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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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Original Article

Renal Safety of Telminuvo, a Single Pill Combination of Telmisartan and S-amlodipine, in Korean Hypertensive Patients: A Multicenter, Retrospective Cohort Study

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ABSTRACT

Background: Effective blood pressure (BP) control is vital for preventing target organ damage, and combination therapy offers added benefits when single-agent treatment is insufficient. This cohort study examined whether Telminuvo, a single-pill combination of telmisartan and S-amlodipine, effectively maintains kidney function as a target organ in a large cohort of Korean patients.
Methods: A total of 4,934 patients from 30 hospitals were treated with Telminuvo for over six months, with BP, estimated glomerular filtration rate (eGFR), electrolyte levels, and adverse events monitored throughout the study period.
Results: Among the participants, 1,463 (29.7%) used Telminuvo for less than 1 year, while the remainder used it for longer. At baseline, the systolic and diastolic BP averaged 140.2 ± 18.4 mmHg and 82.1 ± 13.4 mmHg, respectively, which significantly decreased to approximately 130 and 75 mmHg after the initiation of treatment. The baseline eGFR of 79.3 mL/min/1.73 m^2 remained stable over three years, regardless of the initial eGFR levels. Within the first six months, acute kidney injury (defined as either a ≥ 0.3 mg/dL increase in serum creatinine or a ≥ 50% increase from baseline) occurred in 6.6% of patients, while hyperkalemia (defined as serum potassium levels > 5.5 mmol/L) was observed in 3.2% of patients.
Conclusion: This cohort study demonstrates that Telminuvo effectively reduces blood pressure without compromising kidney function. Furthermore, the findings provide additional insights into drug-related adverse events, which will be valuable for clinicians in the real-world prescribing of Telminuvo.

Keywords: Combination therapy; Hypertension; Kidney function; Safety

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Conflicts of interest
The authors declare the following competing interests: This research was funded by Chong Kun Dang Pharmaceutical Corporation. The funding source had no role in the study design, data collection, analysis, or writing of the manuscript.

Data sharing statement
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions
Conceptualization: MSH, SSH. Data curation: HKK, SUK, MSH, SSH. Formal analysis: HM, SB, DY, SSH. Writing - original draft: HM, SB, SSH. Writing - review & editing: DY, SSH. All authors read and approved the final manuscript.

INTRODUCTION

Hypertension is a significant global health issue, affecting over 30% of adults and playing a major role in cardiovascular morbidity and mortality, particularly in developed countries [1,2]. Effective management of blood pressure (BP) is crucial, especially in high-risk patients, as it can substantially improve their prognosis [3]. Numerous studies have shown that adequate control of hypertension is vital for reducing the risk of cardiovascular events and associated mortality [4,5]. Since more than two-thirds of hypertensive patients do not achieve adequate control with monotherapy, combining medications that have different mechanisms of action is often necessary. For patients with stage 2 or high-risk hypertension, starting combination therapy from the outset is recommended [6-11].

Key classes of antihypertensive agents include those targeting the renin-angiotensin system, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), as well as calcium channel blockers (CCBs) [12]. ACE inhibitors and ARBs are particularly recommended for patients with type 1 or type 2 diabetes who have hypertension and albuminuria [13,14]. These agents are effective in reducing proteinuria and preserving kidney function in conditions like diabetic kidney disease [15]. According to guidelines for managing chronic kidney disease (CKD), ARBs are the preferred choice for patients with stages 1 to 4 CKD, especially when diabetes and hypertension coexist [13]. In contrast, CCBs work by blocking the influx of calcium ions into cardiac and peripheral vascular smooth muscle cells, providing both antihypertensive and antianginal effects [16].

With a wide range of antihypertensive medications available, various combination therapies can be employed [10,11]. 2018 European Society of Hypertension/European Society of Cardiology hypertension guidelines recommend pairing an ARB with a CCB as a first-line combination due to its effectiveness in controlling BP and its ability to alleviate common side effects associated with CCBs, such as peripheral edema [17].

The combination of telmisartan (as an ARB) and S-amlodipine (as a CCB), marketed as Telminuvo, was specifically developed to treat essential hypertension that is inadequately controlled by either agent alone. Considering the importance of monitoring renal function in hypertensive patients, we conducted an observational cohort study—TRUST (a multicenter retrospective study evaluating the renal safety of the Telmisartan/S-Amlodipine combination in patients with essential hypertension treated for over six months)—utilizing data from multiple centers in Korea. In addition to assessing renal safety, we monitored the incidence of major and minor drug-related adverse events not associated with renal function.

METHODS

Ethics statements

The protocol for this multicenter retrospective study, evaluating the renal safety of the telmisartan/S-amlodipine combination in patients with essential hypertension treated for more than six months (the TRUST study), was reviewed and approved by the institutional review boards of all participating centers. These include Seoul National University Hospital (H-2003-165-1112; H-2003-149-1111), Changwon Fatima Hospital (CFH-2020-07), Kyung Hee University Hospital at Gangdong (2020-03-013; 2020-03-014; 2020-03-022; 2020-06-025), Andong Medical Group Hospital (2020-005), Bongseng Memorial Hospital (BSIRB-2021-005;

BSIRB-2021-010), CHA University Bundang Medical Center (2020-01-036), Chonnam National University Hospital (2020-236), Dong-A University Hospital (DAUHIRB-20-053; DAUHIRB-20-054; DAUHIRB-20-066), Dongguk University Medical Center (2020-11-040; 2020-12-015; 2020-12-020), Gachon University Gil Medical Center (GDIRB2020-265; GDIRB2021-420), Gangnam Severance Hospital (2020-1043-006), Haeundae Bumin Hospital (202103-CTDG-029), Hallym University Gangnam Sacred Heart Hospital (2020-05-005; 2020-05-006; 2020-05-007; 2020-08-007), Hanyang University Seoul Hospital (2019-12-016; 2020-03-032; 2020-06-011), Inje university Busan Paik Hospital (2020-01-087; 2020-01-089), Inje University Ilsan Paik Hospital (2020-01-016; 2020-02-038; 2020-02-039), Kangdong Sacred Heart Hospital (2020-02-007; 2020-02-009; 2020-05-006; 2020-05-007; 2020-08-002; 2020-10-002; 2020-10-003), Konkuk University Medical Center (2020-11-010; 2020-11-011; 2021-02-005; 2021-03-009), Korea University Anan Hospital (2020AN0144; 2020AN0151; 2020AN0234), Korea University Guro Hospital (2020GR0578), Kosin University Gospel Hospital (2020-02-026; 2020-03-001), Maryknoll Hospital (MMC/2021-303), Myongji Hospital (2020-08-018), National Health Insurance Service Ilsan Hospital (2020-05-012), Pusan National University Yangsan Hospital (02-2020-046), Seoul National University Bundang Hospital (B-2005-613-103; B-2012-652-103; B-2204-748-401), Soon Chun Hyang University Hospital Bucheon (2020-08-007; 2020-08-011; 2020-10-025), Soonchunhyang University Hospital Seoul (2020-02-014), Yeungnam University Hospital (2020-12-016), and Yongin Severance Hospital (2020-0361-008). The study was conducted in accordance with the ethical standards of the Declaration of Helsinki, and the requirement for written consent was waived due to the retrospective nature of the study.

Study design and patients

This study was designed as a multicenter observational cohort, incorporating demographic and biochemical parameters, with a focus on patients with essential hypertension. Patients were included if they met the following criteria: diagnosed with essential hypertension according to clinical guidelines, at least 19 years old at the start of Telminuvo treatment, on Telminuvo for at least 6 months, and had serum creatinine data available both before and after starting the medication. Exclusion criteria included patients with hypersensitivity to the main components or dihydropyridine derivatives of telmisartan and S-amlodipine, those who were pregnant or possibly pregnant at the start of Telminuvo treatment, or those who were breastfeeding. Additionally, patients who had previously undergone dialysis or received a kidney transplant, or who were otherwise deemed unsuitable for the study at the investigator's discretion, were also excluded.

