jungho Shin, Tae Hyun Ban, Hyung Duk Kim, Yeoree Yang, Sangmo Hong, Eun Joo Cho, on behalf of the Korean Society of Nephrology, the Korean Diabetes Association and the Korean Society of Cardiology

Review Article



Monogenic Kidney Disorders as Hidden Drivers of Electrolyte Imbalance and Hypertension

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ABSTRACT

Hypertension is the leading modifiable risk factor for cardiovascular disease, stroke, and chronic kidney disease worldwide. Although most cases are essential hypertension, a subset of patients harbors monogenic disorders that disrupt how the kidneys control electrolyte balance and blood pressure regulation. These rare conditions provide important insights into the fundamental physiological mechanisms that link tubular sodium transport, extracellular volume homeostasis, and systemic hemodynamics. The distal nephron is crucial in fine-tuning sodium and potassium balance through tightly regulated transport systems, such as the sodium–chloride cotransporter (NCC) in the distal convoluted tubule and the epithelial sodium channel (ENaC) in the collecting duct. Genetic perturbations of these pathways can markedly disrupt electrolyte balance and blood pressure. Monogenic hypertensive disorders exemplify these mechanisms. Liddle syndrome results from gain-of-function mutations in ENaC subunits, resulting in sodium retention, hypokalemia, and suppressed renin–aldosterone levels. Conversely, Gordon syndrome (pseudohypoaldosteronism type II) is caused by the dysregulation of the with-no-lysine (K) kinase–SPS1-related proline/alanine-rich kinase signaling pathway, resulting in NCC overactivation and the paradoxical concurrence of hypertension and hyperkalemia. Apparent mineralocorticoid excess results from deficiency of 11 β -hydroxysteroid dehydrogenase type 2, resulting in the inappropriate activation of the mineralocorticoid receptor by cortisol and subsequent sodium retention. Together, these disorders illustrate how discrete defects in distal nephron transport pathways induce characteristic electrolyte signatures while converging on the shared phenotype of hypertension. Understanding these genetic mechanisms may provide insight into fundamental renal physiology and facilitate the use of precision diagnostic and therapeutic approaches for patients with atypical or treatment-resistant hypertension.

Keywords: Genetic disease, inborn; Hypertension; Ion transport; Kidney tubules, distal; Water-electrolyte balance

INTRODUCTION

Hypertension is the leading preventable risk factor for cardiovascular disease, stroke, and chronic kidney disease worldwide [1]. Although most cases are classified as essential

hypertension, a complex, polygenic condition influenced by environmental factors, lifestyle, and aging, a subset of patients harbor secondary and potentially reversible causes. Among these, monogenic kidney disorders represent rare but clinically important causes of hypertension, accounting for a small proportion of cases in the general population but a substantially higher proportion among individuals with early-onset or treatment-resistant hypertension. These disorders offer valuable insights into the fundamental physiological mechanisms governing blood pressure regulation and fluid–electrolyte homeostasis [2].

Arthur Guyton advanced the kidney-centered model of blood pressure control by establishing that the kidney primarily determines long-term arterial pressure through the pressure–natriuresis relationship [3]. This framework presents that sustained hypertension occurs when renal sodium excretion is impaired, necessitating a higher arterial pressure to achieve sodium balance. Genetic mutations that disrupt kidney sodium regulation or potassium homeostasis effectively shift this pressure–natriuresis curve, resetting the systemic blood pressure set point at a higher level [4,5]. Monogenic kidney disorders exemplify this principle, as mutations that affect tubular transport proteins, ion channels, and regulatory signaling pathways disrupt renal sodium reabsorption, extracellular volume homeostasis, and potassium balance [6,7]. Clinically, these molecular defects manifest as early-onset or treatment-resistant hypertension. These abnormalities are often accompanied by characteristic electrolyte abnormalities and acid–base disturbances. Importantly, these conditions often masquerade as primary hypertension, leading to delayed diagnosis and suboptimal targeted therapy.

This review aimed to explore the molecular mechanisms underlying monogenic hypertensive disorders, which would emphasize the transition from tubular transport defects to systemic clinical phenotypes. Understanding these genetic drivers can help clinicians transition from empirical treatment to precision medicine by targeting specific molecular pathways disrupted.

PATHOPHYSIOLOGY OF TUBULAR SODIUM TRANSPORT AND HEMODYNAMICS

The human kidney filters approximately 180 L of glomerular ultrafiltrate daily; however, only < 1% of the filtered sodium load is ultimately excreted in the urine [8,9]. This remarkable efficiency is attributed to the coordinated activity of specialized transporters distributed along the nephrons. Among these segments, distal nephrons, particularly the distal convoluted tubule (DCT) and collecting duct (CD), play a disproportionate role in blood pressure regulation, as the final hormonally regulated adjustments in sodium and potassium balance occur in the nephrons [10,11].

At the molecular level, the sodium–chloride cotransporter (NCC) primarily mediated sodium reabsorption in the DCT, whereas the principal cells of the CD reabsorb sodium through the epithelial sodium channel (ENaC) [5]. Activities of these transport systems are regulated rather than static under the control of an intricate signaling network that includes serine–threonine kinases (such as the with-no-lysine [K] kinase [WNK] family and their downstream SPS1-related proline/alanine-rich kinase [SPAK]/oxidative stress–responsive kinase 1 [OSR1]) and ubiquitin ligases (notably NEDD4-2) [12–14]. Genetic mutations that enhance the activity or expression of these transporters can lead to increased sodium retention and secondary water reabsorption, leading to extracellular fluid volume expansion. This volume expansion

is associated with increased cardiac output and may contribute to high systemic vascular resistance, thereby sustaining hypertension.

Simultaneously, enhanced sodium reabsorption, particularly via ENaC, enhances the lumen-negative transepithelial potential difference in the distal nephron. These electrical gradients drive potassium and hydrogen ion secretion, predisposing to hypokalemia and metabolic alkalosis [11,15]. These electrolyte and acid–base abnormalities often provide the earliest clinical clues underlying monogenic disorder of tubular sodium handling [6].

MONOGENIC HYPERTENSIVE DISORDERS

Liddle syndrome

This syndrome is the prototypical form of monogenic salt-sensitive hypertension. This autosomal dominant disorder is characterized by severe, early-onset hypertension [16]. The molecular defect most commonly involves gain-of-function mutations in *SCNNIB* or *SCNNIG*, which encode ENaC β - and γ -subunits, respectively [17]. *SCNNIA* (α -subunits) mutations are rare but have also been described [18].

Under physiological conditions, ENaC surface expression is tightly regulated by the E3 ubiquitin ligase NEDD4-2, which recognizes a proline-rich “PY motif” located in the cytoplasmic C-terminus of the β - and γ -subunits and targets the channel for ubiquitination and proteasomal degradation (**Fig. 1**) [5,19]. In Liddle syndrome, truncating or missense mutations disrupt this PY motif, which inhibits NEDD4-2 binding [17]. Consequently, ENaC accumulates at the apical membrane of principal cells in the CD and remains constitutively active.

The clinical phenotype reflects mineralocorticoid excess, often referred to as pseudoaldosteronism. Enhanced ENaC activity leads to increased sodium reabsorption and extracellular volume expansion, which in turn suppresses the renin–angiotensin–aldosterone system to very low or undetectable levels [5,9]. However, given the autonomous and aldosterone-independent nature of sodium reabsorption, hypertension persists despite low plasma renin and aldosterone concentrations [20]. This distinction is clinically important for diagnosis. In contrast to primary aldosteronism, Liddle syndrome is characterized by suppressed aldosterone, rendering mineralocorticoid receptor (MR) antagonists, such as spironolactone, ineffective [16,20]. Alternatively, direct ENaC inhibitors, particularly amiloride or triamterene, produce a marked therapeutic response [16,20].

At the cellular level, high sodium influx through ENaC enhances basolateral Na^+/K^+ -ATPase activity, promoting potassium uptake into cells (**Fig. 1**). Concurrently, augmented apical sodium entry generates a more lumen-negative transepithelial potential difference in distal nephrons. This electrical gradient drives potassium secretion through apical potassium channels, such as renal outer medullary potassium channel (ROMK), and facilitates hydrogen ion secretion by α -intercalated cells [21]. The net effect is renal potassium wasting and increased acid excretion, resulting in hypokalemia and metabolic alkalosis [21,22].

Liddle syndrome reflects how dysregulation of a distal nephron transporter can mimic the hemodynamic and electrolyte phenotype of mineralocorticoid excess without hormonal activation.

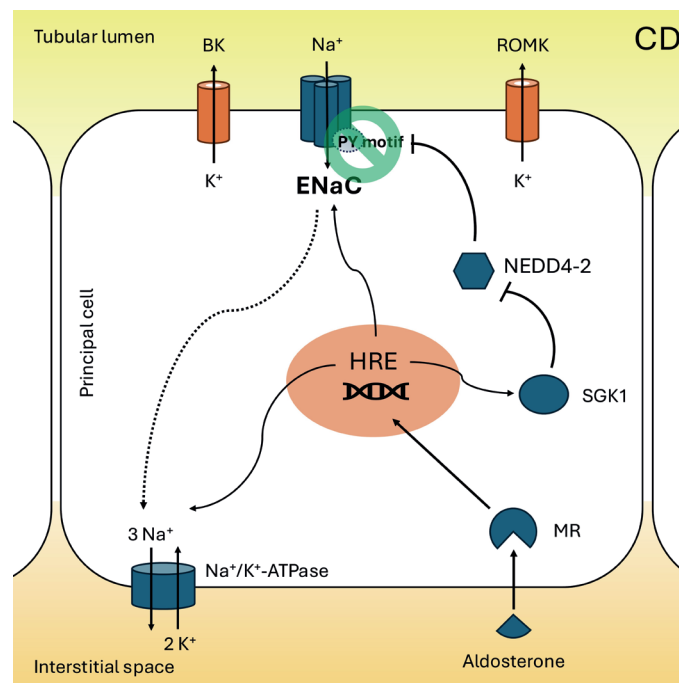


Fig. 1. Physiological regulation of sodium transport in principal cells of the distal nephron and its dysregulation in Liddle syndrome. Under normal conditions, aldosterone binds to the MR, leading to increased transcription of ENaC subunits and SGK1. SGK1 enhances ENaC activity in part by inhibiting the E3 ubiquitin ligase NEDD4-2, which normally binds to the PY motif of ENaC subunits and promotes channel ubiquitination and internalization. This tightly regulated balance maintains appropriate sodium reabsorption. In Liddle syndrome, gain-of-function mutations in ENaC disrupt the PY motif, preventing NEDD4-2-mediated degradation and resulting in constitutive ENaC activation and sodium reabsorption independent of aldosterone. BK, large-conductance calcium-activated potassium channel; CD, collecting duct; ENaC, epithelial sodium channel; HRE, hormone response element; MR, mineralocorticoid receptor; NEDD4-2, neural precursor cell expressed developmentally down-regulated 4-2; ROMK, renal outer medullary potassium channel; SGK1, serum and glucocorticoid-regulated kinase 1.

Gordon syndrome (pseudohypoaldosteronism type II)

This syndrome, also known as pseudohypoaldosteronism type II or familial hyperkalemic hypertension, is a paradoxical form of monogenic hypertension characterized by the triad of hypertension, hyperkalemia, and hyperchloremic metabolic acidosis [23]. In contrast to Liddle syndrome, which is driven by excessive ENaC activity in the CD, Gordon syndrome arises primarily from dysregulated sodium transport in the DCT [24].

The disorder is caused by mutations in genes encoding components of the WNK signaling pathway (e.g., *WNK1*, *WNK4*, *Kelch-like protein 3* [*KLHL3*], and *Cullin 3* [*CUL3*]). *WNK1* and *WNK4* are serine–threonine protein kinases that form a phosphorylation cascade with *SPAK* and *OSR1*, ultimately regulating the activity of cation–chloride cotransporters, particularly the *NCC* (**Fig. 2A**) [25,26]. *WNK*–*SPAK/OSR1* pathway activation enhances *NCC* phosphorylation and increases its activity at the apical membrane of DCT cells [23].

Recent studies have further demonstrated that *WNK* kinases are directly regulated by intracellular chloride [27,28]. Low intracellular chloride concentration, as seen in hypokalemia or reduced effective circulating volume, relieves inhibitory binding at a conserved chloride-binding site within *WNK* kinases, leading to activation of *WNK* kinases (particularly *WNK4*) and the downstream *WNK*–*SPAK/OSR1* signaling cascade [29].

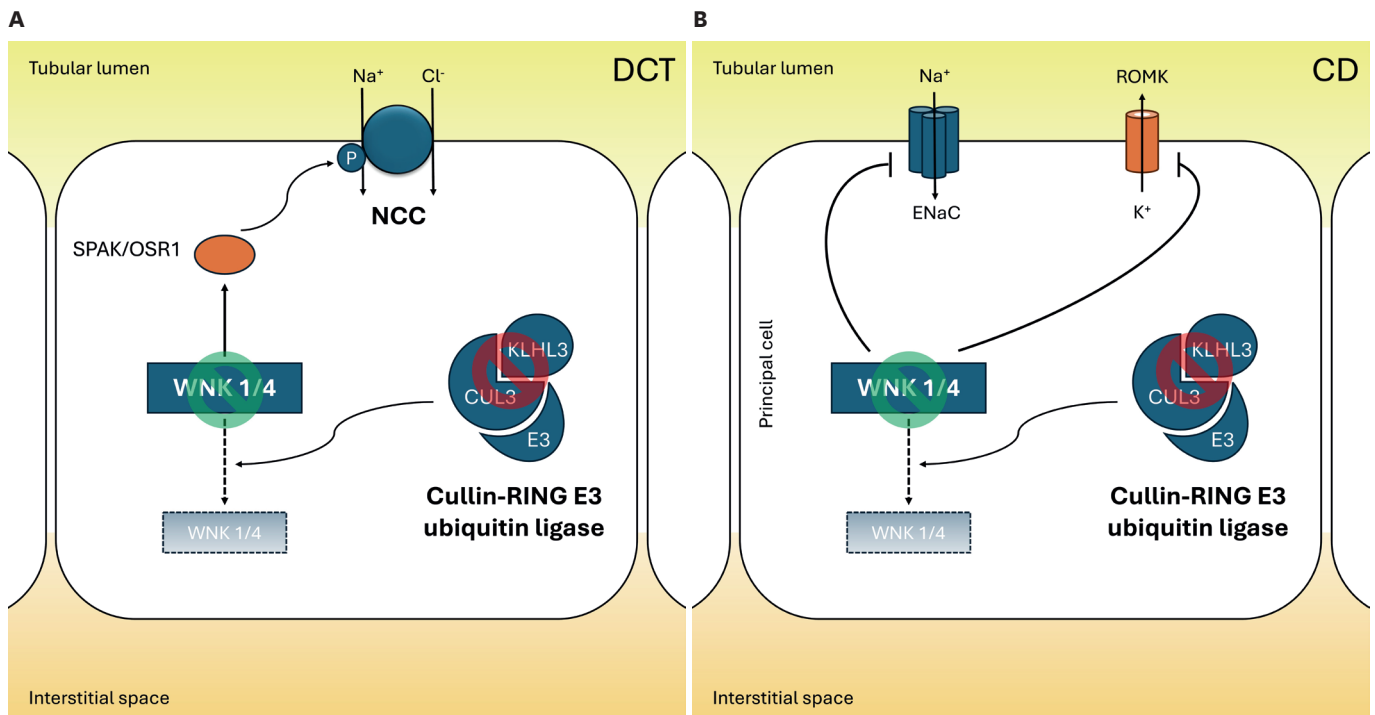


Fig. 2. Mechanisms of Gordon syndrome. (A) In the DCT, activation of the WNK–SPAK/OSR1 signaling cascade increases the activity of the NCC, enhancing sodium and chloride reabsorption. Gain-of-function mutations in *WNK1* or *WNK4* increase WNK kinase activity, whereas loss-of-function mutations in *CUL3* or *KLHL3* impair ubiquitin-mediated degradation of WNK kinases, leading to their accumulation and sustained NCC activation. (B) Increased sodium reabsorption in the DCT reduces distal sodium delivery to the CD, thereby decreasing ENaC-mediated sodium uptake and impairing potassium secretion through apical potassium channels such as ROMK, resulting in hyperkalemia. CD, collecting duct; CUL3, Cullin 3; DCT, distal convoluted tubule; ENaC, epithelial sodium channel; KLHL3, Kelch-like protein 3; NCC, sodium–chloride cotransporter; OSR1, oxidative stress–responsive kinase 1; ROMK, renal outer medullary potassium channel; SPAK, SPK1-related proline/alanine-rich kinase; WNK, with-no-lysine (K) kinase.

This mechanism establishes WNK4 as a key intracellular chloride sensor in the DCT and provides a mechanistic basis for the inverse relationship between dietary potassium intake and NCC activity [29]. In addition, kidney-specific WNK1 functions as a signal amplifier by promoting the formation of WNK bodies, thereby enhancing WNK–SPAK/OSR1-mediated NCC activation in response to changes in potassium balance [30]. This mechanism enables the distal nephron to translate small fluctuations in plasma potassium into robust alterations in sodium transport [30].

Under normal conditions, WNK abundance is tightly controlled by a Cullin-RING E3 ubiquitin ligase complex composed of CUL3 and KLHL3, which targets WNK kinases for ubiquitination and proteasomal degradation (**Fig. 2A**) [24]. *CUL3* or *KLHL3* mutations impair this degradation process, leading to the accumulation of WNK kinases and constitutive activation of NCC [26]. Similarly, gain-of-function *WNK1* or *WNK4* mutations directly enhance NCC activity [23,24]. The net effect is excessive sodium and chloride reabsorption in the DCT.

Previous genotype–phenotype studies have demonstrated substantial clinical variability [25,26]. *CUL3* mutations and recessive *KLHL3* variants are typically associated with earlier onset and more severe phenotypes, whereas dominant *KLHL3*, *WNK4*, and *WNK1* intron 1 deletion tend to produce intermediate forms [25]. Mild phenotypes have shown association with specific *WNK1* acidic motif variants.

The resulting hyperkalemia provides important mechanistic insight. Enhanced NCC-mediated sodium reabsorption in the DCT eases sodium delivery to the downstream CD, where ENaC-dependent sodium uptake normally generates a lumen-negative potential that triggers potassium secretion [23]. Reduced distal sodium delivery diminishes this electrical gradient, impairing potassium secretion through ROMK channels [22,24]. Additionally, WNK signaling directly suppresses ROMK expression and activity, further limiting renal potassium excretion (**Fig. 2B**) [24]. The combined effect of systemic hyperkalemia and reduced hydrogen ion secretion leads to hyperchloremic metabolic acidosis. Gordon illustrates how increased sodium reabsorption at an upstream nephron segment can paradoxically produce hyperkalemia, underscoring the tight coupling between segmental sodium handling and potassium homeostasis [24].

Liddle and Gordon syndromes represent physiologic opposites, demonstrating how different distal nephron sodium transport defects can produce mirror-image potassium phenotypes.

Apparent mineralocorticoid excess (AME)

AME is a rare autosomal recessive disorder characterized by severe, early-onset hypertension, hypokalemia, metabolic alkalosis, and renin and aldosterone suppression [31]. It results from loss-of-function mutations in *HSD11B2*, which encodes the 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) enzyme. 11 β -HSD2 functions as a critical “gatekeeper” for the MR in aldosterone-sensitive tissues, such as distal nephrons [32,33]. Although the MR has a similar affinity for cortisol and aldosterone, circulating cortisol concentrations are several hundredfold higher than those of aldosterone. Under physiological conditions, 11 β -HSD2 protects the MR by rapidly converting cortisol into cortisone, its inactive metabolite, thereby ensuring that aldosterone remains the primary physiological ligand activating the MR [32,34].

In AME, 11 β -HSD2 deficiency prevents this protective cortisol inactivation (**Fig. 3**). Consequently, cortisol freely binds to and activates the MR in distal nephrons, mimicking AME despite low circulating aldosterone levels [31]. MR activation upregulates ENaC activity and basolateral Na⁺/K⁺-ATPase function, promoting sodium retention and extracellular volume expansion [31]. The resulting volume expansion suppresses the renin–angiotensin–aldosterone system, producing the characteristic biochemical profile of low renin and low aldosterone.

Enhanced sodium reabsorption through ENaC also generates a lumen-negative potential difference in the CD, driving potassium and hydrogen ion secretion. Consequently, hypokalemia and metabolic alkalosis occur, closely resembling the electrolyte phenotype observed in Liddle syndrome. However, the underlying mechanism involves inappropriate MR activation rather than intrinsic channel dysregulation.

Clinically, AME typically presents in early childhood with severe hypertension, polyuria, and polydipsia caused by impaired urinary concentrating ability [35]. Affected children often may develop failure to thrive, and nephrocalcinosis. The disease can lead to serious complications, including early-onset stroke [36].

