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References
1. Verbalis JG, Goldsmith SR, Greenberg A, Schrier RW, Sterns RH. Hyponatremia treatment guidelines 2007: expert panel recommendations. Am J Med. 2007;120(11 Suppl 1):S1-S21.
2. Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, Orlandi C. for the SALT Investigators. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for Hyponatremia. N Engl J Med 2006;355:2099-112

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Aims and Scope

Electrolytes & Blood Pressure (EBP; ISSN 1738-5997), formerly known as the Korean Journal of Electrolyte Metabolism, is the official journal of the Korean Society for Electrolyte and Blood Pressure Research (formerly the Korean Society of Electrolyte Metabolism). Since its launch in 2003, the journal has evolved into a respected and internationally recognized publication. As of 2005, it has been published exclusively in English as a peer-reviewed platform dedicated to advancing scientific knowledge in its field. The journal is indexed under the ISO abbreviation Electrolyte Blood Press.

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.

Journal Infomation

The journal is currently indexed in several major international databases, including Scopus, PubMed, PubMed Central (PMC), KoreaMed, KoMCI, EMBASE, Chemical Abstracts Service (CAS), Google Scholar, and Korea Citation Index (KCI), ensuring its accessibility and discoverability within the global scientific community.

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Review Article

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Mechanism of Sodium-Glucose Cotransporter-2 Inhibitors for Uricosuria

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

ABSTRACT

Clinical trials have found that sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce serum urate levels by 0.6–1.5 mg/dL, which might contribute to cardiovascular protection. Urate is the final degradation product of purine nucleotides in humans who lack uricase, unlike most mammals. Thus, the processes of urate handling differ. This review aims to address the handling of urate in humans and the mechanisms through which SGLT2 inhibitors reduce serum urate levels. The kidneys and intestines are respectively responsible for excreting 70% and 30% of urate in humans. Medications that inhibit urate excretion, as well as increased purine intake or production, can cause hyperuricemia and decrease kidney function, which plays a key role in urate excretion. Hyperuricemia is significantly associated with gout, renal stones, mortality, and cardiovascular and chronic kidney diseases. SGLT2 inhibitors lower serum urate by inhibiting its reabsorption through urate anion exchanger 1 in apical membranes of renal proximal tubules and promoting urate excretion through ATP-binding cassette subfamily G member 2 (ABCG2) located in the apical membrane of the proximal tubule and ABCG2 in the intestinal membrane. Further mechanistic studies are needed to elucidate how SGLT2 inhibitors lower serum urate levels. Although the clinical benefits of SGLT2 inhibitors probably do not arise solely from urate reduction, they decrease serum urate levels, suggesting that they could serve as adjunctive therapy for patients with hyperuricemia.

Keywords: Hyperuricemia; Kidney; Sodium-glucose transporter 2 inhibitor; Urate

URATE METABOLISM AND RENAL PROCESSING

Urate is the end product of purine nucleotide degradation in humans. Humans obtain purine nucleotide from three main sources: endogenous synthesis in tissues such as the liver, intestines, and muscle, kidney, and vascular endothelial cells; nucleolysis, which is produced by the breakdown of DNA, RNA, and ATP; and dietary intake. Approximately 80–90% of urate is derived from endogenous metabolism (70–80% is nucleolysis, and 20–30% is endogenous synthesis). The remaining 10–20% is derived from dietary intake [1]. The purine nucleotides adenosine monophosphate (AMP) and guanosine monophosphate are broken down by several enzymes that generate urate as the final product. Two-thirds of urate is

excreted through the kidney, and one-third is eliminated through the gastrointestinal tract [2]. Urate is filtered almost freely at the glomerulus, and ~99% is reabsorbed into the blood in the early renal proximal tubule. Although most other mammals convert urate to more soluble allantoin, humans and other primates have higher serum urate levels due to the absence of uricase. Furthermore, the composition of the urate transporter in the kidney differs between humans and rodents [2]. This review aims to elucidate the handling of urate in humans.

Fig. 1 shows more details on the handling of urate in the kidney. Urate filtered at the glomerulus is reabsorbed from the lumen into cells of the renal proximal tubule through urate anion exchanger 1 (URAT1) encoded by *SLC22A12*, on the apical membrane of the proximal tubule, and anions are exchanged and exported to the lumen through an electrochemical gradient [3]. This reabsorption process involves organic anion transporter (OAT) 4, encoded by *SLC22A11*, on the apical membrane of the proximal tubule. Urate is reabsorbed from cells into the blood *via* the facilitated diffusion of glucose transporter 9 (GLUT9), encoded by *SLC2A9* in the basolateral membrane of the proximal tubule.

In the proximal tubule, urate is transported from blood into the cells *via* OAT1 and 3 respectively encoded by *SLC22A6* and *SLC22A8*, on the basolateral membrane of this

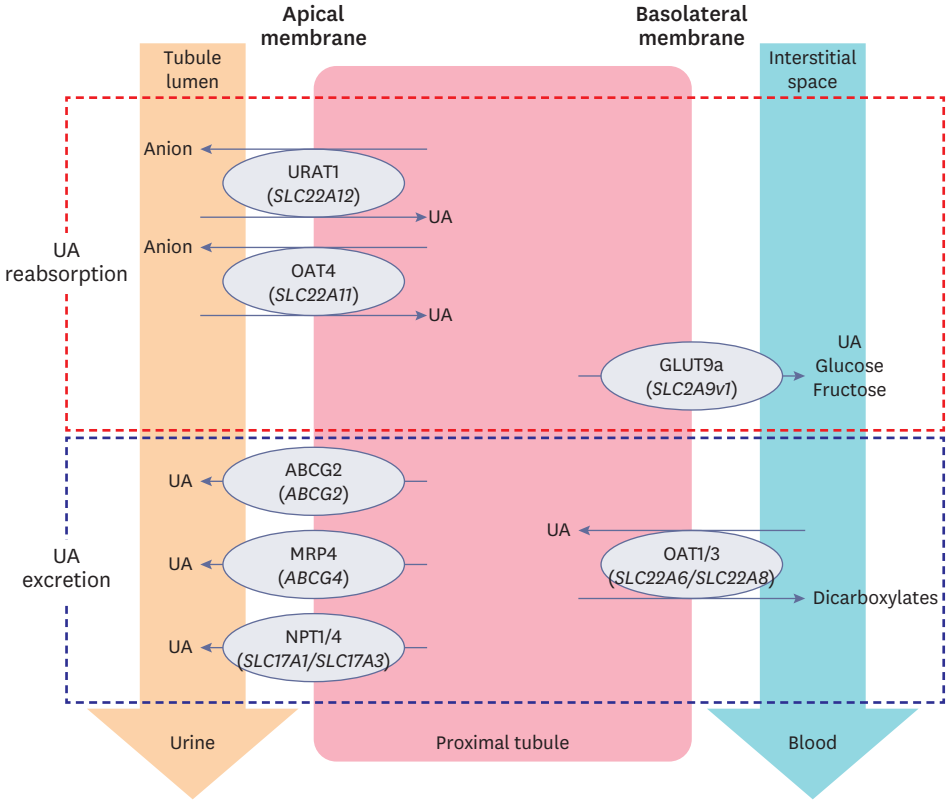

Fig. 1. Mechanisms of urate reabsorption and excretion in proximal tubules of kidneys and involved transporters.
Urate is reabsorbed from lumen into renal tubule cells *via* URAT1 and OAT4 on apical membranes of proximal tubules, then from these cells into interstitial space (blood) *via* GLUT9a on basolateral membranes. Urate is excreted from blood and transported into renal tubular cells by OAT1/3 on basolateral membranes of proximal tubules, and from cells into lumen through ABCG2, MRP4, and NPT 1/4 on apical membrane.
ABCG2, ATP-binding cassette subfamily G member 2; GLUT9a, glucose transporter 9 isoform 9a; MRP4, multidrug resistance-associated protein 4; NPT1, sodium-dependent phosphate transporter 1; NPT4, sodium-dependent phosphate transporter 4; OAT, organic anion transporter; URAT1, urate transporter 1.

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tubule. Urate is then excreted into the lumen through sodium-phosphate transporter (NPT) 1 encoded by *SLC17A1*, NPT4 encoded by *SLC17A3*, and ATP-binding cassette subfamily G member 2 (ABCG2) located apical membrane of the proximal tubule [2-4].

Serum urate is transported to intestinal epithelial cells and secreted into the lumen by ABCG2 expressed on the apical membrane of intestinal epithelial cells [5]. The excreted urate is broken down by intestinal microorganisms in the feces. The intestinal microbiota contributes to urate degradation *via* uricolytic *Bacillus* and *Lactobacillus*, which express uricase [6]. A reduction in uricolytic bacteria leads to dysbiosis associated with elevated serum urate [7]. The intestinal excretion of urate that usually accounts for ~30% increases when kidney function declines.

Polymorphisms in numerous urate transporters contribute to inter-individual differences in urate processing in humans. Loss-of-function variants in *SLC22A12* (URAT1) can cause renal hypouricemia and significantly increase urinary urate excretion [8]. Variants of *SLC2A9* which encodes GLUT9 can also significantly affect serum urate levels by 1.2–6.0% [9]. Common variants in *ABCG2*, such as Q141K, reduce intestinal urate excretion and elevate serum urate [10]. These results indicate that transporter genetics contribute to inter-individual variability in urate homeostasis.

MECHANISMS OF HYPERURICEMIA AND ITS CLINICAL IMPLICATIONS

Urate is a weak acid (pKa, 5.75) and its form depends on pH. At physiological pH, urate exists predominantly in its ionized form and acts as an antioxidant in human plasma by scavenging reactive oxygen species and protecting against oxidative damage [11]. Monosodium urate crystallizes due to low water solubility when urate levels in plasma or tissue fluid exceed the average solubility limit of 6.8 mg/dL [3]. These crystals can lead to immune response activation, inflammation, gout, and kidney stones. Furthermore, elevated urate levels can exert pro-oxidant and pro-inflammatory effects by increasing oxidative stress, impairing endothelial nitric oxide signaling, and activating inflammasome pathways. These actions contribute to vascular and metabolic dysfunction [12,13].

Hyperuricemia is defined as serum urate > 7.0 and > 6.0 mg/dL in men and women, respectively, during excessive urate production or reduced excretion (**Table 1**). A diet rich in purine or fructose contributes to urate production. Ethanol increases ATP breakdown, which

Table 1. Mechanisms of hyperuricemia

Mechanism	Examples or related conditions
Overproduction	
High purine or fructose intake	Purine-rich diet, fructose-rich beverages
Enhanced ATP degradation and purine catabolism	Alcohol (ethanol) increases ATP degradation
Increased cell turnover	Leukemia, lymphoma, tumor lysis syndrome
Increased de novo purine synthesis (enzyme defect)	Lesch–Nyhan syndrome
Underexcretion	
Reduced kidney function	Chronic kidney disease
Drug-induced inhibition of uric acid excretion	Aspirin, loop diuretics, thiazides, cyclosporine, tacrolimus, pyrazinamide, ethambutol, ACE inhibitors, beta-blockers

ACE, angiotensin-converting enzyme; ATP, adenosine triphosphate.

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increases purine breakdown and consequent urate production. Urate production is increased in leukemia, lymphoma, and tumor lysis syndrome, which have increased cell turnover, and sometimes, in Lesch–Nyhan syndrome, which causes excessive purine synthesis due to a deficiency of hypoxanthine-guanine phosphoribosyl transferase that is involved in the purine salvage pathway. Hyperuricemia is particularly likely to develop in patients with chronic kidney disease (CKD). Reduced kidney function plays a crucial role in urate excretion, and drugs such as aspirin, loop diuretics, thiazides, cyclosporin, tacrolimus, pyrazinamide, ethambutol, angiotensin-converting enzyme inhibitors, and beta-blockers inhibit urate excretion.