Study variables

The demographic data collected at the time of Telminuvo administration included age, sex, height, weight, smoking history, comorbidities, Telminuvo dosage, and concomitant medications. Body mass index (BMI) was calculated by dividing weight by height squared. BP measurements were taken at multiple centers during patient visits using a standardized method, which involved taking several readings in the sitting position. Blood tests included measurements of blood urea nitrogen, creatinine, sodium, potassium, chloride, hemoglobin A1c, and lipid panel components such as total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [18]. These variables were extracted from electronic medical records.

Outcome data focused on adverse events following Telminuvo administration. Monitoring occurred at 3, 6, 12, 24, and 36 months post-administration, with particular attention to

kidney dysfunction-related events, such as acute kidney injury (AKI). AKI was defined as either a ≥ 0.3 mg/dL increase in serum creatinine or a ≥ 50% increase from baseline [19]. Hyperkalemia was defined as a serum potassium level > 5.5 mmol/L. Additionally, we monitored other adverse events, including cardiovascular events, peripheral edema, headache, facial flushing, gum hypertrophy, leukopenia, angioedema, and rash, throughout the study period.

Statistical analysis

Categorical data were presented as frequencies and percentages, while continuous data were presented as means (± standard deviations) or medians (interquartile ranges). Each patient's medical history was coded using MedDRA software (version 22.1; International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Geneva, Switzerland). Concomitant medications were classified according to the World Health Organization's Anatomical Therapeutic Chemical index, and the corresponding numbers and percentages were provided based on therapeutic categories. As this was an observational study, no imputation was performed for missing data. Patients could be included in more than one time group, depending on the timing of data collection, which varied among participants. Safety and other data analyses were conducted based on the duration of Telminuvo administration, divided into pre-administration and 3, 6, 12, 24, and 36 months post-administration. If data did not align with the predefined time points, the closest available time point was used. In cases where multiple measurements were taken within the same visit window, the value closest to the designated time point was selected for analysis. Paired t-tests were used to analyze changes in BP over time, comparing baseline values with measurements taken at 3, 6, 12, 24, and 36 months. Differences in variables between pre- and post-administration were estimated using paired t-tests or Wilcoxon signed-rank tests if the assumption of normality was not met. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 4,934 patients from 30 hospitals across South Korea were included in the analysis. Of these, 1,463 (29.7%) used Telminuvo for less than one year, while the remaining patients used it for longer periods. The average age of the patients was 63.3 ± 12.8 years, and 56.8% were male. The median duration of hypertension was 6.4 years (interquartile range: 1.3–12.1 years). The prescribed doses of Telminuvo (telmisartan and S-amlodipine) were 40/2.5 mg, 40/5 mg, 80/2.5 mg, and 80/5 mg, used by 53.1%, 18.8%, 25.8%, and 2.3% of patients, respectively. **Table 1** provides additional clinical details.

The most common comorbidities were metabolism and nutrition disorders, affecting 61.71% of patients, followed by cardiac disorders (30.34%) and nervous system disorders (14.13%). Within the metabolism and nutrition category, hyperlipidemia (26.90%) and diabetes mellitus (26.39%) were the most prevalent. Additional details on comorbidities can be found in **Supplementary Table 1**. Information on transitions from previous medications to Telminuvo is presented in **Supplementary Table 2**, with the most common transitions being from ACE inhibitors or ARBs (22.1%), β-blockers (20.8%), and no prior hypertensive medications (11.6%).

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Table 1. Demographics and baseline characteristics of patients

Variables	Values (n = 4,934)
Male	2,804 (56.8)
Age (yr)	63.3 ± 12.8
Height (cm)	162.8 ± 9.4
Weight (kg)	68.6 ± 13.6
Body mass index (kg/m^2)	25.7 ± 3.8
Duration of hypertension (yr)	8.0 ± 7.7
Smoking history	
Never smoker	2,001 (40.6)
Ex-smoker	488 (9.9)
Current smoker	544 (11.0)
Unknown	1,901 (38.5)

Data are presented as mean ± standard deviation for continuous variables and the number (%) for categorical variables.

BP after Telminuvo administration

At baseline, the systolic and diastolic BPs averaged 140.2 ± 18.4 mmHg and 82.1 ± 13.4 mmHg, respectively. After starting Telminuvo, systolic BP remained at approximately 130 mmHg, while diastolic BP stabilized around 75 mmHg over a 3-year period (**Fig. 1**). Among patients

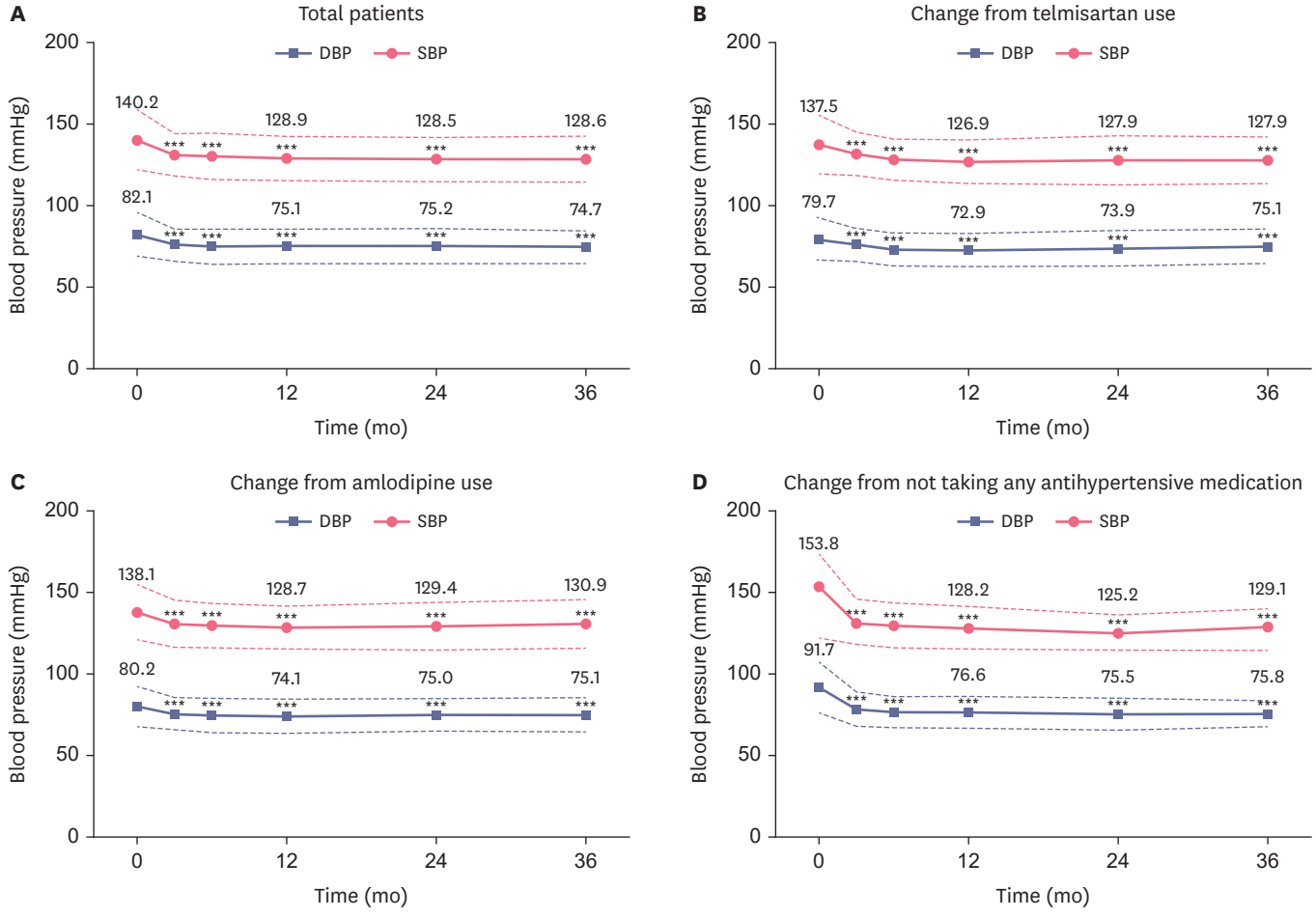

Fig. 1. Blood pressure after administration of Telminuvo.
(A) All patients; (B) Patients previously treated with telmisartan; (C) Patients previously treated with amlodipine; (D) Patients not previously treated with antihypertensive medication.
DBP, diastolic blood pressure; SBP, systolic blood pressure.
***p < 0.001 compared with values at baseline.