Geller syndrome

Geller syndrome is an extremely rare form of autosomal dominant hypertension caused by activating mutations in the MR gene *NR3C2* [6,37]. These mutations alter the ligand specificity of the MR, allowing steroids that normally function as antagonists, particularly

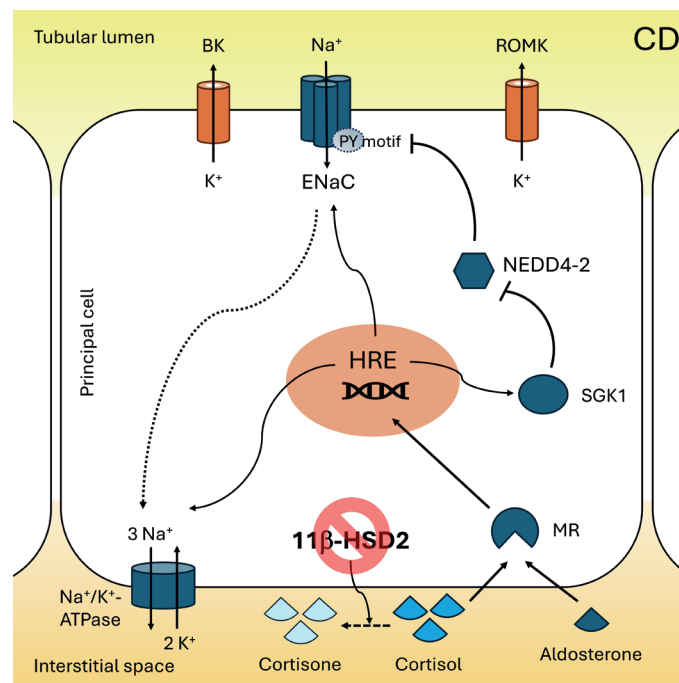


Fig. 3. Mechanisms of apparent mineralocorticoid excess syndrome. In normal physiology, 11β -HSD2 converts cortisol to inactive cortisone, thereby protecting the MR from activation by cortisol. In apparent mineralocorticoid excess syndrome, deficiency of 11β -HSD2 permits cortisol to bind to and activate the MR in the distal nephron, mimicking a state of mineralocorticoid excess despite low circulating aldosterone levels. This results in increased ENaC activity, sodium retention, extracellular volume expansion, and suppression of the renin-angiotensin-aldosterone system.

11β -HSD2, 11β -hydroxysteroid dehydrogenase type 2; BK, large-conductance calcium-activated potassium channel; CD, collecting duct; ENaC, epithelial sodium channel; HRE, hormone response element; MR, mineralocorticoid receptor; NEDD4-2, neural precursor cell expressed developmentally down-regulated 4-2; ROMK, renal outer medullary potassium channel; SGK1, serum and glucocorticoid-regulated kinase 1.

progesterone, to act as potent agonists. Consequently, MR activation stimulates sodium reabsorption in distal nephrons, leading to hypertension, hypokalemia, and renin and aldosterone suppression [37].

Clinically, Geller syndrome often presents as pregnancy-associated hypertension because circulating progesterone levels increase markedly during gestation [38]. In affected individuals, progesterone activates the mutant MR, triggering excessive sodium retention and severe hypertension. Importantly, MR antagonists, such as spironolactone, may paradoxically worsen hypertension in these patients because spironolactone can act as an agonist at the mutant receptor [37]. Therefore, recognition of this disorder helps avoid inappropriate therapy [6].

DIAGNOSTIC APPROACH AND THE SHIFT TOWARD PRECISION MEDICINE

The diagnostic evaluation of genetic kidney disease often begins on the onset of resistant hypertension, defined as blood pressure that remains uncontrolled despite the use of multiple antihypertensive agents. The presence of early-onset hypertension and/or cerebrovascular accident at a young age should prompt further metabolic and endocrine evaluation [39].

Table 1. Monogenic hypertensive disorders affecting distal nephron sodium transport

Disorder	Gene	Inheritance	Age at onset	Key mechanism	Nephron target (transporter)	Electrolyte phenotype	Renin	Aldosterone	Targeted therapy
Liddle syndrome	<i>SCNN1B</i> , <i>SCNN1G</i> (rarely <i>SCNN1A</i>)	AD	Childhood to young adulthood	Gain-of-function ENaC due to impaired NEDD4-2-mediated degradation	Collecting duct (ENaC)	Hypokalemia, metabolic alkalosis	Low	Low	ENaC inhibitors (amiloride, triamterene)
Gordon syndrome	<i>WNK1</i> , <i>WNK4</i> , <i>CUL3</i> , <i>KLHL3</i>	AD or AR	Early childhood to adulthood	Dysregulation of the WNK-SPAK/OSR1 signaling pathway leading NCC overactivation	Distal convoluted tubule (NCC)	Hyperkalemia, hyperchloremic metabolic acidosis	Low	Low to normal	Thiazide diuretics
Apparent mineralocorticoid excess	<i>HSD11B2</i>	AR	Infancy/early childhood	Loss of 11 β -HSD2 activity allowing cortisol activation of MR	Collecting duct (MR-ENaC)	Hypokalemia, metabolic alkalosis	Low	Low	MR antagonists, ENaC blockers
Geller syndrome	<i>NR3C2</i>	AD	Adolescence to adulthood (often pregnancy-associated)	Activating mutation of the MR allowing progesterone or spironolactone to act as agonists	Collecting duct (MR-ENaC)	Hypokalemia (variable)	Low	Low	Amiloride; avoid spironolactone

11 β -HSD2, 11 β -hydroxysteroid dehydrogenase type 2; AD, autosomal dominant; AR, autosomal recessive; ENaC, epithelial sodium channel; MR, mineralocorticoid receptor; NCC, sodium-chloride cotransporter; OSR1, oxidative stress-responsive kinase 1; SPAK, SPS1-related proline/alanine-rich kinase; WNK, with-no-lysine (K) kinase.

The initial screening should include the measurement of plasma renin activity and plasma aldosterone levels, along with a comprehensive metabolic panel to assess potassium and bicarbonate levels [5,6,23]. A biochemical profile characterized by “low-renin, low-aldosterone” is a hallmark of Liddle syndrome or AME, whereas “low-renin, high-aldosterone” suggests primary aldosteronism (**Table 1**). If hyperkalemia and metabolic acidosis occur with hypertension, Gordon syndrome becomes the primary suspect [23].

Definitive diagnosis is increasingly achieved through genetic testing, including targeted gene panels, whole-exome sequencing, and whole-genome sequencing. Identifying the specific genetic mutation is not just an academic exercise; it has direct therapeutic implications. Precision medicine allows clinicians to bypass ineffective standard treatments, such as using angiotensin-converting enzyme inhibitors in a patient with Liddle syndrome and spironolactone in Geller syndrome, and move directly to the molecularly appropriate blocker (**Table 1**) [6,37].

This targeted approach prevents the devastating long-term consequences of uncontrolled hypertension, such as failure to thrive, premature stroke, chronic kidney disease, and heart failure, and improves long-term prognosis [17,23,36,40]. Genetic diagnosis also enables screening of family members, facilitates the identification of asymptomatic carriers, and informs genetic counseling and family planning.

CONCLUSION AND FUTURE PERSPECTIVES

Genetic kidney diseases represent important yet frequently under-recognized drivers of hypertension and cardiovascular morbidity [5,37,41]. Once considered rare textbook curiosities, these disorders are now increasingly recognized as important considerations in the differential diagnosis of early-onset or treatment-resistant hypertension. By elucidating how molecular mechanisms govern sodium transport and hormonal regulation in distal nephrons, these disorders provide a mechanistic framework connecting tubular transport defects to systemic electrolyte imbalance and blood pressure dysregulation [2,14,15,42,43].

Importantly, recognition of these genetic disorders has direct clinical implications. Characteristic biochemical signatures, such as hypokalemia in Liddle syndrome and AME,

or hyperkalemia in Gordon syndrome, can provide important diagnostic clues that guide targeted genetic testing. Mechanism-based therapies, such as ENaC inhibitors, thiazide diuretics, or MR-directed interventions, demonstrate how insights from monogenic diseases can translate directly into precision treatment strategies [6,37,43].

Future studies are increasingly focused on the broader genetic architecture of hypertension. Beyond rare monogenic disorders, emerging studies are exploring polygenic risk scores that incorporate multiple common variants affecting renal sodium transport pathways [44,45]. These low-penetrance variants may help explain inter-individual differences in salt sensitivity and susceptibility to hypertension [46,47].

As genetic testing becomes increasingly accessible, incorporating genomic data into clinical practice may reshape hypertension diagnosis. Future nephrology efforts may focus on mechanism- and genetics-based treatment strategies, in which hypertension management is tailored to the underlying molecular defect, thereby addressing the hidden renal drivers of this global disease.

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Review Article



Dietary Salt Intake and Hypertension in Chronic Kidney Disease

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ABSTRACT

There is a high prevalence of hypertension, which is both a cause and consequence of kidney function decline, among patients with chronic kidney disease (CKD). Impaired sodium excretion and the activation of the renin-angiotensin-aldosterone system (RAAS) are central mechanisms underlying this relationship. In early CKD, compensatory increases in fractional sodium excretion help maintain the balance of sodium in the body; however, as kidney function deteriorates, this compensatory mechanism is overwhelmed, resulting in sodium retention, extracellular volume expansion, and predominantly volume-dependent hypertension. Furthermore, CKD is characterized by heightened salt sensitivity, owing to which blood pressure (BP) responds disproportionately to changes in dietary salt intake. Emerging evidence suggests that non-osmotic sodium storage in tissues, such as alterations in glycosaminoglycan networks, impaired lymphatic clearance, and endothelial glycocalyx dysfunction, further contributes to salt-sensitive hypertension. Together with RAAS activation, these mechanisms promote vascular dysfunction, BP variability, and adverse cardiovascular outcomes. Dietary salt intake is a key modifiable factor in the management of CKD and hypertension. Randomized controlled trials have shown that decreased salt intake lowers BP, reduces proteinuria, and enhances the efficacy of RAAS inhibitors, thereby slowing the progression of CKD and reducing cardiovascular risk. Conversely, increased salt intake is associated with resistant hypertension, increased BP variability, and higher mortality; therefore, current guidelines recommend limiting salt intake to 5 g/day. The role of dietary potassium is increasingly recognized; however, caution is required in patients with advanced CKD due to the risk of hyperkalemia.

Keywords: Kidney failure, chronic; Renin-angiotensin system; Sodium chloride, dietary

INTRODUCTION

The prevalence of hypertension, a common comorbidity in patients with chronic kidney disease (CKD), increases with declining kidney function, with hypertension observed in over 90% of patients with end-stage kidney disease (ESKD) [1,2]. Hypertension is the

Conflicts of interest

Author has no conflicts of interest to declare.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

second leading cause of CKD, while impaired kidney function simultaneously causes and exacerbates hypertension through impaired sodium excretion and activation of the renin-angiotensin-aldosterone system (RAAS), affirming the close relationship between hypertension and CKD [3-5]. Hypertension accelerates the decrease in estimated glomerular filtration rate (eGFR) and leads to increased proteinuria in patients with CKD, resulting in progression of the disease, subsequently increasing the incidence of cardiovascular disease (CVD) and mortality [6,7].

Decreased eGFR restricts sodium excretion in CKD, leading to increased sodium retention and elevated blood pressure (BP). Additionally, owing to RAAS hyperactivity, even a small increase in dietary salt intake can cause a rapid rise in BP. Thus, patients with CKD exhibit a salt-sensitive phenotype, in which BP responds more acutely to dietary salt intake than among individuals in the general population [3,8,9]. Dietary salt intake is a modifiable factor, the reduction of which is an important goal not only to lower BP but also slow the progression of CKD and prevent CVD.

We discuss herein the effects and management of sodium in CKD, the mechanisms of salt-sensitive hypertension, the clinical significance of dietary salt intake in CKD and hypertension, and considerations for ensuring appropriate dietary salt intake.

SODIUM MANAGEMENT IN CKD

As CKD progresses, the number of functional nephrons decreases. In the early stages of the disease, the remaining functional nephrons maintain homeostasis by increasing the fraction excretion of sodium (FENa); however, when eGFR drops below approximately 30 mL/min/1.73 m², the compensatory mechanism reaches its limit, leading to sodium retention, increased BP, and worsening proteinuria [10-13].

In early-to-moderate CKD (stage G1-3), some nephrons are damaged, resulting in decreased eGFR. Consequently, the remaining functional nephrons compensate by inhibiting sodium reabsorption and increasing sodium excretion, leading to an increased FENa. Sodium reabsorption in the proximal tubule is reduced by the release of atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) owing to slightly increased fluid volume and increased peritubular hydrostatic pressure. The increased release of nitric oxide and prostaglandins to maintain renal blood flow and eGFR inhibits sodium reabsorption in the loop of Henle. Additionally, increased ANP/BNP levels inhibit the epithelial sodium channel (ENaC) in the distal tubules, thereby promoting natriuresis (Table 1).

Table 1. Sodium management according to CKD stage

Variables	Early CKD	Advanced CKD
FENa	Increased	Maximized
Total sodium excretion	Maintained (≈ intake)	Decreased
Main handling site	Proximal tubule	Distal tubule, collecting duct
Mechanism	Hyperfiltration, ANP/BNP	RAAS activation, fibrosis
Clinical outcome	Salt sensitivity	Volume overload
Pharmacological consideration	Sodium restriction may enhance the efficacy of RAASi therapy	Monitoring of hyperkalemia and kidney function during RAASi therapy; consider diuretics for volume control

ANP, atrial natriuretic peptide; BNP, B-type natriuretic peptide; FENa, fraction excretion of sodium; RAAS, renin-angiotensin-aldosterone system; RAASi, renin-angiotensin-aldosterone inhibitor.

While there were movements to increase tubular sodium excretion in early CKD, movements to inhibit sodium excretion also began. When the glomerulus recognizes that perfusion pressure is insufficient to compensate for the decrease in eGFR, it initiates renin secretion from the juxtaglomerular apparatus. Angiotensin II constricts the efferent arteriole much more strongly than the afferent arteriole, raising intraglomerular pressure in an attempt to maintain eGFR through compensatory glomerular hyperfiltration. Intrarenal RAAS activation promotes sodium retention and inhibits sodium excretion, contributing to increased fluid volume and salt-sensitive hypertension.

When eGFR drops $< 45 \text{ mL/min/1.73 m}^2$ (CKD stage G3b), the capacity for tubular sodium excretion rapidly declines, leading to increased fluid volume and pronounced systemic RAAS activation. From this stage onwards, ENaC is upregulated by aldosterone, increasing sodium reabsorption in the collecting duct. As CKD progresses to advanced stages (stages G4 and 5), increased Na^+/H^+ exchanger type 3 (NHE3) activity is present in the proximal tubule owing to RAAS activation; however, the decrease in NHE3 activity caused by renal tissue fibrosis and tubular atrophy is greater, resulting in reduced sodium reabsorption in the proximal tubule. RAAS activation triggers sodium chloride (NaCl) cotransporter activity in the distal tubule and ENaC activation in the collecting duct, thereby increasing sodium reabsorption (**Table 1**). This leads to chronic volume expansion, followed by predominantly volume-dependent hypertension, which is often difficult to treat.

From a clinical perspective, pharmacological treatment strategies should be considered alongside dietary sodium restriction. In patients with early CKD, sodium restriction may enhance the antihypertensive and antiproteinuric effects of RAAS inhibitor (RAASi) therapy, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), and steroidal and nonsteroidal mineralocorticoid receptor antagonists (MRAs), by reducing extracellular volume expansion and mitigating compensatory RAAS activation. ACEi and ARBs remain the cornerstone of antihypertensive therapy in CKD and are recommended as first-line agents because they provide both kidney and cardiovascular (CV) protection beyond BP lowering [3,14]. While evidence supporting non-steroidal MRAs has largely been derived from trials involving patients with diabetic CKD, recent findings from the FIND-CKD trial suggest potential renoprotective benefits of finerenone in patients with albuminuric non-diabetic CKD [1,15]. In advanced CKD, however, pharmacological management requires a more individualized approach because impaired sodium excretion is often accompanied by volume overload and an increased risk of hyperkalemia. Loop diuretics may facilitate sodium removal and volume control, whereas careful monitoring of serum potassium and kidney function is necessary when RAASi therapy is used (**Table 1**) [1].

SALT-SENSITIVE HYPERTENSION IN CKD

Salt sensitivity is a condition in which BP changes significantly in response to variations in salt intake, typically assessed by a difference in mean arterial pressure of $> 10\%$ or 5–10 mmHg or more between a high-salt and a low-salt diet [16,17]. Salt-sensitive hypertension is a condition in which BP rises in response to increased salt intake. The kidneys play a significant role in the development of salt-sensitive hypertension, which is highly prevalent in patients with CKD [18,19], owing to the aforementioned impaired sodium handling by the kidneys, and, to a degree, an imbalance in the non-osmotic sodium storage system. Although sodium draws water into the plasma to maintain osmotic pressure and increase fluid volume, recent studies

suggest that a significant amount of sodium is stored non-osmotically by binding to the glycosaminoglycan network in the dermal interstitium, without water retention [20,21].

Sodium homeostasis changes at the tissue level in patients with CKD, extending beyond simple fluid regulation. The structural modifications and reduced sulfation of dermal interstitial glycosaminoglycans impair their sodium-binding capacity, causing sodium to accumulate abnormally within the interstitial layer [20]. Normally, this sodium accumulation stimulates macrophages to secrete vascular endothelial growth factor C and promote lymphangiogenesis, thereby removing excess sodium [22]. However, in the advanced stages of CKD, this immune-lymphatic regulatory mechanism fails to function adequately, limiting the removal of sodium from the tissues. This accumulated sodium contributes to vascular dysfunction and salt-sensitive hypertension [23]. The glycocalyx in the vascular endothelium is also integral in regulating sodium [24]; however, in CKD, chronic inflammation and oxidative stress damage the glycocalyx, leading to a decrease in sodium buffering capacity at the vascular level [25-27]. These changes further exacerbate the increase in vascular resistance and associated rise in BP upon salt intake.

Furthermore, genetic factors are known to be involved in salt-sensitive hypertension. Monogenic disorders associated with salt-sensitive hypertension, including apparent mineralocorticoid excess and Liddle syndrome, provide strong evidence for the role of the kidney in BP regulation. Hypertension in these disorders has been shown to improve after kidney transplantation, further supporting the concept that the kidney is a key determinant of salt-sensitive hypertension [18,28].

As previously mentioned, increased salt sensitivity is characterized by a greater BP response to salt intake, often manifesting as a 5–10 mmHg increase in BP. Importantly, the clinical implications of this BP rise differ according to CKD stage. Patients with CKD already have a reduced capacity for sodium buffering, resulting in a larger standard deviation of systolic BP and, consequently, increased BP variability [29]. Additionally, a “pressure-natriuresis” mechanism is activated in patients with CKD to promote the excretion of sodium retained during the day, leading to nocturnal hypertension and a non-dipping pattern of BP [29]. In the early CKD (stages G1 and 2), even a modest rise in BP driven by salt intake elevates intraglomerular pressure, inducing proteinuria, inflammation, and fibrosis in the tubule and interstitium, thereby accelerating the progression of CKD [30]. In advanced CKD (stages G3-5), where sodium excretion and tissue buffering capacities are severely exhausted, this 5–10 mmHg shift serves as a critical tipping point. In these advanced stages, it directly exacerbates volume overload, precipitates resistant hypertension, and exponentially drives the risk of acute CV events, such as heart failure and stroke [31,32]. These factors—BP variability, nocturnal hypertension, and stage-specific CKD progression—are linked to an increased risk of CVD [29,33].

CLINICAL SIGNIFICANCE OF DIETARY SALT INTAKE IN HYPERTENSION AND CKD

Dietary salt intake, which plays a significant role in the progression of hypertension and CKD, is one of the major factors determining BP. Many previous randomized controlled trials (RCTs) have demonstrated the importance of dietary salt intake. For example, the Dietary Approaches to Stopping Hypertension (DASH)-sodium trial showed that in patients with

hypertension, low-salt intake lowered BP in a dose-dependent manner, with the greatest reduction at the lowest intake level ($\leq 1,500$ mg/day) [34,35]. Furthermore, in patients with CKD, dietary salt restrictions slow the progression of CKD by reducing not only BP but also intraglomerular pressure and proteinuria [36]. RCTs conducted on patients with CKD have shown that a low-salt diet effectively reduces extracellular fluid volume and arterial stiffness, thereby lowering the risk of CVD and progression to ESKD [36,37]. Furthermore, dietary salt intake affects RAAS activation and treatment responsiveness [36]. While a high-salt diet attenuates the antiproteinuric and antihypertensive effects of RAASi therapy, dietary salt restriction significantly improved treatment responsiveness to RAASi therapy [38,39]. In a randomized crossover study of patients with CKD, reducing dietary salt intake resulted in an additional 5–10 mmHg reduction in SBP and a 30–50% reduction in proteinuria compared with the effects achieved with RAASi therapy monotherapy [40]. However, the clinical application of the DASH diet should be differentiated based on the CKD stage, particularly regarding potassium intake. While the high potassium content of the DASH diet offers significant CV benefits and BP control in the early stages of CKD, it poses a critical risk of hyperkalemia in patients with advanced CKD. Therefore, current clinical guidelines recommend regular monitoring of serum potassium levels and individualized modification of the DASH diet according to CKD stage and hyperkalemia risk [1].