Hyperuricemia is associated with increased cardiovascular mortality and all-cause mortality and is significantly associated with cardiovascular disease [14] such as coronary heart disease, myocardial infarction, and stroke [15], heart failure [16], hypertension [17], atrial fibrillation [18], as well as CKD [14,19], renal stone, and gout [19]. Although hyperuricemia is generally associated with poor clinical outcomes, serum urate levels within the physiological range act as a compensatory antioxidant factors in neurodegenerative states, such as Parkinson's disease [20] and cognitive impairment [21]. This raises the question of whether urate is an independent risk factor for poor clinical outcomes or simply a marker reflecting pathophysiological conditions. Whether lowering urate can reduce risk of cardiovascular disease, hypertension, and CKD progression *via* urate-lowering therapy has been investigated. A meta-analysis of randomized controlled trial results among patients with gout found that urate-lowering therapy did not reduce the composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke [22]. Urate-lowering therapy as an antihypertensive agent is not supported by evidence [23]. Reducing urate does not improve all-cause mortality and cardiovascular death in patients with heart failure [24] or significantly reduce estimated glomerular filtration rates among patients with CKD [25].

Although a conclusion remains difficult, urate serves as a marker reflecting pathophysiological conditions rather than as an independent risk factor. Therefore, maintaining serum urate levels within the physiological range is important. If the level is abnormal, efforts should be made to identify and correct the underlying causes.

SODIUM-GLUCOSE COTRANSPORTER-2 (SGLT2) INHIBITORS AND URATE TRANSPORTERS

SGLT2 inhibitors inhibit SGLT2 protein in the S1 segments of renal proximal tubules. Approximately 90% of the glucose and Na^+ filtered by the glomerulus is reabsorbed by SGLT2. Blocking this process allows SGLT2 inhibitors to lower blood glucose levels [26]. Although SGLT2 inhibitors were originally developed as antidiabetic agents, they also protect the kidney and heart via natriuretic effects, reduced blood pressure, and suppressed glomerular hyperfiltration caused by afferent arteriolar constriction [27-29].

SGLT2 inhibitors also reduce serum urate by ~0.5 mg/dL in humans [30]. Among these inhibitors, empagliflozin is the most effective, having reduced urate by 1.12 and 0.43 mg/dL in the EMPEROR-Reduced and exploratory EMPA-KIDNEY trials, respectively [31,32]. Dapagliflozin and canagliflozin reduce urate by 0.51–0.84 mg/dL [33-35] and 0.39–0.69 mg/dL [35,36], respectively, but ertugliflozin and sotagliflozin were less effective (0.23–0.26 mg/dL) [30,37]. Although the extent of urate-lowering effect varies according to drugs and underlying diseases, SGLT2 inhibitors actually do reduce urate levels (**Table 2**).

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Table 2. Effects of SGLT2 inhibitors on serum UA from major clinical or meta-analysis studies

Drug	Study/Analysis	Participants	Change in serum UA
Empagliflozin	EMPEROR-Reduced trial [31]	Heart failure and reduced ejection fraction	1.12 ± 0.04 mg/dL
	Exploratory analysis of EMPA-KIDNEY trial [32]	CKD (eGFR ≥ 20 but < 45 mL/min/1.73 m^2 or eGFR ≥ 45 but < 90 mL/min/1.73 m^2 with a urinary albumin creatinine ratio ≥ 200 mg/g)	0.43 mg/dL
	Meta-analysis [30]		0.77 mg/dL
Dapagliflozin	Single-center retrospective [33]	CKD stage 3–5	0.8 mg/dL
	Post-hoc analysis of DAPA-HF [34]	Heart failure and reduced ejection fraction	0.84 mg/dL
	Meta-analysis [35]		0.51–0.70 mg/dL
Canagliflozin	Post-hoc analysis of CANVAS Program [36]	Type 2 DM and an elevated risk of cardiovascular disease with an eGFR ≥ 30 mL/min/1.73 m^2	0.39 mg/dL
	Meta-analysis [35]		0.61–0.69 mg/dL
Ertugliflozin	Post-hoc analysis of VERTIS CV trial [37]	Type 2 DM and established ASCVD with an eGFR ≥ 30 mL/min/1.73 m^2	0.26 mg/dL
Sotagliflozin	Meta-analysis [30]		0.23 mg/dL
Overall SGLT2 inhibitors	Meta-analysis and observational studies [30]		0.54 mg/dL

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose cotransporter 2 inhibitors; UA, uric acid.

The first mechanism through which SGLT2 inhibitors lower serum urate is by blocking SGLT2 in the proximal tubule, which increases glucose and sodium delivery to downstream tubules. Glucosuria and natriuresis augment tubular flow, which dilutes luminal urate and leads to downregulated URAT1, which enhances urinary urate excretion (**Fig. 2**) [4,38-40]. A review [4] and a preclinical proteome analysis [38] have shown that SGLT2 inhibitors significantly decrease expression of the *SLC22A12* (URAT1 protein-encoding) in the proximal tubules of wild-type mice [39]. SGLT2 inhibitors increase the fractional excretion of urate in patients with

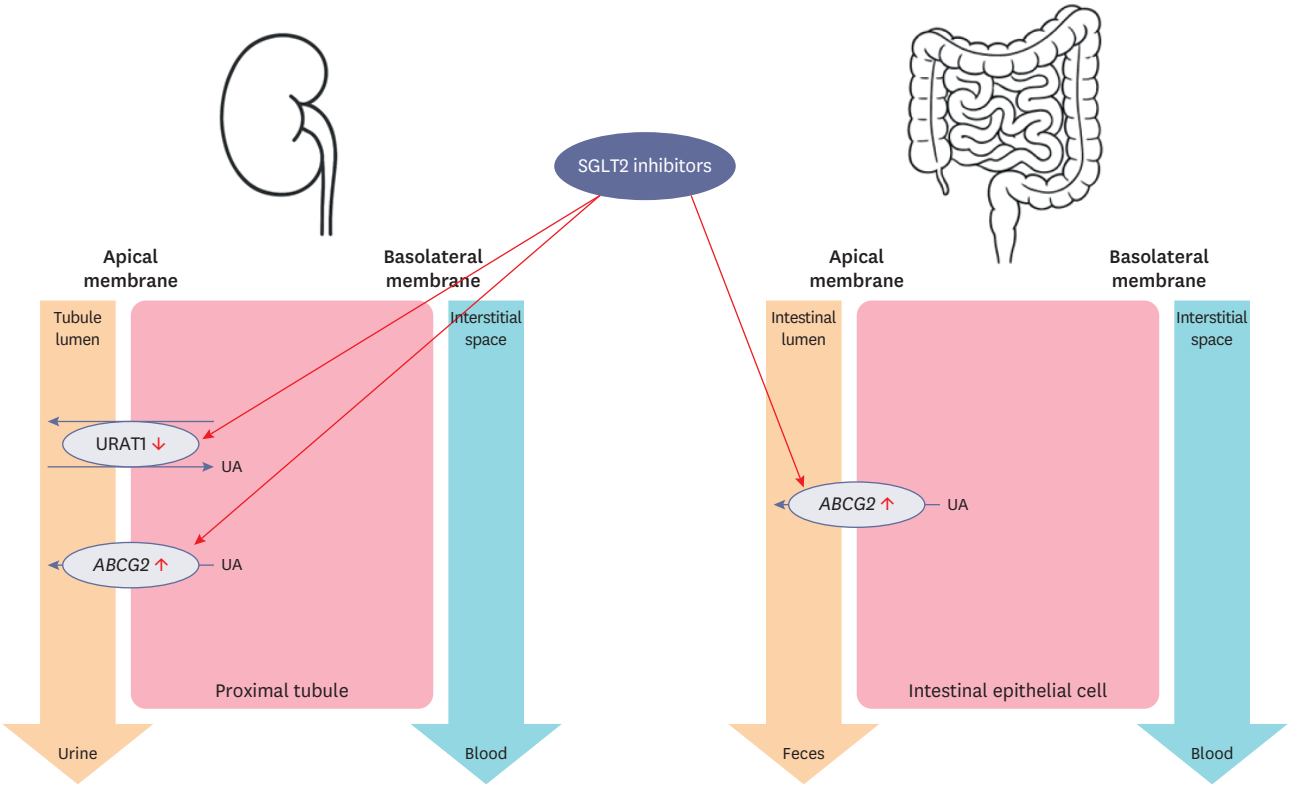

Fig. 2. Mechanisms and transporters involved in lowering urate induced by SGLT2 inhibitors. SGLT2 inhibitors block URAT1 on apical membranes of renal proximal tubules, preventing urate reabsorption. Activated ABCG2 on the apical membranes of renal proximal tubules and intestinal epithelial cells promotes urate excretion. ABCG2, ATP-binding cassette subfamily G member 2; SGLT2, sodium-glucose cotransporter 2; URAT1, urate transporter 1.

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type 2 diabetes mellitus, and that pharmacological blockade of URAT1 using benzbromarone attenuated the urate excretion effect of SGLT2 inhibitors [40]. Preclinical data have found that SGLT2 inhibitors increase urate excretion by inhibiting GLUT9 and URAT1 functions [41]. However, the uricosuric effect of SGLT2 inhibitors might be dependent on URAT1, while GLUT9 may be dispensable [42]. Therefore, the uricosuric effects of SGLT2 inhibitors *via* GLUT9 require further investigation and cannot be definitively concluded.

The secretion of urate from the proximal tubule and intestinal epithelial cells into the lumen is mediated by ABCG2 (**Fig. 2**). A loss of ABCG2 function reduces intestinal urate excretion, leading to elevated serum urate levels in mice [5]. Intestinal urate secretion in humans *in vivo* is mediated by ABCG2 and polymorphisms that reduce ABCG2 function result in elevated serum urate [43]. In addition, preclinical findings of a rat model of CKD have shown increased intestinal ABCG2 expression under conditions of reduced renal urate excretion [44]. SGLT2 inhibitors might also upregulate ABCG2, thus promoting urate secretion [45]. Although the exact mechanism is unknown, SGLT2 inhibitors enhance cellular antioxidant defenses by increasing intracellular ATP consumption, which leads to AMP accumulation and subsequent AMP-activated protein kinase (AMPK) activation. This promotes the nuclear translocation of Forkhead Box Protein O3 and Nuclear factor erythroid 2-related factor 2 (Nrf2) [46,47]. Activated AMPK and Nrf2 signaling can upregulate the urate efflux transporter ABCG2, which increases renal and intestinal urate excretion [45]. However, evidence supporting ABCG2 upregulation and its mechanism by SGLT2 inhibitors is either preclinical [45,46] or a review [47]. Therefore, they have limitations that warrant further investigation in humans.

Whether SGLT2 inhibitors can improve the unfavorable clinical outcomes associated with hyperuricemia by lowering urate levels awaits further investigation. SGLT2 inhibitors significantly reduce serum urate levels, the risk of gout [48], renal stones [49], cardiovascular disease and hospitalization for heart failure, and kidney disease progression. However, using SGLT2 inhibitors to lower urate as a primary outcome has not been investigated, so a causal relationship between the beneficial effects of SGLT2 inhibitors and urate-lowering has not been established. Furthermore, clear evidence that lowering urate improves outcomes is currently insufficient. Taken together, current outcomes suggest that the clinical benefits of SGLT2 inhibitors probably do not arise solely from lowering urate. However, we reviewed how SGLT2 inhibitors lower urate and identified other metabolic or renal benefits that are associated with decreasing urate levels. Therefore, SGLT2 inhibitors could serve as adjuvant therapy for patients with hyperuricemia.

In conclusion, SGLT2 inhibitors lower serum urate levels through numerous interconnected mechanisms, including increased urate excretion, ABCG2, and URAT1. However, the precise mechanism remains unknown, and further investigation is needed.