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who transitioned from renin-angiotensin system agents or CCBs to Telminuvo, systolic BP decreased by about 9 mmHg and diastolic BP by 5 mmHg over the 3 years. For those transitioning from no prior antihypertensive medication to Telminuvo, the reduction was more pronounced, with systolic BP decreasing by 25 mmHg and diastolic BP by 16 mmHg over the same period (**Fig. 1**). Patients were stratified by baseline eGFR, and temporal trends in serum potassium, eGFR, and blood pressure were analyzed separately (**Supplementary Fig. 1**). In this stratified analysis, both SBP and DBP showed statistically significant reductions across all time points.

Renal safety after Telminuvo administration

The baseline eGFR was 79.3 ± 22.1 mL/min/1.73 m^2, with 80.9% of patients having an eGFR of 60 mL/min/1.73 m^2 or higher. While eGFR initially decreased after 6 and 12 months of Telminuvo administration, it returned to baseline levels after one year (**Fig. 2**), suggesting a protective effect from long-term ARB use or effective BP control on target organs [20,21]. The overall annual change in eGFR was less than 1 mL/min/1.73 m^2, consistent with the natural decline in eGFR seen in healthy aging [22]. Notably, no significant decrease in eGFR was observed in patients with reduced kidney function at baseline (e.g., eGFR of 60–89 mL/min/1.73 m^2 or below 60 mL/min/1.73 m^2) (**Table 2**). However, a significant reduction was noted in patients with an eGFR above 90 mL/min/1.73 m^2, though the maximum decrease was only 4 mL/min/1.73 m^2, and eGFR levels remained above 90 mL/min/1.73 m^2 (**Fig. 2**).

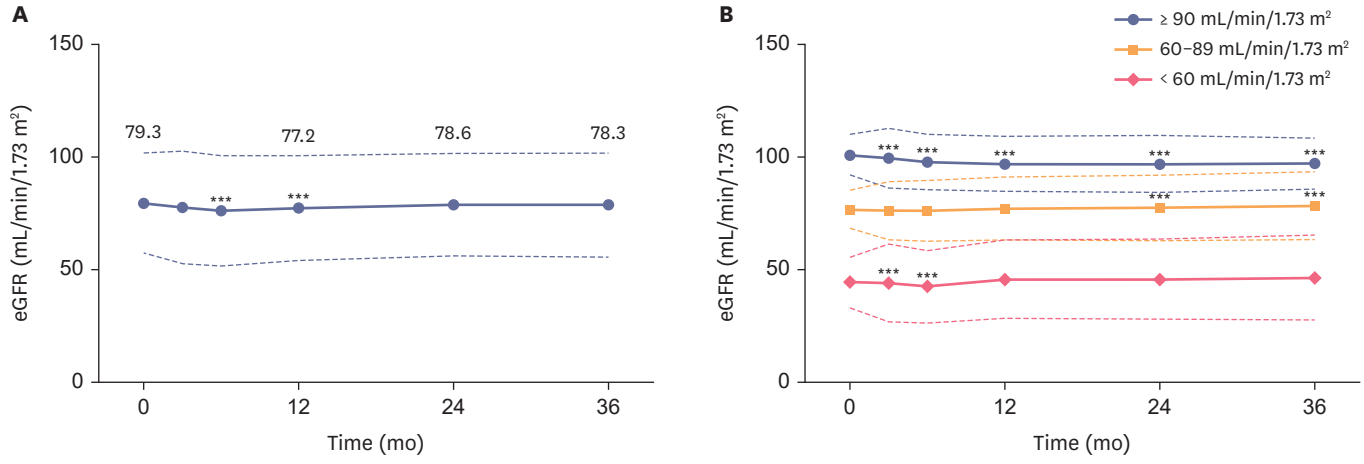

Fig. 2. Kidney function parameters after administration of Telminuvo.
(A) All patients; (B) Stratified analysis by baseline kidney function.
eGFR, estimated glomerular filtration rate.
***p < 0.001 compared with values at baseline.

Table 2. Changes in kidney function parameters after the administration of Telminuvo

Variables	Baseline		3 mo		6 mo		12 mo		24 mo		36 mo	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Total	4,934	79.3 ± 22.1	801	77.4 ± 25.1	1,422	75.9 ± 24.5***	1,696	77.2 ± 23.3***	1,395	78.6 ± 22.6	894	78.3 ± 23.0
eGFR (mL/min/1.73 m^2)												
≥ 90	1774	100.9 ± 9.2	293	99.5 ± 13.2**	474	97.9 ± 12.3***	577	96.9 ± 12.2***	466	97.0 ± 12.6***	284	97.3 ± 11.4***
60–89	2,220	76.7 ± 8.7	324	76.4 ± 12.8	630	76.2 ± 13.5	759	77.2 ± 13.9	687	77.6 ± 14.5*	437	78.6 ± 15.0***
< 60	940	44.7 ± 11.5	184	44.2 ± 17.2*	318	42.6 ± 16.2*	360	45.8 ± 17.3	242	45.9 ± 17.8	173	46.6 ± 18.9

Comparison analyses are performed when the baseline group serving as a reference.
eGFR, estimated glomerular filtration rate; SD, standard deviation.
*p < 0.05, **p < 0.01, and ***p < 0.001.

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Table 3. Changes in the serum potassium concentration after the administration of Telminuvo

Variables	Baseline		3 mo		6 mo		12 mo		24 mo		36 mo	
	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
Total	2,931	4.32 ± 0.48	452	4.42 ± 0.48	821	4.45 ± 0.49***	1,049	4.38 ± 0.48**	820	4.34 ± 0.43	555	4.38 ± 0.47*
eGFR (mL/min/1.73 m²)												
≥ 90	969	4.19 ± 0.39	147	4.22 ± 0.38	229	4.26 ± 0.36*	337	4.26 ± 0.37***	259	4.25 ± 0.38	159	4.19 ± 0.35
60–89	1,301	4.29 ± 0.44	178	4.38 ± 0.43	362	4.38 ± 0.44*	451	4.31 ± 0.40	395	4.31 ± 0.40	267	4.35 ± 0.43*
< 60	661	4.57 ± 0.56	127	4.68 ± 0.54	230	4.74 ± 0.56	261	4.64 ± 0.57	166	4.57 ± 0.49	129	4.69 ± 0.54***

Comparison analyses are performed when the baseline group serving as a reference.
eGFR, estimated glomerular filtration rate; SD, standard deviation.
*p < 0.05, **p < 0.01, and ***p < 0.001.

AKI occurred in 6.6% of patients within the first 6 months of Telminuvo administration, increasing slightly to 7.4% within 3 years. Hyperkalemia was observed in 1.6% and 3.2% of patients within 3 and 6 months, respectively, while 2.0% experienced this condition over 3 years. Long-term increases in serum potassium were primarily observed in patients with an eGFR below 90 mL/min/1.73 m², rather than those with an eGFR ≥ 90 mL/min/1.73 m² (**Table 3**). No kidney-related events were linked to the dosage of Telminuvo (**Supplementary Table 3**).