Increased dietary salt intake is associated with treatment-resistant hypertension as well as increased BP variability and nocturnal hypertension, which are closely linked to worsening CVD prognoses and increased mortality. Conversely, the restriction for dietary salt improves these abnormal BP patterns and reduces the overall risk of CVD [34,41].

APPROPRIATE DIETARY SALT INTAKE

According to Kidney Disease: Improving Global Outcomes, optimal dietary salt intake is < 5 g (approximately 2,000 mg of sodium) to reduce the risk of hypertension and CVD in patients with hypertension and CKD [1,3]. While stricter dietary salt restrictions, such as $\leq 1,500$ mg/day of sodium, show a more potent BP-lowering effect [42], observational studies have shown a J-shaped relationship between dietary salt intake and mortality and CV events, and very low salt intake may require caution as it can lead to inadequate nutritional intake and nutritional imbalance, particularly in elderly patients and those with advanced CKD [43].

There is a paucity of research on whether the type of dietary salt is related to clinical outcomes or on which diet should be followed. However, according to the results of the Salt Substitute and Stroke Study, replacing regular sodium chloride with potassium-fortified salt substitutes significantly lowered the risk of stroke and major CVDs compared with regular salt [44]. Furthermore, it has been reported that increased dietary potassium intake is associated with lower BP, improved vascular function, and a reduced risk of CVD [45]. In particular, the sodium-potassium ratio appears to be a more powerful predictor of hypertension and CVD outcomes than dietary salt intake alone [46]. Increased dietary potassium intake promotes sodium excretion and regulates sodium-chloride cotransporter activity in the distal tubules, thereby mitigating the hypertensive effects of sodium [47]. Therefore, even with the same dietary salt intake, a potassium-rich diet, such as the DASH diet, can help improve CV risk and metabolic parameters and control BP [1,48]. However, in patients with advanced CKD (stages G3b–G5) or RAASi therapy, caution is required when using the DASH diet or potassium-containing salt substitutes owing to the risk of hyperkalemia [3,49]. Therefore, for

these high-risk patients, regular monitoring of serum potassium levels and kidney function, and individualized dietary counseling are essential to safely balance the risk of electrolyte imbalance with the benefits of salt restriction.

In conclusion, impaired sodium handling in CKD leads to salt-sensitive hypertension and adverse outcomes; therefore, appropriate dietary salt restrictions are essential, accounting for individualized consideration of disease stage and potassium balance.

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Review Article



Overcorrection of Hyponatremia: A Complicated Story

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ABSTRACT

Overcorrection is a frequently encountered issue in the treatment of severe hyponatremia, which is defined as a serum sodium concentration below 120–125 mmol/L in symptomatic patients. Severe hyponatremic symptoms, including persistent vomiting, cardiorespiratory arrest, seizures, and reduced consciousness, clearly indicate the use of hypertonic (e.g., 3%) saline infusion to immediately elevate serum sodium levels. In the chronic phase, however, overcorrection is a major concern because an overly rapid increase in serum sodium concentration is an important cause of osmotic demyelination syndrome (ODS). Although risk groups for ODS are well known, saline infusion and water diuresis are 2 common factors underlying the overcorrection of hyponatremia. We propose that isotonic saline initially be infused (1 mL/kg/h) when encountering hyponatremic patients with moderately severe symptoms, such as confusion, headache, or nausea. Although this empirical therapy may not be consistent with current guidelines, it may reduce the risk of overcorrection and be effective in cases with unrecognized hypovolemia or waning vasopressin hyperactivity. We believe that hypertonic saline should be reserved for patients with severely symptomatic hyponatremia. In practice, urine sodium and osmolality should then be measured, along with follow-up serum sodium levels. Subsequent intravenous fluids can be selected according to the response of serum sodium levels and the differential diagnosis of hyponatremia. Because water diuresis is a critical contributor to overcorrection, urine output and urine sodium, potassium, and osmolality should be monitored during fluid therapy. Appropriate use of 5% dextrose in water and/or desmopressin may be necessary to re-lower serum sodium levels.

Keywords: Desmopressin; Hyponatremia; Overtreatment; Saline solution

TREATMENT OF SEVERE HYPONATREMIA

Hyponatremia is a low serum sodium concentration resulting from an excess of extracellular water relative to sodium. Based on changes in sodium balance, hyponatremia is classified as hypovolemic, euvoletic, or hypervolemic. This classification is important because treatment principles are different depending on whether to restore sodium balance.

Irrespective of the sodium status, however, acute treatment of the severe hyponatremia aims to elevate the serum Na^+ concentration. Usually, the hyponatremia is considered severe when the serum Na^+ level is below 120–125 mmol/L and the patient is symptomatic [1,2]. For acute treatment of severe hyponatremia, guidelines recommend 3% NaCl solution using either bolus (100–150 mL over 10–20 minutes) therapy or continuous infusion (0.5–1 mL/kg/h) until a 5 mmol/L elevation of serum Na^+ over 1–4 hours is reached [2]. The SALSA randomized clinical trial reported that rapid intermittent administration of hypertonic saline was preferred because bolus therapy had a lower incidence of therapeutic relowering treatment and tended to have a better efficacy in achieving serum Na^+ within 1 h than continuous infusion [3].

Here, we present 2 cases with severe hyponatremia and describe their courses after an intravenous bolus of 100 mL 3% NaCl. With a literature review, strategies to avoid overcorrection of hyponatremia are discussed.

CASE VIGNETTE

Case 1

A 71-year-old female visited the emergency room (ER) due to confusion. She was previously diagnosed to have senile dementia and was taking an uncertain antihypertensive medication. Her oral intake was poor during the past week, but drinking water was not limited. The initial laboratory results were as follows: serum Na^+ 110 mmol/L, K^+ 2.4 mmol/L, Cl^- 77 mmol/L, total CO_2 12.5 mmol/L and creatinine 0.56 mg/dL, and blood urea nitrogen (BUN) 3.3 mg/dL. Her brain imaging (computed tomography [CT] and magnetic resonance [MR]) revealed mild diffuse brain atrophy. After 100 mL 3% saline was infused over 20 min, 0.9% saline containing potassium chloride (KCl) was continued. The follow-up labs taken 5 hours after the initial sampling were as follows: serum osmolality 236 mOsm/kg H_2O , Na^+ 116 mmol/L, K^+ 2.6 mmol/L, Cl^- 85 mmol/L, total CO_2 18.0 mmol/L and uric acid 3.4 mg/dL, and urine osmolality 151 mOsm/kg H_2O , Na^+ 40 mmol/L, K^+ 14 mmol/L, Cl^- 39 mmol/L and creatinine 10.6 mg/dL. In the meantime, urine output was 1,600 mL.

Follow-up laboratory data were reported nine hours later when the patient was admitted to a ward: serum Na^+ 123 mmol/L, K^+ 2.2 mmol/L, Cl^- 90 mmol/L, and total CO_2 19.0 mmol/L. She was still confused or stuporous despite an increase in serum Na^+ level. The tonicity of intravenous fluid was lowered to half-isotonic. However, the follow-up serum Na^+ taken eight hours later was 129 mmol/L. Therefore, the increase in serum Na^+ was 19 mmol/L over 22 hours. To lower the serum Na^+ level, the half-isotonic fluid was switched to 5% dextrose in water (40 mL/h). The daily intake/output was assumed 2,400/5,050 mL, and the follow-up urine data were as follows: osmolality 104 mOsm/kg H_2O , Na^+ 12 mmol/L, K^+ 9.5 mmol/L, Cl^- 16 mmol/L and creatinine 17.6 mg/dL.

The consciousness of the patient was improved, and verbal communication became possible. Nonetheless, the follow-up serum Na^+ was not lowered and was 132 mmol/L nine hours later. The duty physician decided to use desmopressin, and the serum Na^+ was lowered to 127 mmol/L in 10 hours.

Case 2

Another 71-year-old female visited the ER due to a seizure. The seizure movement subsided when she arrived at the ER. However, she was confused and nauseated. The initial

laboratory results were as follows: serum Na^+ 116 mmol/L, K^+ 3.5 mmol/L, Cl^- 84 mmol/L, total CO_2 13.3 mmol/L, and creatinine 0.49 mg/dL, and BUN 6.8 mg/dL. Her brain imaging (CT and MR) revealed no remarkable findings. After 100 mL 3% saline was infused over 20 min, 0.9% saline was continued at a rate of 60 mL/h.

She became alert when she was admitted to the intensive care unit (ICU). With a Foley catheter inserted, the urine output was initially 1,100 mL and subsequently 500 mL over one hour. The follow-up serum data taken six hours after the initial sampling were Na^+ 126 mmol/L and uric acid 3.0 mg/dL. When another six hours had passed, serum Na^+ reached 137 mmol/L. Therefore, the increase in serum Na^+ was 21 mmol/L over 12 hours. The isotonic saline was switched into half-isotonic (60 mL/h), and her consciousness became clear.

Eight hours later, however, she complained of headache and nausea. The serum Na^+ level was stationary (138 mmol/L). Although the half-saline was replaced by 5% dextrose in water (80 mL/h), the serum Na^+ was not lowered. The daily urine output exceeded intake, and urine osmolality fluctuated between 562 and 150 mOsm/kg H_2O . Only after the use of desmopressin, the serum Na^+ was lowered to 129 mmol/L over 6 hours. Her headache and nausea were relieved along with the reduction of urine output.

MORBIDITY AND MORTALITY OF HYPONATREMIA

In addition to the level of plasma Na^+ , the rapidity of hyponatremia development is critical in determining the severity of hyponatremia. Therefore, hyponatremia is classified as acute or chronic depending on whether it develops within 48 hours or not. Acute hyponatremia is usually symptomatic and requires urgent therapy because patients with acute hyponatremia have a risk of cerebral edema [4]. The symptoms of hyponatremia can be grouped as moderately severe and severe; whereas moderately severe symptoms are headache, nausea, and confusion, severe symptoms include vomiting, cardiorespiratory distress, abnormal and deep somnolence, seizures, and coma [1]. Our cases seemed to have moderately severe symptoms when they arrived at the ER, and their hyponatremia may be considered chronic because of unclear onset. Although the seizure had ceased upon arrival at the ER, case 2 was eligible for treatment with 3% hypertonic saline because of the severity of hyponatremia. This case suggests that avoiding overcorrection of hyponatremia may be difficult when using the traditional approach.

After the acute phase, chronic changes in extracellular tonicity occur for long-term adjustment through the efflux of organic osmolytes [5]. This compensation should be considered when chronic hyponatremia is corrected because rapid correction of extracellular tonicity can lead to a neurological disorder called osmotic demyelination.

Gait disturbances and cognitive impairment are frequently noted in patients with chronic hyponatremia due to altered neuronal activity in brain [6]. Chronic hyponatremia also induces calcium release from bone cells and lead to bone demineralization, osteoporosis and an increased risk of fractures [7].

Hyponatraemia, even when mild, is associated with increased mortality [8]. Acute hyponatremia can be life-threatening due to neurological deficits, and chronic hyponatremia is also associated with increased all-cause and cardiovascular mortality

[9]. Recently, hyponatraemia was found to promote vascular calcification through Rac1-Akt pathway activation [10]. Although patients with hyponatremia usually have comorbid conditions, hyponatremia is consistently identified as an independent contributor to increased mortality [11].

OVERCORRECTION OF HYPONATREMIA AND OSMOTIC DEMYELINATION SYNDROME (ODS)

Temporary or permanent brain damage associated with rapid correction of chronic hyponatremia clinically presents 1 to 7 days after treatment [12]. This delayed onset of neurologic symptoms has been called ODS, and pontine and extrapontine myelinolysis can be demonstrated by magnetic resonance images or autopsy in severely affected patients. Brain astrocyte death and disruption of the blood–brain barrier precedes the development of ODS [13].

The first report of central pontine myelinolysis, a major component of ODS, was documented by autopsy in two middle aged women with severe, diuretic-induced hyponatremia (serum Na⁺, 96 and 100 mmol/L) and a history of protracted vomiting and drowsiness, who deteriorated neurologically after treatment with 3% saline increased their serum sodium concentration by 25 and 32 mmol/L over 48 hours [14]. Subsequent clinical and experimental studies confirmed that overly rapid correction of serum sodium can be associated with ODS [12]. The risk of ODS is increased in patients with liver disease, alcohol use, hypokalemia, severe hyponatremia, and malnutrition [15]. Our cases of severe hyponatremia were malnourished and had low levels of serum potassium.

However, the incidence of ODS is very low even in severe hyponatremia, whereas overcorrection is frequently associated with the treatment of hyponatremia. A bolus of hypertonic saline has the advantage of an immediate effect with little risk of overcorrection [16], but in the SALSA clinical trial, cumulative overcorrection occurred in 15 of 87 (17.2%) patients who were treated with bolus therapy [3].

In a large, a multicenter cohort study of 22,858 hospital admissions of adult patients whose serum Na⁺ < 130 mmol/L, rapid correction of serum Na⁺ (>8 mmol/L over 24 hours) was frequent (17.7%), but ODS was rare (0.05%) [17]. ODS occurred in 3 of 1,000 who had an initial serum sodium level of less than 120 mmol/L, and the incidence of ODS was 0.14% even when the analysis was limited to the patients with the rapid correction of serum Na⁺. Seven (58%) patients who developed ODS did not have rapid correction of serum Na⁺ [17], compatible with the notion that ODS is of multifactorial nature.

Moreover, ODS is infrequent even when correction rates exceed current guidelines, and faster correction may actually lower in-hospital mortality. In a recent systematic review and meta-analysis involving 16 studies and 11,811 patients, slow (< 8 or 6–10 mmol/L over 24 hours) and very slow (< 4–6 mmol/L over 24 hours) correction of severe hyponatremia (serum sodium < 120 or < 125 mmol/L plus severe symptoms) were associated with an increased risk of mortality and hospital length of stay compared to rapid correction. Notably, rapid correction was not associated with a statistically significant increase in the risk of ODS [18]. Healthier patients may tolerate faster correction better, while sicker patients may be more prone to both ODS and mortality.

CAUSES FOR OVERCORRECTION OF HYPONATREMIA

Treatment of severe hyponatremia is delicate because of the 2 sequential strategies; the initial correction must be rapid during the first few hours to decrease cerebral edema, and a slow correction < 10 mmol/L over 24 hours should be followed to avoid the development of ODS [19]. The strict goal of serum Na⁺ lowering was proposed as 4 to 8 mmol/L per day for patients at high risk of overcorrection or ODS (**Table 1**) [15,20-22].

The use of hypertonic saline solution is advantageous for the initial rapid correction, but is prone to later overcorrection. Repeat doses of intravenous bolus therapy would increase the risk of overcorrection. In our cases, however, serum Na⁺ levels were too rapidly corrected despite a single bolus infusion of 100 mL 3% NaCl. In terms of sodium load, the risk of overcorrection can be lessened by the use of isotonic saline. In a Japanese single-center retrospective study on the patients with severe hyponatremia visiting the ER, the lower risk of overcorrection was associated in the 0.9% saline users compared with 3% saline users [23].

In principle, intravenous administration of isotonic saline solution is indicated for treating hypovolemic hyponatremia. Continuous infusion of isotonic saline at a rate of 1 mL/kg/h seems to be safe and effective, aiming an increase in serum Na⁺ between 4–7 mmol/L over the first 24 hours in patients with hypovolemic hyponatremia [24]. In a typical syndrome of inappropriate antidiuresis (SIAD), the serum Na⁺ concentration may actually decrease during the infusion of isotonic saline if the urine Na⁺ plus K⁺ concentration is much higher than 154 mmol/L [12]. Patients given large volumes of isotonic saline may be more likely to overcorrect than patients given low volumes of hypertonic saline [25].

In addition to an excess sodium load to the extracellular fluid, spontaneous water diuresis is an important cause for overcorrection of hyponatremia [26]. Appropriate and inappropriate stimuli of vasopressin release can be attenuated or ceased by the administration of saline, volume repletion, discontinuing hyponatremia-inducing drugs or stress relief, leading to hypoosmotic polyuria. As shown in our cases, water diuresis, defined as urine flow ≥ 2 mL/kg/h and urine Na⁺ plus K⁺ concentration ≤ 50 mmol/L, is common during the treatment for severe hyponatremia and typically occurs within the first 24 hours [27]. Polyuria was remarkable in our cases, and their urine chemistry was compatible with water diuresis. Therefore, physicians should pay attention not only to changes in serum Na⁺ levels but also to the diuretic response. Electronic alert systems may provide rapid notifications during the treatment of hyponatremia, enabling timely intervention by physicians and nursing staff.

Table 1. Risk groups for overcorrection and ODS in hyponatremia

Overcorrection	ODS
Low solute intake	Serum sodium < 105 mmol/L
Hypovolemia	Hypokalemia
Adrenal insufficiency	Malnutrition
Transient SIAD ^a	Alcoholism
Thiazide diuretics	Advanced liver disease
Prior use of desmopressin	V2R antagonist therapy
Body weight < 60 kg	

ODS, osmotic demyelination syndrome; SIAD, syndrome of inappropriate antidiuresis; V2R, vasopressin-2 receptor.

^aTransient SIAD may be caused by nausea, hypoxia, surgery, pain, or stress.

Table 2. Major causes for overcorrection of hyponatremia

Major causes
Sodium load to extracellular fluid
Spontaneous water diuresis
Potassium administration
Application of the Adrogué-Madias formula
Small body size

Hypertonic saline induces more water diuresis than isotonic saline during the treatment of hyponatremia because hypertonicity acts as a potent osmotic stimulus to pull water into the intravascular space, facilitating the excretion of free water in excess of sodium [20,28]. We could not avoid overcorrection in our cases although isotonic saline infusion was followed by a single bolus of 3% hypertonic saline. Close monitoring of serum Na^+ is advisable, initially every 1–2 hours and then every 4 hours, particularly if urine output is high ($> 150 \text{ mL/h}$ or 2 mL/kg/h) [19,28]. Overcorrection might have been lessened if we had monitored urine output hourly from the beginning of treatment.

Intracellular free water uptake is another cause for overcorrection of hyponatremia [26]. Some patients with hyponatremia accompanies K^+ deficiency (e.g., thiazide-induced hyponatremia), and K^+ administration can increase serum Na^+ concentration primarily through osmotic water shifts; as potassium is taken up into cells, it creates an osmotic gradient that draws water out of the extracellular space. Additionally, to maintain electrical neutrality, intracellular K^+ uptake can lead to an equivalent movement of Na^+ out of cells into the extracellular fluid. According to the Edelman equation, serum Na^+ concentration is determined by the total amount of exchangeable Na^+ and K^+ divided by total body water [29]. We had to intravenously supplement potassium to correct hypokalemia, and thiazide-induced hyponatremia might have underlain case 1 [30]. To treat thiazide-induced hyponatremia, the intravenous administration of 1–2 L of isotonic saline containing 40 mmol KCl over 24 hours may be optimal in conjunction with stopping the thiazides [19].

The Adrogué-Madias formula is typical in aiding fluid prescription to correct hyponatremia [31]. However, it frequently underestimates the increase in serum Na^+ after hypertonic saline infusion because of ignoring renal water losses and variable active water excretion, such as sudden suppression of vasopressin release (e.g., in syndrome of inappropriate antidiureis or volume depletion) [32].

Finally, we need to be more cautious about overcorrection of hyponatremia when the patients are old females like our cases with a small body size. According to a single-center, retrospective study, bolus infusion of 100 or 150 mL 3% NaCl may expose patients with low ($\leq 60 \text{ kg}$) and high ($\geq 100 \text{ kg}$) body weight to more overcorrection and undercorrection, respectively. **Table 2** summarizes the major causes for overcorrection of hyponatremia.

USE OF DESMOPRESSIN TO PREVENT OVERCORRECTION IN SEVERE HYPONATREMIA

Hyponatremia is often spontaneously improved by water diuresis when the causative factors such as hypovolemia, medications, and pain or stress, are reversed. We saw in our cases that spontaneous excretion of dilute urine raised the serum Na^+ by $> 2 \text{ mmol/L/h}$, exceeding

therapeutic limits within a few hours. Three regimens of therapeutic re-lowering of serum Na^+ are feasible: intravenous 5% dextrose in water, parenteral desmopressin, or both. We used less amount of 5% dextrose solution compared with the guidelines (3 mL/kg/h or 10 mL/kg over 1 hour) [1,15]. Therefore, we had to use desmopressin for rescue.

Three different strategies of desmopressin administration for prevention or treatment of overcorrection in hyponatremia [20,22]: 1) proactive, in anticipation of water diuresis; 2) reactive, in response to water diuresis and impending overcorrection; and 3) rescue, after overcorrection had already occurred. The proactive strategy starts immediately when the patients whose serum Na^+ is less than 115 mmol/L have risk factors for overcorrection or ODS (**Table 1**). Along with hypertonic saline bolus or continuous infusion, desmopressin 2–4 μg is administered intravenously or subcutaneously every 6–8 hours. The reactive strategy starts when a high urine flow ($> 1 \text{ mL/kg/h}$ or $> 100 \text{ mL/h}$) is noted in patients whose serum Na^+ increase was $\leq 6 \text{ mmol/L}$ in a 24-hour period. It also uses intravenous or subcutaneous desmopressin 2–4 μg every 6–8 hours. The rescue strategy is applied when overcorrection (serum Na^+ elevation $\geq 8 \text{ mmol/L}$ in a 24-hour period) has occurred. Along with 5% dextrose in water (3 mL/kg/h), desmopressin 2–4 μg is administered intravenously or subcutaneously every 6–8 hours.