REFERENCES

1. Song Y, Li Q, Lu J, et al. Dietary purines and health: metabolism, impact, and regulation. *Trends Food Sci Technol* 2025;163:105191. CROSSREF
2. Bobulescu IA, Moe OW. Renal transport of uric acid: evolving concepts and uncertainties. *Adv Chronic Kidney Dis* 2012;19:358-371. PUBMED | CROSSREF
3. Kim SH, Shin J, Son HE, Kang DH. Role of urate transporters in the kidneys and intestine in uric acid homeostasis. *Kidney Res Clin Pract* 2025 Jun 18 [Epub]. DOI: 10.23876/j.krcp.24.321 PUBMED | CROSSREF

4. Zapf AM, Woodward OM. SGLT2 Inhibitors and uric acid homeostasis. *Gout Urate Cryst Depos Dis* 2024;2:157-172. CROSSREF
5. Takada T, Ichida K, Matsuo H, et al. ABCG2 dysfunction increases serum uric acid by decreased intestinal urate excretion. *Nucleosides Nucleotides Nucleic Acids* 2014;33:275-281. PUBMED | CROSSREF
6. Terkeltaub R, Dodd D. The gut microbiome in hyperuricemia and gout. *Arthritis Rheumatol* 2025;77:955-965. PUBMED | CROSSREF
7. Liu X, Ke L, Lei K, et al. Antibiotic-induced gut microbiota dysbiosis has a functional impact on purine metabolism. *BMC Microbiol* 2023;23:187. PUBMED | CROSSREF
8. Tin A, Woodward OM, Kao WH, et al. Genome-wide association study for serum urate concentrations and gout among African Americans identifies genomic risk loci and a novel URAT1 loss-of-function allele. *Hum Mol Genet* 2011;20:4056-4068. PUBMED | CROSSREF
9. Le MT, Shafiu M, Mu W, Johnson RJ. SLC2A9--a fructose transporter identified as a novel uric acid transporter. *Nephrol Dial Transplant* 2008;23:2746-2749. PUBMED | CROSSREF
10. Woodward OM, Köttgen A, Coresh J, Boerwinkle E, Guggino WB, Köttgen M. Identification of a urate transporter, ABCG2, with a common functional polymorphism causing gout. *Proc Natl Acad Sci U S A* 2009;106:10338-10342. PUBMED | CROSSREF
11. Becker BF, Reinholz N, Ozçelik T, Leipert B, Gerlach E. Uric acid as radical scavenger and antioxidant in the heart. *Pflugers Arch* 1989;415:127-135. PUBMED | CROSSREF
12. Sautin YY, Johnson RJ. Uric acid: the oxidant-antioxidant paradox. *Nucleosides Nucleotides Nucleic Acids* 2008;27:608-619. PUBMED | CROSSREF
13. Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. *Semin Nephrol* 2005;25:39-42. PUBMED | CROSSREF
14. Zheng L, Zhu Y, Ma Y, et al. Relationship between hyperuricemia and the risk of cardiovascular events and chronic kidney disease in both the general population and hypertensive patients: a systematic review and meta-analysis. *Int J Cardiol* 2024;399:131779. PUBMED | CROSSREF
15. Bos MJ, Koudstaal PJ, Hofman A, Witteman JC, Breteler MM. Uric acid is a risk factor for myocardial infarction and stroke: the Rotterdam study. *Stroke* 2006;37:1503-1507. PUBMED | CROSSREF
16. Huang H, Huang B, Li Y, et al. Uric acid and risk of heart failure: a systematic review and meta-analysis. *Eur J Heart Fail* 2014;16:15-24. PUBMED | CROSSREF
17. Kuwabara M, Hisatome I, Niwa K, et al. Uric acid is a strong risk marker for developing hypertension from prehypertension: a 5-year Japanese cohort study. *Hypertension* 2018;71:78-86. PUBMED | CROSSREF
18. Tamariz L, Agarwal S, Soliman EZ, et al. Association of serum uric acid with incident atrial fibrillation (from the Atherosclerosis Risk in Communities [ARIC] study). *Am J Cardiol* 2011;108:1272-1276. PUBMED | CROSSREF
19. Oh YJ, Shin JM, Hur JW, Son CN. Association between serum urate, gout and chronic kidney disease: a scoping review of systematic reviews and meta-analyses. *J Rheum Dis* 2025;32:241-251. PUBMED | CROSSREF
20. Weisskopf MG, O'Reilly E, Chen H, Schwarzschild MA, Ascherio A. Plasma urate and risk of Parkinson's disease. *Am J Epidemiol* 2007;166:561-567. PUBMED | CROSSREF
21. Euser SM, Hofman A, Westendorp RGJ, Breteler MMB. Serum uric acid and cognitive function and dementia. *Brain* 2009;132:377-382. PUBMED | CROSSREF
22. Zhang T, Pope JE. Cardiovascular effects of urate-lowering therapies in patients with chronic gout: a systematic review and meta-analysis. *Rheumatology (Oxford)* 2017;56:1144-1153. PUBMED | CROSSREF
23. Gois PHF, Souza ERM. Pharmacotherapy for hyperuricemia in hypertensive patients. *Cochrane Database Syst Rev* 2017;4:CD008652. PUBMED | CROSSREF
24. Xu H, Liu Y, Meng L, Wang L, Liu D. Effect of uric acid-lowering agents on patients with heart failure: a systematic review and meta-analysis of randomised controlled trials. *Front Cardiovasc Med* 2021;8:639392. PUBMED | CROSSREF
25. Kimura K, Hosoya T, Uchida S, et al. Febuxostat therapy for patients with stage 3 CKD and asymptomatic hyperuricemia: a randomized trial. *Am J Kidney Dis* 2018;72:798-810. PUBMED | CROSSREF
26. Vallon V. State-of-the-art-review: mechanisms of action of SGLT2 inhibitors and clinical implications. *Am J Hypertens* 2024;37:841-852. PUBMED | CROSSREF
27. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 dabetes. *N Engl J Med* 2015;373:2117-2128. PUBMED | CROSSREF
28. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016;375:323-334. PUBMED | CROSSREF
29. Jiang B, Cheng Z, Wang D, et al. Unveiling the podocyte-protective effect of sodium-glucose cotransporter-2 inhibitors. *Kidney Res Clin Pract* 2025;44:69-78. PUBMED | CROSSREF

30. Yang S, Hu Q, Liu K, Xiao B, Zhang B, Su N. Serum uric acid reduction through SGLT2 inhibitors: evidence from a systematic review and meta-analysis. *Front Pharmacol* 2025;16:1551390. PUBMED | CROSSREF

31. Doehner W, Anker SD, Butler J, et al. Uric acid and sodium-glucose cotransporter-2 inhibition with empagliflozin in heart failure with reduced ejection fraction: the EMPEROR-reduced trial. *Eur Heart J* 2022;43:3435-3446. PUBMED | CROSSREF

32. Mayne KJ, Sardell RJ, Staplin N, et al. Empagliflozin lowers serum uric acid in chronic kidney disease: exploratory analyses from the EMPA-KIDNEY trial. *Nephrol Dial Transplant* 2025;40:720-730. PUBMED | CROSSREF

33. Iwata Y, Notsu S, Kawamura Y, et al. The effect of dapagliflozin on uric acid excretion and serum uric acid level in advanced CKD. *Sci Rep* 2023;13:4849. PUBMED | CROSSREF

34. McDowell K, Welsh P, Docherty KF, et al. Dapagliflozin reduces uric acid concentration, an independent predictor of adverse outcomes in DAPA-HF. *Eur J Heart Fail* 2022;24:1066-1076. PUBMED | CROSSREF

35. Kochanowska A, Rusztyn P, Szczerkowska K, et al. Sodium-glucose cotransporter 2 inhibitors to decrease the uric acid concentration-a novel mechanism of action. *J Cardiovasc Dev Dis* 2023;10:268. PUBMED | CROSSREF

36. Li J, Badve SV, Zhou Z, et al. The effects of canagliflozin on gout in type 2 diabetes: a post-hoc analysis of the CANVAS program. *Lancet Rheumatol* 2019;1:e220-e228. PUBMED | CROSSREF

37. Sridhar VS, Cosentino F, Dagogo-Jack S, et al. Effects of ertugliflozin on uric acid and gout-related outcomes in persons with type 2 diabetes and cardiovascular disease: post hoc analyses from VERTIS CV. *Diabetes Obes Metab* 2024;26:5336-5346. PUBMED | CROSSREF

38. Sanchez-Lozada LG, Lanaspa MA, Rodriguez-Iturbe B, Brown JM, Madero M, Johnson RJ. Sodium-glucose cotransporter 2 inhibitors and uric acid. *Nephron* 2025;149:488-492. PUBMED | CROSSREF

39. Billing AM, Kim YC, Gullaksen S, et al. Metabolic communication by SGLT2 inhibition. *Circulation* 2024;149:860-884. PUBMED | CROSSREF

40. Suijk DLS, van Baar MJB, van Bommel EJM, et al. SGLT2 inhibition and uric acid excretion in patients with type 2 diabetes and normal kidney function. *Clin J Am Soc Nephrol* 2022;17:663-671. PUBMED | CROSSREF

41. Ng HY, Leung FF, Kuo WH, Lee WC, Lee CT. Dapagliflozin and xanthine oxidase inhibitors improve insulin resistance and modulate renal glucose and urate transport in metabolic syndrome. *Clin Exp Pharmacol Physiol* 2021;48:1603-1612. PUBMED | CROSSREF

42. Novikov A, Fu Y, Huang W, et al. SGLT2 inhibition and renal urate excretion: role of luminal glucose, GLUT9, and URAT1. *Am J Physiol Renal Physiol* 2019;316:F173-F185. PUBMED | CROSSREF

43. Miyazaki R, Ohashi Y, Sakurai T, Iwamoto T, Ichida K, Saruta M. First verification of human small intestinal uric acid secretion and effect of ABCG2 polymorphisms. *J Transl Med* 2025;23:257. PUBMED | CROSSREF

44. Yano H, Tamura Y, Kobayashi K, Tanemoto M, Uchida S. Uric acid transporter ABCG2 is increased in the intestine of the 5/6 nephrectomy rat model of chronic kidney disease. *Clin Exp Nephrol* 2014;18:50-55. PUBMED | CROSSREF

45. Lu YH, Chang YP, Li T, et al. Empagliflozin attenuates hyperuricemia by upregulation of ABCG2 via AMPK/AKT/CREB signaling pathway in type 2 diabetic mice. *Int J Biol Sci* 2020;16:529-542. PUBMED | CROSSREF

46. Wang Y, Ding Y, Sun P, et al. Empagliflozin-enhanced antioxidant defense attenuates lipotoxicity and protects hepatocytes by promoting FoxO3a- and Nrf2-mediated nuclear translocation via the CAMKK2/AMPK pathway. *Antioxidants* 2022;11:799. PUBMED | CROSSREF

47. Packer M. Hyperuricemia and gout reduction by SGLT2 inhibitors in diabetes and heart failure: JACC review topic of the week. *J Am Coll Cardiol* 2024;83:371-381. PUBMED | CROSSREF

48. Lai SW, Hwang BF, Kuo YH, Liu CS, Liao KF. Sodium-glucose cotransporter-2 inhibitors use and the risk of gout: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)* 2023;14:1158153. PUBMED | CROSSREF

49. Shin A, Shin JY, Kang EH. Risk of nephrolithiasis associated with SGLT2 inhibitors versus DPP4 inhibitors among patients with type 2 diabetes: a target trial emulation study. *Diabetes Care* 2025;48:193-201. PUBMED | CROSSREF

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Original Article

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Relationship Between Cardiac Autonomic Control and Intradialytic Hypotension in Senegalese Chronic Hemodialysis Patients: A Single Center Prospective Study

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ABSTRACT

Background: Intradialytic hypotension (IDH) increases cardiovascular morbidity and mortality in chronic hemodialysis patients and cardiac autonomous neuropathy (CAN) might be involved. To assess cardiac autonomic control in hemodialysis patients and describe its relationship with IDH.
Methods: We conducted a prospective study at Ouakam Military Hospital in Senegal from January 1st to March 31st, 2023. Fifty-two patients (31 men, mean age 47.54 years) were included and had 3 measurements of heart rate variability (HRV): before, during and after an index hemodialysis session. They were classified according to changes in systolic blood pressure (SBP) during hemodialysis into three groups: 14 patients in group I (increase > 10 mmHg in mean intradialytic SBP), 13 in group II (decrease ≥ 20 mmHg in mean intradialytic SBP or MAP > 10 mmHg) and 25 in group III (others). HRV frequency domain indices between groups were compared.
Results: In pre-dialysis, patients in group II showed higher values in total power (650.30 vs. 94.94 and 108.11 ms^2, p = 0.02), high frequency (199.24 vs. 25.05 and 25.90 ms^2, p = 0.03) and low frequency (225.36 vs. 42.30 and 53.76 ms^2, p = 0.01) compared to those in groups I and III. Also, they presented less severe CAN (16.2% vs. 57.2% and 56%, p = 0.03). Measures after dialysis found no difference in HRV parameters among the three groups.
Conclusion: Our results found that HRV was similar between patients with and without IDH suggesting the influence of other risk factors that need to be explored in further studies.