Other safety events after Telminuvo administration

Adverse events unrelated to kidney dysfunction were also recorded (**Supplementary Table 4**). A total of 1,463 patients received Telminuvo for less than 1 year, during which 61 adverse events were reported. The most common was peripheral edema (n = 8, 0.55%), followed by generalized edema and dizziness, which occurred in 2 (0.14%) and 3 (0.21%) patients, respectively. A total of 15 patients (2.43%) discontinued treatment, with dizziness and hypotension being the primary adverse events leading to discontinuation. No deaths were reported during the study period. Further details on other adverse events can be found in **Supplementary Table 4**.

DISCUSSION

Clinicians require detailed evaluations of individual medications, as efficacy and the frequency of complications can vary even among drugs within the same class. This study focused on kidney-related outcomes and complications associated with Telminuvo, a single-pill combination of telmisartan and S-amlodipine. Over 3 years of use, kidney function remained largely stable, with rates of AKI and hyperkalemia recorded at 7.4% and 2.0%, respectively. Notably, patients with pre-existing kidney impairment did not experience a decline in eGFR. These findings suggest that the appropriate use of Telminuvo may help prevent further deterioration of kidney function in hypertensive patients [23]. Additionally, various complications were investigated, and common adverse effects such as edema and dizziness, which are frequently seen with drugs in the same class, occurred at very low rates. This may be due to the specific characteristics of the study population. On the other hand, BP control was notably effective. These findings provide valuable data for anticipating and addressing potential issues when using Telminuvo in real-world clinical practice.

Antihypertensive drugs are among the most commonly prescribed medications worldwide [24]. There is a well-established positive correlation between BP and the risk of stroke, coronary artery disease, heart failure, and the development and progression of kidney dysfunction [25-28], a relationship that applies across all age groups and ethnicities [29]. While improving lifestyle habits can lower BP and reduce overall cardiovascular

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risk, most hypertensive patients require antihypertensive medications alongside lifestyle interventions [30]. Several classes of antihypertensive drugs are available, with ARBs being the most commonly prescribed in Korea, followed by CCBs [12]. In this study, we focused on Telminuvo, a single-pill combination that may enhance patient compliance and lead to improved clinical outcomes [6]. However, before this study, no reports had explored the use of Telminuvo in real clinical settings, particularly in relation to kidney outcomes.

Over the 3-year period of Telminuvo use, no significant deterioration in kidney function was observed. Although eGFR may decrease in the early phase of treatment due to the effects of ARBs, long-term follow-up showed sustained kidney function [31]. This is likely attributable to BP-lowering effect of Telminuvo. The incidence of AKI and hyperkalemia was low, at around 7% and 2%, respectively, indicating that these events are rare. Furthermore, since these complications mainly occurred in patients with advanced kidney dysfunction, Telminuvo appears to be very safe for hypertensive patients with preserved kidney function.

This study also discusses several other events associated with the use of Telminuvo. Peripheral edema is a common complication linked to CCBs, with rates exceeding 5% in various cohort studies. This side effect may be influenced by the molecular structure of CCBs. Telminuvo contains S-amlodipine, which has a lower incidence of edema compared to amlodipine, which consists of both S- and R-amlodipine [32]. Additionally, the inclusion of telmisartan in Telminuvo may further reduce the risk of peripheral edema typically associated with CCBs. These findings suggest that Telminuvo could be a beneficial option for patients who experience peripheral edema, whether or not it is related to other drug use.

While the study provides valuable insights, it also has several limitations. As a retrospective study, it cannot definitively establish causal relationships, particularly regarding Telminuvo use and the rise in potassium levels. Hyperkalemia can be influenced by various factors, including underlying diseases, dietary habits, concomitant medications, and the use of potassium-lowering agents, which were not fully accounted for. The lack of proteinuria data limits the comprehensive evaluation of renal outcomes. These limitations highlight the need for future prospective studies to address such variables. Moreover, the inclusion criteria required patients to have been on Telminuvo therapy for at least six months, which could introduce bias, as patients who experienced early onset of AKI or hyperkalemia and discontinued treatment were excluded, potentially leading to lower observed incidence rates.

Since the cohort consisted solely of Korean patients and hospitals, the results may reflect specific characteristics of this population, and the findings may not be directly applicable to other countries or ethnic groups. Additionally, the lack of imputation for missing data could introduce bias and reduce the statistical power of the study. Furthermore, the absence of a comparison between Telminuvo and other ARB-CCB combination therapies limits the study to descriptive observations, highlighting the need for future studies with comparison groups to draw stronger conclusions.

Conclusions

This study provides evidence supporting the use of Telminuvo in hypertensive patients by thoroughly analyzing its renal safety. Additionally, the findings offer valuable insights for clinical practice, demonstrating effectiveness of Telminuvo in lowering BP and its low incidence of associated complications. Future research will focus on investigating its impact on other target organs beyond the kidneys.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Comorbidities at baseline

Supplementary Table 2
Information on antihypertensive medications

Supplementary Table 3
Occurrence of major adverse events based on the Telminuvo dose

Supplementary Table 4
Occurrence of other adverse events according to the period of Telminuvo administration

Supplementary Fig. 1
Comparative trends.

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Case Report

Cytotoxic Lesions of the Corpus Callosum Preceding Osmotic Demyelination Syndrome in Hypernatremia and Hyperosmolar Hyperglycemic State: A Case Report

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ABSTRACT

Osmotic demyelination syndrome (ODS) is a rare neurological disorder associated with osmotic imbalances. Traditionally, ODS has been known to occur following the rapid correction of hyponatremia; however, ODS has also been reported concerning hypernatremia and hyperglycemia. Cytotoxic lesions of the corpus callosum (CLOCC), identified using transient magnetic resonance imaging, can arise from various causes, including drugs, vascular diseases, infections, and metabolic disturbances such as electrolyte imbalances and dysglycemia. The simultaneous occurrence of ODS and CLOCC is extremely rare. Here, we report a case whereby a 57-year-old male initially developed CLOCC via severe hypernatremia and hyperosmolar hyperglycemic state (HHS) was also subsequently identified with ODS. Physicians should know CLOCC may be an early radiologic finding in ODS associated with severe hypernatremia and HHS. Therefore, proactive brain imaging should be considered in these patients to facilitate the early detection of neurological complications.

Keywords: Consciousness; Corpus callosum; Hyperglycemia; Hypernatremia; Magnetic resonance imaging

INTRODUCTION

Generally, hypernatremia and hyperglycemia can lead to brain damage, including cerebral edema, hemorrhage, and thrombosis [1]. Meanwhile, osmotic demyelination syndrome (ODS) and cytotoxic lesions of the corpus callosum (CLOCC) have been identified using brain imaging methods in relation to these conditions.

ODS, which includes both central pontine myelinolysis and extrapontine myelinolysis, is characterized by acute demyelination lesions occurring in brain cells [2]. Traditionally, ODS has been described in patients with rapid osmotic shifts, especially rapid correction of hyponatremia or severe hypernatremia [3]. However, several case reports have documented the occurrence of ODS, even in hyperglycemia [4].

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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
Supervision: CSK. Writing - original draft: HJP, SHS[1]. Writing - review & editing: SHS[2], HSC, EHB, SKM, SWK, CSK. All authors read and approved the final manuscript.

SHS[1], Su Hyun Song; SHS[2], Sang Heon Suh.

CLOCC is a transient signal alteration on magnetic resonance imaging (MRI), typically involving the splenium of the corpus callosum (SCC). CLOCC exhibits hyperintensity on diffusion-weighted imaging (DWI) sequences with corresponding hypo-intensity on apparent diffusion coefficient (ADC) maps. Various diseases and conditions have been associated with CLOCC, including trauma, drug-related, infections, vascular diseases, and metabolic disorders [5]. CLOCC caused by electrolyte imbalance is commonly observed hyponatremia, whereas it is relatively rare in hypernatremia [6]. These lesions usually recover within one to several weeks after correcting the underlying cause [5].