In our cases, the rescue desmopressin was used. Earlier applications of desmopressin might have prevented or relieved overcorrection of hyponatremia. Although favored by some experts, the proactive strategy may prolong the hospital stay [20]. We think the reactive strategy should be optimal [33], and vigilant urine output monitoring particularly during the first 24–48 hours is necessary.

CONCLUSION

Severe hyponatremia is vulnerable to overcorrection during saline infusion, and spontaneous water diuresis is a critical mechanism leading to overcorrection. The greater the amount of sodium administered to the plasma, the higher the risk of overcorrection. Therefore, hypertonic saline should be reserved for patients with severely symptomatic hyponatremia. We prefer the use of isotonic saline rather than hypertonic saline in patients with moderately severe symptoms who present to the ER. Unrecognized hypovolemia may respond to isotonic saline infusion, and some patients with transient SIAD may also improve with isotonic saline. The decision to switch to hypertonic saline can be made after evaluating follow-up changes in serum Na^+ and urine parameters, including hourly urine flow, Na^+ , K^+ , and osmolality (**Fig. 1**). During the first 24–48 hours of treatment, vigilant monitoring of urine output is essential to avoid overcorrection of hyponatremia.

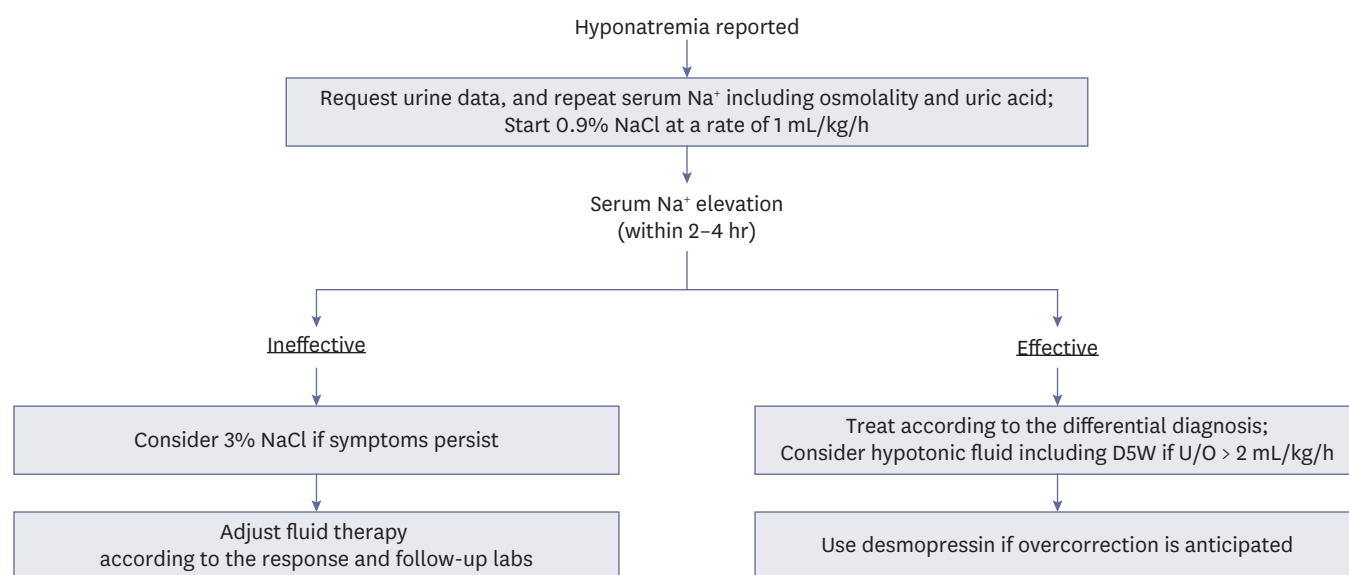


Fig. 1. Exemplary therapeutic approach for patients with moderately severe symptomatic hyponatremia who present to the emergency room and are awaiting admission. The initial serum sodium concentration is usually below 125 mmol/L, and patients typically present with confusion, headache, or nausea, but without persistent vomiting, cardiorespiratory arrest, seizures, or reduced consciousness. This scheme is intended to avoid overcorrection of hyponatremia. D5W, 5% dextrose in water; U/O, urine output.

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Review Article



Impact of the Four Pillars on Electrolyte Derangements during State-of-the-Art Therapy for Diabetic Kidney Disease

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ABSTRACT

The pharmacological management of diabetic kidney disease (DKD) has shifted toward a “four-pillar” approach that offers robust cardiorenal protection. While traditional renin-angiotensin system (RAS) inhibitors carry well-documented electrolyte risks, the distinct electrolyte profiles of novel therapies—sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and non-steroidal mineralocorticoid receptor antagonists (nsMRAs)—warrant a comprehensive understanding. This review examines these drug-induced electrolyte derangements. SGLT2 inhibitors demonstrate a highly favorable safety profile; despite inducing osmotic diuresis, they are notably associated with a reduced risk of hyperkalemia. Similarly, GLP-1 RAs possess an exceptionally low risk of direct renal electrolyte wasting, with imbalances occurring primarily secondary to severe gastrointestinal intolerance. Conversely, nsMRAs, such as finerenone, introduce a mild risk of hyperkalemia, though their unique receptor selectivity significantly diminishes this risk compared to traditional steroidal mineralocorticoid receptor antagonists. Crucially, combining SGLT2 inhibitors and nsMRAs creates a physiological synergy that attenuates hyperkalemic adverse effects while maximizing antiproteinuric benefits. By integrating these complementary mechanisms alongside routine electrolyte monitoring, clinicians can safely sustain these indispensable combination therapies and optimize clinical outcomes in DKD.

Keywords: Glucagon-like peptide-1 receptor agonists; Hyperkalemia; Mineralocorticoid receptor antagonist; Sodium-glucose transporter 2 inhibitor

INTRODUCTION

The establishment of the “four-pillar” of pharmacological therapy has reshaped the management of diabetic kidney disease (DKD), rendering a comprehensive understanding of these mechanistically distinct agents essential. In particular, recognizing drug-induced electrolyte imbalances is a critical priority for prescribing clinicians, which, in turn, requires a fundamental grasp of the baseline electrolyte vulnerabilities inherent to the

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

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pathophysiology of DKD. The diabetic intrarenal environment is characterized by progressive neurohormonal and structural alterations that predispose patients to severe electrolyte derangements even prior to any pharmacological intervention.

The most prominent pathophysiological hallmark of advanced DKD is hyporeninemic hypoaldosteronism, which clinically manifests as type 4 renal tubular acidosis. Persistent chronic hyperglycemia and microvascular ischemia lead to the hyalinization of the afferent arteriole and subsequent damage to the juxtaglomerular apparatus, impairing renin synthesis and release [1]. Concurrently, autonomic neuropathy and impaired conversion of prorenin to active renin further suppress the renin-angiotensin system (RAS) axis. This deficit in aldosterone-mediated sodium-potassium exchange in the principal cells of the cortical collecting duct directly results in chronic potassium retention [2]. Consequently, DKD patients exhibit a significantly higher propensity for developing hyperkalemia at a much earlier stage of chronic kidney disease (CKD) compared to those with non-diabetic etiologies. This underlying defect drastically narrows the safety margin when introducing standard-of-care cardiorenal therapies.

Advanced DKD accompanied by nephrotic-range proteinuria introduces complex hemodynamic and metabolic shifts that alter electrolyte homeostasis. First, the profound loss of oncotic pressure induces arterial underfilling, triggering secondary hyperaldosteronism and non-osmotic antidiuretic hormone (ADH) release that result in chronic dilutional hyponatremia [3], while acute glycemic spikes concurrently induce transcellular fluid shifts that manifest as hyponatremia. In parallel, massive proteinuria leads to the co-excretion of vitamin D-binding protein, significantly compromising the intrarenal generation of active $1,25(\text{OH})_2\text{D}_3$ [4,5]. This deficit in active vitamin D, paired with phosphate retention from a declining estimated glomerular filtration rate (eGFR), precipitates hypocalcemia and accelerates secondary hyperparathyroidism. Finally, the combination of heavy proteinuria and osmotic diuresis facilitates substantial urinary magnesium loss, which is worsened by the hyperglycemia-induced downregulation of tubular magnesium transporters [6], thereby establishing a highly vulnerable electrolyte baseline.

Recognizing these multifaceted baseline disturbances is critical, as they form the precarious pathophysiological backdrop against which modern pharmacotherapies operate. By anticipating adverse effects and implementing rigorous monitoring based on a deeper understanding of these medications, clinicians can successfully overcome these electrolyte-related hurdles. Given that RAS inhibitor-induced electrolyte disturbances have been extensively covered in previous literature, this review will focus on the electrolyte imbalances associated with the remaining three therapeutic pillars: sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and non-steroidal mineralocorticoid receptor antagonists (nsMRAs). The distinct electrolyte profiles and clinical considerations for each class are summarized in **Table 1**. Furthermore, we explore how combination therapies involving these agents can mitigate electrolyte derangements, ultimately offering patients optimal treatment strategies.

RAS INHIBITORS

Among the four pillars, RAS inhibition serve as the cornerstone of DKD treatment. Agents such as angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor

Table 1. Electrolyte profiles and clinical considerations of novel pharmacotherapies in diabetic kidney disease

Class	Main electrolyte effects	Primary mechanism	Clinical caveats & monitoring
SGLT2 inhibitors	Potassium: Reduced risk of hyperkalemia Magnesium: Mild increase	Promotes distal sodium delivery and osmotic diuresis, enhancing K ⁺ secretion; augments renal Mg ²⁺ reabsorption.	Generally safe; monitor for volume depletion. Clinical vigilance for hypernatremia in acute illness.
GLP-1 RAs	Potassium: Neutral/mild decrease Sodium: Neutral/hyponatremia	Low intrinsic renal effect; electrolyte imbalances are typically secondary to GI side effects.	Monitor electrolytes primarily in patients with severe GI intolerance (nausea, vomiting, diarrhea) to prevent secondary dehydration.
nsMRAs (e.g., finerenone)	Potassium: Mild to moderate increase Sodium: Potential dilutional hyponatremia	Antagonizes MR in the distal tubule, reducing ENaC-mediated Na ⁺ reabsorption and K ⁺ excretion.	Lower risk of hyperkalemia than steroidal MRAs due to unique receptor selectivity; requires routine K ⁺ monitoring.
Synergistic combination (SGLT2 inhibitors + nsMRA)	Potassium: Attenuated hyperkalemia risk	Physiological Synergy: SGLT2 inhibitors-induced distal Na ⁺ delivery and flow offset the K ⁺ -retaining effect of nsMRAs.	The “Ideal Synergy”: Maximizes cardiorenal and antiproteinuric benefits while neutralizing the primary limiting adverse effect (K ⁺).

ENaC, epithelial sodium channel; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MR, mineralocorticoid receptor; nsMRA, non-steroidal mineralocorticoid receptor antagonist; SGLT2, sodium-glucose cotransporter-2.

blockers (ARBs) directly confer renoprotection by reducing intraglomerular pressure and proteinuria, addressing specific intrarenal hemodynamic pathways [7,8]. Notably, the landmark Irbesartan Diabetic Nephropathy Trial demonstrated that the renoprotective benefits of irbesartan extend far beyond blood pressure control. Historically, the dual blockade of ACEi and ARBs has not been recommended due to an increased risk of adverse events, primarily hyperkalemia [8]. Today, however, the fear of hyperkalemia rarely deters clinicians from optimizing RAS inhibitor therapy.

Recent meta-analyses have shown that the concurrent use of novel potassium binders, such as patiromer and sodium zirconium cyclosilicate, increases the achievement rate of optimal RAS inhibitor doses by approximately 14% and significantly lowers the risk of hyperkalemia compared to placebo in patients with heart failure and CKD [9]. Furthermore, real-world data indicate that maintaining RAS inhibitor therapy with the strategic aid of these potassium-lowering agents is associated with reduced all-cause mortality and lower hospitalization rates [10,11].

SGLT2 INHIBITORS

SGLT2 inhibitors reduce hyperfiltration and improve metabolic control, exerting renoprotective effects through mechanisms beyond glucose reduction. Clinical studies have demonstrated that SGLT2 inhibitors improve cardiac and renal outcomes in diabetic [12-14] and non-diabetic conditions, including CKD [15] and heart failure [16]. Based on these findings, SGLT2 inhibitors have emerged as an important pillar in preventing kidney function decline in patients with DKD. SGLT2 inhibitors block glucose and sodium reabsorption in the kidneys, promote natriuresis, and restore tubuloglomerular feedback, which consequently results in a decrease in glomerular hyperfiltration and albuminuria. Through their unique mechanism of blocking renal tubular channels, SGLT2 inhibitors exert diverse effects beyond reducing blood glucose levels, conferring renal and cardiovascular protective benefits.

Initially, SGLT2 inhibitors were considered to have a relatively neutral profile regarding electrolyte homeostasis. However, as real-world clinical experience has accumulated, distinct electrolyte shifts have become evident. On one hand, the profound glycosuria-induced osmotic diuresis has been reported to cause hypernatremia in certain vulnerable

clinical scenarios. On the other hand, early theoretical concerns regarding the potential for SGLT2 inhibitors to induce hyperkalemia have been largely alleviated. In fact, clinical evidence indicates a lower incidence of hyperkalemia and occasionally even the occurrence of mild hypokalemia associated with their use. This unexpected potassium-lowering tendency has proven to be a significant clinical advantage; it effectively offsets the hyperkalemic risks associated with RAS inhibitors, thereby permitting the safe and sustained concurrent use of these foundational therapies in clinical practice.

Water-sodium balance

Hypernatremia primarily arises from glucosuria-induced osmotic diuresis, which promotes renal free-water clearance. Although SGLT2 inhibitors initially acutely induce osmotic diuresis and mild volume contraction, they rarely lead to hypernatremia due to robust physiological compensatory mechanism. The initial volume depletion activates the body's water conservation system, leading to a significant accumulation of urea in the renal medulla [17]. The resulting elevation in medullary osmolality establishes a potent osmotic gradient that facilitates free-water reabsorption into the systemic circulation. Owing to this urea-driven renal water conservation, the baseline risk of hypernatremia remains inherently low during SGLT2 inhibitor therapy. Nevertheless, clinicians must remain vigilant during intercurrent illnesses (often termed 'sick days') characterized by acute gastrointestinal fluid losses or when voluntary water intake is severely restricted. In such vulnerable states, these compensatory mechanisms can be easily overwhelmed, predisposing patients to profound volume depletion and subsequent electrolyte derangements.

Recently, SGLT2 inhibitors have emerged as a promising and safe off-label treatment modality for the syndrome of inappropriate antidiuresis (SIAD). By inducing glycosuria and subsequent osmotic diuresis, these agents promote aquaresis—the excretion of solute-free water—thereby effectively elevating serum sodium levels. Consequently, they are increasingly considered a viable pharmacological alternative or adjunct to traditional fluid restriction.

The current evidence base, though limited to two small-scale randomized controlled trials (RCTs), supports their therapeutic potential. These agents have demonstrated significant efficacy in raising serum sodium concentrations compared to placebo in both acute hospitalized settings [18] and chronic outpatient scenarios [19]. Furthermore, they proved effective when combined with varying degrees of fluid restriction, ranging from standard limitation (< 1,000 mL/day) to more liberal regimens (1,500–1,600 mL/day). Importantly, SGLT2 inhibitors were well-tolerated in these SIAD cohorts, with no reported incidences of hypoglycemia or clinically significant hypotension.

Despite these promising preliminary data, several limitations warrant caution. The current evidence is restricted by small sample sizes, short study durations, and modest absolute efficacy, yielding placebo-subtracted sodium increases of only 3.0–4.1 mmol/L. Additionally, the safety of combining SGLT2 inhibitors with strict fluid restriction (< 500 mL/day) remains unknown, and their use in acute settings carries a potential risk of overly rapid sodium correction and transient renal impairment [18].

Beyond these clinical concerns, a critical practical caveat limits their immediate translation into real-world clinical practice. Both aforementioned RCTs utilized empagliflozin at a dose of 25 mg daily to treat SIAD. In contrast, the standard approved dosage for primary indications such as DKD and heart failure in real-world practice is typically 10 mg. Given

this significant dosage discrepancy, extrapolating the safety and efficacy profiles of the 25 mg trial dose to routine clinical care warrants careful consideration. Until large-scale investigations validate the efficacy of the standard 10 mg dose in this context, the off-label prescription of SGLT2 inhibitors for SIAD should be approached with caution.

Potassium derangement

A core renoprotective mechanism of SGLT2 inhibitors involves afferent arteriolar vasoconstriction, which effectively mitigates glomerular hyperfiltration. This hemodynamic adjustment typically results in a transient reduction in the eGFR within the first 2 to 4 weeks of treatment initiation—a clinical phenomenon widely recognized as the “initial dip.” Historically, this acute decline prompted significant concern regarding a potential impairment in renal potassium excretory capacity. Given that many patients with DKD already exhibit compromised potassium homeostasis and are frequently prescribed concurrent RAS inhibitors, there was a rational clinical suspicion that this initial dip might precipitate life-threatening hyperkalemia.

These early apprehensions were reinforced by initial data, particularly from trials involving canagliflozin, which reported a modest increase in hyperkalemic episodes among patients with moderate-to-severe renal impairment or those on concomitant RAS inhibitors [20]. This observation even led to an official Food and Drug Administration label warning. However, these concerns were effectively dispelled with the publication of the CANVAS program and subsequent trials. Comprehensive analyses demonstrated no clinically meaningful differences in serum potassium levels between the canagliflozin and placebo groups, regardless of dose, baseline eGFR, or concomitant RAS inhibitor use [21]. Furthermore, recent meta-analyses have shown that SGLT2 inhibitors are associated with a lower risk of hyperkalemia [22], particularly in patients with DKD who concurrently receive RAS inhibitors or mineralocorticoid receptor antagonists (MRAs) [23].

Several mechanisms have been proposed to explain how SGLT2 inhibitors mitigate hyperkalemia risk despite the initial dip in eGFR. As detailed in a recent physiological review [24], these agents promote potassium excretion through multiple interconnected tubular pathways. By inhibiting proximal glucose reabsorption, they induce a persistent osmotic diuresis that significantly increases distal tubular flow and sodium delivery. This high-flow state creates a potent, continuous stimulus for electrogenic potassium secretion. Concurrently, SGLT2 inhibitors suppress the sodium-hydrogen exchanger 3 (NHE3) in the proximal tubule, resulting in luminal alkalinization. This alkaline shift provides an additional defense mechanism by allosterically activating renal outer medullary potassium (ROMK) channels, further promoting renal potassium excretion.

Beyond direct tubular effects, systemic neurohormonal shifts also play a crucial role in maintaining potassium homeostasis [25]. The mild natriuresis and subsequent plasma volume reduction induced by SGLT2 inhibitors can activate the renin-angiotensin-aldosterone system. When this increased mineralocorticoid activity is coupled with enhanced distal sodium delivery, it strongly augments potassium secretion, particularly during the initial phase of therapy. Furthermore, the forced glycosuria alters systemic energy metabolism, leading to a reduction in insulin and an elevation in circulating glucagon levels. Glucagon acts directly on receptors along the distal nephron, exerting a rapid stimulatory effect on potassium secretion and completing a robust physiological defense against hyperkalemia.

Despite this theoretical propensity for potassium loss, SGLT2 inhibitors rarely induce hypokalemia due to the concurrent activation of sophisticated intrarenal compensatory mechanisms that restrict excessive excretion [25]. First, by increasing sodium delivery to the macula densa and decreasing sympathetic tone, SGLT2 inhibitors attenuate the overactivation of the renin-angiotensin-aldosterone system, thereby limiting aldosterone-driven potassium secretion. Second, the increased delivery of glucose to the distal nephron allosterically sensitizes the calcium-sensing receptor, which consequently upregulates the activity of the sodium-chloride cotransporter (NCC). Third, the enhanced distal delivery of α -ketoglutarate functions as an intrarenal paracrine signal that inhibits the epithelial sodium channel (ENaC) while promoting electroneutral sodium reabsorption. Ultimately, these coordinated tubular adaptations facilitate sodium reabsorption without provoking electrogenic potassium loss, effectively limiting the diuretic impact of the therapy while providing a robust physiological defense against the development of hypokalemia.

Ultimately, the dynamic interplay of these interconnected and compensatory mechanisms provides a compelling theoretical rationale for the generally favorable electrolyte safety profile of SGLT2 inhibitors. By balancing appropriate potassium excretion with safeguards against excessive loss, these agents help maintain potassium homeostasis. Consequently, this physiological balance substantially alleviates historical concerns regarding hyperkalemia, providing reassurance for their use even in vulnerable populations, such as patients with DKD. Nevertheless, while the absolute risk of severe dyskalemia is substantially attenuated, maintaining appropriate clinical vigilance and routine electrolyte monitoring remains a prudent standard of care in these high-risk cohorts.