Keywords: Autonomic nervous system; Heart rate; Hypotension; Renal dialysis; Senegal

INTRODUCTION

Intradialytic hypotension (IDH) is a common complication of hemodialysis and is associated with increased morbidity and mortality, especially from cardiovascular causes [1-3].
Its prevalence varies significantly across studies due to differing definitions. According to

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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: ILS, AKS, BC, BM, SMS; Data curation: ILS, BM; Formal analysis: ILS, AKS, BM, SMS; Investigation: ILS, AKS, BC, BM, SMS; Methodology: ILS, AKS, SMS; Project administration: BC; Resources: BC, BM; Supervision: SMS; Validation: AKS, BC, BM, SMS; Writing - review & editing: BM, SMS.

the Kidney Disease Outcomes Quality Initiative and the European Best Practice Guidelines, IDH is a fall in systolic blood pressure (SBP) ≥ 20 mmHg or a fall in mean arterial pressure (MAP) of at least 10 mmHg associated with a clinical event and/or requiring nursing intervention [4,5]. This condition is particularly concerning because it often results in insufficient perfusion of vital organs, especially the heart and brain, which increases the risk of cardiovascular events and mortality.

The pathophysiology of IDH is multifactorial and not yet fully understood. However, hypovolemia induced by ultrafiltration (UF) during hemodialysis is considered as the primary etiological factor. In response to hypovolemia, the organism activates compensatory mechanisms to restore blood volume and maintain organ perfusion. These mechanisms include fluid exchange between interstitial and intracellular compartments to refill plasma volume, cardiovascular adaptations to sustain cardiac output and venous return, and arteriolar vasoconstriction to increase total peripheral resistance [6]. All of these processes are primarily regulated by the sympathetic nervous system. Thus, any dysfunction in the autonomous nervous system (ANS), such as cardiac autonomous neuropathy (CAN) may impair these compensatory mechanisms, thereby increasing the risk of IDH [7-9].

Cardiac autonomic function can be noninvasively assessed through the measurement of heart rate variability (HRV) that provides time and frequency domain parameters. Frequency domain parameters improve the diagnosis of CAN by 3 times compared to time domain parameters [10]. However, current data supporting the clinical validation of HRV to predict IDH in hemodialysis patients are still inconsistent [11]. Previous studies have shown that during hemodialysis, the sympathetic response is normally activated, particularly in patients without CAN while in patients experiencing IDH, this sympathetic response is often impaired, particularly in the later phases of dialysis, contributing to the occurrence of hypotension [12]. Conversely, Sapoznikov et al. [13] observed that the arterial baroreflex mechanism is preserved and adequately activated during hemodialysis in patients with IDH, suggesting that the pathophysiology of IDH may be complex and not solely attributable to sympathetic dysfunction.

While several studies explored the relationship between cardiac autonomic function and IDH, there is a lack of data on this topic among African dialysis patients who have different demographic characteristics and comorbidities. This study was designed to assess cardiac autonomic control in chronic hemodialysis patients at Ouakam Military Hospital in Senegal and to explore its potential relationship with IDH.

METHODS

Type, setting and study period

This was a cross-sectional, single center study from January 1 to March 31, 2023. Participants were recruited from the hemodialysis unit of Ouakam Military Hospital (Dakar).
HRV recordings were read and interpreted by a physiologist at the Physiology and Functional Explorations Laboratory at Cheikh Anta Diop University in Dakar.

Study population

All patients over 18 years of age who had been on regular chronic hemodialysis for at least 3 months, who consented to participate in the study and who had not been hospitalized for an acute disease during the month prior to data collection, were included. Patients with

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cardiac arrhythmias or pacemakers, and those with a short life expectancy due to a chronic disease such as terminal cancer, were not included.

Ethics approval and consent to participate

The participation to this study was voluntary. All participants provided informed consent. The principles of anonymity and confidentiality of data were respected during this study. The study was approved by the Institutional Review Board at the Ouakam Military Hospital (Reference: 02/2022/CER/HMO; Clinical trial number: not applicable).

Study procedure

For each included patient, we first conducted a thorough and targeted interview to assess, among other factors, sociodemographic information, medical history, and current treatments particularly antihypertensive medications (calcium channel blockers and blockers of the renin angiotensin aldosterone system). A general examination was then carried out, including measurements of blood pressure (BP), weight and HRV recording during an index hemodialysis session. All included patients were treated with the same type of machine (BBRAUN) for 4 hours. The dialysis bath had the same composition in all patients (Ca^{2+}: 1.5 mmol/L; Na^{+}: 138 mmol/L; K^{+}: 2 mmol/L; Mg^{2+}: 0.5 mmol/L; HCO_3−: 32 mmol/L and glucose: 1 g/L) during the index hemodialysis session. Their treatment had not been modified or stopped during the study period. Hemodialysis parameters for the index session and biological data were collected from dialysis and medical records respectively. Finally, the data were entered into a Microsoft Excel version 16.77.1 file (Microsoft, Redmond, WA, USA) and analyzed using R software (R Foundation for Statistical Computing, Vienna, Austria).

BP monitoring and patients' classification

BP was meticulously measured using a single, reliable and validated electronic BP monitor before and after the hemodialysis sessions (OMRON®, Osaka, Japan). Intradialytic BP data were taken from the BBRAUN hemodialysis monitor.

Pre-dialysis measurement

BP was measured 30 minutes prior to the start of the hemodialysis session under controlled conditions: in a quiet, well-lit room at ambient temperature to minimize external factors affecting BP and from an arm without an arterio-venous fistula. The patient was positioned in the supine position and in the orthostatic position to assess orthostatic BP changes.

Intradialytic measurement

During the hemodialysis session, BP was regularly measured every 30 minutes using the BBRAUN hemodialysis monitor. The BP measurements were taken at rest, ensuring the patient remained as calm and relaxed as possible. It was also measured at the lowest level of symptoms experienced by the patient.

Post-dialysis measurement

After the hemodialysis session, BP was measured after a 30-minute rest in the supine position, in a manner similar to the pre-session measurements.

Patients' classification

Following the international guidelines on IDH [5], all included patients were classified into three groups according to their intradialytic BP variations. Group I consisted of patients whose mean SBP raised by more than 10 mmHg during the session, compared with the resting pre-

dialysis SBP. Group II comprised patients with a decrease in mean SBP ≥ 20 mmHg or a fall in MAP of at least 10 mmHg associated with a clinical event and/or requiring nursing intervention during hemodialysis session [4,5]. This corresponded to patients prone to IDH. Group III included all patients who could not be classified into either of these two groups.

HRV monitoring and analysis

HRV was recorded using an *AR4plus Schiller*® ECG Holter (SCHILLER, Baar, Switzerland), a lightweight, patient-comfortable device with 5 electrodes. The electrodes were placed on the patient's bare torso in the supine position 30 minutes before the session and removed 30 minutes later. The HRV was recorded throughout this period. We took measures during early, middle and late phases of the dialysis session [14].

Pre-dialysis HRV monitoring

The first HRV recorded was measured for 10 minutes in the supine position to assess baseline autonomic function. Following this, a second set of recording was taken for 7 minutes in the standing position to observe the effects of postural changes on autonomic regulation.

Post-dialysis HRV monitoring

It was measured during 10 minutes in the supine position, 20 minutes after the session.

Intradialytic HRV monitoring

During the hemodialysis session, HRV data were collected in 5-minute intervals, resulting in a total of 48 segments throughout the 4-hour session. This allowed for continuous monitoring of autonomic function during different phases of dialysis. For statistical analysis, the hemodialysis session was divided into three phases based on the timing of monitoring: early phase: corresponding to segments 1 and 2 (the first 10 minutes of the session), middle phase: corresponding to segments 24 and 25 (approximately the halfway point of the session) and the late phase: corresponding to segments 47 and 48 (the last 10 minutes of the session). Each phase consisted of 2 consecutive 5-minute segments, and the mean value of the two segments was used as the final variable for analysis. This approach helped to mitigate the natural variability of HRV and provided a more stable and accurate estimate of autonomic function during each phase of hemodialysis.

HRV data analysis

The HRV recordings were analyzed using Kubios HRV Standard software (Kubios Oy, Kuopio, Finland), which is a widely recognized tool for HRV analysis. The software provided various frequency domain parameters, each reflecting different aspects of autonomic control over the heart. High frequency (HF) explored parasympathetic activity while low frequency (LF) reflected sympathetic activity in particular. Very low frequency (VLF) reflected long-term heart rate regulatory mechanisms such as thermoregulation and hormonal mechanisms. The total power (TP) represented the total variance and corresponds to the sum of the LF, HF and VLF spectral bands. The LH/HF ratio represents an indicator of sympatho-vagal balance, with high values reflecting the dominance of the sympathetic system and low values reflecting the dominance of the parasympathetic system.

CAN diagnosis

CAN was retained using the criteria proposed by Bellavere et al. [15] with a TP measured in supine position at rest lower than the average—two standard deviation (2SD) of its diabetic population without CAN.

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CAN was rated moderate if HFpw and LFpw were below the mean—2SD of their values in the moderate CAN population.

It was severe if HFpw and LFpw are lower than the mean—2SD of the values in their diabetic population with a severe form of CAN.

Patients who had low TP with LFpw and HFpw values greater than the mean—2SD of the HFpw and LFpw values found in the moderate form of CAN were classified as borderline.

Statistical analysis

Data analysis was performed using R software version 4.3.2. Continuous data were tested for normality using the Shapiro test. Data following a normal distribution were expressed as the means ± standard deviations or medians (interquartile ranges) for those not following a normal distribution. Categorical data were expressed as frequencies (proportions, %). A χ^2 test or Fisher's exact test will be used to compare categorical data. Comparisons of variables following a normal distribution between groups was carried out by analysis of variance, and in the event of significance, Tukey's post-hoc test was used. For non-normally distributed data, medians were compared using the nonparametric Kruskal-Wallis test and if the results were significant, the Wilcoxon post-hoc test was used. Individual variability between different HRV measurement conditions was studied using a paired Student's t-tests. The significance threshold was set at $p < 0.05$.

RESULTS

Patient characteristics

Fifty-two patients were included and classified into group I (n = 14; 26.9%), group II (n = 13; 25%) and group III (n = 25; 48.1%) (**Fig. 1**). The mean age of the patients was 47.54 ± 15.08 years with a male predominance (59.6%). Patients in the group II were significantly older than those in the group III. The most common cause of end-stage renal disease was undetermined nephropathy. Arterial hypertension was the most prevalent

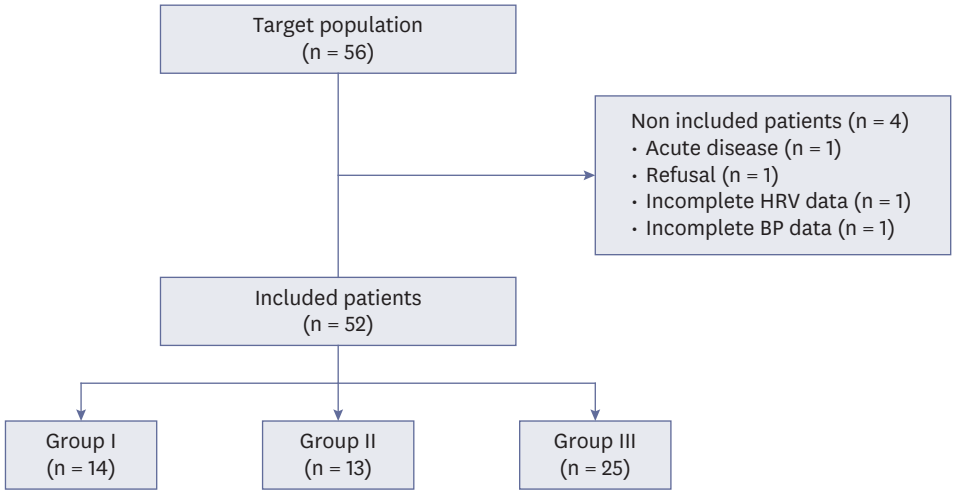

Fig. 1. Flow chart of patients. Group I: patients with BP increase in dialysis. Group II: patients with intradialytic hypotension. Group III: patients neither in Group I nor in Group II.
BP, blood pressure; HRV, heart rate variability.

