Identification of osteopontin as a urinary biomarker for autosomal dominant polycystic kidney disease progression

PKD patients and the level of extracellular OPN secretion were decreased, the levels of OPN in urine were tested by ELISA. The levels of OPN were significantly lower in the urine of ADPKD patients than in that of normal individuals, demonstrating the potential for the use of OPN as a biomarker for the diagnosis of ADPKD (Fig. 4A).

In addition, we selected only subjects with estimated glomerular filtration rates (eGFRs) of >60 mL/min/1.73 m² to determine the ability of using OPN level to diagnose disease progression in early stages. Patients with ADPKD were divided into two groups according to the Mayo classification (class 1A–1E): a rapid progressor group (n = 11) in which disease was classified as class 1C–1E and a slow progressor group (n = 11) in which disease was classified as class 1A–1B [22] (Table 1). The protein levels of OPN in the urine were significantly lower in the rapid progressor group than in the slow progressor group (mean ± standard deviation, 0.1217 ± 0.06629 μg/mg creatinine; p = 0.03) (Fig. 4B). This demonstrates the potential for the use of OPN as a urinary biomarker to predict the severity of ADPKD progression.

Discussion

The diagnosis of ADPKD and the prediction of its progression remain difficult. Identification of biomarkers that...
Aims and Scope

*Kidney Research and Clinical Practice* (KRCP; formerly The Korean Journal of Nephrology; ISSN 1975-9460, launched in 1982), the official journal of the Korean Society of Nephrology, is an international, peer-reviewed journal published in English. Its ISO abbreviation is *Kidney Res Clin Pract*.

The journal considers articles on all aspects of nephrology and hypertension as well as molecular genetics, anatomy, pathology, physiology, pharmacology, and immunology related to kidney disease. In particular, the journal focuses on translational renal research that helps bridging laboratory discovery with the diagnosis and treatment of human kidney disease. The journal publishes the topics covered basic science with possible clinical applicability and the papers on the pathophysiological basis of the kidney disease. Original studies from areas of diagnostic and interventional nephrology or dialysis access are also welcomed. Major article types considered for publication include original research and reviews on current topics of interest.

To provide an efficient venue for dissemination of knowledge and discussion of topics related to basic research, translational study and clinical practice in nephrology, the journal offers online only open access, in which all published articles are free for everyone to read and download.

The journal is currently indexed in Science Citation Index Expanded (SCIE), Scopus, ScienceDirect, PubMed, PubMed Central (PMC), Directory of Open Access Journals (DOAJ), DOI/Crossref, Google Scholar, KoMCI, KoreaMed, ScienceCentral, CAS, Current Content Clinical Medicine and Essential Science Indicators.

This journal was supported by the Korean Federation of Science and Technology Societies Grant funded by the Korean Government (Ministry of Education).

Open Access

Every peer-reviewed research article in this journal is freely available via our website ([https://www.krcp-ksn.org](https://www.krcp-ksn.org)). Articles published in KRCP are distributed under the terms of the Creative Commons Attribution Non-Commercial and No Derivatives License ([https://creativecommons.org/licenses/by-nc-nd/4.0/](https://creativecommons.org/licenses/by-nc-nd/4.0/)), which permits unrestricted non-commercial use, distribution of the material without any modifications, and reproduction in any medium, provided the original works properly cited. ANY USE of the open access version of this Journal in whole or in part must include the customary bibliographic citation, including author and publisher attribution, date, article title, *Kidney Research and Clinical Practice* (Kidney Res Clin Pract), and the URL [https://www.krcp-ksn.org](https://www.krcp-ksn.org) and MUST include a copy of the copyright notice. If an original work is subsequently reproduced or disseminated not in its entirety but only in part or as a derivative work this must be clearly indicated. For any commercial use of material from the open access version of the journal, permission MUST be obtained from KRCP. If necessary, please contact the Editorial Board through our editorial office (registry@ksn.or.kr). Proprietary rights notice for KRCP online were available at: [https://www.krcp-ksn.org/authors/permission.php](https://www.krcp-ksn.org/authors/permission.php).

Publisher The Korean Society of Nephrology
Editor-in-chief Tae-Hyun Yoo, MD., PhD

Editorial office
The Korean Society of Nephrology
#301, (Miseung Bldg.) 23, Apgujenog-ro 30-gil, Gangnam-gu, Seoul 06022, Korea
Tel: +82-2-3486-8736  Fax: +82-2-3486-8737  E-mail: registry@ksn.or.kr

Publishing office
M2PI
8th FL, DreamTower, 66 Seongsui-ro, Seongdong-gu, Seoul 04784, Korea
Tel: +82-2-6966-4930  Fax: +82-2-6966-4945  E-mail: support@m2-pi.com

Published on November 30, 2022

Editorials
637  A troubled mind troubles the kidney: a brain-to-kidney axis?
Keun You Kim, Eosu Kim

640  The effects of nitric oxide and 8-iso-prostaglandin F2α on chloride absorption in cortical thick ascending limb
Tae-Hwan Kwon

Review Articles
644  Healthy aging and chronic kidney disease
Reshma Aziz Merchant, Anantharaman Vathsala

657  Nutrition and quality of life in chronic kidney disease patients: a practical approach for salt restriction
Kunitoshi Iseki

670  Why should we focus on high-volume hemodiafiltration?
Sug-Kyun Shin, Young-II Jo

682  Advances in the management of diabetic kidney disease: beyond sodium-glucose co-transporter 2 inhibitors
Anthony T. P. Chan, Sydney C. W. Tang

Original Articles
699  Nitric oxide–inhibited chloride transport in cortical thick ascending limbs is reversed by 8–iso-prostaglandin–F2α
Pablo D. Cobral, Guillermo B. Silva, Sandra T. Baigorria, Luis I. Juncos, Ebenezer I. O. Ajayi, Néstor H. García

707  Clinical relevance of postoperative proteinuria for prediction of early renal outcomes after kidney transplantation
Junseok Jun, Kyungho Park, Hyun Suk Lee, Kyo Won Lee, Jung Eun Lee, Joe Berm Park, Kyunga Kim, Wooseong Huh, Yoon-Goo Kim, Dae Joong Kim, Hye Ryoun Jang

717  Hospital mortality and prognostic factors in critically ill patients with acute kidney injury and cancer undergoing continuous renal replacement therapy
Da Woon Kim, Geum Suk Jang, Kyoung Suk Jung, Hyuk Jae Jung, Hya Jin Kim, Harin Rhee, Eun Young Seong, Sang Heon Song
Identification of osteopontin as a urinary biomarker for autosomal dominant polycystic kidney disease progression