Magnesium

Evidence from multiple randomized controlled trials demonstrates that SGLT2 inhibitors induce a modest yet significant increase in serum magnesium levels (approximately 0.08–0.2 mEq/L) [24], with canagliflozin exhibiting a distinct dose-dependent effect that is further amplified in patients with reduced renal function [26]. Notably, these agents have been shown to effectively normalize magnesium concentrations in patients with type 2 diabetes (T2D) who often present with hypomagnesemia [27]. From a clinical perspective, this mild elevation in serum magnesium—often accompanied by slight increases in serum potassium—is hypothesized to exert antiarrhythmic effects. Consequently, these favorable electrolyte shifts may partially underpin the remarkable cardiovascular benefits and reduced arrhythmia risks observed in landmark cardiovascular outcome trials, such as EMPA-REG OUTCOME [28] and CANVAS [12,29].

The elevation of serum magnesium concentrations induced by SGLT2 inhibitors is mediated by a complex interplay of several physiological mechanisms. Primarily, these agents mitigate the renal magnesium wasting characteristic of diabetes by improving insulin resistance, which subsequently restores the activity of transient receptor potential melastatin 6 (TRPM6) channels in the distal convoluted tubules [30]. This restorative effect is further supported by favorable hormonal shifts; Specifically, SGLT2 inhibitors elevate circulating glucagon levels, which directly enhances distal tubular magnesium reabsorption, and decrease insulin levels, which prevents the intracellular sequestration of magnesium and promotes its redistribution to the extracellular space [31–33]. Additionally, the mild extracellular volume depletion resulting from osmotic diuresis and natriuresis contributes to a relative increase in serum magnesium through hemoconcentration [24].

Interestingly, these magnesium-conserving mechanisms operate in opposition to inherent counter-regulatory forces. The same diuretic-induced hypovolemia that causes hemoconcentration also stimulates aldosterone secretion, which typically promotes renal magnesium excretion [34]. Nevertheless, the combined effects of TRPM6 restoration, favorable hormonal redistribution, and hemoconcentration robustly counterbalance the magnesiuic influence of aldosterone. Ultimately, this dynamic physiological interplay results in the net modest elevation of serum magnesium levels characteristically observed in clinical practice.

Phosphate

Regarding phosphate homeostasis, although SGLT2 inhibitors induce a mild elevation in serum phosphate—driven by a compensatory increase in proximal tubular $\text{Na}^+3\text{PO}_4^{3-}$ cotransport following decreased sodium reabsorption [35]—this physiological shift does not universally increase bone fracture risk. Theoretically, this subtle hyperphosphatemia triggers a compensatory hormonal cascade involving elevated parathyroid hormone and fibroblast growth factor 23, which subsequently suppresses vitamin D synthesis and intestinal calcium absorption, hypothetically threatening bone mineral density. However, while initial data from the CANVAS trial linked canagliflozin to increased fractures [36,37], robust subsequent evidence from the EMPA-REG OUTCOME trial [29] and comprehensive meta-analyses [38,39] clarified that this is likely a drug-specific phenomenon rather than a class effect. Ultimately, clinical data demonstrate that these theoretical pathways of bone resorption do not translate into actual skeletal fragility for the majority of SGLT2 inhibitors.

GLP-1 RAs

Alongside their established cardiorenal benefits [40–42], GLP-1 RAs induce mild natriuresis similar to SGLT2 inhibitors [43]. By inhibiting proximal NHE3, they increase distal sodium delivery and elevate urinary pH, collectively promoting renal potassium excretion [44]. Consequently, clinical evidence shows a significantly lower incidence of hyperkalemia with GLP-1 RAs compared to dipeptidyl peptidase-4 inhibitors [45].

However, the renal physiology of GLP-1 RAs differs fundamentally from that of SGLT2 inhibitors. While GLP-1 RAs modulate tubular function via the gut-kidney axis, they do not drive profound osmotic diuresis or direct tubular electrolyte wasting. Instead, their renoprotection is predominantly mediated by pleiotropic effects, such as eGFR stabilization and albuminuria reduction. Thus, severe electrolyte derangements under GLP-1 RA therapy are typically secondary systemic phenomena rather than primary renal mechanisms. For instance, recent reports of severe hypokalemia (2.5–2.7 mmol/L) following semaglutide use were explicitly attributed to severe reductions in oral intake and gastrointestinal losses from severe nausea and vomiting [46]. Similarly, GLP-1 RA-induced hyponatremia is primarily driven by the syndrome of inappropriate antidiuretic hormone secretion—triggered by severe nausea and delayed gastric emptying—rather than mild diuresis [47]. Given their exceptionally low risk of hyperkalemia, GLP-1 RAs may be considered a favorable foundational therapy for susceptible populations, potentially facilitating safer concurrent treatment with RAS inhibitors or MRAs.

nsMRAs

nsMRAs represent a critical advancement in DKD pharmacotherapy, designed to overcome the limitations of traditional steroidal agents by providing potent anti-inflammatory and anti-fibrotic benefits. By utilizing a distinct, bulky non-steroidal structure, agents like finerenone

achieve high receptor selectivity and offer a theoretically improved safety margin. Nevertheless, because they fundamentally antagonize aldosterone action, precise understanding and management of their impact on electrolyte derangements remain essential.

Hyperkalemia

MRAs effectively overcome the “aldosterone breakthrough” of standard RAS inhibition, offering additive anti-inflammatory and antifibrotic benefits [48]. However, the substantial hyperkalemia risk associated with traditional steroidal MRAs severely limits their clinical use—especially in patients with impaired eGFR—underscoring the critical need for safer alternatives. To address this, finerenone has emerged as a promising nsMRA. Compared to traditional steroidal MRAs, finerenone exhibits greater mineralocorticoid receptor selectivity and binding affinity, affording higher therapeutic potency with a theoretically lower risk of hyperkalemia. The cardiorenal efficacy of finerenone in patients with T2D on a background of maximal RAS inhibition has been robustly demonstrated in 2 large RCTs. The FIDELIO-DKD study [49] demonstrated significant benefits in patients with advanced CKD (urine albumin-to-creatinine ratio [UACR] 30 to < 300 mg/g with eGFR 25 to < 60 mL/min/1.73 m², or UACR 300 to 5,000 mg/g with eGFR 25 to < 75 mL/min/1.73 m²) over a median follow-up of 2.6 years. Subsequently, the FIGARO-DKD [50] study expanded these findings to patients with T2D and less advanced CKD. Results showed a 29% risk reduction in heart failure hospitalizations and a 23% relative risk reduction in the kidney composite outcome (2.9% vs. 3.8%). While initial reports from these individual trials suggested that overall adverse events were comparable to placebo and severe hyperkalemia was uncommon, the FIDELITY pooled analysis [51] clarified that hyperkalemia events were indeed more frequent in the finerenone group than in the placebo group, particularly among patients with a low baseline eGFR.

Despite this increased risk relative to placebo, finerenone demonstrates a remarkably superior potassium safety profile when directly compared to traditional steroidal MRAs. In the phase 2 ARTS study [52], which evaluated finerenone (5–10 mg/day) versus spironolactone (25–50 mg/day) in patients with concurrent heart failure with reduced ejection fraction and CKD (eGFR 30–60 mL/min/1.73 m²), finerenone was associated with significantly smaller mean increases in serum potassium (0.04–0.30 vs. 0.45 mmol/L, $p < 0.0001$ –0.0107) and a substantially lower incidence of hyperkalemia (5.3% vs. 12.7%, $p = 0.048$). This favorable safety profile was further corroborated by a comparative post hoc analysis [53] matching data from the FIDELITY program with the AMBER trial [54]. In populations with treatment-resistant hypertension and moderate-to-advanced CKD, the incidence of hyperkalemia was markedly lower in the finerenone cohort compared to the spironolactone cohort (12% vs. 64%). Furthermore, treatment discontinuation due to hyperkalemia was nearly negligible for finerenone compared to spironolactone (0.3% vs. 23%).

The improved potassium safety profile of finerenone relative to spironolactone is driven by distinct pharmacokinetic and pharmacodynamic mechanisms. First, unlike spironolactone, which accumulates in the kidneys and consequently drives excessive potassium retention, finerenone exhibits a balanced 1:1 tissue distribution between the heart and kidneys [55,56]. Second, finerenone has a short half-life of 2–3 hours and lacks active metabolites, preventing the unpredictable drug accumulation commonly seen with the long-acting active metabolites of spironolactone in patients with CKD [57]. Lastly, the bulky non-steroidal structure of finerenone induces a distinct conformational change in the mineralocorticoid receptor. This unique binding confers superior selectivity, potentially

inhibiting pro-inflammatory and pro-fibrotic pathways with minimal disruption to normal electrolyte handling [58].

nsMRA in combination with SGLT2 inhibitors

The implementation of a “four-pillar” therapeutic strategy in DKD has proven highly effective in reducing both CKD progression and all-cause mortality [59], establishing combination therapy as an indispensable standard of care. Ideally, such combination regimens should capitalize on complementary safety profiles to mutually offset specific adverse events.

The physiological rationale for combining SGLT2 inhibitors and nsMRAs lies in their complementary effects on distal potassium handling (**Fig. 1**). While nsMRAs carry an inherent risk of hyperkalemia by inhibiting potassium secretion mediated by the ROMK channel, SGLT2 inhibitors provide robust compensatory shunt. Crucially, the mineralocorticoid receptor-antagonistic effect of finerenone exerts a dominant transcriptional suppression on ROMK channels [60] that overrides any potential up-regulation induced by SGLT2 inhibitor-mediated luminal alkalinization [25]. Consequently, even though SGLT2 inhibitors significantly increase distal sodium delivery and urinary flow by blocking proximal reabsorption, ROMK activity remains pharmacologically suppressed under combination therapy. This high-flow state, however, serves as a potent mechanical stimulus that activates flow-sensitive Big Potassium (BK) channels in the distal nephron [61], thereby facilitating ‘flow-dependent potassium secretion’ to bypass the blocked ROMK pathway.

In line with these biological mechanisms, early post-hoc analyses from the FIDELITY program generated optimism, demonstrating that baseline SGLT2 inhibitor use significantly lowered the incidence of finerenone-induced hyperkalemia. This premise was prospectively evaluated in the CONFIDENCE trial, which confirmed that combining empagliflozin and finerenone achieves a profound, synergistic reduction in albuminuria compared to either monotherapy. While initial reports sparked hopes of superior potassium safety, a recent 180-day secondary analysis of the CONFIDENCE trial [62] provided a more complex clinical picture. Although the incidence of hyperkalemia remained numerically lower in the combination arm (15.1%) than in the finerenone monotherapy arm (18.8%), this reduction did not reach statistical significance. Ultimately, while SGLT2 inhibitors do not completely neutralize the hyperkalemia risk associated with nsMRAs, severe events necessitating treatment discontinuation are exceedingly rare. Given the overwhelming antiproteinuric benefits, the concurrent use of SGLT2 inhibitors and nsMRAs remains a highly recommended therapeutic strategy, provided it is accompanied by routine potassium monitoring.

Hyponatremia

Finerenone is associated with a marginally higher incidence of hyponatremia compared to placebo across eGFR subgroups (approx. 1.1–1.2% vs. 0.5–0.8%), although it rarely necessitates treatment discontinuation [63]. Although finerenone possesses a distinct non-steroidal structure, its fundamental mineralocorticoid antagonism can still contribute to the development of hyponatremia through two primary renal mechanisms. First, by blocking aldosterone action in the distal tubule and collecting duct, finerenone inhibits the synthesis of ENaC [64]. This disruption of Na^+/K^+ exchange promotes direct renal sodium wasting. Second, it impairs the kidney’s urinary diluting capacity, which can precipitate dilutional hyponatremia even in the absence of pronounced hypovolemia [65]. Notably, these dose-dependent effects are clinically more evident in patients with mild-to-moderate, rather than severe, CKD [66].

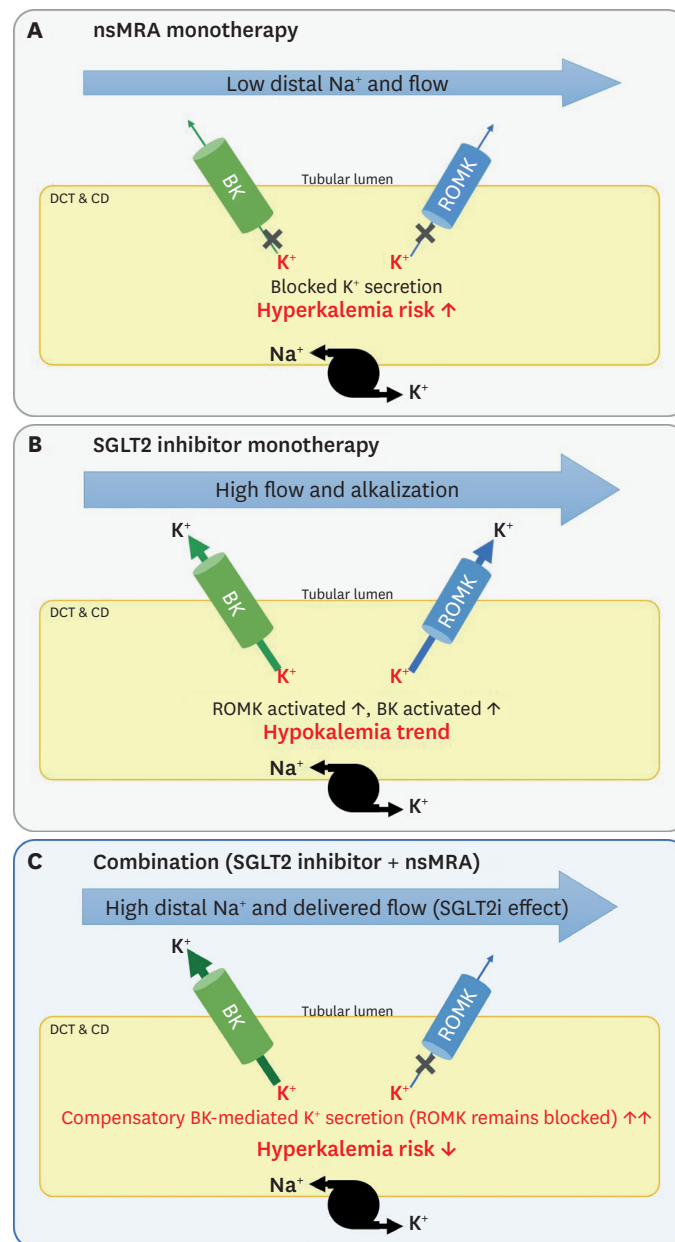


Fig. 1. Potential complementary effects of SGLT2i and nsMRA combination on distal potassium (K^+) secretion via ROMK and BK channels (A) nsMRA monotherapy: nsMRAs, such as finerenone, potentially block aldosterone action in the DCT & CD. This blockade potentially leads to the transcriptional and functional suppression of the ROMK channel. Because the downstream luminal delivery of Na^+ and urinary flow rate remain low under monotherapy, the flow-sensitive BK channel cannot be mechanically activated. Consequently, overall distal K^+ secretion is blocked, shifting the clinical balance toward an increased risk of hyperkalemia. (B) SGLT2 inhibitor monotherapy: SGLT2 inhibitors block proximal tubular reabsorption, resulting in a high-flow state and increased delivery of Na^+ and fluid to the distal nephron. This process also induces luminal alkalization. The luminal alkalization provides a chemical stimulus that upregulates ROMK channel activity. Simultaneously, the pronounced increase in delivered flow acts as a potent mechanical stimulus that activates the flow-sensitive, high-conductance BK channels. This dual activation may accelerate distal K^+ wasting, driving a clinical trend toward hypokalemia. (C) Combination therapy (SGLT2 inhibitor + nsMRA): When an SGLT2 inhibitor is co-administered with an nsMRA, their distinct physiological pathways intersect. Crucially, the MR-antagonistic effect of finerenone potentially exerts a dominant transcriptional suppression on ROMK channels that may override the potential upregulation induced by SGLT2 inhibitor-mediated luminal alkalization; thus, the ROMK pathway remains pharmacologically blocked. However, the persistent high distal Na^+ delivery and delivered flow generated by the SGLT2 inhibitor serve as a robust, continuous mechanical stimulus that can activate the flow-dependent BK channels. This proposed compensatory BK-mediated shunt appears to bypass the blocked ROMK pathway, facilitating sufficient K^+ secretion and effectively mitigating the baseline hyperkalemia risk associated with nsMRA monotherapy. BK, big potassium channel; CD, collecting duct; DCT, distal convoluted tubule; K^+ , potassium; MR, mineralocorticoid receptor; Na^+ , sodium; nsMRA, non-steroidal mineralocorticoid receptor antagonist; ROMK, renal outer medullary potassium; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

CLINICAL CONSIDERATIONS FOR ELECTROLYTE MONITORING

Ultimately, translating the clinical benefits of these state-of-the-art therapeutic classes into safe clinical practice requires structured and individualized electrolyte monitoring. To optimize patient safety, post-prescription electrolyte monitoring intervals must be clearly defined and individualized based on the patient's baseline renal function. For standard-risk patients initiating either nsMRA monotherapy or combination therapy, the first electrolyte follow-up should be scheduled within a specific 2- to 4-week window following initiation or dose escalation. Crucially, for high-risk individuals—particularly those with advanced CKD and a baseline eGFR below 30 mL/min/1.73 m²—this monitoring interval for serum potassium and renal function must be significantly shortened to 1 to 2 weeks following the initiation or dose escalation of either nsMRAs or combination therapy. This closer clinical oversight provides a critical safety window to proactively detect and manage potential electrolyte derangements as patients approach end-stage renal disease.

Beyond these routine clinical checks, implementing “sick day rules” during acute, dehydrating illnesses (such as severe vomiting or diarrhea) is widely recommended to protect patients during intercurrent events [67]. In these acute scenarios, the temporary suspension of SGLT2 inhibitors, RAS inhibitors, or nsMRAs should be considered a prudent and effective approach to proactively prevent acute kidney injury.

CONCLUSION

The pharmacological management of DKD has been revolutionized by the “four-pillar” approach, shifting the paradigm beyond traditional RAS inhibition. While these novel therapeutic classes offer robust cardiorenal protection, understanding their distinct impacts on electrolyte homeostasis is essential for safe clinical practice. SGLT2 inhibitors present a highly favorable electrolyte profile; their unique mechanisms of osmotic diuresis and tubular transport modulation are notably associated with a reduced risk of hyperkalemia. Similarly, GLP-1 receptor agonists carry an exceptionally low intrinsic risk of direct renal electrolyte wasting, with rare derangements such as hypokalemia occurring primarily as secondary systemic consequences of severe gastrointestinal intolerance.

Despite these reassuring safety profiles, the integration of nsMRAs introduces a mild risk of hyperkalemia and dilutional hyponatremia. However, their distinct pharmacokinetic properties and unique receptor selectivity significantly diminish these risks compared to traditional steroidal MRAs. Crucially, harnessing the complementary physiological mechanisms of these pillars—particularly the concurrent administration of SGLT2 inhibitors and nsMRAs—creates a highly synergistic strategy that attenuates this hyperkalemic adverse effect while maximizing antiproteinuric benefits.

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Original Article



Unsupervised Clustering of Intradialytic Blood Pressure Patterns and Their Associations With Body Composition in Patients Undergoing Chronic Hemodialysis

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ABSTRACT

Background: Intradialytic blood pressure (BP) abnormalities are common in patients undergoing chronic hemodialysis (HD), however, their relationship with body composition remains unclear. We investigated the association between intradialytic BP patterns and body composition using an unsupervised clustering approach.

Methods: Adult outpatients receiving chronic HD who underwent segmental multifrequency bioelectrical impedance analysis were included. Systolic blood pressure (SBP) trajectories during HD were mapped to prespecified 30-minute time points from 0 to 240 minutes, and changes relative to predialysis SBP were clustered using k-means clustering. Body composition parameters were compared across BP clusters. Linear mixed-effects models with a random intercept for patient identifier were used to account for repeated HD sessions.

Results: Among 928 HD sessions from 179 patients, three SBP patterns were identified: marked decreasing (16.8%), mild decreasing (46.2%), and rising (37.0%) patterns. Body mass index did not differ across clusters. However, fat-free mass index and skeletal muscle mass index increased from the marked decreasing to the mild decreasing and rising clusters, whereas percent body fat decreased. The extracellular water-to-total body water ratio was highest in the rising cluster, and visceral fat area showed a decreasing trend from the marked decreasing cluster to the rising cluster. These associations remained significant after adjustment. Similar findings were observed in sensitivity analyses.

Conclusion: Unsupervised clustering identified reproducible intradialytic BP phenotypes that closely associated with volume status and body composition in patients undergoing chronic HD.

Keywords: Blood pressure; Body composition; Clustering; Hemodialysis

INTRODUCTION

Cardiovascular disease is the leading cause of morbidity and mortality in patients with end-stage kidney disease undergoing chronic hemodialysis (HD) [1]. Blood pressure (BP) is a major determinant of cardiovascular risk; therefore, it should be controlled within acceptable

Conflicts of interest

All authors have no conflicts of interest to declare.

Data sharing statement

Data supporting the findings of this study are available from the corresponding author upon request.