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comorbidity affecting 94.23% of patients, followed by left ventricular hypertrophy that was present in 40.40% of patients (**Table 1**).

There were no significant differences between the groups regarding SBP or diastolic blood pressure before the hemodialysis session. However, as expected, SBP at the end of the session was significantly higher in patients in the group I compared to those in the other groups (**Table 1**).

Table 1. Comparison of sociodemographic characteristics; comorbidities; and clinical, biological and dialysis parameters between the 3 groups

Data	Total (n = 52)	Group I (n = 14)	Group II (n = 13)	Group III (n = 25)	p-value
Sociodemographic parameters and comorbidities					
Age (yr)	47.54 ± 15.08	52.5 ± 11.2	54.08 ± 16	41.36 ± 14.4*	0.01
Male gender	31 (59.6)	5 (35.7)	7 (53.8)	19 (76)††	0.04
Duration on dialysis (mo)	46.60 ± 0.26	48.60 ± 0.3	47.90 ± 0.2	44.6 ± 0.2	0.52
Initial kidney disease undetermined	24 (46.2)	6 (42.9)	6 (46.2)	12 (48)	0.81
Nephropathy attributed to hypertension	14 (26.9)	5 (35.7)	4 (30.8)	5 (20)	
Diabetic nephropathy	3 (5.8)	0 (0)	0 (0)	3 (12)	
Others	11 (21.2)	3 (21.4)	3 (23.1)	5 (20)	
Arterial hypertension	49 (94.23)	13 (92.86)	12 (92.31)	24 (96)	0.86
Diabetes	4 (7.69)	0 (0)	0 (0)	4 (16)	0.09
Smoking	1 (1.9)	0 (0)	1 (7.7)	0 (0)	0.21
Alcohol	1 (1.9)	0 (0)	0 (0)	1 (4)	0.57
LVEF < 55%	4 (7.7)	1 (7.1)	1 (7.6)	2 (8)	0.78
LVH	21 (40.4)	5 (35.7)	7 (53.8)	9 (36)	0.10
Clinical parameters					
BMI (kg/m^2)	22.3 ± 5.6	22.72 ± 7.6	24.73 ± 6.2	20.74 ± 3.4	0.11
SBP (before HD)	161.1 ± 23.1	156.9 ± 18.7	168.3 ± 23.7	159.7 ± 24.9	0.4
DBP (before HD)	99.17 ± 16.1	93.29 ± 12.2	99.77 ± 16.6	102.2 ± 17.3	0.25
HR (before HD)	80.65 ± 13.9	77.14 ± 12.9	78.15 ± 13.8	83.92 ± 14.3	0.26
SBP (ortho)	162.5 ± 23.3	168.8 ± 14	166.1 ± 22.6	157.4 ± 27.2	0.29
DBP (ortho)	102.5 ± 16.1	100.86 ± 11.2	100.92 ± 22.2	104.1 ± 15.5	0.78
HR (ortho)	88.02 ± 15.6	84.69 ± 13.97	87.58 ± 17.3	89.96 ± 15.8	0.62
HR (Valsalva)	78.58 ± 13.6	78.57 ± 13.3	74.62 ± 14	80.64 ± 13.7	0.44
SBP (after HD)	166.0 ± 29.7	189.4 ± 23.1	147.5 ± 25††	162.5 ± 25††	0.0001
DBP (after HD)	99.02 ± 17.7	104.2 ± 14.05	90.31 ± 18.62	100.6 ± 16.23	0.07
HR (after HD)	79.17 ± 13.97	79.86 ± 14.13	79 ± 13.26	78.8 ± 14.94	0.97
RAASB	36 (69.23)	9 (64.29)	9 (69.23)	18 (72)	0.88
BB	9 (17.31)	4 (28.57)	2 (15.38)	3 (12)	0.38
Biological parameters					
Hemoglobin (g/dL)	8.81 ± 1.58	8.50 ± 1.43	9.5 ± 1.41	8.72 ± 1.69	0.32
Hematocrit (%)	26.13 ± 3.99	24.66 ± 2.43	29.2 ± 2.09	25.33 ± 4.68	0.13
Calcemia (mg/L)	83.82 ± 12.55	81.45 ± 15.26	87.29 ± 14.76	83.93 ± 9.84	0.69
Phosphatemia (mg/L)	34.96 ± 19.14	34.32 ± 22.4	40.24 ± 21.09	32.92 ± 17.47	0.72
iPTH (pg/mL)	520 (1,092)	265 (1,038)	546 (1,286)	587 (808)	0.67
Albuminemia (g/L)	39.5 ± 6.56	40.5 ± 13.43	41 ± 2.82	37 ± 2.82	0.87
Dialysis session parameters					
AVF	40 (76.92)	13 (92.86)	11 (84.62)	16 (64)	0.09
Blood flow	300.4 ± 30.2	292.9 ± 27.85	303.1 ± 35.68	303.2 ± 29.39	0.56
Hourly UF	593.4 ± 182	491.5 ± 236.4	587.7 ± 127.5	653.5 ± 53.4†	0.02
Mean SBP	160.1 ± 27.2	176.9 ± 18.4	146.2 ± 22.4††	157.9 ± 23.8†	0.002
Mean DBP	82.54 ± 17.1	75.07 ± 13.52	85 ± 18.87	85.44 ± 16.67	0.15
Mean HR	76.88 ± 12.2	73.3 ± 13.87	78.54 ± 14.6	77.96 ± 10.12	0.47
KT/V	1.29 ± 0.25	1.36 ± 0.26	1.41 ± 0.24	1.21 ± 0.23*	0.04
URR (%)	71.66 ± 7.76	73.00 ± 7.77	72.66 ± 8.04	72.66 ± 7.7	0.54

Data are expressed as mean ± standard deviation, number (%).
AVF, arteriovenous fistula; BB, betablockers; BMI, body mass index; DBP, diastolic blood pressure (mmHg); HD, hemodialysis; HR, heart rate (bpm); iPTH, intact parathormone; LVEF, left ventricular systolic ejection fraction; LVH, left ventricular hypertrophy; RAASB, renin angiotensin aldosterone system blocker; SBP, systolic blood pressure (mmHg); UF, ultrafiltration; URR, urea reduction rate.
The p-value between groups II and III, *$p < 0.05$.
The p-value between group II and other groups, †$p < 0.05$, ††$p < 0.01$.

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Table 2. Comparison of HRV parameters between the three groups

Data	Total (n = 52)	Group I (n = 14)	Group II (n = 13)	Group III (n = 25)	p-value
Supine position					
TP (ms^2)	128.13 (301.15)	94.94 (219.48)	650.30 (832.20)*	108.11 (255.1)	0.02
HF (ms^2)	40.73 (138.51)	25.05 (68.8)	199.24 (516.22)*	25.90 (109.62)	0.03
LF (ms^2)	58.13 (173.56)	42.30 (122.42)	225.36 (457.72)	53.76 (99.86)†	0.01
VLF (ms^2)	16.36 (29.01)	10.99 (20.64)	28.17 (30.25)	14.48 (23.33)	0.07
LF/HF	1.72 (2.17)	1.83 (1.67)	1.74 (2.17)	1.72 (2.46)	0.76
Orthostatism					
TP (ms^2)	110.30 (220.1)	106.00 (134.6)	257.85 (504.8)	58.33 (182.39)	0.05
HF (ms^2)	19.22 (53.88)	22.79 (36.87)	60.50 (205.9)	15.31 (28.03)	0.19
LF (ms^2)	41.94 (127.49)	39.23 (65.97)	152.30 (233.1)*	33.01 (117.6)†	0.04
VLF (ms^2)	15.74 (31.56)	17.26 (28.11)	25.52 (33.07)	13.35 (16.85)	0.13
LF/HF	1.78 (3.12)	1.72 (2.78)	1.59 (2.98)	2.14 (4.86)	0.99
After hemodialysis session					
TP (ms^2)	243.97 (682.2)	193.31 (469.4)	623.40 (624.4)	177.09 (542.2)	0.23
HF (ms^2)	85.96 (276.44)	35.58 (206.34)	253.16 (145.29)	76.57 (119.92)	0.39
LF (ms^2)	127.16 (432.4)	129.23 (236.2)	133.09 (471.84)	112.30 (435.2)	0.25
VLF (ms^2)	22.48 (39.67)	20.81 (26.28)	23.28 (96.35)	19.72 (45.31)	0.24
LF/HF	1.79 (2.38)	1.75 (1.65)	2.57 (3.84)	1.70 (1.97)	0.62

Table 2 shows that markers of autonomous nervous system activity in the three groups are significantly different before hemodialysis session with those in group II presenting higher variability and better response when they shift to orthostatic position. Patients in the group III with low values of TP, LF and HF presented a poor response to orthostatism probably due to severe dysautonomia. However, those differences between groups disappeared after the hemodialysis session.
HF, high frequency; HRV, heart rate variability; LF, low frequency; TP, total power; VLF, very low frequency.
*p-value between group II and the other groups, $p < 0.05$.
†p-value between groups II and III, $p < 0.05$.

Regarding the session parameters, the mean hourly UF rate of patients in the group III was significantly higher than those in group I. The KT/V of the patients in the group II was significantly higher than that of patients in the group III (**Table 1**).

HRV before the hemodialysis session

In the decubitus position, patients in the group II showed higher values in TP (650.30 vs. 94.94 and 108.11 ms^2, p = 0.02), HF (199.24 vs. 25.05 and 25.90 ms^2, p = 0.03) and LF (225.36 vs. 42.30 and 53.76 ms^2, p = 0.01) compared to than those in groups I and III. Also, they exhibited a lower prevalence of severe CAN (16.2% vs. 57.2% and 56%, p = 0.03) (**Table 2**). Additionally, the severity of CAN in these patients was less pronounced than in the other groups (**Table 3**).

In orthostatic position, the LF values of patients in the group II were significantly higher compared to those in the other groups (**Table 2**). Upon transitioning to orthostatism, patients in groups II and III exhibited a significant reduction in TP, with no notable changes observed in other HRV parameters or SBP. In contrast, group I showed no significant variation in HRV parameters during the transition to orthostatism. Additionally, arterial baroreflex was significantly impaired in the majority of patients (**Fig. 2**).

Table 3. Patients' level of cardiac autonomic control

Data	Group I (n = 14)	Group II (n = 13)	Group III (n = 25)	p-value
Normal	0 (0.0)	3 (23.1)	1 (4.0)	0.05
Borderline	3 (21.4)	4 (30.1)	3 (12.0)	0.36
Moderate CAN	3 (21.4)	4 (30.1)	7 (28.0)	0.84
Severe CAN	8 (57.2)	2 (16.7)*	14 (56.0)†	0.03
p-value	0.005	0.77	0.0001	

CAN, cardiac autonomous neuropathy.
*p-value between group II and the other groups, $p < 0.05$.
†p-value between groups II and III, $p < 0.05$.

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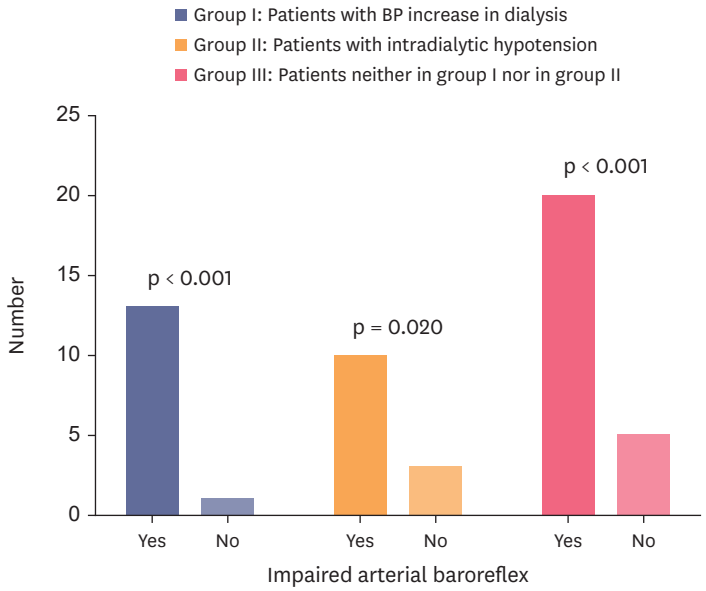

Fig. 2. Arterial baroreflex status according to patient group.
BP, blood pressure.