We report an exceptionally rare case of CLOCC initially manifested in a patient with concurrent hypernatremia and hyperosmolar hyperglycemic state (HHS), followed by the subsequent development of ODS.

CASE REPORT

A 57-year-old man presented to the emergency department with confusion and irritability. The patient also complained of anorexia and vomiting for 2 weeks before the visit, and had a weight loss of approximately 10 kg over the past six months. He denied any history of trauma or alcohol use. The patient had no known underlying medical conditions and was not taking any medications. However, he did report a habitual excessive intake of dietary sugar.

On admission, the patient appeared confused, producing incomprehensible sounds. His vital signs were measured: blood pressure of 130/60 mmHg, heart rate of 97 beats/min, body temperature of 36.2°C, and oxygen saturation of 100% on room air. A physical examination revealed a dry tongue and decreased skin turgor, which suggested severe dehydration. His laboratory results were as follows: serum creatinine, 2.4 mg/dL (0.5–1.3 mg/dL); serum sodium, 176 mEq/L (136–146 mEq/L); serum potassium, 3.2 mEq/L (3.5–5.1 mEq/L); serum magnesium, 2.5 mg/dL (1.6–2.6 mg/dL); serum inorganic phosphorus, 3.0 mg/dL (2.5–4.5 mg/dL); serum osmolality, 401 mOsm/kg (280–295 mOsm/kg); urine osmolality, 353 mOsm/kg (300–900 mOsm/kg); hemoglobin A1c, 15.1% (4.4–6.4%); blood glucose, 525 mg/dL (60–100 mg/dL). The corrected serum sodium level was 186 mEq/L. The serum pH was 7.40 (7.35–7.45), and the bicarbonate level was 26.6 mmol/L (21–28 mmol/L), indicating an absence of acidosis. The ketone body level was mildly elevated at 155.7 μmol/L (28–120 μmol/L). A detailed summary of the patient's laboratory findings on the first hospital day is presented in **Table 1**.

Brain MRI was performed to evaluate the altered mental status of the patient and demonstrated a diffusion-restricted lesion in the SCC, appearing hyperintense on DWI and fluid-attenuated inversion recovery (FLAIR) sequences, with corresponding hypointensity on the ADC maps (**Fig. 1**).

The patient was treated using hypotonic fluids and continuous intravenous insulin infusion to correct hypernatremia and hyperglycemia. Hypernatremia was gradually corrected over several days to prevent overcorrection. Insulin therapy for glycemic control was transitioned from continuous infusion to multiple daily injection regimens, followed by oral hypoglycemic agents—metformin and linagliptin. We included a summary table to illustrate the daily trends in serum sodium, glucose, osmolality, potassium, blood urea nitrogen, and creatinine during the early course of hospitalization (**Table 2**). On the 14th day of hospitalization, the patient did not fully recover consciousness despite serum sodium levels and osmolality

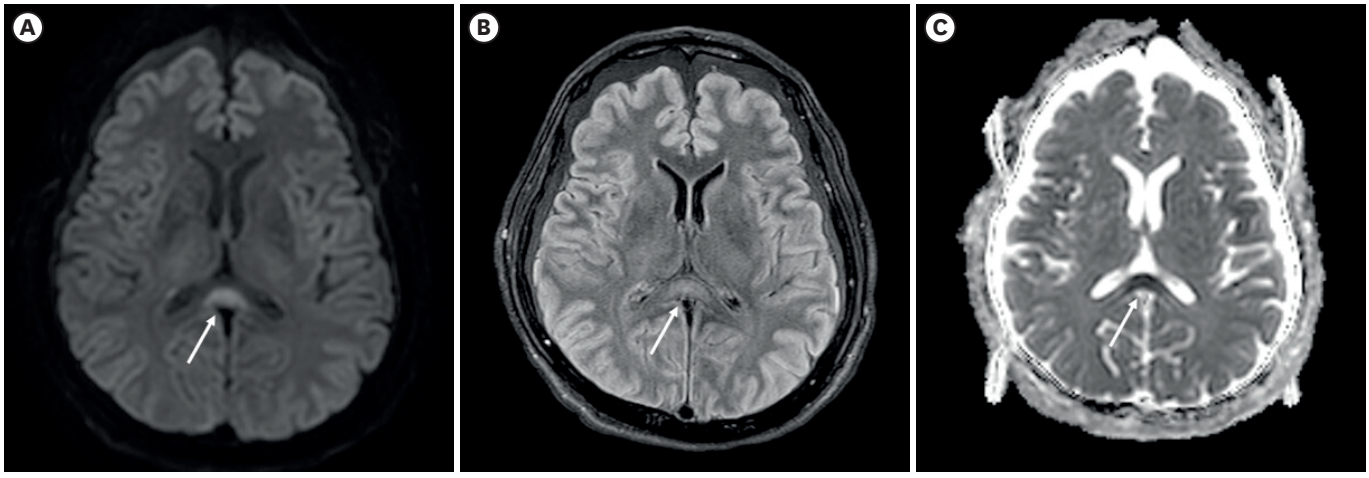

Fig. 1. Magnetic resonance imaging findings in cytotoxic lesions of the corpus callosum. (A) Diffusion-weighted imaging and (B) fluid-attenuated inversion recovery show high signal intensity. (C) The apparent diffusion coefficient map shows hypointense signals in the same lesion, indicating restricted diffusion (arrow).

Table 1. Laboratory findings on the first hospital day

Laboratory parameter	Result	Reference range
White blood cell count (μL)	6,100	4,000–10,000
C-reactive protein (mg/dL)	0.78	0–0.3
Aspartate aminotransferase (U/L)	31	13–39
Alanine aminotransferase (U/L)	54	7–52
Serum albumin (g/dL)	3.5	3.5–5.2
Serum creatinine (mg/dL)	2.4	0.5–1.3
Serum sodium (mEq/L)	176	136–146
Serum potassium (mEq/L)	3.2	3.5–5.1
Serum magnesium (mg/dL)	2.5	1.6–2.6
Serum inorganic phosphorus (mg/dL)	3.0	2.5–4.5
Serum osmolality (mOsm/kg)	401	280–295
Urine osmolality (mOsm/kg)	353	300–900
Hemoglobin A1c (%)	15.1	4.4–6.4
Blood glucose (mg/dL)	525	60–100
Serum pH	7.40	7.35–7.45
Bicarbonate (mmol/L)	26.6	21–28
Ketone bodies (μmol/L)	155.7	28–120

Table 2. Daily laboratory results during hospitalization

Laboratory parameter	HD 1	HD 2	HD 3	HD 7	HD 14
Serum sodium (mEq/L)	176	168	161	145	142
Serum glucose (mg/dL)	525	391	222	171	163
Serum osmolality (mOsm/kg)	401	385	350	294	293
Serum potassium (mEq/L)	3.2	3.0	3.9	3.7	4.1
BUN (mg/dL)	43.0	37.4	22.1	21.9	18.7
Creatinine (mg/dL)	2.42	2.08	1.76	0.90	0.79

BUN, blood urea nitrogen; HD, hospital day.

appearing normalized. A follow-up brain MRI showed a resolution of the SCC lesions; however, new lesions consistent with ODS were revealed, affecting the external capsules, thalami, hippocampi, and pons (**Fig. 2**). After one month, the patient had fully regained consciousness.