Hyunsuk Kim, Jinmo Sung, Ju Young Bae, Poongyeon Lee, Yun Kyu Oh, Hyunho Kim

Association of sarcopenia and its components with clinical outcomes in patients undergoing peritoneal dialysis

Seok Hui Kang, A Young Kim, Jun Young Do

Associations among Alzheimer disease, depressive disorder, and risk of end-stage kidney disease in elderly people

Shin Chan Kang, Hee Byung Koh, Hyung Woo Kim, Young Su Joo, Seung Hyeok Han, Tae-Hyun Yoo, Shin-Wook Kang, Jung Tak Park

Correspondence

Successful provision of hemodialysis to patients with confirmed COVID–19 in Korea: the role of a cooperative network between public and private medical systems

Ji-Young Choi, Jeong-Hoon Lim, Seungryeup Han, Seung-Chan Park, Hee-Yeon Jung, Jang-Hee Cho, Chah-Duck Kim, Yang-Lim Kim, Sun-Hee Park

Treatment of acute tacrolimus toxicity with phenytoin after Paxlovid (nirmatrelvir/ritonavir) administration in a kidney transplant recipient

Eun-Jeong Kwon, Gi-Ae Yun, Seokwoo Park, Sejoong Kim, Dong-Wan Chae, Hyung Sub Park, Taeseung Lee, Jong Cheol Jeong

The image on the front cover: Kim et al reported the osteopontin as a urinary biomarker for autosomal polycystic kidney disease progression. Osteopontin expression is reduced in PKD2−/− porcine fibroblasts. Please see the text for more details (pp. 730–740).
Dementia and depression are among the so-called 3Ds (dementia, depression, and delirium), which are most frequently encountered in geriatric psychiatry [1]. A recent report by Kang et al. [2] has shown that older adults (aged >60 years) with Alzheimer dementia (AD) or depression have increased risk of end-stage kidney disease (ESKD) by 67% and 44%, respectively [2]. These figures seem to go beyond the common expectation that aging-associated illnesses are more likely to coexist.

It is recognizable that impaired renal function can increase the risk to brain health in various ways. Chronic kidney disease (CKD) has been associated with increased risk of depression, anxiety, and cognitive decline [3]. However, the opposite relationship has not been studied well. A recent study of Kang et al. [2] highlights the topic by supporting the existence of a brain-to-kidney axis [4]. This concept has been proposed based on findings that acute brain injuries from trauma or ischemic or hemorrhagic stroke coincide with acute kidney injury [5]. However, it is unknown which factors could be involved in such long-term crosstalk between depression, dementia, and ESKD. First, any factors that mediate brain and kidney function could mediate the relationship bidirectionally (Fig. 1A). For instance, humoral factors such as proinflammatory cytokines can arise from pathological conditions of either of the two organs and affect the other. Indeed, depression and AD have long been associated with systemic as well as neuronal inflammation [6,7]. Second, metabolic conditions such as hypertension, diabetes, and hypercholesterolemia may contribute to the link since they cause vascular dysfunction (Fig. 1B); not only vascular dementia but also AD have been related to vascular pathology. Vascular dysfunction has also been regarded as an important depressogenic factor, especially in elderly depression, which prompted the term, ‘vascular depression’ [8]. The brain and kidney share a common feature of microvasculature, function of which is crucial to their normal operation. This common microvascular pathogenesis might have influenced the brain first (inducing depression or dementia) and then the kidney, resulting in ESKD as a final step. As well as vasculopathy, several adipokines (adiponectin, leptin, and clusterin) and myokines (irisin) could mediate or moderate the relationship between metabolic disease and AD [9–11].
proteins might have the potential to convey or implicate dysfunctions in the kidney as well. Third, attention should be paid to a recent conceptualization of ‘brain-gut-kidney axis’ (Fig. 1C). This may be an extended concept based on the above-mentioned pathways between the brain and kidney, suggesting that the gut microbiome can affect both the brain and kidney through metabolic, immune, and autonomic nervous systems [12, 13].

Future study efforts should aim to elucidate clinical and therapeutic implications of the brain-kidney axis. First, as mentioned above, gut microbiota could be added as a key potential mediator between brain and kidney functions. Second, the long-term influence of antidepressants on kidney function should be reexamined. Third, a prospective study should identify metabolic, immune, or microbiotic factors, which are commonly found in patients who have simultaneous depression/dementia and ESKD/CKD compared to those who have only one. Such studies will provide valuable information on a promising target of intervention with which renal function may be protected in elderly patients with depression or dementia. Given the high prevalence of these conditions in old age, the impact of such intervention would be not insignificant, as suggested by Kang et al. [2].

Conflicts of interest
The author has no conflicts of interest to declare.

Funding
None.

Authors’ contributions
Conceptualization, Project administration, Supervision, Visualization: EK
Validation: KYK
Writing–original draft: KYK, EK
Writing–review & editing: KYK, EK
All authors read and approved the final manuscript.

ORCID
Keun You Kim, https://orcid.org/0000-0001-7192-2828
Eosu Kim, https://orcid.org/0000-0001-9472-9465

Figure 1. Proposed model for a brain-kidney axis. (A) Factors initiated by the brain can affect the kidney and vice versa. For instance, circulating cytokines associated with neuroinflammation can damage the kidney. (B) Common factors may influence both organs but do so sequentially. Hypertension, diabetes, and other metabolic/vascular risk factors may affect the brain first, causing depression or dementia, and then the kidney. (C) The brain-gut-kidney axis [13] involves inflammation, metabolic dysfunction, and sympathetic activation as mediators of brain-kidney crosstalk, and gut microbiota are highly involved in this interplay.
References

The effects of nitric oxide and 8-iso-prostaglandin F2α on chloride absorption in cortical thick ascending limb

Tae-Hwan Kwon

Department of Biochemistry and Cell Biology, Kyungpook National University School of Medicine, Daegu, Republic of Korea

Introduction

In this issue of Kidney Research and Clinical Practice, Cabral et al. [1] studied the effects of nitric oxide (NO) on chloride absorption (J Cl) in the isolated perfused cortical thick ascending limb (cTAL) of rabbit kidneys. They also examined the effects of 8-iso-prostaglandin F2α (8-iso-PGF2α), an isoprostane produced by the nonenzymatic peroxidation of arachidonic acid in membrane phospholipids, on J Cl in the presence of NO donor treatment. They concluded that 1) NO significantly decreases J Cl in the cTAL, which is reversed by 8-iso-PGF2α; 2) 8-iso-PGF2α stimulates J Cl via a cyclic adenosine 3’5’-monophosphate (cAMP)-dependent mechanism despite the presence of NO donor treatment; and 3) 8-iso-PGF2α requires protein kinase A (PKA) activity to reverse the NO-induced inhibition of J Cl. The study found that the effects of 8-iso-PGF2α on sodium reabsorption in cTAL prevailed over the natriuretic effects of NO and that activation of PKA was required for such interaction. Thus, it is likely that sodium retention may prevail over sodium excretion in clinical conditions associated with an increased 8-iso-PGF2α level in plasma and urine, such as several chronic inflammatory and metabolic diseases, including coronary heart disease, hypertension, diabetes mellitus, obesity, hypercholesterolemia, and non-alcoholic fatty liver disease.