Patients with IDH exhibited the best HRV prior to the hemodialysis session. However, the sympathetic response during the transition to orthostatism was impaired in the majority of patients.

HRV during the hemodialysis session

The TP, HF and LF of the middle phase of patients in the group II were significantly higher than those in the group III. There was no significant difference in these parameters during this phase between patients in the group II and those in group I. During the early and late phases of the hemodialysis session, the HRV parameters were comparable among the three groups (**Fig. 3**). Patients with IDH seemed to have the best HRV during the middle phase of the hemodialysis session.

HRV after the hemodialysis session

At the end of the hemodialysis session, there were no significant differences in HRV parameters between the three groups (**Table 2**). However, patients in the group I showed a slight impairment in TP, while those in the group III exhibited more severe alteration of autonomic function (low values of TP and LF). In contrast, there was no significant change in HRV values pre- and post-dialysis for patients in the group II. This shows a better adaptation capacity in these patients.

DISCUSSION

ANS dysfunction is a major cause of IDH because it impairs the body's ability to regulate BP during hemodialysis.

Several previous studies assessing the clinical significance of HRV in dialysis patients has been demonstrated in association with IDH [16], vascular accesses failure [17], major adverse

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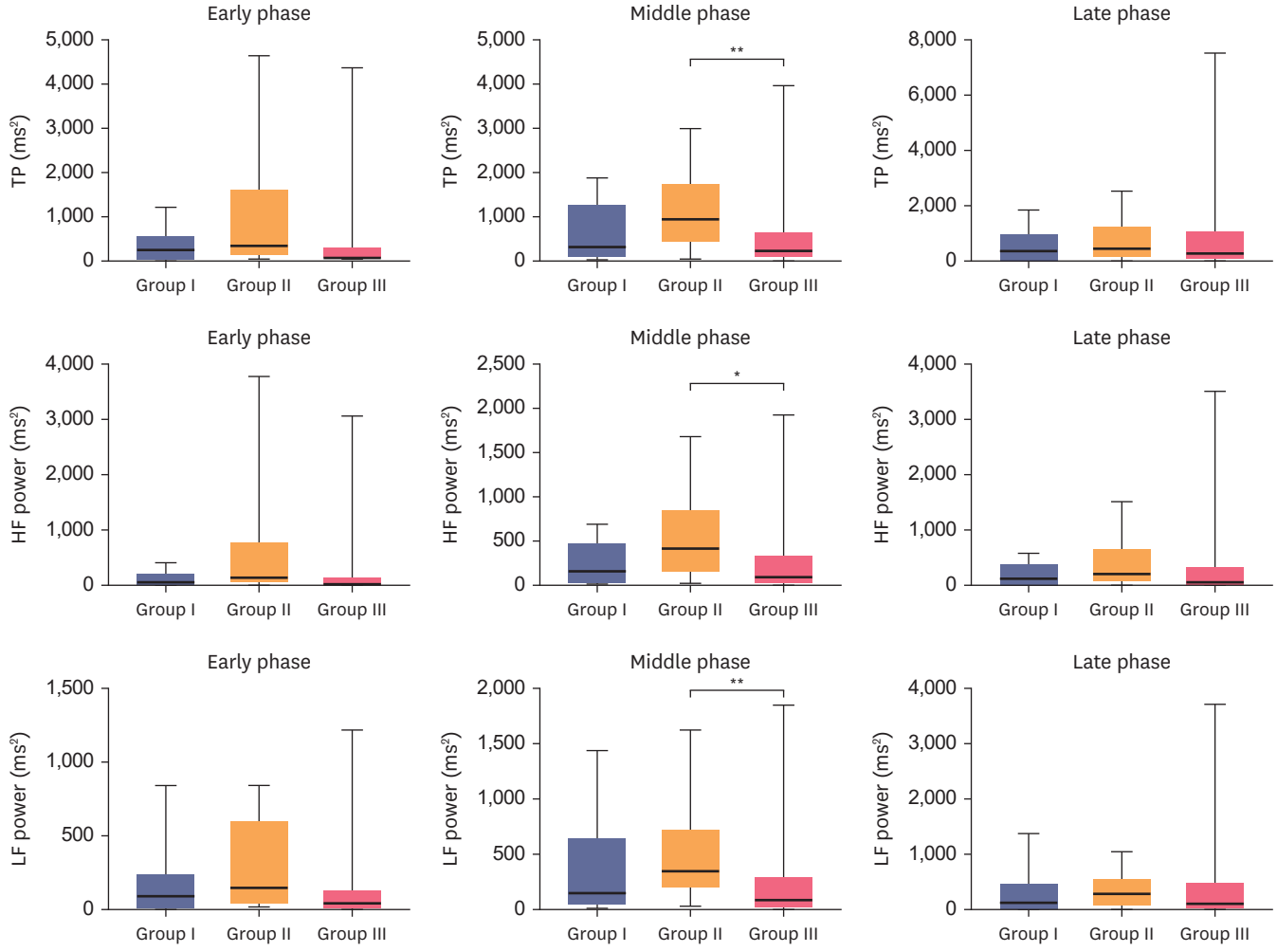

Fig. 3. Comparison of frequency-domain parameters during the dialysis session.
Group I: patients with blood pressure increase in dialysis. Group II: patients with intradialytic hypotension. Group III: patients neither in group I nor in group II.
HF, high frequency; LF, low frequency; TP, total power.
The p-value between groups II and III, *p < 0.05, **p < 0.01.

cardiovascular events [18], and mortality [7] in hemodialysis patients. To our knowledge, the present study is the first one in African patients.

Patients with IDH presented the best HRV values before the hemodialysis session. This was evidenced by TP and LF parameters, which were significantly higher in patients belonging to group II (with IDH) than those in the other groups. In addition, severe CAN was significantly more common in patients in groups I and III (**Table 3**). This finding is in contradiction with majority of data in the literature that reported a significantly higher incidence of IDH among patients with CAN [2,6,9,12]. However, similarly to our results, Straver et al. [7] found no significant difference in resting cardiac autonomic control between patients with and without IDH. Furthermore, a study by Chang et al. [19] did not find any significant difference in resting HRV parameters in patients with an increase in SBP > 20 mmHg and those with a decrease in SBP > 20 mmHg.

The absence of significant link between ANS dysfunction and incidence of IDH in our study could be explained by several factors. In their study, Straver et al. [7] measured HRV with

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spectral analysis and demonstrated its superiority in detecting vegetative dysautonomia compared to traditional tests. Skin sympathetic nerve activity is another methods that can help assessing noninvasively the sympathetic nerve activity and detect early dysfunction [2]. Other parameters that may influence the HRV tests in our patients include their young age and short dialysis vintage that make them less prone to autonomic nervous dysfunction, preserved autonomic, impaired vascular resistance or plasma refill. In the study by Chang et al. [19], patients were older (61.70 ± 12.60 vs. 54.08 ± 16) and with more comorbidities such as diabetic nephropathy (44.40% vs. 0%), ischemic heart disease (22.20% vs. 0%) or heart failure (15.60% vs. 7.60%). These conditions are known to have a negative influence on HRV values [20-22]. Moreover, dialysis parameters dialysate composition, ultrafiltration rate might interfere with CAN control mechanism and induce hypotension during dialysis [11].

The sympathetic response during the transition to orthostatism was impaired in all our patients. There are few data in the literature evaluating changes in HRV indices during the transition to orthostatism by the spectral method in chronic hemodialysis patients. González et al. [23] reported a stimulated sympathetic activity, from supine position to orthostatism, in chronic hemodialysis patients. This stimulation is marked by a decrease in RR and increases in standard deviation of NN intervals, LFnu and Ln LF/HF. In our study, the absence of significant variability in HRV parameters between the supine and orthostatic positions found corroborates the impaired arterial baroreflex noted in the majority of them and reflects a poor cardiac autonomic control.

Patients with IDH had better HRV during the middle phase of hemodialysis as demonstrated by the TP, LF and HF of this phase, which were significantly higher in patients in group II compared to group III. The other HRV parameters did not significantly differ between the groups during this phase. These results are similar to those reported by Sapoznikov et al. [13] who noted that episodes of IDH were associated with significant increases in LF and HF mainly in patients with severe IDH without LF/HF variation. The magnitude of the increase in these indices was proportional to the decrease in BP. Thus, the results of Sapoznikov et al. [13] showed a preserved and adequately activated baroreflex during IDH. Chang et al. [19] noted an increase in the LF/HF ratio in patients undergoing dialysis, with a decrease in both LF and HF (with a more marked decrease in HF than LF) at rest and during the dialysis session. However, as mentioned above, those patients with IDH were older and presented with more comorbidities such as diabetes and cardiovascular disease which could influence HRV values at rest and during the hemodialysis session [20-22]. CAN leads to poorer HRV due to impaired autonomic control, particularly in diabetes and other chronic conditions. However, our findings suggest that patients who experience IDH, actually had preserved HRV implying that other factors besides CAN might be more prominent the occurrence of IDH.

Moreover, HRV seems to improve during the hemodialysis session in some of our patients. When comparing pre- and post-session values, a significant improvement in HRV was noted in groups I and III. In contrast, patients in the group II exhibited no significant variation in HRV parameters between the two periods.

Indeed, previous studies reported a significant correlation between HRV and Kt/V indices, suggesting a beneficial effect of dialysis adequacy on ANS [24]. Further studies are needed to confirm whether this represents a sustained improvement.

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Limitations of the study

Our study has several limitations that should be considered when interpreting the results.

First, the cross-sectional nature can limit causal conclusions and the small sample size may affect the statistical power. Additionally, not all patients underwent a comprehensive cardiovascular assessment to identify potential cardiac abnormalities contributing to IDH, nor did we perform a full hormonal work-up, such as plasma catecholamine assays.

Second, we excluded patients with arrhythmias but not those taking these antihypertensive medications (beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II) due to the limited number of participants. However, the distribution of these medications was similar across the three groups (**Table 1**). Third, HRV was measured during only one dialysis session and may not reflect intra-individual variability. The cut-off values used for HRV were derived from studies in diabetic populations and may not be validated in hemodialysis patients. Finally, the absence of synchronized continuous BP and HRV monitoring limits a precise assessment of baroreflex function and real-time fluctuations in BP during hemodialysis.

Conclusion

Our results suggest that chronic hemodialysis patients who are prone to IDH had better HRV at rest and during the middle phase of the hemodialysis session. This contradictory finding suggest the existence of other risk factors such as young age, intravascular volume changes, vascular resistance, and cardiovascular reflexes that interfere with the occurrence of IDH. The improved HRV observed in some patients at rest and during the middle phase might reflect a preserved ANS or a compensatory response to hemodynamic changes. Further studies are necessary to better explore the determinants of IDH in African patients.