Authors' contributions

Conceptualization: JS; Data curation: HK, SK, JHH, JS; Formal analysis: JS; Investigation: JS; Supervision: SK, JHH, JS; Writing - original draft: HK, JS.

target ranges [2,3]. However, in patients on chronic HD, the association between BP levels and cardiovascular outcomes is less straightforward than in general population, particularly with the distinctive patterns of BP measurements influenced by the HD treatment [4]. In routine chronic HD care, office BP measurements, including peridialytic and intradialytic BP, are frequently recorded and are essential for ensuring safe and effective HD treatment. Despite their clinical utility, the mechanisms underlying HD-related BP changes remain incompletely understood, and the management of abnormal intradialytic BP patterns, such as intradialytic hypotension and hypertension, remains unsatisfactory. Moreover, heterogeneous and arbitrary definitions of abnormal intradialytic BP patterns may further hinder a clear understanding of their nature.

Recent advances in body composition assessment have increased its accessibility in clinical practice and enhanced our understanding of its clinical implications. In many HD centers, body composition analysis is regularly performed to guide dry weight adjustment and identify abnormal conditions such as malnutrition and sarcopenia [5]. Emerging evidence suggests a strong connection between body composition and intradialytic BP patterns. During HD treatment, BP decreases as retained extracellular water (ECW) is removed [4]. Excessive ECW removal beyond an individual's tolerance can precipitate a BP drop and contribute to the development of intradialytic hypotension [6], whereas ECW overload has been associated with intradialytic hypertension [7]. These findings support the role of volume status as a key determinant of abnormal intradialytic BP patterns. In addition, prior studies have reported the associations between intradialytic hypotension and low muscle and fat mass [8,9]. Taken together, body composition analysis can help characterize intradialytic BP patterns and provide insights into the pathophysiologic mechanisms underlying intradialytic hypotension and hypertension.

In this study, we investigated the association between intradialytic BP patterns and body composition in patients undergoing chronic HD. We classified intradialytic BP patterns into clusters using an unsupervised approach to minimize investigator-driven bias. We then explored how these clusters were related to volume status and to muscle and fat mass.

METHODS

Patients

This retrospective study included adult patients with end-stage kidney disease who underwent outpatient chronic HD and body composition analysis between October 2016 and October 2023. Among 185 eligible patients, six were excluded because of missing baseline laboratory data or insufficient BP measurements (BP recordings available for < 180 minutes). Ultimately, 179 patients receiving chronic HD were included, contributing 928 paired BP and body composition measurements.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Chung-Ang University Hospital (number: 2310-022-19496). The requirement for written informed consent was waived because of the retrospective nature of the study and the use of anonymized data.

Data collection

Demographic and clinical data were obtained from electronic medical records, including age, sex, dialysis vintage, cause of end-stage kidney disease, and comorbidities. Comorbidity

burden was assessed using the modified Charlson Comorbidity Index [10]. Additionally, dialysis-related parameters including interdialytic weight gain, dry weight, ultrafiltration volume, and calculated ultrafiltration rate were retrieved. The number of prescribed antihypertensive medications was also collected. Fasting blood samples were obtained before the midweek dialysis session to measure hemoglobin, albumin, blood urea nitrogen, creatinine, calcium, phosphorus, uric acid, sodium, potassium, total carbon dioxide, and total cholesterol. Postdialysis blood urea nitrogen was measured to assess dialysis adequacy.

Body composition analysis

Body composition was assessed every 6 months in outpatients undergoing chronic HD using a segmental multifrequency bioelectrical impedance analysis (BIA) device (InBody S10; BioSpace, Seoul, Korea). Measurements were performed after midweek dialysis sessions in the supine position. Eight tactile electrodes were placed on the tips of the thumbs and middle fingers of both hands and between the malleoli and calcanei of both feet. The device was regularly calibrated and operated by trained nursing staff according to the manufacturer's instructions.

Parameters obtained from BIA included fat-free mass, skeletal muscle mass, percent body fat (PBF), visceral fat area (VFA), and the ratio of ECW to total body water (ECW/TBW). Body mass index (BMI), fat-free mass index (FFMI), and skeletal muscle mass index (SMI) were calculated as the corresponding mass divided by height squared (kg/m^2).

BP measurement

HD was performed using either Fresenius 5008S (Fresenius Medical Care, Homburg, Germany) or Artis (Gambro Dasco SpA, Medolla, Italy) machines. Patients were treated with bicarbonate-based dialysate at standard temperature two or three times weekly for 4 hours per session, with a blood flow rate of 200–350 mL/min.

BP measurements, including predialysis, postdialysis, and intradialytic BP, were obtained in the supine position using automated devices built into the HD machines, which underwent regular calibration. BP data were collected on the same day as the BIA measurements. All systolic and diastolic BP measurements were recorded from predialysis (0 minute) to at least 180 minutes. Because all sessions were scheduled for 4 hours, incomplete BP series were primarily attributable to missed recordings or early session termination.

Clustering of intradialytic BP patterns

Systolic blood pressure (SBP) values were mapped to prespecified 30-minute time points (0, 30, 60, 90, 120, 150, 180, 210, and 240 minutes). For each time point, measurements obtained within a ± 15 -minute window were assigned, and the mean value was used when multiple measurements were available within the window. The change in SBP at each time point was calculated relative to the predialysis SBP ($\Delta\text{SBP}_t = \text{SBP}_t - \text{SBP}_0$). For sporadically missing SBP values between recorded measurements, missing values were imputed using within-session linear interpolation. Because the last SBP value could not be imputed, sessions yielded three types of complete trajectories through 180, 210, or 240 minutes, depending on the availability of the final measurements.

Unsupervised clustering was performed using k-means in a complete-case subset of sessions that included ΔSBP values at all time points from 0 to 240 minutes. Nonstandardized raw ΔSBP values were used for clustering to preserve the clinical meaning of absolute BP changes

and to allow cluster distinctions reflecting both trajectory magnitude and shape. Candidate numbers of clusters ($k = 2-8$) were evaluated using the within-cluster sum of squares (elbow method), and cluster separability was assessed using the mean silhouette width based on Euclidean distance. K-means was fitted with 50 random starts ($nstart = 50$) and a maximum of 1,000 iterations per run ($iter.max = 1,000$).

Sessions with complete data up to 180 or 210 minutes but missing later measurements were assigned to the nearest centroid derived from the 0–240-minutes k-means model. Euclidean distances between the session vector and each centroid were computed at the prespecified time points, and the cluster with the minimum distance was assigned.

Statistical analysis

Continuous variables were expressed as means $\pm$ standard deviations, and categorical variables as numbers (%). Between-group differences were compared using one-way analysis of variance for continuous variables and the χ^2 test for categorical variables. Because multiple HD sessions could belong to the same patient, linear mixed-effects models with a random intercept for each patient were fitted to account for repeated sessions within individuals. In the adjusted models, cluster membership, age, sex, predialysis SBP, and ultrafiltration rate were included as fixed effects. Adjusted marginal means were estimated, and pairwise comparisons among clusters were performed using Bonferroni correction.

We performed sensitivity analyses to evaluate the robustness and reproducibility of the identified BP clusters. First, a repeated random one-session-per-patient resampling was conducted to address potential bias from multiple sessions per patient. For each of 200 iterations, one HD session was randomly selected from each patient from the complete-case training dataset. Second, we repeated the clustering using an alternative number of clusters to assess whether the associations between BP patterns and body composition were preserved regardless of the specific choice of k . All statistical analyses were performed using R software (version 4.4.2; R Foundation for Statistical Computing, Vienna, Austria). A two-sided p -value < 0.05 was considered statistically significant.

RESULTS

Study population and dataset preparation

A total of 928 HD sessions from 179 patients were included in the final analysis dataset. The median number of sessions per patient was 3 (1, 8). The mean age was 68.2 ± 13.0 years, and 55.9% of the patients were male. The prevalence of diabetes and hypertension was 58.1% and 80.4%, respectively.

Of the 928 HD sessions, 826 (89.0%) had complete intradialytic BP measurements through 240 minutes and were used for k-means model training. The remaining sessions were assigned to clusters using centroid-based classification if complete measurements were available through 210 minutes ($n = 75$ [8.1%]) or 180 minutes ($n = 27$ [2.9%]).

Intradialytic BP clustering

Clustering was performed using the 826 sessions with complete dataset. The elbow profile supported $k = 3$, with a pronounced decrease in the within-cluster sum of squares from $k = 2$ to $k = 3$, followed by progressively smaller reductions thereafter (**Supplementary Fig. 1**).

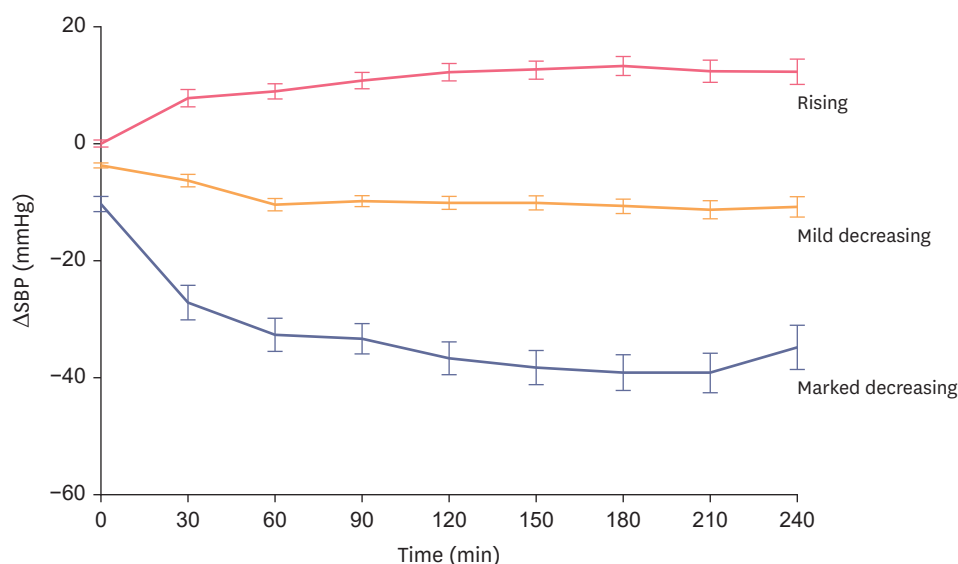


Fig. 1. Intradialytic SBP trajectories according to clusters. Mean changes in SBP relative to predialysis value are shown for the three clusters identified by k-means clustering ($k = 3$). Error bars indicate standard deviations. The marked decreasing, mild decreasing, and rising clusters included 156, 429, and 343 hemodialysis sessions, respectively. SBP, systolic blood pressure.

The mean silhouette width also favored $k = 3$ over $k = 4$ (0.293 versus 0.237). Based on these criteria, $k = 3$ was selected as the primary clustering scheme, whereas $k = 4$ was retained for sensitivity analysis of phenotype characterization.

After integration of the trained clustering model with centroid-based assignment, all 928 HD sessions were classified into three clusters according to their characteristic intradialytic SBP patterns: marked decreasing ($n = 156$, [16.8%]), mild decreasing ($n = 429$ [46.2%]), and rising ($n = 343$ [37.0%]) (**Fig. 1**). Characteristics across the intradialytic BP clusters are summarized in **Table 1**. The marked decreasing cluster had significantly higher ultrafiltration rate than the mild decreasing cluster, whereas patients in the rising cluster were prescribed a significantly higher number of antihypertensive drugs.

Association between intradialytic BP clusters and body composition analysis

We compared body composition parameters across intradialytic BP clusters (**Table 1**). Significant differences across clusters were observed for FFMI, SMI, PBF, VFA, and ECW/TBW, whereas BMI did not differ significantly.

After accounting for repeated measurements using linear mixed-effects models adjusted for age, sex, predialysis SBP, and ultrafiltration rate, the overall pattern remained evident (**Fig. 2**). Compared with the mild decreasing cluster, the rising cluster showed higher ECW/TBW, FFMI, and SMI, but lower PBF. In contrast, the marked decreasing cluster showed lower FFMI and SMI than the mild decreasing cluster. BMI did not differ across the clusters.

In addition, we further adjusted for ECW/TBW to determine whether the association between intradialytic BP patterns and muscle and fat mass was independent of volume status. The overall pattern of associations was largely preserved (**Table 2**).

Table 1. Cluster-specific session-level clinical, dialysis-related, and body composition characteristics according to intradialytic blood pressure pattern

Variable	Marked decreasing (n = 156)	Mild decreasing (n = 429)	Rising (n = 343)	Overall p-value
Demographic & comorbidities				
Age (yr)	68.1 ± 11.3	69.7 ± 11.5	69.4 ± 12.3	0.286
Males	77 (49.7)	231 (54.6)	187 (55.5)	0.466
Hemodialysis duration (mo)	70.2 ± 62.8*	52.3 ± 57.8	40.1 ± 56.2*	< 0.001
Charlson Comorbidity Index	2.7 ± 1.9	2.6 ± 2.0	2.8 ± 2.1	0.324
Diabetes	103 (66.5)	236 (55.8)	170 (50.4)	0.004
Hypertension	119 (76.8)	346 (81.8)	264 (78.3)	0.308
Laboratory results				
Hemoglobin (g/dL)	10.8 ± 1.9	10.6 ± 1.5	10.1 ± 1.4*	0.002
Albumin (g/dL)	3.7 ± 0.4	3.8 ± 0.4	3.7 ± 0.5	0.118
Sodium (mmol/L)	135.7 ± 3.4	136.2 ± 3.0	136.6 ± 3.2	0.009
Potassium (mmol/L)	4.7 ± 0.6	4.7 ± 0.7	4.6 ± 0.7	0.397
Kt/Vurea	1.7 ± 0.2	1.7 ± 0.3	1.7 ± 0.3	< 0.001
Hemodynamic & dialysis parameters				
Predialysis systolic BP (mmHg)	169.3 ± 21.8*	144.8 ± 22.3	133.1 ± 20.8*	< 0.001
Number of antihypertensive drugs	1.2 ± 1.0	1.2 ± 1.1	1.5 ± 1.2*	< 0.001
Interdialytic weight gain (kg)	2.3 ± 1.0	2.1 ± 1.2	1.8 ± 1.5*	< 0.001
Dry weight (kg)	57.5 ± 10.1	56.9 ± 11.3	56.8 ± 11.5	0.653
Ultrafiltration volume (kg)	2.0 ± 1.0	1.8 ± 0.8	1.6 ± 0.9*	< 0.001
Ultrafiltration rate (mL/kg/hr)	9.0 ± 4.3*	8.3 ± 3.6	7.1 ± 4.1*	< 0.001
Body composition parameters				
BMI (kg/m ²)	22.7 ± 3.7	22.1 ± 3.6	22.1 ± 3.6	0.169
FFMI (kg/m ²)	15.8 ± 2.2	15.9 ± 2.3	16.4 ± 2.3*	0.001
SMI (kg/m ²)	8.4 ± 1.4	8.5 ± 1.5	8.7 ± 1.4*	0.009
PBF (%)	29.0 ± 13.0	27.2 ± 10.8	24.5 ± 10.6*	< 0.001
VFA (cm ²)	88.2 ± 57.2*	77.1 ± 44.2	69.0 ± 40.8*	< 0.001
ECW/TBW (%)	39.8 ± 1.9	39.6 ± 1.5	39.9 ± 1.4*	0.048

Data are expressed as mean ± standard deviation or number (%). The p-values indicate the overall significance of differences across clusters.

BMI, body mass index; BP, blood pressure; ECW/TBW, extracellular water-to-total body water ratio; FFMI, fat-free mass index; PBF, percent body fat; SMI, skeletal muscle mass index; VFA, visceral fat area.

*Indicates a significant difference compared with the mild decreasing group after Bonferroni correction ($p < 0.05$). Because clustering was performed at the hemodialysis-session level, the table summarizes session-level profiles.

Table 2. Adjusted body composition parameters after additional adjustment for ECW/TBW

Variable	Marked decreasing	Mild decreasing	Rising	p-value
BMI (kg/m ²)	22.4 (21.8–23.0)	22.4 (21.8–23.0)	22.4 (21.9–23.0)	0.893
FFMI (kg/m ²)	15.9 (15.5–16.2)*	16.1 (15.8–16.4)	16.5 (16.2–16.8)*	< 0.001
SMI (kg/m ²)	8.4 (8.2–8.6)*	8.6 (8.4–8.8)	8.8 (8.6–8.9)*	< 0.001
PBF (%)	28.1 (26.5–29.7)	27.1 (25.7–28.5)	25.4 (23.9–26.8)*	< 0.001
VFA (cm ²)	82.0 (74.8–89.2)	77.1 (70.8–83.4)	72.8 (66.4–79.2)	0.004

Data are expressed as adjusted means (95% confidence intervals). The p-values indicate the overall significance of cluster differences across clusters in linear mixed-effects models adjusted for age, sex, predialysis systolic blood pressure, ultrafiltration rate, and ECW/TBW, with a random intercept for each patient.

BMI, body mass index; ECW/TBW, extracellular water-to-total body water ratio; FFMI, fat-free mass index; PBF, percent body fat; SMI, skeletal muscle mass index; VFA, visceral fat area.

*Indicates a significant difference compared with the mild decreasing group after Bonferroni correction ($p < 0.05$).

Results of sensitivity analysis

We evaluated whether the findings were maintained in sensitivity analyses. The repeated random one-session-per-patient resampling analysis with $k = 3$ preserved the general trajectory structure of the three clusters, but the degree of stability differed across clusters (**Supplementary Fig. 2**). The marked decreasing and rising centroids showed high similarity to the original centroids, with mean correlations of 0.965 and 0.981, respectively. In contrast, the mild decreasing cluster showed lower correlation-based stability (mean correlation, 0.054), although its root mean square error was 6.08 mmHg, consistent with relatively small absolute deviation for a flat trajectory. Overall, the repeated resampling analysis supported preservation of the three-trajectory structure.

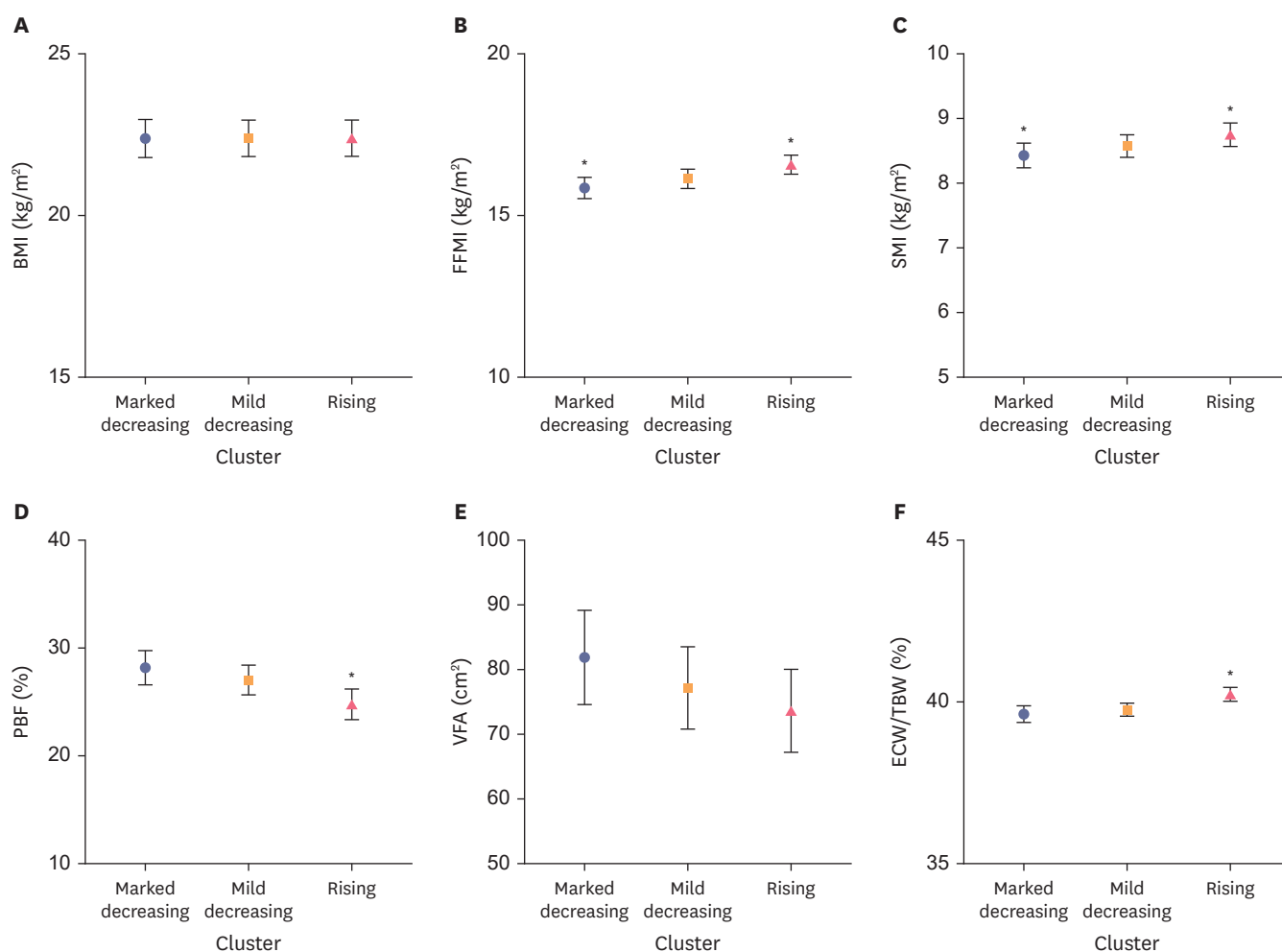


Fig. 2. Adjusted body composition parameters according to intradialytic blood pressure pattern clusters. Adjusted marginal means with 95% confidence intervals are shown for each cluster. (A) BMI did not differ across clusters. (B, C) FFMI and SMI were higher in the rising cluster and lower in the marked decreasing cluster. (D, E) PBF and VFA showed overall differences across clusters, although pairwise differences were attenuated after Bonferroni correction. (F) ECW/TBW was highest in the rising cluster. BMI, body mass index; ECW/TBW, extracellular water-to-total body water ratio; FFMI, fat-free mass index; SMI, skeletal muscle mass index; PBF, percent body fat; VFA, visceral fat area.