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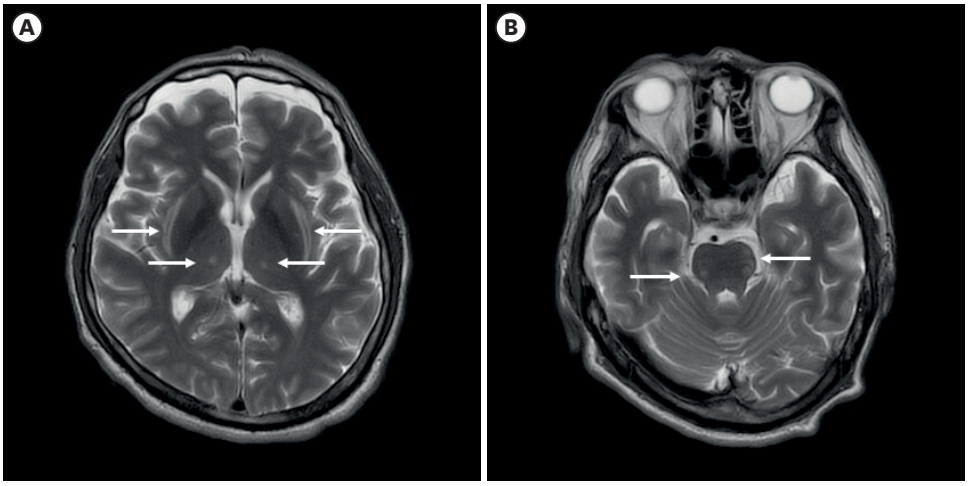

Fig. 2. A follow-up brain magnetic resonance imaging (hospital day 14). Symmetrical T2 hyperintensities in the (A) external capsules, thalami, (B) hippocampi, and peripheral pons. These findings suggest metabolic encephalopathy, such as osmotic demyelination syndrome (arrows).

Ethics statement

This study was approved by the Chonnam National University Hospital (study approval number: CNUH-EXP-2025-099).

DISCUSSION

We present a case in which ODS was subsequently identified in a patient who developed CLOCC as a result of hypernatremia and HHS. ODS is a rare neurological disorder characterized by demyelination of brain cells, encompassing both central pontine myelinolysis and extrapontine myelinolysis [2]. The most widely recognized precipitating factor in clinical practice is the rapid correction of chronic hyponatremia, but in some cases, its association with hypernatremia and hyperglycemia has also been revealed [3,4]. In ODS, seizures or encephalopathy may manifest initially. As the disease progresses, dysarthria, dysphagia, oculomotor dysfunction, and variable degrees of quadriplegia may develop. Radiological findings on brain MRI are hyperintense lesions in the central pons or associated extrapontine structures on T2-weighted and FLAIR sequences with corresponding hypointensity on T1-weighted sequences. While ODS has historically been considered a condition with a poor prognosis, recent studies indicate favorable recovery is not uncommon [2].

The term CLOCC was first proposed by Starkey et al. [7] in 2017. Prior to this, these lesions were referred to as mild encephalitis/encephalopathy with reversible splenial lesion, reversible or transient splenial lesions, and reversible splenial lesion syndrome. MRI shows these lesions exhibit hyperintensity on T2-weighted imaging, FLAIR, and DWI while demonstrating hypointensity on ADC. On T1-weighted imaging, these lesions exhibit either hyperintensity or isointensity. In most cases, contrast enhancement is not observed. Clinical manifestations are usually nonspecific and varied. Meanwhile, fever and headache are commonly observed, while cognitive impairment, behavioral change, confusion, seizures, and loss of consciousness can also occur. CLOCC is associated with diverse causes, including trauma, drugs, viral or bacterial infections, vascular diseases, and metabolic disorders such as electrolyte disturbances and dysglycemia. The exact mechanism underlying splenial

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lesions remains unclear, but the high density of excitatory amino acid receptors in the corpus callosum may contribute to its vulnerability to cytokine-mediated injury. These lesions generally resolve within a few weeks following correction of the underlying cause [5].

In our patient, we hypothesized that diabetes mellitus developed but remained untreated, leading to uncontrolled hyperglycemia. Moreover, as no findings were observed on the computed tomography scan of the neck, chest, and abdomen that indicated the existence of malignant tumors, the 10 kg weight loss over six months was thought to be a manifestation of diabetes mellitus. Osmotic diuresis was induced afterward, and hypernatremia is presumed to have worsened due to polyuria and inadequate oral intake. Although most cases of CLOCC are linked to hyponatremia [6], CLOCC has also been reported in the context of hypernatremia and hyperglycemia [8-10]. Thus, we suggest that hypernatremia and hyperglycemia contributed to the development of CLOCC in this case. A follow-up MRI performed three weeks later revealed imaging findings consistent with ODS. To our knowledge, the simultaneous occurrence of CLOCC and ODS is extremely rare, with only a single case previously reported by Zhang et al. [10] in 2024, in which CLOCC and ODS were induced by hypernatremia. In that case, the patient recovered consciousness within five days; in our case, complete recovery required several weeks. We hypothesized the reasons for this occurred in two ways. Since our patient presented to the emergency department, determining the baseline sodium level and continuously monitoring the levels was challenging. Additionally, the exact timing of deterioration was unclear, leading to a delayed diagnosis of hypernatremia and HHS. Another reason is related to the coexistence of hypernatremia and hyperglycemia. Both serum sodium and glucose play essential roles in regulating serum osmolality, and their coexistence leads to delayed recovery from ODS, as the condition is influenced by changes in serum osmolality.

In conclusion, CLOCC lesions are important radiologic findings and may be observed early in ODS caused by severe hypernatremia and HHS. Therefore, physicians should consider performing proactive brain imaging, and further research is needed to explain the pathological mechanisms associated with CLOCC and ODS.

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Case Report

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A Case of Cystinuria With Compound Heterozygous Mutations Both in *SLC3A1* and *SLC7A9* Genes

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ABSTRACT

Cystinuria is an autosomal recessively inherited genetic disorder, and is typically classified into type A, caused by mutations in *SLC3A1*, or type B, caused by mutations in *SLC7A9*. While the predominance of the genotypes varies among countries, due to lack of a large scale cohort, the characterization of mutations in *SLC3A1* or *SLC7A9* is still limited in East Asia. A 61-year-old male patient admitted to the department of nephrology, with a chief complaint of fever, chillness and left flank pain for a week. The patient had a past history of recurrent urolithiasis, with a frequency of at least 1 to 2 times a year. Computed tomography visualized 1 cm-sized stone at distal ureter, which was removed by retrograde ureteroscopy. The stone analysis documented 100% of cystine, indicating an underlying genetic disorder, cystinuria. Whole genome sequencing from peripheral blood unveiled 3 heterozygous missense mutations in coding exons of *SLC3A1* gene, and 2 heterozygous missense mutations in coding exons of *SLC7A9* gene. We here report a case of cystinuria with compound heterozygous mutations both in *SLC3A1* and *SLC7A9* genes, with a total of 5 mutant alleles in a patient.

Keywords: Cystinuria; Heterozygote; Mutation

INTRODUCTION

Cystinuria is an autosomal recessively inherited genetic disorder characterized by increased urinary excretion of cystine and dibasic amino acids, ornithine, lysine, and arginine (COLA) [1-3]. Due to the low solubility of cysteine, the affected individuals are prone to repeated episodes of urolithiasis. Excess urinary excretion of COLA results from the functional defects of COLA transporter, $b^{0,+}$, located in the apical membrane of renal proximal tubules. As the transporter, $b^{0,+}$, is a heterodimer, *SLC3A1*, located on chromosome 2p16.3, and *SLC7A9*, located on chromosome 19q13.1, encode its subunits rBAT and $b^{0,+}$ AT, respectively [4,5]. The genotypes classify the patients with cystinuria into type A, caused by mutations in *SLC3A1*, or type B, caused by mutations in *SLC7A9* [6]. Type AB is originally defined as one mutation on each of *SLC3A1* or *SLC7A9*, although the cysteine stone forms only if both copies of either *SLC3A1* or *SLC7A9* are mutated [7].

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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.