Expression of sodium (co)transporters in renal tubule

Renal tubular sodium and water reabsorption depend on active sodium transport through sodium transporters and osmotic water transport through aquaporins expressed in the renal tubular epithelial cells [2,3]. The proximal tubule reabsorbs the majority of the filtered sodium and water through glomerular ultrafiltration. The electrochemical gradient driving the reabsorption is generated by the pumping function of the sodium-potassium adenosine triphosphatase (Na/K-ATPase). The Na/K-ATPase is expressed basolaterally in all renal tubular segments, where it pumps three Na+ ions out of the cells and two K+ ions into the cells. In the proximal tubule, sodium is reabsorbed through the apically expressed Na/H exchanger (Na/H exchanger type 3 [NHE3]; solute carrier family 9, isoform A3 [SLC9A3]) and basolaterally expressed Na/K-ATPase and Na-HCO3 cotransporter (electrogenic NBC1 encoded by the gene SLC4A4). The sodium-glucose cotransporters...
(SGLT-2; SLC5A2) and type II Na-Pi cotransporters (NaPi-2; mainly NPT2a [SLC34A1] and NPT2c [SLC34A3]) are also expressed apically in the proximal tubule and play a role in sodium reabsorption, in addition to glucose or phosphate transport, respectively.

Establishing and maintaining a hyperosmotic medullary interstitium is a prerequisite to urine concentration. The loop of Henle generates a high medullary osmolality by driving countercurrent multiplication, which is mediated by active NaCl reabsorption (Fig. 1). In the medullary thick ascending limb (mTAL), the apically expressed Na-K-2Cl cotransporter (NKCC2; rat type 1 bumetanide-sensitive cotransporter [BSC-1]; solute carrier family 12 member 1 [SLC12A1]) and NHE3, as well as basolaterally expressed Na/K-ATPase, are the components mediating sodium reabsorption. In addition, the apical potassium channel (Kir 1.1 or renal outer medullary potassium channel) and basolateral chloride channels (ClC-kb) also play a role in the reabsorption of sodium and chloride in the mTAL. Urinary dilution in the tubular lumen is further mediated by NaCl absorption in the cTAL and distal convoluted tubule (DCT). Micropuncture studies have shown that the DCT receives approximately 4% to 20% of the filtered sodium, of which it reabsorbs approximately 80% to 90%, primarily mediated by the sodium-chloride cotransporter (NCC, thiazide-sensitive cotransporter [TSC], solute carrier family 12 member A3 [SLC12A3]). The following collecting duct (CD) is the renal tubular segment for the fine regulation of sodium reabsorption and excretion into the urine, where the epithelial sodium channel (ENaC) and Na/K-ATPase are involved. ENaC is apically expressed in the late DCT, connecting tubule, and CD in the kidney tubule, where the regulation of ENaC controls extracellular fluid (ECF) volume and blood pressure.

**Regulation of sodium (co)transporters**

The regulation of renal sodium transporters is importantly involved in controlling sodium balance and ECF volume [2]. The NHE3 mediates a major fraction of the transcellular sodium and bicarbonate reabsorption. The proximal convoluted tubules from NHE3-deficient mice exhibited a significant reduction in fluid and HCO₃⁻ reabsorption by 69% and 61%, respectively. The findings indicate that NHE3 is importantly involved in sodium, fluid, and bicarbonate reabsorption in the proximal tubule. NKCC2 expression in the TAL plays a significant role in the urinary concentration mechanism. An increase in the delivery of NaCl to the loop of Henle by chronic oral saline loading or vasopressin treatment upregulates NKCC2 expression. In contrast, hypercalciemia or hypokalemia is associated with decreased NKCC2 expression associated with polyuria. Since the vasopressin V2 receptor is coupled with the activation of adenylyl cyclase, vasopressin-induced upregulation of NKCC2 is likely to be a result of an elevated intracellular cAMP level. The reduction in the intracellular concentration of chloride activates NKCC2 by phosphorylation, which requires the interaction of WNK3 and SPAK [4]. ENaC is regulated by the

![Figure 1. Main sodium and chloride transporters expressed in the thick ascending limb (TAL).](image-url)

CIC-kb, chloride channel kb; NHE3, Na-H exchanger type 3; NKCC2, Na-K-2Cl cotransporter; ROMK, renal outer medullary potassium channel (Kir1.1).
adrenal mineralocorticoid, vasopressin, and insulin, which increase the apical permeability of the CD to sodium. The importance of ENaC in ECF volume regulation has been demonstrated as the basis of the pathogenesis of Liddle’s syndrome as well as type I pseudohypoaldosteronism.

The renin-angiotensin-aldosterone system plays a critical role in the regulation of renal sodium and water metabolism. Aldosterone increases sodium reabsorption in part by increasing the NCC expression in the DCT cells and the α-subunit of the ENaC (α-ENaC) in the CD principal cells. In contrast, the administration of spironolactone, a mineralocorticoid receptor antagonist, substantially decreases the expression of the NCC and the α-ENaC. Moreover, angiotensin II (Ang II) has known effects on the regulation of renal hemodynamics and glomerular filtration rate, as well as direct effects on the renal tubule. Increased NHE3 expression in the proximal tubule brush border and mTAL cells was observed in response to Ang II treatment [5]. Renal sodium transporters play a critical role in renal sodium handling, and dysregulation could be the underlying mechanism for clinical conditions with altered urine concentration and/or deranged renal sodium excretion and ECF volume.