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REFERENCES

1. Wu Y, Lu J, Wang T, Zhu X, Xue J, You L. Association of frequent intradialytic hypotension with the clinical outcomes of patients on hemodialysis: a prospective cohort study. *Ren Fail* 2024;46:2296612. PUBMED | CROSSREF
2. Zhang Y, Su S, Chen Z, et al. Prediction of intradialytic hypotension based on heart rate variability and skin sympathetic nerve activity using LASSO-enabled feature selection: a two-center study. *Ren Fail* 2025;47:2478487. PUBMED | CROSSREF
3. Stefánsson BV, Brunelli SM, Cabrera C, et al. Intradialytic hypotension and risk of cardiovascular disease. *Clin J Am Soc Nephrol* 2014;9:2124-2132. PUBMED | CROSSREF
4. Kooman J, Basci A, Pizzarelli F, et al. EBPG guideline on haemodynamic instability. *Nephrol Dial Transplant* 2007;22 Suppl 2:ii22-ii44. PUBMED | CROSSREF
5. K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis* 2005;45 Suppl 3:S1-S153. PUBMED

6. Reeves PB, Mc Causland FR. Mechanisms, clinical implications, and treatment of intradialytic hypotension. *Clin J Am Soc Nephrol* 2018;13:1297-1303. PUBMED | CROSSREF
7. Straver B, de Vries PM, ten Voorde BJ, Roggekamp MC, Donker AJ, ter Wee PM. Intradialytic hypotension in relation to pre-existent autonomic dysfunction in hemodialysis patients. *Int J Artif Organs* 1998;21:794-801. PUBMED | CROSSREF
8. Kersh ES, Kronfield SJ, Unger A, Popper RW, Cantor S, Cohn K. Autonomic insufficiency in uremia as a cause of hemodialysis-induced hypotension. *N Engl J Med* 1974;290:650-653. PUBMED | CROSSREF
9. Sato M, Horigome I, Chiba S, et al. Autonomic insufficiency as a factor contributing to dialysis-induced hypotension. *Nephrol Dial Transplant* 2001;16:1657-1662. PUBMED | CROSSREF
10. Strobescu E, Graur M. The cardiovascular reflex tests in autonomic cardiac neuropathy diagnosis. *Rev Med Chir Soc Med Nat Iasi* 2002;106:746-752. PUBMED
11. Jhen RN, Wang PC, Chang YM, Kao JL, Wu EC, Shiao CC. The clinical significance and application of heart rate variability in dialysis patients: a narrative review. *Biomedicines* 2024;12:1547. PUBMED | CROSSREF
12. Pelosi G, Emdin M, Carpeggiani C, et al. Impaired sympathetic response before intradialytic hypotension: a study based on spectral analysis of heart rate and pressure variability. *Clin Sci (Lond)* 1999;96:23-31. PUBMED | CROSSREF
13. Sapoznikov D, Backenroth R, Rubinger D. Baroreflex sensitivity and sympatho-vagal balance during intradialytic hypotensive episodes. *J Hypertens* 2010;28:314-324. PUBMED | CROSSREF
14. Park S, Kim WJ, Cho NJ, et al. Predicting intradialytic hypotension using heart rate variability. *Sci Rep* 2019;9:2574. PUBMED | CROSSREF
15. Bellavere F, Balzani I, De Masi G, et al. Power spectral analysis of heart-rate variations improves assessment of diabetic cardiac autonomic neuropathy. *Diabetes* 1992;41:633-640. PUBMED | CROSSREF
16. Rubinger D, Backenroth R, Sapoznikov D. Sympathetic nervous system function and dysfunction in chronic hemodialysis patients. *Semin Dial* 2013;26:333-343. PUBMED | CROSSREF
17. Huang YT, Chang YM, Chen IL, et al. Heart rate variability during hemodialysis is an indicator for long-term vascular access survival in uremic patients. *PLoS One* 2017;12:e0172212. PUBMED | CROSSREF
18. Muhadi M, Nasution SA, Putranto R, Harimurti K. The ability of detecting heart rate variability with the photoplethysmography to predict major adverse cardiac event in acute coronary syndrome. *Acta Med Indones* 2016;48:48-53. PUBMED
19. Chang YM, Shiao CC, Chang KC, et al. Heart rate variability is an indicator for intradialytic hypotension among chronic hemodialysis patients. *Clin Exp Nephrol* 2016;20:650-659. PUBMED | CROSSREF
20. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. *Diabetes Care* 1985;8:491-498. PUBMED | CROSSREF
21. Comi G, Sora MG, Bianchi A, et al. Spectral analysis of short-term heart rate variability in diabetic patients. *J Auton Nerv Syst* 1990;30 Suppl:S45-S49. PUBMED | CROSSREF
22. Ewing DJ. Cardiovascular reflexes and autonomic neuropathy. *Clin Sci Mol Med* 1978;55:321-327. PUBMED | CROSSREF
23. González H, Infante O, Pérez-Grovas H, Jose MV, Lerma C. Nonlinear dynamics of heart rate variability in response to orthostatism and hemodialysis in chronic renal failure patients: recurrence analysis approach. *Med Eng Phys* 2013;35:178-187. PUBMED | CROSSREF
24. Laaksonen S, Voipio-Pulkki L, Erkinjuntti M, Asola M, Falck B. Does dialysis therapy improve autonomic and peripheral nervous system abnormalities in chronic uraemia? *J Intern Med* 2000;248:21-26. PUBMED | CROSSREF

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Case Report

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Unusual Presentation of Hyponatremia: Persistent Hiccups

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ABSTRACT

Hyponatremia is a common electrolyte disturbance with well-recognized neurological and gastrointestinal symptoms. However, it rarely presents with atypical manifestations, such as persistent hiccups. We report a case of a 36-year-old woman with necrotizing tonsillitis who developed persistent hiccups 3 days prior to hospitalization. Laboratory evaluation revealed severe hyponatremia (serum sodium [Na] 122.4 mEq/L), consistent with the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Despite symptomatic treatment, hiccups persisted until serum Na levels were gradually corrected with hypertonic saline and fluid restriction. Hiccups resolved with improved Na levels. This case underscores the importance of considering hyponatremia in the differential diagnosis of persistent hiccups and highlights SIADH as a potential underlying cause.

Keywords: Hiccup; Hyponatremia; Inappropriate ADH syndrome; Tonsillitis

INTRODUCTION

Hyponatremia, defined as a serum sodium (Na) concentration < 135 mEq/L, is the most common electrolyte disorder in clinical practice [1]. It typically presents with a range of neurological and gastrointestinal symptoms, particularly in acute cases, including headache, confusion, nausea, seizures, and even coma. However, in rare instances, hyponatremia may present with atypical or nonspecific symptoms.

Persistent hiccups, often regarded as benign and self-limiting, can occasionally serve as subtle clinical indicators of a more serious underlying pathology. Although uncommon, intractable hiccups have been associated with various conditions including intracranial lesions, gastrointestinal disorders, and metabolic and electrolyte abnormalities [2].

The underlying pathophysiological mechanism remains unclear; however, it has been postulated that hyponatremia contributes to the development of hiccups through its effects on central nervous system (CNS) excitability and brainstem function.

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
Supervision: SWH; Writing - original draft: SL; Writing - review & editing: HWS, JL, MYY.

Here, we report a case of persistent hiccups as the initial manifestation of severe hyponatremia that resolved after correction of underlying electrolyte abnormalities.

CASE REPORT

A 36-year-old woman presented to the emergency department with a 14-day history of sore throat, cough, sputum production, and dyspnea. She had been on treatment for a severe sore throat, and a biopsy confirmed necrotizing tonsillitis (**Figs. 1** and **2**). Three days before admission, she developed persistent hiccups that did not respond to the initial symptomatic management.

On physical examination, the patient was hemodynamically stable with no signs of dehydration or edema. Her vital signs were as follows: blood pressure, 149/77 mmHg; heart

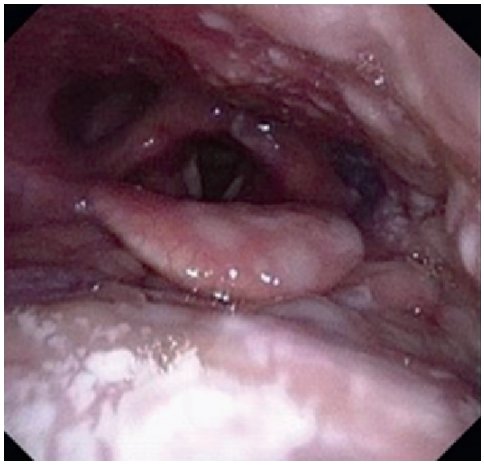

Fig. 1. On physical examination of the larynx, the endoscopic photo showed multiple ulcerative lesions on the left epiglottic surface and oropharynx.

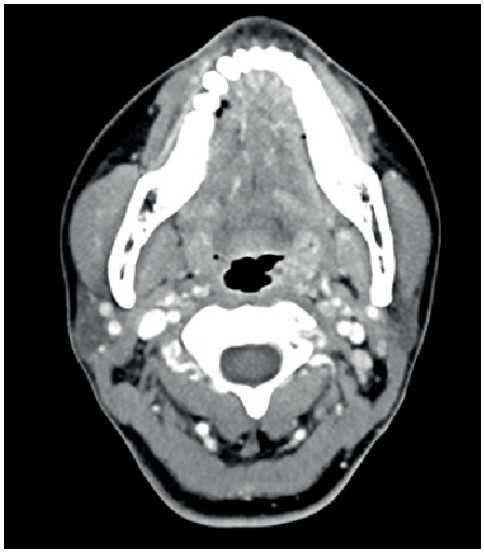

Fig. 2. Neck CT axial image reveals mild asymmetric swelling with heterogeneous enhancement of the left palatine tonsil and aryepiglottic folds, probable pharyngotonsillitis.
CT, computed tomography.

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rate, 74 beats per minute; respiratory rate, 18 breaths per minute; and body temperature, 37.0°C. The initial laboratory evaluation revealed significant electrolyte abnormalities, including severe hyponatremia (serum Na 122.4 mEq/L) and hypokalemia (serum K 2.9 mEq/L). Additional findings included low serum osmolality (246 mOsm/kg) and reduced serum uric acid (1.7 mg/dL). Renal function was within normal limits (serum creatinine 0.4 mg/dL, blood urea nitrogen 6.4 mg/dL), and inflammatory markers were unremarkable (C-reactive protein 0.1 mg/dL). Urinalysis showed elevated urine Na (Na 103 mEq/L) and osmolality (241 mOsm/kg), consistent with the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The fractional excretion of uric acid was 12.7%. The endocrine evaluation revealed a normal thyroid-stimulating hormone (0.30 μIU/mL), adrenocorticotropic hormone (25.4 pg/mL), and basal cortisol level (26.0 μg/dL), with a mildly elevated free T4 (2.13 ng/dL). These results rule out adrenal insufficiency and hypothyroidism. The plasma antidiuretic hormone (ADH) concentration was 4.51 pg/mL, which was inappropriately normal in the context of hyponatremia. Arterial blood gas analysis revealed respiratory alkalosis. The complete blood count, brain CT and chest radiography findings were unremarkable, and no lesions that could have caused hyponatremia were identified.

The patient was managed with fluid restriction, an intravenous bolus, and a continuous infusion of 3% hypertonic saline. Despite corrective efforts, hiccups persisted, Na level decreased to 118.3 mEq/L on day 2 and 116.4 mEq/L on day 3 (**Fig. 3**). Pharmacological interventions included baclofen, and metoclopramide for hiccup control.

The hiccups lasted until the fifth day, and resolved on the sixth day of hospitalization. Serum Na level began to improve slowly 2 days before the resolution of hiccups, without overcorrection. Serum Na concentrations were 120 mEq/L on day 4, 123.1 mEq/L on day 5, 127.7 mEq/L on day 6, and 131.4 mEq/L on day 7, when hypertonic saline administration was discontinued (**Fig. 3**). The patient was discharged in a stable condition on the eighth day of hospitalization.

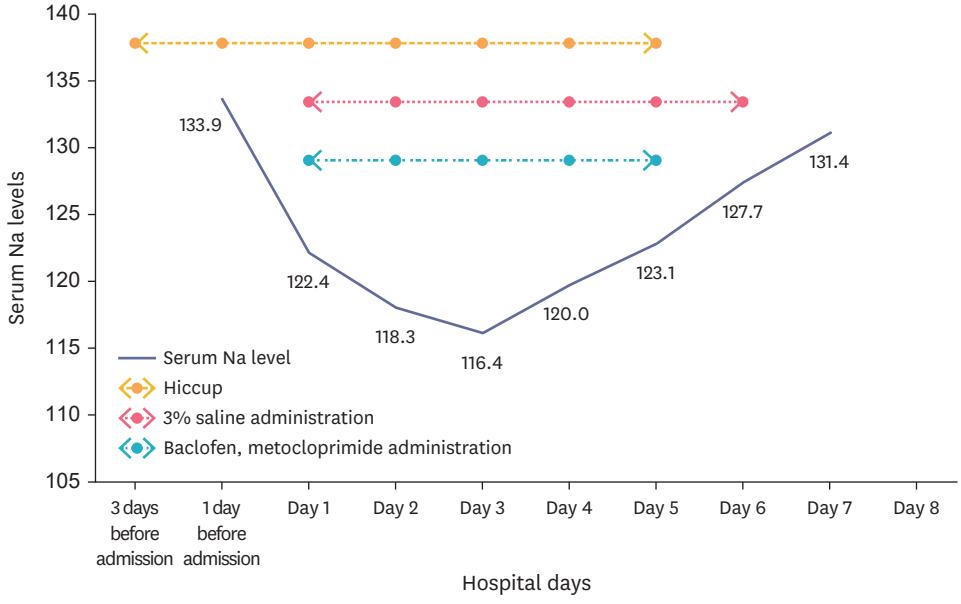

Fig. 3. Symptoms, therapeutic drugs, fluid administration, and changes in serum Na levels.
Na, sodium.