While the predominance of type A or type B genotype and the frequent mutations vary among countries [7-9], due to lack of a large scale cohort, the characterization of mutations in *SLC3A1* or *SLC7A9* is still limited in East Asia [10,11]. We here describe a case of cystinuria, who presented with post-renal acute kidney injury (AKI). In the present case, whole genome sequencing from peripheral blood revealed compound heterozygous mutations both in *SLC3A1* and *SLC7A9*.

CASE REPORT

A 61-year-old male patient admitted to the department of nephrology, with a chief complaint of fever, chillness and left flank pain for a week. The patient had a past history of recurrent urolithiasis, with a frequency of at least 1 to 2 times a year. The patient stated that, as the attack is so frequent that the patient himself is 'adapted' to the pain, and, at this presentation, had been waiting for the spontaneous relief of the pain. While no previous history of chronic kidney disease was documented in the patient, the familial history revealed that his brother had been on chronic hemodialysis. Elevated blood urea nitrogen (25.4 mg/dL), serum creatinine (2.37 mg/dL) and C-reactive protein (5.84 mg/dL) levels in the laboratory study and left-sided hydronephrosis in the ultrasonography imaging (**Fig. 1A**) collectively suggested post-renal AKI combined with urinary tract infection.

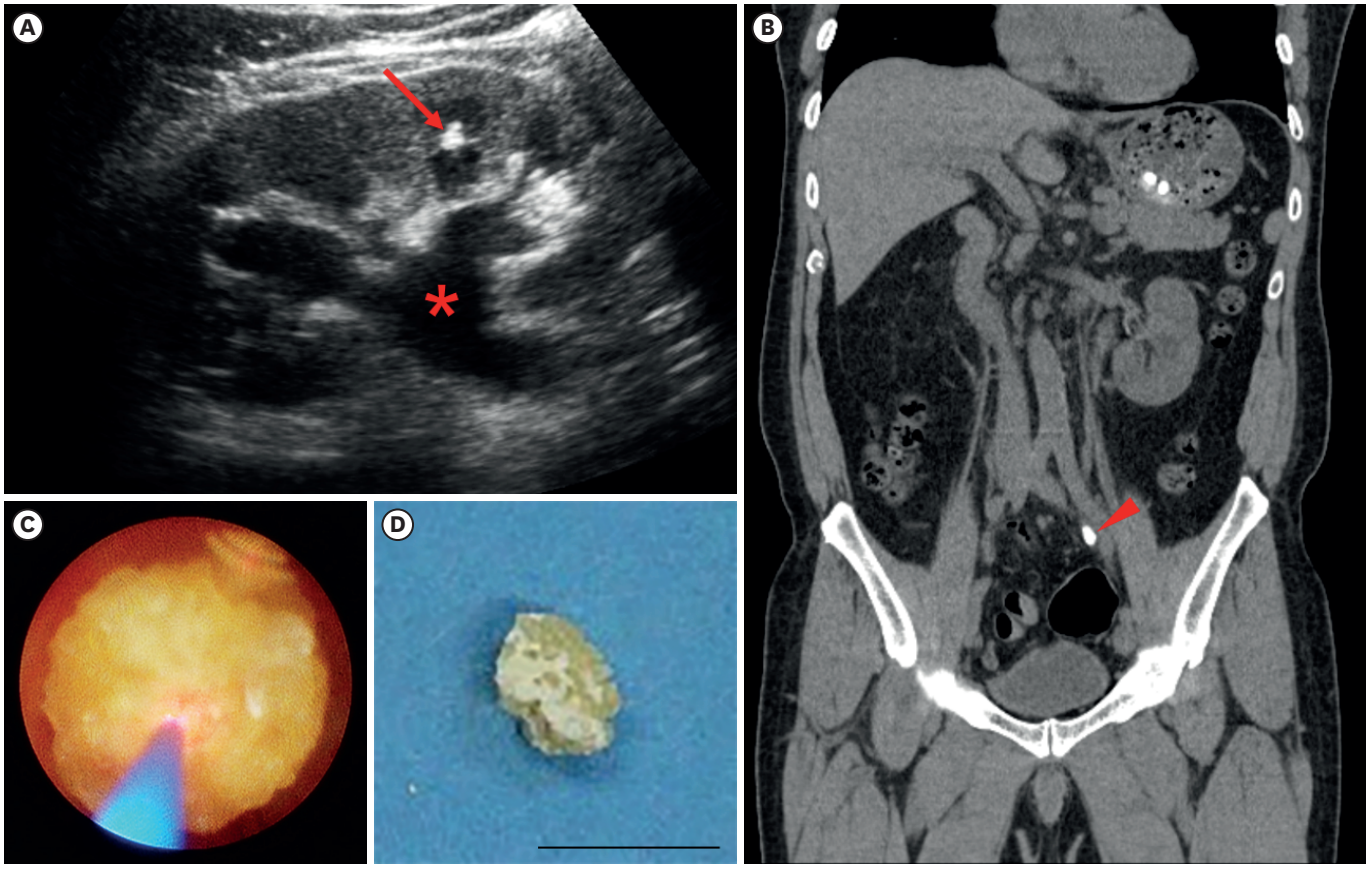

Fig. 1. Clinical findings on the diagnostic work-up for cystinuria. Findings of ultrasonography (A), computed tomography (B), retrograde ureteroscopy (C), and gross appearance of the cystine stone (D).

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Table 1. Summary of mutations in exon regions of *SLC3A1* and *SLC7A9*

Gene	Position	Nucleotide change	Predicted protein	Variant type	dbSNP ID
SLC3A1	Exon 1	c.460G>C	p.(Ala154Pro)	Missense	rs766140035
	Exon 7	c.1364C>T	p.(Ser455Leu)	Missense	rs949704245
	Exon 10	c.1854G>A	p.(Met618Ile)	Missense	rs698761
SLC7A9	Exon 3	c.399C>T	p.(Ser133Ser)	Synonymous	rs35170371
	Exon 3	c.425T>C	p.(Val142Ala)	Missense	rs12150889
	Exon 4	c.507C>T	p.(Ser169Ser)	Synonymous	rs11084673
	Exon 4	c.667C>A	p.(Leu223Met)	Missense	rs1007160
	Exon 5	c.687C>T	p.(Leu229Leu)	Synonymous	rs1007161
	Exon 9	c.1143C>T	p.(Ala381Ala)	Synonymous	rs2287881

Note that all the mutations listed above are heterozygous.

Authors' contributions

Conceptualization: SHS[1]; Data curation: SHS[1]; Formal analysis: SHS[1]; Funding acquisition: SWK, SKM; Investigation: SHS[1]; Methodology: SHS[1]; Supervision: SWK, SKM; Validation: SHS[2], HSC, CSK, EHB; Visualization: SHS[1]; Writing - original draft: SHS[1]; Writing - review & editing: SHS[1], SHS[2], HSC, CSK, EHB, SWK, SKM.

SHS[1], Sang Heon Suh; SHS[2], Su Hyun Song

All authors read and approved the final manuscript.

To cope with AKI and urinary tract infection, percutaneous nephrostomy was ipsilaterally placed on hospital day (HD) 1. Empirical antibiotics were also initiated. To further define the etiology of ureteral obstruction, computed tomography checked on HD 4 visualized a 1 cm-sized stone at distal ureter (**Fig. 1B**). To eliminate the lesion, stone removal by retrograde ureteroscopy was performed on HD 5 (**Fig. 1C and D**). The stone analysis documented 100% of cystine, suggesting an underlying disorder, cystinuria.

Whole genome sequencing (Macrogen, Seoul, Korea) from peripheral blood unveiled compound heterozygous mutations both in *SLC3A1* and *SLC7A9* genes (**Table 1**). We found 3 heterozygous missense mutations in coding exons of *SLC3A1* gene. We also observed 2 heterozygous missense mutations and 4 synonymous variants in coding exons of *SLC7A9* gene.