The action of renal nitric oxide on sodium and chloride transport

Renal NO increases the urinary excretion of water and solutes by inhibiting tubular sodium reabsorption [6]. The effects of NO on sodium reabsorption in the proximal tubule are associated with decreased activity of apical Na-H exchange and basolateral Na/K-ATPase. In TAL, as Cabral et al. [1] demonstrated in this issue, exogenous and endogenous NO, acting as an autacoid, decreases sodium and chloride absorption, which could be mediated by the inhibition of NKCC2 and NHE3. Interestingly, a previous study demonstrated the reduced ability of NO to inhibit sodium transport in TAL in Dahl salt-sensitive rats, which might account for the salt sensitivity of blood pressure in this strain [7]. In the CD, NO affects tubular sodium reabsorption by inhibiting amiloride-sensitive ENaC. Accordingly, mice with CD-specific knockout of NO synthase 1 (NOS1) have salt-sensitive hypertension associated with impaired urinary sodium excretion [8]. Nephron-specific disruption of NOS3 in mice also results in hypertension and impaired urinary sodium excretion [9]. In addition, NO inhibits vasopressin-induced osmotic water permeability in the cortical CD. The effects may be due to the cyclic guanosine 3’5’-monophosphate (cGMP)-dependent protein kinase-mediated decrease in vasopressin-stimulated cAMP content [10].

The action of renal 8-iso-prostaglandin-F2α on sodium and chloride transport

Cabral et al. [11] previously demonstrated that 8-iso-PGF2α stimulates sodium and chloride transport in cTAL via a PKA-dependent mechanism. The administration of 8-iso-PGF2α to the lumen of the isolated cTALs increased $J_{\text{Cl}^-}$ by 54%, and adding it to the bath enhanced $J_{\text{Cl}^-}$ by 35%. In contrast, the 8-iso-PGF2α-induced increase in $J_{\text{Cl}^-}$ was significantly diminished by adding furosemide, an inhibitor of NKCC2. Since 8-iso-PGF2α, a product of non-enzymatic peroxidation of arachidonic acid, increases in plasma and urine in disease conditions such as hypertension, chronic kidney disease, and liver cirrhosis, the high levels of 8-iso-PGF2α could contribute to NaCl retention.

Summary

In this issue of *Kidney Research and Clinical Practice*, Cabral et al. [1] further reported that 8-iso-PGF2α could override NO’s natriuretic effects in the cTAL. This finding suggests that sodium retention may prevail over sodium excretion in the renal tubule in clinical conditions, particularly when they are associated with an increased 8-iso-PGF2α level and blunted NO production. Further studies are warranted to elucidate the effects of 8-iso-PGF2α on the phosphorylation and intracellular trafficking of NKCC2 and the expression of other ion transporters expressed in TAL and different renal tubular segments.

Conflicts of interest

The author has no conflicts of interest to declare.

Funding

This work was supported by grants from the Korea Health Technology R&D Project through the Korea Health Indus-
try Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Korea (HI15C0001).

ORCID

Tae-Hwan Kwon, https://orcid.org/0000-0002-1561-6508

References


Healthy aging and chronic kidney disease

Reshma Aziz Merchant1,2, Anantharaman Vathsala2,3

1 Division of Geriatric Medicine, Department of Medicine, National University Hospital, Singapore, Singapore
2 Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore
3 Division of Nephrology, Department of Medicine, National University Hospital, Singapore, Singapore

The world population is aging and the prevalence of noncommunicable diseases such as chronic kidney disease (CKD) will increase significantly. With advances in medical treatment and public health, the human lifespan continues to outpace the health span and the last decade of life is generally spent in poor health. In 2015, the World Health Organization defined healthy aging as ‘the process of developing and maintaining the functional ability that enables wellbeing in older age.’ CKD is increasingly being recognized as a model of accelerated aging and is associated with physical performance decline, cognitive decline, falls and fractures, poor quality of life, loss of appetite, and inflammation. Frailty and dementia are the final pathways and key determinants of disability and mortality independent of underlying disease. CKD, dementia, and frailty share a triangular relationship with synergistic actions and have common risk factors wherein CKD accelerates frailty and dementia through mechanisms such as uremic toxicity, metabolic acidosis and derangements, anorexia and malnutrition, dialysis-related hemodynamic instability, and sleep disturbance. Frailty accelerates glomerular filtration decline as well as dialysis induction in CKD and more than doubles the mortality risk. Anorexia is one of the major causes of protein-energy malnutrition, which is also prevalent in the aging population and warrants screening. Healthcare systems across the world need to have a system in place for the prevention of CKD amongst high-risk older adults, focusing on screening for poor prognostic factors amongst patients with CKD such as frailty, poor appetite, and cognitive impairment and providing necessary person-centered interventions to reverse underlying factors that may contribute to poor outcomes.

Keywords: Anorexia, Chronic kidney disease, Cognitive impairments, Frailty, Healthy aging

Introduction

The world population is aging at an exponential rate and demographic transition will have a major impact on health and social care costs. The lifespan continues to outpace healthspan, resulting in older adults spending their last decade in poor health. In the aging population, the prevalence of noncommunicable diseases such as chronic kidney disease (CKD), cardiovascular disease, diabetes, hyperlipidemia, and neurodegenerative diseases with associated frailty and dementia is expected to increase significantly. By 2040, CKD is projected to be the fifth leading cause of death across the world [1]. The world report on aging and health published by the World Health Organization (WHO) in 2015 defined ‘healthy aging’ as ‘the process of developing and maintaining the functional ability that

Received: May 26, 2022; Revised: June 18, 2022; Accepted: July 3, 2022
Correspondence: Reshma Aziz Merchant
Division of Geriatric Medicine, Department of Medicine, National University Hospital, 1E Kent Ridge Road, Singapore 119228, Singapore.
E-mail: reshmama@nuhs.edu.sg
ORCID: https://orcid.org/0000-0002-9032-0184

Copyright © 2022 by The Korean Society of Nephrology
© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial and No Derivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/) which permits unrestricted non-commercial use, distribution of the material without any modifications, and reproduction in any medium, provided the original works properly cited.
enables wellbeing in older age’ with a particular focus on intrinsic capacities such as sensory impairment, cognition, nutrition, mobility, and depression [2,3]. The trajectory of aging is determined by multiple complex processes, including genetic susceptibility as well lifestyle, chronic diseases, behavioral, environmental, and dietary factors. Frailty and dementia are the main determinants of disability and are associated with increased morbidity and mortality independent of the underlying disease.