* $p < 0.05$ versus the mild decreasing cluster after Bonferroni correction.

In a 4-cluster solution, the overall phenotypic structure observed in the 3-cluster analysis was preserved. Among the 928 HD sessions, 61 (6.6%), 269 (29.0%), 374 (40.3%), and 224 (24.1%) were classified as severe decreasing, moderate decreasing, near-stable, and rising patterns, respectively (**Supplementary Fig. 3**). The 4-cluster solution represented a finer stratification of the same underlying trajectory structure.

Body composition differences across the 4-cluster solution were consistent with those observed in the primary 3-cluster analysis (**Supplementary Table 1**). In the adjusted mixed-effects models, FFMI and SMI remained highest in the rising cluster, whereas PBF and VFA were highest in the severe decreasing cluster. In addition, ECW/TBW was lowest in the severe decreasing cluster. BMI remained similar across the clusters. These findings support the robustness of the primary results.

DISCUSSION

In this study, we used an unsupervised clustering approach to objectively classify dynamic intradialytic BP trajectories and evaluated their independent associations with body composition parameters. We identified three distinct, reproducible intradialytic BP phenotypes: marked decreasing, mild decreasing, and rising clusters. These clusters were strongly and independently associated with the patients' volume status, muscle mass, and fat mass, even after rigorous adjustment for dynamic fluid removal stress.

Intradialytic BP monitoring is fundamental for ensuring patient safety during HD. Importantly, extreme intradialytic BP deviations—such as intradialytic hypotension and hypertension—are well-established risk factors for subsequent all-cause and cardiovascular mortality [11-14]. Given this established prognostic significance, understanding the underlying pathophysiological drivers of these high-risk BP trajectories is of paramount clinical importance. However, clinical decision-making based on arbitrary diagnostic cutoffs and binary thresholds may overlook the continuous physiological heterogeneity among patients [15-17]. In contrast, machine learning techniques like clustering learn directly from data, which helps elucidate the true relationship between clinical phenotypes and underlying pathophysiology. Using an unsupervised clustering approach, we visualized that intradialytic SBP alterations exist on a continuous spectrum and demonstrated that these data-driven phenotypes are intricately linked to the patients' body composition characteristics.

Through the k-means clustering algorithm, we identified three distinct intradialytic BP phenotypes based on their trajectories over the HD session. Notably, these trajectory features were consistently maintained both when the repeated random one-session-per-patient resampling analysis with 200 iterations and when a 4-cluster solution ($k = 4$) was selected in the sensitivity analyses. We initially anticipated that the algorithm might differentiate the phenotypes based on the specific timing of the BP changes (e.g., early versus late drops); however, the clusters were primarily distinguished by the absolute magnitude and direction of the BP alterations. The features were confirmed both in the repeated random resampling analysis and the 4-cluster solution. A previous study by Wang et al. [18] determined intradialytic BP patterns using a dynamic time warping algorithm and applied normalization to the BP sequences, proposing five patterns based on density peak clustering, distinguishable by the timing and shape of the BP change. In contrast, we considered both the specific time interval after HD initiation and the absolute amount of change in SBP to be clinically crucial. This methodological choice allowed our clustering to capture the true magnitude of hemodynamic shifts, effectively revealing the trajectories representing highly reproducible biological signatures with the exceptional numerical stability.

Our clustering approach revealed that the dynamic intradialytic BP alterations are intricately linked to patients' fluid status and body composition. It is noteworthy that a continuous, stepwise gradient in volume, muscle, and fat parameters was observed across the clusters, which was robustly confirmed in our 4-cluster sensitivity analysis. ECW/TBW indicates volume status and has been used to guide dry weight adjustment [5]. Based on our results, ECW/TBW tended to increase as the trajectory shifted from a marked decreasing to a rising pattern, while the lowest interdialytic weight gain and ultrafiltration rate and the highest number of antihypertensive drugs were observed in the rising cluster. The association between hypervolemia and intradialytic hypertension has been well demonstrated in previous literature [7,14]. Taken together, these findings suggest a state of volume overload

in which the prescribed dry weight may be higher than the true euvoletic state. On the other hand, the excessive or rapid removal of ECW can precipitate a profound BP decline during HD [6]. Our results support the importance of individualized dry weight assessment and volume management for stable HD treatment, with attention to both marked decreasing and rising intradialytic BP patterns.

Indicators of muscle mass, such as FFMI and SMI, exhibited a stepwise increase toward the rising cluster, while indicators of fat mass, such as PBF and VFA, a stepwise decrease. These findings should be interpreted with extreme caution. Because BIA inherently estimates fat-free mass based on TBW, ECW excess can lead to a substantial overestimation of muscle mass [19]. However, there is research supporting the association between sarcopenia and intradialytic hypotension [8], and some evidence even shows the protective effect of intradialytic exercise against intradialytic hypotension [20]. Furthermore, visceral adiposity acts as an active endocrine organ secreting pro-inflammatory cytokines [21,22], which may exacerbate endothelial and autonomic dysfunction, rendering patients highly vulnerable to BP drops. Our finding aligns with a previous study by Tian et al. [9], which reported that sarcopenic obesity, the combination of high fat mass and low lean mass, conferred the highest risk of intradialytic hypotension. Our results support previous findings, highlighting the critical role of sarcopenic obesity and adipose tissue in hemodynamic alterations over the HD course.

This study has several limitations that should be acknowledged. First, this was a retrospective, single-center study, which limits the generalizability of our findings to broader HD populations. Furthermore, this study design precludes causal inference regarding the relationship between intradialytic BP patterns and body composition parameters. Second, this study assessed body composition using BIA, which can limit the interpretation since it is easily affected by volume status, although we used a multifrequency BIA and measured following the recommended protocol [19]. Third, BP was measured using automated devices built into the HD machines. This approach may introduce measurement discrepancies compared to standardized measurement.

In conclusion, our unsupervised clustering successfully classified the dynamic trajectories of intradialytic BP into three distinct, reproducible phenotypes: marked decreasing, mild decreasing, and rising patterns. These data-driven BP trajectories are intricately linked to the patients' underlying body composition parameters. This insight provides actionable therapeutic targets, such as more rigorous volume assessment in the rising pattern and nutritional and physical interventions for sarcopenic obesity in the marked decreasing pattern. Ultimately, integrating routine body composition and volume assessments into clinical practice can improve the interpretation of intradialytic BP patterns, paving the way for more individualized management strategies for patients undergoing chronic HD.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Adjusted values of body composition parameters according to the 4-cluster solution

Supplementary Fig. 1

Elbow plot for selecting the number of clusters for intradialytic BP trajectories. Total WSS is plotted against the number of clusters ($k = 2-8$) for k-means clustering based

on raw intradialytic changes in systolic BP from sessions with complete 0–240 minutes measurements. A marked reduction in the WSS was observed from 1,816,039.9 at $k = 2$ to 1,383,281.5 at $k = 3$, followed by progressively smaller decreases thereafter, supporting $k = 3$ as the primary clustering solution.

Supplementary Fig. 2

The three intradialytic SBP clusters in repeated one-session-per-patient resampling. One hemodialysis session was randomly selected from each patient, and k -means clustering ($k = 3$) was repeated over 200 iterations. Gray lines indicate the cluster centroids from each resampled dataset, while black lines represent centroids from the original full training dataset. The overall three-trajectory structure was preserved across resampling iterations, although the mild decreasing pattern showed greater dispersion than the marked decreasing and rising patterns.

Supplementary Fig. 3

Intradialytic systolic blood pressure trajectories according to the 4-cluster solution. The 4-cluster solution identified four distinct phenotypes: severe decreasing, moderate decreasing, near-stable, and rising patterns, supporting finer stratification of the primary 3-cluster trajectory structure.

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Case Report



Long-Standing Hypokalemia and Hypomagnesemia in a 61 Year-Old Woman: A Delayed Diagnosis of Gitelman Syndrome

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ABSTRACT

Background: Gitelman syndrome (GS) is an autosomal recessive renal tubular disorder characterized by a distinct biochemical profile, including hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria. Due to its often mild or nonspecific clinical presentation, GS is frequently misdiagnosed as idiopathic hypokalemia, leading to prolonged symptomatic treatment without a definitive etiologic diagnosis.

Case Presentation: We report the case of a 61-year-old female with a one-year history of unexplained, refractory hypokalemia and hypomagnesemia. The diagnosis had been delayed as clinical efforts were primarily focused on escalating electrolyte supplementation. Systematic evaluation of renal electrolyte handling revealed inappropriate urinary potassium and magnesium wasting in conjunction with marked hypocalciuria. In addition, a symptom-oriented family history, documenting chronic fatigue and muscle cramps in her sibling, served as a critical diagnostic clue. Genetic testing confirmed the diagnosis by identifying compound heterozygous variants in the *SLC12A3* gene. Following diagnosis, the patient was enrolled in the Korean National Medical Expense Support Program for rare diseases, ensuring structured long-term management.

Conclusions: This case underscores the importance of an etiologic approach over a purely treatment-focused one in patients with recurrent electrolyte imbalances. GS may be more prevalent than currently recognized, particularly among adults receiving empirical therapy for hypokalemia. Early clinical suspicion, grounded in urinary electrolyte indices and careful family history, is essential for timely diagnosis.

Keywords: Gitelman syndrome; Hypokalemia; Magnesium; Renal tubular transport; Inborn errors; Solute carrier family 12, member 3

INTRODUCTION

Gitelman syndrome (GS) is an inherited renal tubular disorder caused by loss-of-function mutations in the *SLC12A3* gene, which encodes the thiazide-sensitive Na-Cl cotransporter

Conflicts of interest

All authors have no conflicts of interest to declare.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

Conceptualization: SYL, MYY; Supervision: MYY; Writing - original draft: SYL; Writing - review & editing: SWH, JL, MYY.

(NCC) in the distal convoluted tubule [1,2]. Dysfunction of NCC leads to impaired sodium and chloride reabsorption, resulting in a characteristic biochemical profile, including hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria [2,3].

Despite these distinctive laboratory findings, its diagnosis is frequently delayed in clinical practice. Patients often present with nonspecific symptoms such as fatigue, muscle cramps, or gastrointestinal complaints, or are incidentally found to have electrolyte abnormalities during evaluation for unrelated conditions. This diagnostic delay is particularly common in adult patients, in whom GS often presents with subtle or nonspecific manifestations. In many cases, hypokalemia is managed with repeated electrolyte replacement without sufficient effort to identify the underlying cause, leading to prolonged symptomatic treatment and delayed etiologic diagnosis [2,3].

Here, we report a case of genetically confirmed GS in a patient with long-standing, unexplained hypokalemia and hypomagnesemia. This case underscores the importance of clinical suspicion and systematic diagnostic reasoning in patients with recurrent electrolyte abnormalities.

CASE PRESENTATION

A 61-year-old woman presented to the emergency department with abdominal pain and diarrhea. She had experienced abdominal discomfort for 3 days prior to presentation and developed up to seven episodes of watery diarrhea on the day of admission. She had a known history of dyslipidemia and hypothyroidism, for which she had been taking levothyroxine (50 µg/day), but had no prior use of diuretics, laxatives, or herbal medicines.

Blood pressure was 102/58 mmHg, and other vital signs were within normal limits. Physical examination was unremarkable, and electrocardiography showed no abnormal findings. Initial laboratory evaluation revealed hyponatremia (serum sodium 123.4 mmol/L), hypokalemia (2.5 mmol/L), hypochloremia (85.4 mmol/L), hypomagnesemia (1.4 mg/dL), and mild metabolic alkalosis, reflected by a serum total CO₂ level of 27 mmol/L. Renal function was preserved, with a serum creatinine level of 0.63 mg/dL and an estimated glomerular filtration rate of 97.1 mL/min/1.73 m².

Mild hypophosphatemia (3.0–3.9 mg/dL) and low-normal serum uric acid levels (3.5–3.8 mg/dL) were also observed. Serum calcium, liver function tests, and inflammatory markers were within normal ranges. Thyroid function tests revealed markedly elevated thyroid-stimulating hormone (87.5 µIU/mL) and low free thyroxine (0.7 ng/dL), consistent with inadequately controlled hypothyroidism. Accordingly, the dose of levothyroxine was increased from 50 to 100 µg/day during hospitalization. Although hypothyroidism may have contributed to the hyponatremia, it does not account for the persistent hypokalemia and hypomagnesemia observed in this patient.

Given her diarrhea, gastrointestinal potassium loss was initially considered, and the patient was admitted for electrolyte correction and monitoring. However, medication reconciliation revealed that she had been taking high-dose oral potassium chloride (4,800 mg/day) along with oral magnesium supplementation (magnesium lactate hydrate 470 mg per tablet, 4 tablets twice daily). She also reported intermittent diarrhea during magnesium supplementation. Further history taking confirmed that she had experienced intermittent

fatigue for 2 years. Fourteen months prior to admission, she was evaluated at a local nephrology clinic and started on potassium and magnesium supplementation. Despite progressive dose escalation over the following year, serum potassium and magnesium levels remained persistently low.

In addition, family history revealed that her younger sister had experienced chronic fatigue and recurrent muscle cramps, requiring multiple medical visits and ongoing follow-up at a neurology outpatient clinic for similar symptoms. No prior laboratory data were available at the time of initial assessment.

Given the long-standing electrolyte abnormalities and the suggestive family history, further etiologic evaluation was pursued rather than continued symptomatic correction alone.

A 24-hour urine study revealed low urinary calcium excretion (101 mg/day), consistent with hypocalciuria. Urinary potassium (70.7 mmol/day) and magnesium (273 mg/day) excretion remained inappropriately elevated despite hypokalemia and low-normal serum magnesium levels. The fractional excretion of potassium and magnesium, calculated from the 24-hour urine collection, were 20.7% and 18.4%, respectively. Additionally, spot urine analysis demonstrated an elevated transtubular potassium gradient (5.2), supporting inappropriate renal electrolyte wasting due to an intrinsic tubular defect rather than extrarenal loss.

Based on these findings, genetic testing was performed. Next-generation sequencing identified 2 heterozygous variants in the *SLC12A3* gene: a pathogenic splice-site variant, *c.964+1G>A*, and a likely pathogenic missense variant, *c.403C>T* (*p.Arg135Cys*). These findings were consistent with autosomal recessive GS.

Subsequent family evaluation confirmed that her sibling was also diagnosed with GS. The patient was enrolled in the Korean National Medical Expense Support Program for rare diseases and initiated on structured long-term management, including potassium and magnesium supplementation and potassium-sparing therapy. Following treatment initiation, serum potassium and magnesium levels gradually increased and remained stable (**Fig. 1**).

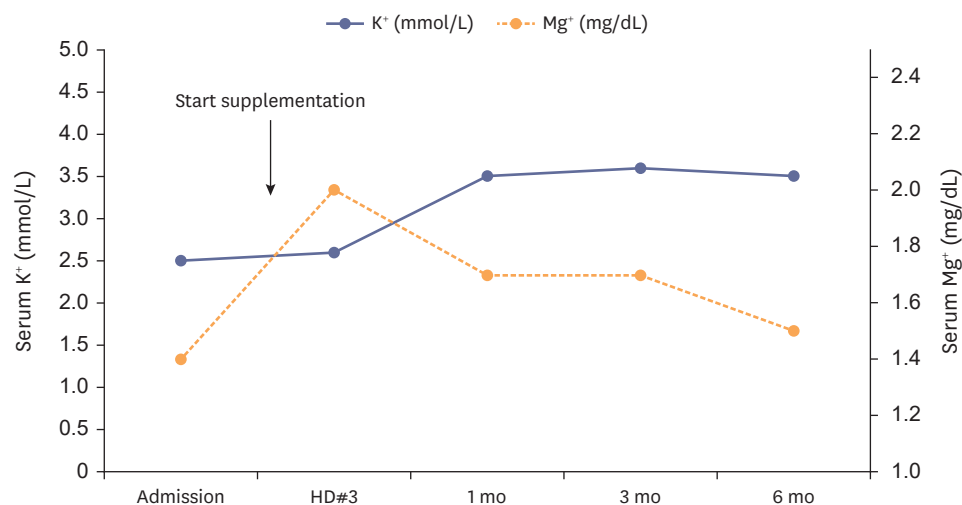


Fig. 1. Longitudinal trends in serum K⁺ and Mg²⁺ levels. HD, hospital day; K⁺, potassium; Mg²⁺, magnesium.

DISCUSSION

This case illustrates a common clinical pitfall in adult patients with chronic electrolyte disturbances, where hypokalemia is repeatedly treated without sufficient effort to determine its underlying cause. The diagnosis in this case was not prompted by worsening laboratory abnormalities but was made during evaluation for unrelated gastrointestinal symptoms.

At presentation, hypokalemia secondary to gastrointestinal potassium loss was appropriately considered in the acute setting. However, systematic reassessment redirected the diagnostic focus. Careful history taking revealed that hypokalemia and hypomagnesemia had clearly preceded the onset of diarrhea, concomitantly with magnesium supplementation. High-dose magnesium supplementation is a well-recognized cause of osmotic diarrhea and likely contributed to the patient's watery diarrhea. This may have further complicated long-term maintenance of electrolyte supplementation. More importantly, urinary electrolyte analysis demonstrated inappropriate renal potassium and magnesium excretion despite low serum levels, findings incompatible with extrarenal electrolyte loss. The presence of hypocalciuria further supported an intrinsic distal tubular defect, allowing differentiation from secondary hypokalemia and other tubulopathies.

Although metabolic alkalosis is a hallmark of GS, it may be milder in adult-onset or late-diagnosed patients than in classic pediatric presentations. Consequently, serum bicarbonate or total CO₂ levels may remain within the upper-normal range despite the presence of an underlying metabolic alkalosis. This case demonstrates the diagnostic value of simple urinary electrolyte assessment. Even without complex or invasive testing, basic urine studies, including urinary potassium, magnesium, and calcium excretion, can provide critical insight into renal tubular function. Early incorporation of urinary electrolyte analysis into the diagnostic workup of chronic or unexplained hypokalemia allows clinicians to suspect renal tubular disorders at an early stage and to pursue targeted etiologic evaluation.

Despite its characteristic biochemical profile, GS is frequently underdiagnosed because of its nonspecific and variable clinical presentation. Many patients experience only mild symptoms or remain asymptomatic for years, and chronic electrolyte abnormalities are often attributed to idiopathic or acquired causes [4].

The key diagnostic step in this case was clinical suspicion based on the chronicity of electrolyte abnormalities, reinforced by structured evaluation including detailed history taking and urinary electrolyte analysis. Recognition of symptom-based family history, chronic fatigue and muscle cramps in the patient's sibling, provided an additional diagnostic clue. Family history should not be limited to confirmed diagnoses, but should also encompass symptom patterns suggestive of inherited disease.

GS is characterized by substantial intrafamilial phenotypic variability, such that affected individuals within the same family may present with different patterns and severities of electrolyte abnormalities. This variability is thought to result from differences in residual function of the thiazide-sensitive NCC due to distinct combinations of *SLC12A3* variants, modifier genes, hormonal factors, and environmental exposures [5,6]. For this reason, family history should include careful inquiry into a broad range of symptoms, such as fatigue, muscle cramps, weakness, or recurrent medical visits. A symptom-oriented approach to history taking may therefore raise clinical suspicion for GS even when biochemical presentations differ among family members.

In Korea, GS is classified as a rare disease and is included in the National Medical Expense Support Program. Diagnostic criteria require demonstration of characteristic electrolyte abnormalities on blood and urine testing and confirmation of loss-of-function mutations in the *SLC12A3* gene, making genetic testing essential for definitive diagnosis. Because GS is a lifelong, non-curable condition requiring chronic management, accurate diagnosis has important implications beyond academic interest, enabling access to structured medical surveillance and financial support. From this perspective, active diagnostic efforts are not only clinically meaningful but also beneficial for patients within the Korean healthcare system. While routine genetic testing is not warranted for all patients with hypokalemia, this case exemplifies the value of targeted genetic evaluation when clinical features strongly suggest an inherited renal tubular disorder. Furthermore, identification of GS has implications beyond the affected individual, as family members may benefit from clinical screening and genetic evaluation.