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DISCUSSION

Hiccups are repeated involuntary, spasmodic, and temporary contractions of the diaphragm accompanied by sudden closure of the glottis [3]. They are mediated by a reflex arc that involves afferent pathways (phrenic, vagal, and sympathetic nerves), a central processing center in the medulla oblongata, and efferent pathways to the respiratory muscles. Physical and chemical irritants, inflammatory, and neoplastic conditions involving the hiccup reflex may cause hiccups [4].

Persistent hiccups have been associated with a variety of central and peripheral causes. The central causes of hiccups include stroke, space-occupying lesions, and injury, whereas peripheral causes include lesions along the arc such as tumors, myocardial ischemia, herpes infection, gastroesophageal reflux disease, and instrumentation applied to the human body [4]. Notably, metabolic and electrolyte disturbances have been implicated in disrupting the reflex arc [2].

Although rare, hyponatremia has been reported to cause persistent hiccups, likely through interference with CNS inhibitory mechanisms. Hyponatremia may precipitate hiccups by disrupting normal neuronal function in the brainstem hiccup reflex arc [2]. Several case reports have described persistent hiccups as early signs of hyponatremia, especially in the elderly or neurologically compromised individuals [2]. A case-control study involving hospitalized patients reported that the likelihood of developing hiccups increased 17-fold with every 10 mEq/L reduction in serum Na levels [5].

In the present case, the diagnosis of the SIADH was made based on the patient's euvolemic status, decreased serum osmolality, inappropriately concentrated urine with elevated Na levels, and normal adrenal and thyroid function. Plasma ADH levels were inappropriately normal, given the degree of hyponatremia, further supporting the diagnosis.

The underlying etiology of hyponatremia in this patient was likely multifactorial. First, non-osmotic stimuli, such as pain, nausea, and emotional stress are known to provoke vasopressin (ADH) secretion, leading to dilutional hyponatremia. Although excessive water intake due to hiccup-related discomfort could be a contributing factor, the patient had no history of polydipsia. Second, pharyngotonsillitis may have played a role. Hyponatremia is a frequently observed abnormality in pediatric and adult patients with respiratory tract infections. Although the exact mechanism remains unclear, SIADH is thought to result from inflammatory cytokine-mediated ADH secretion or transient resetting of the osmostat in response to fever and dehydration. Recent studies have suggested that interleukin (IL)-mediated pathways contribute to inappropriate hormone release [6]. Furthermore, previous studies have shown that inflammatory cytokines such as IL-1β and IL-6 can cause hyponatremia in inflammatory conditions. In a study evaluating the hypothalamic–pituitary–adrenal axis response following intravenous administration of IL-6 in cancer patients, an increase in plasma arginine vasopressin levels was observed [7]. Additionally, an animal study demonstrated that IL-1β stimulates both central and peripheral vasopressin release [8]. Although CRP elevation was not observed in our patient, leukocytosis was present—white blood cell count was initially 11,300 × 10^3/μL on day 1, increased to 15,900 × 10^3/μL on day 3, then decreased to 11,700 × 10^3/μL on day 6 and 8,400 × 10^3/μL on day 7—and the timing of its normalization closely corresponded to the improvement of hyponatremia. Third, opioid use may have exacerbated SIADH. The patient was prescribed tramadol 5 days before admission,

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which is 2 days before hiccup appeared, for neck pain. Tramadol was discontinued at the time of hospitalization, Dihydrocodeine was initiated on hospital day 3 to control her cough, continued for 7 days during the hospital stay, and further prescribed for 15 days at discharge. In this patient, tramadol may be considered one of the causes because it was administered before the onset of symptoms. Opioids are well-documented SIADH inducers. Tramadol may increase ADH secretion directly via opioid receptors and indirectly via enhanced serotonin activity, which in turn promotes vasopressin release. However, most reported cases of tramadol-induced hyponatremia occurred in elderly patients and often involved higher doses [9,10]. Fourth, although evidence is limited regarding hypokalemia as an isolated cause of hiccups, other accompanying electrolyte imbalances such as hypokalemia may also contribute to their development. Hypokalemia can cause neuromuscular irritability and has been implicated in various arrhythmias and muscle disorders [11]. In this patient, the potassium levels were 2.9 mEq/L on day 1, 3.4 mEq/L on day 2, and 3.0 mEq/L on day 3, respectively and potassium was supplemented through both intravenous administration on day 1 to 2, and oral medication on day 3 to 7. The temporal correlation between the onset of persistent hiccups and the development of hyponatremia and their resolution following correction of serum Na levels supports the hypothesis that hiccups may be an early and underrecognized symptom of severe hyponatremia in some patients.

In this patient, hyponatremia was not severe on the day before admission. Initially, tonsillitis may have been the cause of the hiccups. It can be presumed that severe hyponatremia during hospitalization, caused by multiple factors, acted as a sustaining factor for the intractable hiccups. This case highlights a rare and atypical presentation of SIADH-induced hyponatremia, with persistent hiccups as the initial symptom. Clinicians should be vigilant for metabolic and electrolyte abnormalities in patients presenting with unexplained or intractable hiccups. In addition to symptomatic and pharmacological management, a thorough evaluation of the underlying causes, including hyponatremia, should be a part of the diagnostic approach in such cases.

In conclusion, the present report emphasizes the importance of evaluating serum electrolytes—particularly Na—in patients with persistent hiccups, since prompt recognition and management of hyponatremia (as seen here in the context of SIADH) may alleviate an otherwise unexplained symptom.

REFERENCES

1. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med* 2013;126:S1-S42. PUBMED | CROSSREF
2. Jones JS, Lloyd T, Cannon L. Persistent hiccups as an unusual manifestation of hyponatremia. *J Emerg Med* 1987;5:283-287. PUBMED | CROSSREF
3. Sampath V, Gowda MR, Vinay HR, Preethi S. Persistent hiccups (singultus) as the presenting symptom of lateral medullary syndrome. *Indian J Psychol Med* 2014;36:341-343. PUBMED | CROSSREF
4. Chang FY, Lu CL. Hiccup: mystery, nature and treatment. *J Neurogastroenterol Motil* 2012;18:123-130. PUBMED | CROSSREF
5. George J, Thomas K, Jeyaseelan L, Peter JV, Cherian AM. Hyponatraemia and hiccups. *Natl Med J India* 1996;9:107-109. PUBMED
6. Park SW, Shin SM, Jeong M, et al. Hyponatremia in children with respiratory infections: a cross-sectional analysis of a cohort of 3938 patients. *Sci Rep* 2018;8:16494. PUBMED | CROSSREF

https://doi.org/10.5049/EBP.2025.23.e6

7. Mastorakos G, Weber JS, Magiakou MA, Gunn H, Chrousos GP. Hypothalamic-pituitary-adrenal axis activation and stimulation of systemic vasopressin secretion by recombinant interleukin-6 in humans: potential implications for the syndrome of inappropriate vasopressin secretion. *J Clin Endocrinol Metab* 1994;79:934-939. PUBMED | CROSSREF

8. Landgraf R, Neumann I, Holsboer F, Pittman QJ. Interleukin-1 beta stimulates both central and peripheral release of vasopressin and oxytocin in the rat. *Eur J Neurosci* 1995;7:592-598. PUBMED | CROSSREF

9. Akl A, Alwagdani M, Aziz AA, Saad R, Baslaim G, Aldhaheri F. Tramadol-induced hyponatremia: case report highlighting the mechanism and review of literature. *Urol Nephrol Open Access J* 2021;9:75-77. CROSSREF

10. Falhammar H, Calissendorff J, Skov J, Nathanson D, Lindh JD, Mannheimer B. Tramadol- and codeine-induced severe hyponatremia: a Swedish population-based case-control study. *Eur J Intern Med* 2019;69:20-24. PUBMED | CROSSREF

11. Kardalas E, Paschou SA, Anagnostis P, Muscogiuri G, Siasos G, Vryonidou A. Hypokalemia: a clinical update. *Endocr Connect* 2018;7:R135-R146. PUBMED | CROSSREF

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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1.1. Online Submission

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3) Confirmation that all listed authors have approved the manuscript
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- **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, Bomback AS, et al, eds. Primer on kidney disease. 7th ed. Elsevier; 2018. p. 68-76.
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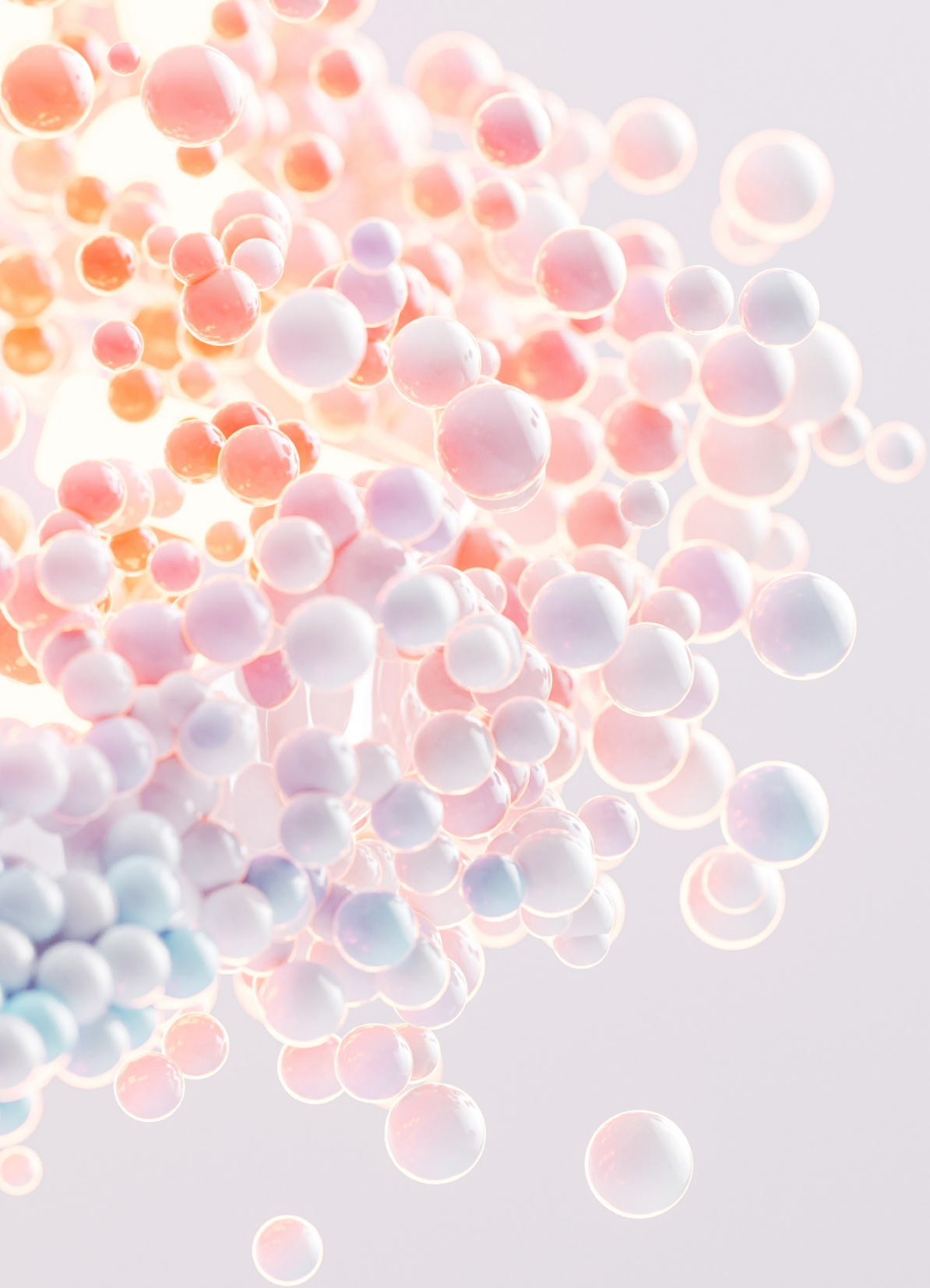

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