The current disease-centric and acute reactive healthcare model is not sustainable in countries with a fast-growing aging population and for conditions like CKD where there is a high prevalence of polypharmacy, multimorbidity, and heterogeneity. The healthcare systems of many countries are moving from a reactive state to a proactive one focusing on preventive care [4]. Redesigning of healthcare care is necessary and the WHO has published guidelines advocating on proactive assessments (e.g., comprehensive geriatric assessment) of individual impairments, slowing the decline in capacity with personalized care plans and providing interventions to improve nutrition and physical exercise and referrals to specialists for those with impairments [3,5].

With aging, the kidney undergoes functional and structural changes. Microscopic changes include glomerulosclerosis, interstitial fibrosis, thickening of the glomerular basement membrane, arteriosclerosis and tubular atrophy with a consequent decline in renal mass, glomerular filtration, and autoregulatory function [6]. In addition to the reduced functional reserve, chronic diseases such as diabetes, nephrotic polypharmacy, and sepsis are more prevalent in this group, and—together with underlying physiological changes such as a lack of thirst—can increase susceptibility to acute kidney injury [7]. CKD is considered a model of accelerated aging and is associated with a decline in physical performance, cognitive decline, fatigue, falls and fractures, poor quality of life (QoL), loss of appetite, and inflammation [8]. The term ‘senescent nephropathy’ is used to describe the synergistic decline in renal and physical function and is thought to be caused by increased inflammation in both aging and CKD [9]. While low-grade inflammation is not uncommon in aging, inflammation in CKD can be caused by dialysis-related factors (biocompatible membranes, dialysate [e.g., endotoxins], vascular access [e.g., prosthetic arteriovenous grafts/catheters], uremic toxicity, volume overload, subclinical infections, and alterations in the gut microbiome) [10]. Early identification of frailty and cognitive impairment in older patients with CKD will guide risk stratification and, when accompanied by personalized interventions, may promote aging free from disability as well as better self-rated health.

**Frailty, cognitive impairment, and chronic kidney disease**

There is a triangular relationship between dementia/cognitive impairment, frailty, and CKD with aging (Fig. 1) [11,12]. The common pathophysiology and risk factors include comorbidities that often coexist in older adults, vascular risk factors such as arteriosclerosis, physical inactivity, inflammation, mitochondrial dysfunction, nutrition, depression, and impairments of the senses such as vision and hearing. Management of extrarenal complications such as frailty and cognitive impairment is a rapidly developing area in nephrology and there is lack of consensus on screening, interventions, and intended outcomes. Frailty is a dynamic, multidimensional state affecting multiple physiological systems that increases vulnerability to stressors, resulting in functional decline, falls, and increased morbidity and mortality rates [13]. The prevalence of frailty and pre-frailty in older adults worldwide varies from 43%–60% to 78% in hemodialysis (HD) patients [14]. It is an independent marker for diabetes and declines in kidney function and cognition [12,15–19]. The prevalence of frailty in pre-dialysis patients is as high as 43% and they are 2.5 times more likely to die or to begin dialysis [9,12]. Frailty may be reversible, especially before the onset of disability, with targeted interventions such as nutrition, exercise, polypharmacy, and oral health management [16,20]. However, despite its poor outcomes, frailty screening has not been incorporated into routine care by nephrologists.

Albuminuria and CKD serve as complimentary risk factors for cognitive decline. Risk factors for cognitive decline can broadly be divided into three main groups: traditional risk factors applicable to older adults in general; dialysis-related factors; and nontraditional risk factors such as malnutrition, anemia, and inflammation [12,21].

There is a significant symptom burden among patients with CKD, some of which could be attributed to frailty and cognitive impairment, which is not often assessed in a clinical setting. In patients with CKD stage 4 to 5 managed
without dialysis, weakness was found in 75%, poor mobility in 75%, poor appetite in 58%, pain in 56%, pruritus in 56%, and dyspnea in 49% [22].

Frailty and chronic kidney disease

A low estimated glomerular filtration rate (eGFR) is associated with a greater risk of frailty, and frail patients with CKD do much worse. In pre-dialysis patients, frailty is associated with a faster decline in eGFR, accelerated dialysis initiation, poor QoL, and increased mortality [9]. In dialysis patients, frailty is associated with increased risk of falls, readmission to the hospital, and more than double odds of mortality in 1 year [9,23]. Decreased energy and food intake with declining eGFR, in addition to other factors like metabolic acidosis, uremia, dialysis-related catabolism, hospital admissions, and metabolic derangement, contributes to sarcopenia and physical frailty (Fig. 1) [13,24]. Sarcopenia is a component of physical frailty defined as a progressive loss of skeletal muscle mass, quality and strength that is highly prevalent in CKD and has recently been shown to be associated with intradialytic hypotension in addition to other adverse outcomes such as mortality [25].

The operational definition of frailty is based on two principal concepts: the Fried Phenotype Model of Physical Frailty and the Cumulative Deficit Model of Frailty. The Fried Phenotype Model of Physical Frailty was validated in the Cardiovascular Health Study and is based on quantification, which requires measurements such as gait speed, handgrip strength, and physical activity in addition to weight loss and exhaustion [26]. The fatigue, resistance, ambulation, illnesses, and loss of weight (FRAIL) scale is based on a similar concept but relies on self-reported questionnaire responses pertaining to items such as fatigue, difficulty walking one block of 50 m, difficulty climbing a flight of stairs, weight loss and ≥5 illnesses [27,28]. The Rockwood Mitnitsky Frailty Index is a 70-item multi-domain frailty phenotype based on self-reported data initially validated in the Canadian study of health and aging that determines deficits in functional, cognitive, and social domains. The number of domains can be simplified and frailty is measured based on a ratio of the number of health deficits present over the number of health deficits measured [29]. The common physical function and frailty assessment tools are listed in Table 1 [3,9,26,27,29–36].

The short physical performance battery test covers three domains: balance, gait speed, and sit-to-stand. The test has been shown to be associated with disease progression and increased mortality [9]. Gait speed alone has been shown to correlate with frailty and predict cognitive impairment,
hospitalization, and mortality [30,37]. van Loon et al. [14] compared various frailty screening tools, including the Fried Frailty Phenotype, Groningen Frailty Indicator, Geriatric 8, the Identification of Seniors at Risk and the Hospital Safety Program, where the sensitivity ranged from 48% (Fried Frailty Phenotype) to 88% (Geriatric 8). Anderson et al. [38] compared the Frailty Index, Frailty Phenotype, Edmonton Frail Scale, and Clinical Frailty Scale in HD patients and found that agreement between different frailty tools was weak and the tools themselves were not interchangeable. The selection of an optimal frailty screening tool requires the balance between utility in decision-making, interventions or outcomes intended and ease of administration.