In summary, this case serves as a reminder that chronic hypokalemia should not be managed solely as a laboratory abnormality. Persistent hypokalemia warrants etiologic investigation, particularly when urinary electrolyte indices indicate inappropriate renal electrolyte wasting. Early recognition of inherited renal tubular disorders through systematic history taking, urinary electrolyte assessment, and targeted genetic testing can facilitate timely diagnosis, appropriate long-term management, and family screening.

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Letter to the Editor



From Specialty Silos to Integrated Care: A Korean Initiative for Cardiovascular-Kidney-Metabolic Health

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on behalf of the Korean Society of Nephrology, the Korean Diabetes Association
and the Korean Society of Cardiology

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Cardiovascular disease (CVD), chronic kidney disease (CKD), diabetes, obesity, and various metabolic disorders have traditionally been managed within distinct clinical and academic domains [1]. However, these conditions rarely exist in isolation. They share risk factors and pathophysiological pathways, accelerate one another, and increasingly share therapeutic strategies. Beyond renin-angiotensin system inhibitors, the emergence of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists, and nonsteroidal mineralocorticoid receptor antagonists has further blurred conventional organ-based therapeutic boundaries [2]. Consequently, therapies once viewed through organ-specific indications are increasingly shared across cardiology, nephrology, and endocrinology to achieve cardiovascular, kidney, and metabolic protection.

The concept of cardiovascular-kidney-metabolic (CKM) syndrome provides a framework for addressing these interconnections. In 2023, the American Heart Association (AHA) formally defined CKM syndrome as a systemic disorder reflecting interactions among metabolic risk factors, CKD, and the cardiovascular system [3]. More recently, the '2026 AHA/ACC/ADA/ASN Guideline for the Prevention, Detection, Evaluation, and Management of Cardiovascular-Kidney-Metabolic Syndrome' provided the first comprehensive clinical practice guideline for CKM syndrome, transitioning the concept toward practical implementation by introducing a stage- and risk-based approach and recommending interdisciplinary care teams with a CKM coordination point person [4]. This development represents an important shift from managing individual diseases toward managing the whole patient across traditional specialty boundaries.

This transition is particularly relevant to Korea. Cardiology, nephrology, and endocrinology/metabolism have each achieved substantial advances in clinical care, research, education,

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Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

Writing - original draft: SC, JY, JS, THB, HDK, YY, SH, EJC; Writing - review & editing: SC, JY, JS, THB, HDK, YY, SH, EJC.

and health policy. Yet these efforts have largely evolved within their respective specialty frameworks. A patient with diabetes, CKD, and CVD may therefore encounter multiple specialists, separate clinical pathways, and disease-specific recommendations despite having a single interconnected disease continuum. The challenge is no longer simply to strengthen each specialty independently, but to connect their expertise around the needs of the same patient.

Against this background, representatives of the Korean Society of Nephrology (KSN), Korean Society of Cardiology (KSC), and Korean Diabetes Association (KDA) held their first working-level meeting on August 24, 2026, to discuss the establishment of a national CKM collaborative framework, tentatively referred to as the Korean CKM Alliance. The significance of this initiative lies not merely in bringing three professional societies together. Rather, it represents a transition from parallel efforts by individual specialties toward a shared approach to an interconnected disease spectrum. At the meeting, the three societies identified the development of a Korean CKM care model adapted to the Korean healthcare environment as a key long-term goal. Proposed areas of collaboration include multidisciplinary CKM care models and clinical practice guidelines, joint academic and professional education programs, CKM registries and real-world data infrastructure, collaborative clinical research, public and professional awareness initiatives, and coordinated health policy proposals (**Fig. 1**). As an initial academic collaboration, a joint CKM session is planned for the 11th Congress of the Asian Pacific Society for Dialysis Access (APSDA) in conjunction with the 47th Annual Meeting of the KSN (APSDA × KSN 2027) in Seoul. These activities may provide a foundation for moving CKM care from a conceptual framework toward practical implementation.

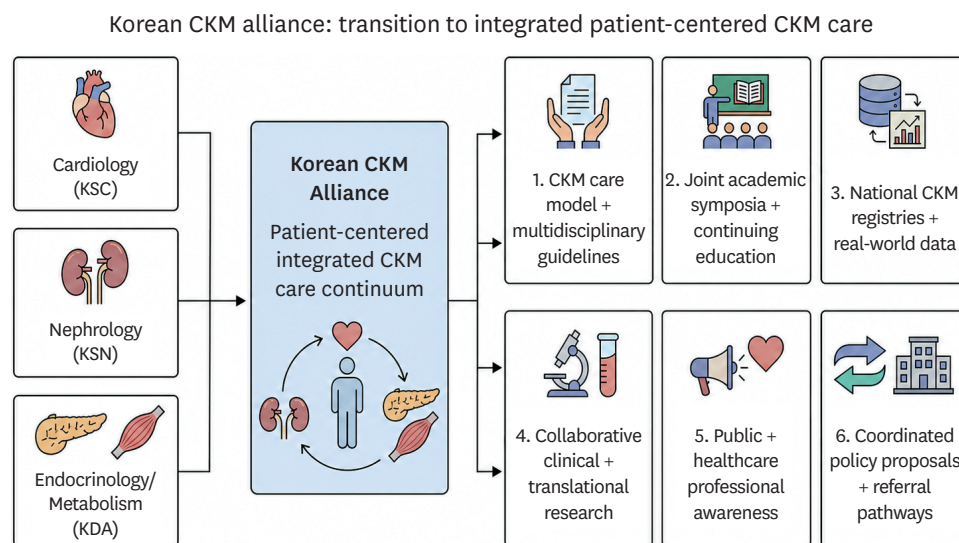


Fig. 1. A proposed framework for integrated CKM care in Korea.

Schematic representation illustrating the transition from traditional specialty silos (Cardiology [KSC], Nephrology [KSN], and Endocrinology/Metabolism [KDA]) toward a patient-centered, integrated care continuum. The alliance is structured around 6 core strategic pillars: (1) Korean CKM care model development and multidisciplinary clinical practice guidelines, (2) joint academic symposia and continuing medical education programs, (3) national CKM registries and real-world data infrastructure, (4) collaborative clinical and translational research, (5) public and healthcare professional awareness campaigns, and (6) coordinated health policy proposals and primary-specialist referral pathways.

CKM, cardiovascular-kidney-metabolic; KDA, Korean Diabetes Association; KSC, Korean Society of Cardiology; KSN, Korean Society of Nephrology.

A Korean CKM model must not merely replicate other frameworks, rather, it should be tailored to Korea's unique healthcare landscape. Korea's nationwide health screening infrastructure may provide a unique platform for systematic CKM risk assessment. However, important gaps remain, including the absence of quantitative albuminuria testing in the current national health screening program and the need to incorporate CKM-specific cardiovascular risk stratification. At the same time, clinical care remains largely organized around individual specialties and diseases. Developing effective referral and co-management pathways, defining the respective roles of primary care physicians and specialists, and identifying appropriate points for multidisciplinary intervention will therefore be essential. Each discipline brings a distinct but complementary perspective to CKM health. From a cardiology perspective, CKD, diabetes, and obesity are major determinants of cardiovascular risk, heart failure, and atherosclerotic cardiovascular disease, making their early recognition and management integral to cardiovascular prevention [5]. Nephrologists address that cardiovascular and metabolic disorders are major drivers of CKD development and progression, while CKD itself markedly amplifies cardiovascular risk, positioning kidney protection as an essential component of CKM care [6]. From an endocrinology perspective, diabetes, obesity, and insulin resistance are important metabolic drivers of both cardiovascular and kidney disease, creating opportunities for early intervention before irreversible target-organ damage develops [7]. These complementary perspectives are increasingly connected by therapies that provide benefits across organ systems rather than within a single traditional specialty. Existing specialty-based initiatives can also provide building blocks for this shared framework. For example, the KSN's Kidney Health Plan 2033, which emphasizes CKD prevention and attenuation of disease progression, is closely aligned with the broader direction of integrated CKM health [8].

Important challenges remain. Governance, practical care pathways, shared outcome measures, data infrastructure, and policy priorities will require careful consensus among participating societies. More importantly, multidisciplinary care should not simply add more specialists to an already complex patient journey. Its value should be judged by whether it reduces fragmentation, improves implementation of evidence-based therapies, facilitates communication among clinicians, and ultimately improves patient-centered outcomes.

The first meeting among the KSN, KSC, and KDA is only an initial step, but it signals an important change: from specialty-based silos toward collaboration around the patient. CKM syndrome challenges the traditional boundaries on which medical specialties have been organized. The task ahead is not to eliminate those boundaries, but to build effective bridges between them. Developing and evaluating a Korean CKM care model may provide an opportunity to translate this principle into clinical practice and national health policy and, ultimately, to reduce the growing burden of cardiovascular, kidney, and metabolic diseases in Korea.

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Electrolytes & Blood Pressure (EBP; pISSN 1738-5997, eISSN 2092-9935), the official journal of the Korean Society for Electrolyte and Blood Pressure Research, is a peer-reviewed publication dedicated to advancing research in renal physiology, hypertension, and the cardiovascular system. The journal welcomes original research and reviews addressing glomerular filtration, tubular transport, hormonal regulation, fluid and electrolyte balance, acid-base homeostasis, blood pressure regulation, and toxin elimination. Topics of interest further include the renin-angiotensin-aldosterone system, renovascular and secondary hypertension, and hypertension-related kidney disease—emphasizing the complex interplay between renal function and cardiovascular health. *EBP* accepts contributions from researchers worldwide, across all related disciplines.

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- List up to six authors. If more than six, list the first three followed by “et al.”
- Journal titles must be abbreviated according to Index Medicus standards.

Examples:

- **Journal article:** Lee EK, Yang WS. Use of Fludrocortisone for Hyperkalemia in Chronic Kidney Disease Not Yet on Dialysis. *Electrolyte Blood Press* 2024;22:8-15.
- **Supplement:** Kim GH, Han JS. Therapeutic approach to hypokalemia. *Nephron* 2002;92(Suppl 1):28-32.
- **Online publication but not yet in print:** Chao CT, Kovesdy CP, Merchant RA. Sarcopenia, sarcopenic obesity, and frailty in individuals with chronic kidney disease: a comprehensive review. *Kidney Res Clin Pract* 2025 Jan 21 [Epub]. DOI: 10.23876/j.krcp.24.207
- **Entire Book:** Daugirdas JT, Blake PG, Ing TS. Handbook of dialysis. 5th ed. Wolters Kluwer; 2015.
- **Book chapter:** Verbalis JG. Hyponatremia and hypoosmolar disorders. In: Gilbert SJ, Weiner DE, Bombardieri AS, et al, eds. *Primer on kidney disease*. 7th ed. Elsevier; 2018. p. 68-76.
- **Website:** National Cancer Information Center. Cancer incidence [Internet]. National Cancer Information Center, c2009 [cited 2009 Oct 20]. Available from: <http://www.cancer.gov/cancer/cancerstats>

2.8. Tables and Figures

Tables and figures must be cited in numerical order.

- Table titles should be concise (≤ 15 words), with legends (≤ 300 words) placed below each table.
- Figure titles and legends should be provided in the main manuscript file.
- All non-standard abbreviations must be defined.
- Use superscript lowercase letters (e.g., *, †, ‡) for table/figure notes.
- Figures must be submitted as separate files (not embedded), in high-resolution TIFF, EPS, or JPEG (≥ 300 dpi for color, ≥ 1200 dpi for line art).

2.9. Supplementary Materials

Supplementary files should be clearly labeled and submitted

separately using the “supplementary” designation. All supplementary materials must be cited in the manuscript (e.g., “Supplementary Figure 1”).

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Non-native English speakers must upload a certificate from a professional editing service. Native English speakers should submit a placeholder file labeled “Certificate of English Editing (empty).”

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Manuscripts are acknowledged within one week of submission. Submissions not adhering to technical standards may be returned without review. Each manuscript undergoes blind peer review by at least two external experts. Final publication decisions rest with the Editor-in-Chief.

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Authors of original articles are encouraged to submit a visual abstract summarizing the study graphically. Visual abstracts may be used for online promotion and engagement.

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- Original/Review Articles, Case Reports: KRW 1,000,000 (Korea) / USD 1,000 (international)
- Letters to the Editor: KRW 500,000 (Korea) / USD 500 (international)
- Member Benefit: Fees are waived for corresponding authors who are active members of the Korean Society for Electrolyte and Blood Pressure Research.
- Invited Articles: Publication fees are waived.
- Waivers: Authors from low-income countries may apply for a waiver by contacting the Editorial Office.

The primary objective of peer review is to provide the editorial team with a scientifically informed, balanced, and evidence-based assessment of submitted manuscripts, ensuring that all editorial decisions meet the journal's rigorous standards. In addition, peer review should aid authors in improving their manuscripts, regardless of the final publication decision. Review reports recommending rejection should include a clear explanation of the manuscript's principal weaknesses, thus assisting authors in refining their work for submission to another journal if applicable.

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Electrolytes & Blood Pressure (EBP) sincerely appreciates the time, expertise, and thoughtful input contributed by our reviewers. Reviewers play a critical role in maintaining the scientific integrity and academic quality of the journal. When feasible, reviewers are encouraged to assess revised versions of manuscripts they originally reviewed to ensure continuity and coherence in the evaluation process.

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Reviewers must not contact authors directly under any circumstances during the peer review process. Any required communication should occur solely through the editorial office.

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Reviewers must not involve colleagues, students, or collaborators in the review process without prior written permission from the editorial office. If assistance is obtained with prior approval, the names and affiliations of those who contributed to the review must be disclosed, and proper acknowledgment will be recorded by the journal.

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Reviewers must assess whether any conflicts of interest exist that could compromise the impartiality of their evaluation. Review invitations should be declined if any of the following apply:

- Recent collaboration with any of the authors (within the last 36 months), including co-authorship or ongoing submissions
- Shared institutional affiliation with one or more authors
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Reviewers must remain unbiased and refrain from judgments based on authors' nationality, gender, institutional affiliation, religious or political beliefs, or other personal characteristics. The evaluation should focus solely on scientific merit.

4. Review Reports and Recommendations

4.1. Role of the Reviewer Recommendation

Reviewers are invited to provide a recommendation regarding acceptance, revision, or rejection. The editorial decision will be based on the review reports and the editorial team's judgment, and may not always align with individual reviewer recommendations.

4.2. Focus of the Review

Reviews should prioritize the scientific content of the manuscript

and its alignment with the scope of *EBP*. Minor issues related to formatting and stylistic conventions will be addressed by the editorial office and should not be the focus of the review unless they impede understanding.

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Reviewers are asked to assess manuscripts based on the following:

- Relevance and significance of the topic to the field
- Originality and novelty of the findings
- Rigor and appropriateness of the study design, methodology, and analysis
- Transparency and reproducibility of the data, methodology, and interpretation
- Ethical integrity, including potential issues related to plagiarism, image/data manipulation, redundant publication, authorship disputes, or undisclosed conflicts of interest
- Clarity and quality of the writing, structure, figures, tables, and reference list

4.4. Constructive Feedback

Reviewers should aim to be objective, respectful, and helpful in their feedback. Comments should be specific, actionable, and

framed in a professional tone. Authors should be guided toward improving their work, regardless of the final recommendation.

Suggested Review Structure

- **General Overview:** Provide a brief summary of the manuscript, including its objectives, main findings, and overall relevance. Comment on the significance of the study and its contribution to the field.
- **Major Comments:** Discuss substantive concerns such as study design flaws, inadequate data interpretation, lack of novelty, methodological weaknesses, or the need for additional experiments.
- **Minor Comments:** Address less critical issues such as unclear phrasing, inconsistent terminology, typographical or numerical errors, minor referencing concerns, and formatting of tables and figures.

We thank our reviewers for their invaluable service to *Electrolytes & Blood Pressure*. Our reviewers' expertise and commitment to rigorous peer review are essential to upholding the journal's standards and advancing the field.

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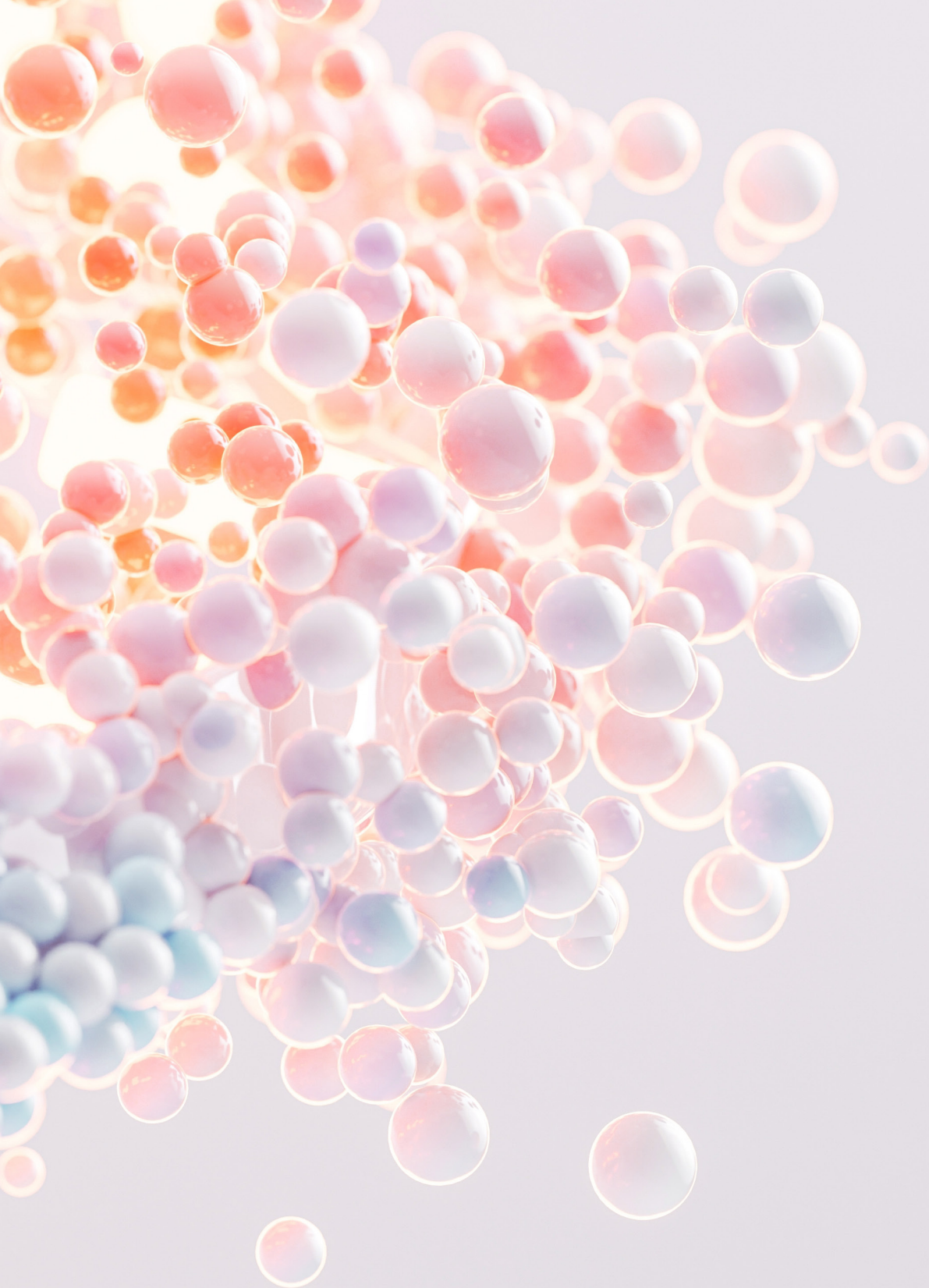
카로스현탁액

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[제품요약정보] [전문의약품] ■ 제품명_아가메이트현탁액 ■제회사_JW중외제약 ■ 주성분·함량_이 약 1포 중 폴리스티렌설포산칼륨 5g ■ 효능·효과_고칼륨혈증억제
■용법·용량_성인: 폴리스티렌설포산칼륨으로서 1일 15~30g을 2~3회 나누어 경구투여 한다. 연령증상에 따라 적절히 증감한다.
■금기_배합금기: 칼슘염과 반응하는 물질 또는 칼슘에 흡수가 저해되는 약물과의 배합은 피한다.
■신중투여_변비가 자주 발생하는 환자, 장관협착증환자, 소화관궤양환자
■주요이상반응_변비, 식욕부진, 구역
■보험수가: 698원/포 ■ 보험코드_644913491 ■ 포장단위_20포/Box

[제품요약정보] [전문의약품] ■ 제품명_카로스현탁액 ■제회사_(주)휴온스 ■ 주성분·함량_이 약 1포 중 폴리스티렌설포산칼륨 5g ■ 효능·효과_고칼륨혈증억제
■용법·용량_성인: 폴리스티렌설포산칼륨으로서 1일 15~30g을 2~3회 나누어 경구투여 한다. 연령증상에 따라 적절히 증감한다.
■금기_배합금기: 칼슘염과 반응하는 물질 또는 칼슘에 흡수가 저해되는 약물과의 배합은 피한다.
■신중투여_변비가 자주 발생하는 환자, 장관협착증환자, 소화관궤양환자
■주요이상반응_변비, 식욕부진, 구역
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