To prevent the recurrence of urolithiasis, the patient was advised to restrict dietary intake of sodium and protein, and was encouraged to drink free water adequately. Medication of potassium citrate also prescribed for the alkalization of urine. The treatment was so effective in the present case that the attack did not recur thereafter for more than 3 years, and the kidney function was returned to normal, with a serum creatinine level of 0.97 mg/dL.

DISCUSSION

We here report a case of cystinuria with a digenic inheritance affected by a total of 5 compound heterozygous mutations from *SLC3A1* and *SLC7A9* genes. According to a previously proposed molecular classification, type A cystinuria is caused by biallelic variations that affect the *SLC3A1* gene (genotype AA), type A heterozygote individuals have normal urinary amino acid excretion; type B cystinuria is due to pathogenic variants in both *SLC7A9* alleles (genotype BB), type B heterozygote individuals may have normal or enhanced urinary excretion of dibasic amino acid; type AB (genotype AB) has been proposed with a possible digenic inheritance [6]. In this study from Italy, among 125 patients completed with gene analyses, 98.4% could be classified to either type A or type B, and only 1.6% were classified to type AB, where the classification system is missing the cases with *trans* compound heterozygous mutations affecting only one of the 2 genes, as, by virtue of definition, type AB is defined as a case with one mutation on each of the genes [6]. A case series of 8 unrelated patients with cystinuria in China reported that compound heterozygous mutations in either *SLC3A1* or *SLC7A9* genes were observed in all patients except but one [10], where no one with more than 2 mutant alleles were reported. Recent reports demonstrated that patients with an AB genotype have a third variant leading to genotype AAB or ABB [12,13]. A French cohort of 112 patients completed the genotyping in 99 patients, where only 4 patients had

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3 mutant alleles (3 patients with type AAA, and one patient with type AAB) [14]. Similarly, the genotype of the present case could be defined as 'type AAABB,' which had never been identified before. It is, therefore, unique and worth noting that 5 mutated alleles are found in a patient. Even though the previous study reported that some of the mutations in the current case report was identified as non-pathogenic in that case (i.e., those in *SLC3A1* exon 10 and *SLC7A9* exons 3 and 4) [14], it is likely that the remaining 2 heterozygous variants could be still pathogenic with a *trans* compound heterozygous mutation (i.e., type AA).

A potential implication for the identification of genetic etiology is the individualization of therapeutics. While the genotype of patients with cystinuria was believed not to be closely associated with the phenotypes (i.e., the amount of urinary excretion of cysteine), their relationships now begin to be elucidated. Indeed, a series of recent studies with genetic models of cystinuria reported that hyper-excretion of cysteine was observed in the mice with 2 mutant copies of *Slc3a1*, but not in the mice with one mutant copy [15]. In contrast, elevated excretion of cysteine was reported both in homozygous and heterozygous *Slc7a9* knockout mice, although the amount of excreted amino acid was larger in the homozygotes [16]. This obviously indicates that the contribution of either gene in the phenotype of cystinuria may be differential. Likewise, we assume that various mutant sites within a gene may differentially determine the functional defect of final product protein, whereas the systematic approach to uncover the genotype-phenotype association using genotype database in human subjects has not been reported yet. As the treatment of cystinuria is still unsatisfactory [7], and up to 70% of patients with cystinuria eventually develop chronic kidney disease [9,17], a special concern should be given to the early identification of high risk individuals, who are unlikely to response to conventional managements, such as lifestyle modification and urine alkalization. In this context, we propose that the genetic counseling for the suspected or even biochemically diagnosed patients with cystinuria may help the risk stratification of kidney function decline.

The sequencing of non-coding intronic regions of *SLC3A1* and *SLC7A9* genes remains to be determined. Despite approximately 400 mutations in either *SLC3A1* or *SLC7A9* gene so far reported, 5% of cases identify only one mutant allele or even fail to identify the mutation [3,9,14,17]. Although we did not confirm the pathogenic role of the mutations in non-coding regions, it is expected that the prevalent adoption of whole genome sequencing may facilitate the answer to the cases with previously unclear genetic etiology.

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■ 신중투어_ 변비가 자주 발생하는 환자, 장관협착증환자, 소화관궤양환자
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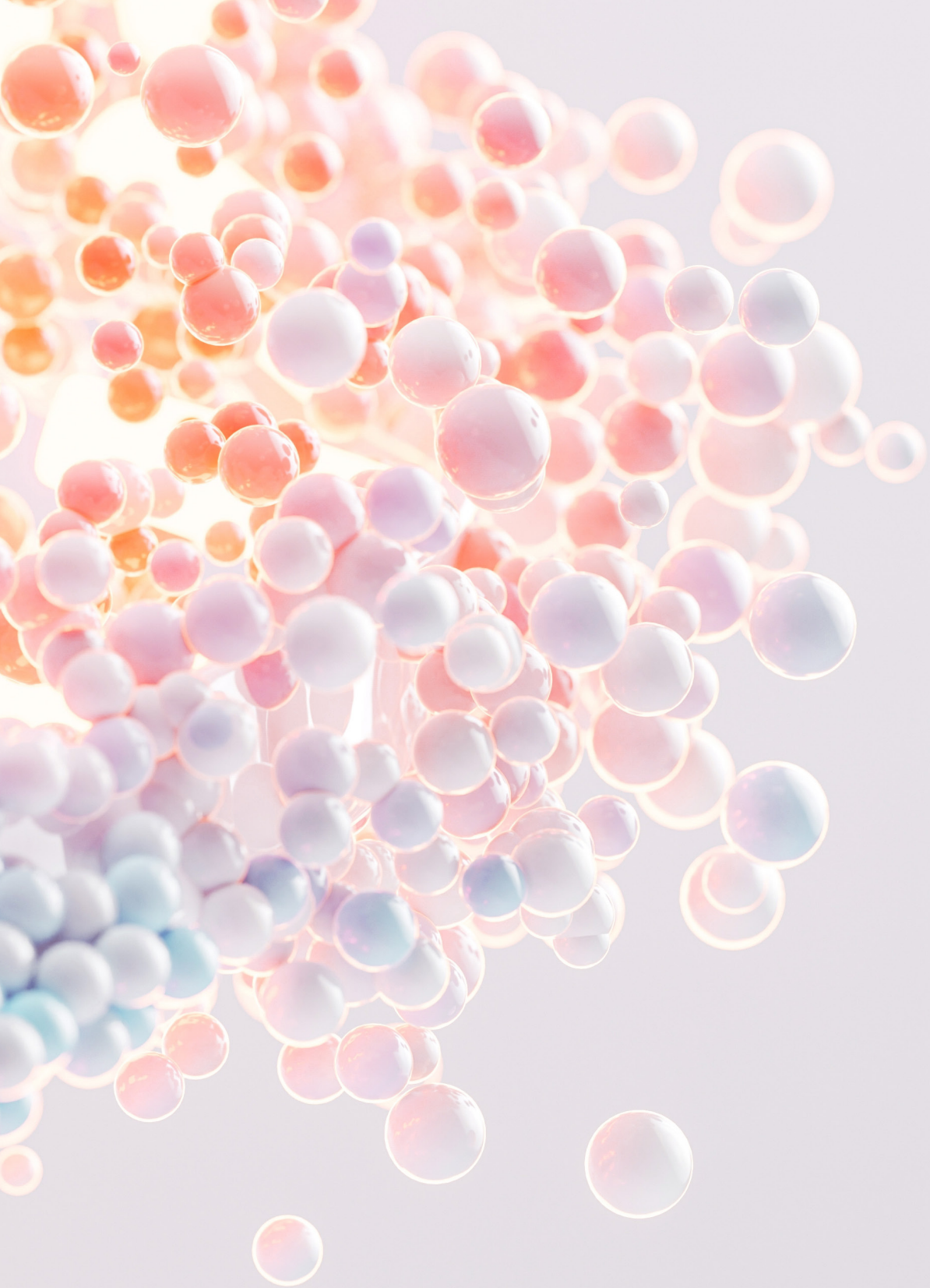

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