**Cognitive impairment and chronic kidney disease**

The presence of cognitive impairment in patients with CKD was first described by Dr. Thomas Addison in 1839 and, despite its significant association with poor treatment compliance, decision-making, readmissions, worsening kidney function, falls, and mortality, screening for cognitive impairment is not routinely conducted in the nephrology clinic [39]. More than half of HD patients with cognitive impairment are nonadherent to their medications [40]. It is estimated that every 10 mL/min/1.73 m² decrease in

<table>
<thead>
<tr>
<th>Table 1. Physical function and frailty assessment tools</th>
<th>Description</th>
<th>Estimated time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical function assessment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short physical performance battery test [31]</td>
<td>Measures the functional performance of the lower extremities using a set of 3 static balance tests, gait speed, and five times sit-to-stand test</td>
<td>≤10</td>
</tr>
<tr>
<td>Gait speed (4, 6, or 10 m or 6 min)</td>
<td>Gait speed can be measured for 4, 6, or 10 m or 6 min. The 6-min gait test assesses endurance and aerobic capacity. Gait speed is also highly correlated with cognitive function [30,32]. Most sarcopenia guidelines use &lt; 1 m/sec as a cutoff [33].</td>
<td>≤5</td>
</tr>
<tr>
<td>Sit-to-stand (5 repetitions)</td>
<td>The time required to rise from the chair repeatedly 5 times. The measure of lower limb power and the ability to stand up after a fall. The cutoff for possible sarcopenia is ≥12 sec [33] and that for mobility limitation (ICOPE WHO) is &gt;14 sec [3].</td>
<td>≤5</td>
</tr>
<tr>
<td>Timed up and go [34]</td>
<td>Participants need to stand up from a chair unassisted, walk 3 m, turn, walk back to the chair, and sit down. The test is used as a screening tool for falls and mobility.</td>
<td>≤5</td>
</tr>
<tr>
<td><strong>Frailty assessment tool</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRAIL scale [27]</td>
<td>5-item scale assessing fatigue, resistance, ambulation, ≥5 illnesses, and loss of weight</td>
<td>≤5</td>
</tr>
<tr>
<td>Clinical Frailty Scale [35]</td>
<td>9-Point scale ranging from very fit to severely frail to terminally ill</td>
<td>≤5</td>
</tr>
<tr>
<td>Fried's Frailty Phenotype Scale [26]</td>
<td>5-item scale (requires physical measurement) assessing muscle strength, walking speed, physical activity, weight loss, and exhaustion</td>
<td>5–10</td>
</tr>
<tr>
<td>Rockwood Mitnitsky Frailty Index [29]</td>
<td>Cumulative deficits (pre-determined list)</td>
<td>20–30</td>
</tr>
<tr>
<td>Groningen Frailty Indicator [9]</td>
<td>Includes 15 questions across 8 domains covering mobility, vision, hearing, nutrition, comorbidity, cognition, psychosocial, and physical fitness. The test has limited sensitivity, especially for physical fitness.</td>
<td>≤10</td>
</tr>
<tr>
<td>Edmonton Frail Scale [36]</td>
<td>Based on the following 9 components: cognition, general health, functional independence, social support, medication use, nutrition, mood, continence, and functional performance</td>
<td>≤10</td>
</tr>
</tbody>
</table>

FRAIL scale, the fatigue, resistance, ambulation, illnesses, and loss of weight scale. ICOPE, Integrated Care for Older People; WHO, World Health Organization.
eGFR is associated with an 11% increase in cognitive impairment prevalence amongst those aged >55 years. There is a rapid decline in cognition for those with eGFR of <30 mL/min/1.73 m², where more than three quarters of those undergoing dialysis and up to 2/3 of pre-dialysis patients may have underlying cognitive impairment [32,39]. The initiation of dialysis can cause a stepwise decline in cognition, especially executive function [41]. Lacunar infarcts, white matter disease, and cerebrovascular disease are also common in CKD patients, especially those on dialysis, and intradialytic hemodynamic disturbances can precipitate cerebral ischemia with a cumulative impact on cognitive function [42]. Other factors often overlooked include sleep disturbance due to obstructive sleep apnea or restless leg syndrome, depression, anemia, and nutrient deficiencies [43]. While kidney transplantation is the gold standard for improvement in cognition in those with end-stage kidney disease, peritoneal dialysis (PD) also appears to be ‘protective’ in some studies [44].

There is still an ongoing debate about which is the best practical test to assess cognitive impairment in patients with CKD. Similar to frailty, the choice of test is dependent on its utility, time taken, threshold for intervention, and intended outcome overall. Cognitive tests (Table 2) [39,45–52] can vary from neuropsychological assessment, which takes >60 minutes in some patients and is costly to perform, to brief methods of triage, such as a single screening question or the Rapid Cognitive Screen or Mini-Cog exam [45]. Multidomain screening methods, such as the Mini-Mental State Examination and the Montreal Cognitive Assessment (which takes up to 15 minutes) are frequently used in clinical practice [39,46,47]. There are many interventions that can improve or slow down cognitive decline, requiring further validation in larger CKD populations while considering aspects such as cooled dialysis, type of dialysis, renal transplantation, anemia correction, supplements, nutrition, and exercise [39].

### Table 2. Cognition assessment tools

<table>
<thead>
<tr>
<th>Tool</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Triage tool</strong></td>
<td></td>
</tr>
<tr>
<td>Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [47,48]</td>
<td>26-item structured informant questionnaire. The final score is based on the ratio of total scores (26–130 points) over the total number of completed items (1–5). It is available in multiple language translations (<a href="https://nceph.anu.edu.au/research/tools-resources/informant-questionnaire-cognitive-decline-elderly">https://nceph.anu.edu.au/research/tools-resources/informant-questionnaire-cognitive-decline-elderly</a>).</td>
</tr>
<tr>
<td>Mini-Cog [49]</td>
<td>Includes 3-item recall and clock-drawing (visuospatial).</td>
</tr>
<tr>
<td>Rapid Cognitive Screen [45]</td>
<td>Includes the following three items from the Veterans Affairs SLUMS examination: i) recall of five words (testing recall), ii) a clock-drawing test (testing visuospatial function), and iii) the ability to remember a story and convert the fact (testing insight and executive function).</td>
</tr>
<tr>
<td>Abbreviated Mental Test Score [50]</td>
<td>10-item assessment. The test is easy to administer in the ambulatory care setting.</td>
</tr>
<tr>
<td><strong>Multidomain screening tool</strong></td>
<td></td>
</tr>
<tr>
<td>Mini-Mental State Examination [39,51]</td>
<td>30-Point assessment. The test evaluates attention and orientation, registration, recall, memory, calculation, language, and ability to draw a complex polygon.</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment [39,46]</td>
<td>30-Point assessment. The test evaluates short-term memory, visuospatial ability, executive function, attention, concentration and working memory, language, and orientation. It is available in multiple language translations (<a href="https://www.mocatest.org/about/">https://www.mocatest.org/about/</a>).</td>
</tr>
<tr>
<td><strong>Multidomain formal assessment</strong></td>
<td></td>
</tr>
<tr>
<td>Neuropsychological battery</td>
<td>Often conducted by psychologist within an acute setting. The test takes &gt; 60 min and is useful for the diagnosis of dementia and/or amnestic mild cognitive impairment.</td>
</tr>
</tbody>
</table>
Anorexia of aging and chronic kidney disease

Anorexia of aging (AA) is defined as a reduced desire to eat or a loss of appetite in older adults, which is associated with weight loss, frailty, sarcopenia, hospitalization, disability, and mortality. The decrease in appetite may affect food intake and/or type of food intake, affecting overall energy intake and causing a loss of weight, which in turn is a precursor of frailty and loss of muscle mass. AA can be caused by the dysfunctional release of hormones (e.g., cholecystokinin, ghrelin, leptin), which also occurs in CKD, underlying diseases and polypharmacy, a decline in physical or mental health (including depression and dementia), a decrease in fundal compliance, poor oral health, xerostomia, and social factors such as loneliness (Fig. 2) [53,54]. In addition to the above factors, causes of anorexia in patients with CKD with/without dialysis can include a low acylghrelin level, high leptin concentration, proinflammatory cytokines, metabolic acidosis, uremic toxins, changes in gut microbiomes, dialysis-related factors such as fatigue, nausea, vomiting, impaired gastric emptying and bloating, metabolic derangement, and altered taste perception [55–57]. The combination of anorexia and dietary restrictions not personalized to age, function, culture, comorbidities, or goals of treatment in the background of inflammation are major causes of protein-energy malnutrition (PEM) in CKD.

The commonly used tools in studies and clinical practice for the evaluation of anorexia or loss of appetite are listed in Table 3 [58–64]. The Simplified Nutrition Assessment Questionnaire (SNAQ) is a simplified version of the Council on Nutrition Appetite Questionnaire that is simple to use, has been validated worldwide and was shown to be associated with depression, number of medications, poor self-rated health, and eating alone [59,60,65]. The prevalence of AA is 12% to 70% depending on the tools used and the participants studied. Among patients with CKD, the prevalence of anorexia is between 35% and 50%, and it is significantly associated with increasing age, poor QoL, and mortality [66,67].

Person-centered care in older patients with chronic kidney disease

With growth of the aging population, the number of older patients with CKD will continue to increase. The aging

---

**Figure 2. Causes of anorexia associated with aging or due to CKD.**

CCK, cholecystokinin; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HD, hemodialysis; PYY, peptide YY.
Table 3. Appetite assessment tools

<table>
<thead>
<tr>
<th>Tool</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>The Council on Nutrition Appetite Questionnaire (CNAQ) [60]</td>
<td>Contains 8 questions related to appetite, food intake, satiety, and number of meals consumed per day derived from the AHSPQ. The total appetite score ranges from 8 (worst appetite) to 40 points (best appetite).</td>
</tr>
<tr>
<td>The Simplified Nutrition Assessment Questionnaire (SNAQ) [60]</td>
<td>Contains four questions related to appetite, food intake, satiety, and number of meals consumed per day. A total score of ≤14 points indicates a significant risk of ≥5% weight loss in the next 6 months.</td>
</tr>
<tr>
<td>Appetite and Diet Assessment Tool (ADAT) [61]</td>
<td>44-item self-administered questionnaire divided into three sections about appetite and eating habits in general, on dialysis, and on non-dialysis days, respectively. It takes 10 min to complete.</td>
</tr>
<tr>
<td>Self-assessment of appetite changes [58]</td>
<td>Compares present appetite vs. appetite over the last month (increased, decreased, or unchanged).</td>
</tr>
<tr>
<td>Subjective assessment of appetite [58]</td>
<td>Compares present appetite vs. appetite last week (increased, decreased, or unchanged). The test was adapted from the ADAT.</td>
</tr>
<tr>
<td>Visual analogue scale (VAS) [62]</td>
<td>Determines present appetite indicated with a line on a scale (scale extremities: 0 mm, ‘no hunger’; 100 mm, ‘hunger’). The scale is a quantitative measure of appetite. Scoring: &gt;50 mm, good appetite</td>
</tr>
<tr>
<td>FAACT-ESSEN score (based on a subset of the FAACT, in particular the AC/S) [63]</td>
<td>12 Questions related to appetite and food intake, each of which allows for five answers (i.e., not at all, a little bit, somewhat, quite a bit, or very much).</td>
</tr>
<tr>
<td>The Anorexia questionnaire (AQ) [58]</td>
<td>Developed for the diagnosis of anorexia associated with chronic diseases, including CKD and ESRD.</td>
</tr>
<tr>
<td>Appetite and Food Satisfaction Questionnaire (AFSQ) [64]</td>
<td>Assesses the level of appetite using a facial hedonic scale and five other questions adapted from the Buckner and Dwyer tool that assesses some aspects related to food satisfaction.</td>
</tr>
</tbody>
</table>

AC/S, anorexia/cachexia subscale; AHSPQ, Appetite, Hunger and Sensory Perception Questionnaire; CKD, chronic kidney disease; ESRD, end-stage renal disease; FAACT, Functional Assessment of Anorexia/Cachexia Therapy.

CKD population with/without dialysis will have an increased prevalence of loss of appetite, sarcopenia, frailty, cognitive impairment, and PEM, which are all associated with poor outcomes including hospitalization, disability, and mortality [11]. Healthcare systems across the world need to have systems in place for the prevention of CKD amongst high-risk older adults (e.g., diabetics), screening for poor prognostic factors amongst patients with CKD (e.g., frailty, poor appetite, cognitive impairment) and provide necessary interventions to reverse underlying factors that may contribute to poor outcomes.

Screening for frailty and cognitive impairment will enable us to manage patients with CKD better with shared decision-making where treatment options such as dialysis may prolong life but cause significant physical and psychological burdens and poor QoL. In other situations, frailty could be reversed or optimized before kidney transplantation, although this may lead to patients not being put on the transplant list. With limited numbers of geriatricians worldwide, close collaboration between geriatricians and nephrologists is required to implement assessment (e.g., comprehensive geriatric assessment) and interventions. The Rapid Geriatric Assessment tool (Fig. 3), which is available in the Epic electronic health records (https://www.epic.com/about) and as an app to screen for frailty (FRAIL), sarcopenia (SARC-F), AA (SNAQ) and cognition (Rapid Cognitive Screen) with an assisted management pathway, may be useful in centers with limited geriatric resources [45,68]. While several intervention strategies have been shown to be useful, two key approaches that warrant mention include nutrition and exercise training.

Nutrition

The National Kidney Foundation’s Kidney Disease Outcomes Quality Initiative (KDOQI) continues to revise clinical practice guidelines on the management of nutrition based on new evidence and to focus on six key areas: nutritional assessment, medical nutrition therapy, protein and energy intake, nutritional supplementation, micronutrients, and electrolytes [69]. A loss of appetite requires evaluation to exclude treatable or reversible factors based on the mnemonic ‘Meal on Wheels,’ such as medications, emotion (e.g., depression) and alcohol/substance or elder abuse, etc., as shown in Fig. 4.

For protein intake in metabolically stable CKD stage 3 to
5 patients, the KDOQI recommends a low-protein (0.55–0.60 g of dietary protein/kg body weight/day) or very-low-protein (0.28–0.43 g of dietary protein/kg body weight/day) diet with additional keto acid/amino acid analogs to meet protein intake needs. A protein intake of 0.6 to 0.8 g/kg body weight per day is recommended for CKD stage 3 to 5 patients with diabetes. For those on dialysis, regardless of diabetes, a dietary protein intake of 1.0 to 1.2 g/kg body weight per day is recommended [69]. A prescription of energy intake of 25 to 35 kcal/kg body weight per day is recommended in CKD stage 1 to 5D to maintain nutritional status [69]. Oral nutritional solutions in non-dialysis and dialysis patients with CKD have been shown to improve nutrition and inflammation [70,71]. The KDOQI recommends a minimum of a 3-month trial of oral nutritional supplements to improve dietary status in those who failed to respond to dietary counseling to meet nutritional requirements.

**Figure 3. Rapid geriatric assessment with an assisted management pathway.**
FRAIL, fatigue, resistance, ambulation, illnesses, and loss of weight; MCI, mild cognitive impairment; SARC-F, strength, ambulation, rising from a chair, climbing stairs, and falls questionnaire; SNAQ, Simplified Nutrition Assessment Questionnaire.

**Figure 4. Evaluation of loss of appetite in older adults.**
The role of appetite stimulants like megestrol acetate requires further evaluation in larger randomized control trials [72]. As the aging population and those with CKD are very heterogeneous, personalized assessments, which assess psychosocial aspects, environment, comorbidities with associated polypharmacy, frailty, and dementia, are necessary before providing intervention for loss of appetite, malnutrition, and/or PEM. Poor dietary compliance is often caused by contradictory and complicated dietary regimes without taking personal preference into account [73]. For those in a hypercatabolic state, malnourished and/or frail, there should be some flexibility in dietary recommendations.

Exercise

Exercise is considered a poly-pill for primary prevention and a multitude of medical diagnoses, including frailty and dementia, where no cure is available [20]. Older patients with CKD have multimorbidity’s, poor effort tolerance, fatigue, poor QoL, and poor appetite and are at increased risk of social isolation. While renal rehabilitation includes recommendations on diet and water management, pharmacotherapy, education, and psychological support, exercise is a core tenet of renal rehabilitation [74]. Insufficient physical activity increased with disease progression and increasing age in CKD patients [75]. While 34% of CKD stage 1 to 2 patients were physically active, only 11% of CKD stage 5, 6% of HD patients, and 8% of PD patients were physically active in the same study [75]. Physical inactivity is one of the causes of a high symptom burden and leads to a loss of muscle mass and strength with a consequent functional decline, disability, poor QoL, and mortality [76].

Exercise is beneficial in both CKD non-dialysis and CKD dialysis patients, being partially possibly mediated through a muscle-bone crosstalk mechanism [77]. The DOPPS (Dialysis Outcomes and Practice Pattern Study) showed that CKD patients on maintenance HD who participated in aerobic physical activity had better QoL, survival and fewer depression symptoms [78]. Moraes et al. [79] found that 6 months of resistance exercise increased physical function (as assessed by the 36-Item Short Form Survey), plasma concentrations of appetite hormones (acyl-ghrelin), body composition, and nutritional status in HD patients. Intradialytic exercise (Fig. 5) is increasingly encouraged in dialysis centers worldwide as it is associated with increased dialysis efficacy, better QoL, and improved physical function [80,81]. Specific exercises need to be prescribed and must include aerobic, strength, and flexibility exercises performed 2 to 3 days/wk. Each exercise should have ≤2 sets of 12 to 15 reps, and common modalities include cycle ergometer, weights/resistance bands, and static stretching [82].

Systematic reviews on the benefits of exercise in pre-dialysis patients showed that it improved eGFR, blood pressure, body mass index, inflammatory markers, maximal oxygen uptake peak, and QoL [83–85]. A lower decline in glomerular filtration and improvements in muscle strength were reported in a 12-week randomized study combining resistance exercise with a low-protein diet by Castaneda et al. [86]. While there is limited evidence for dual-task exercise in CKD patients, it has been shown to improve gait speed, cognition, pain, and perceived health in at-risk community-dwelling older adults [87].

Future studies

The literature on frailty in older patients with CKD has increased significantly in the last 5 years, but significant gaps remain, which warrants further research. Despite a large number of frailty screening tools, there is still a lack of optimal screening tools in patients with CKD. Most researchers and dialysis centers worldwide are using physical performance tools, such as the sit-to-stand test or the gait speed test, which allow objective comparisons across different time points. Given the reversibility of frailty and pre-frail-
ty in the general population, it remains unclear whether interventions to alter the trajectory of frailty, such as nutrition and exercise, will help to slow CKD progression. Future studies should focus on the role of various different types of intervention in delaying the onset of frailty in pre-dialysis or dialysis patients. There is very little literature on the impact of frequency or dosage of dialysis and reducing HD complications on frailty and cognitive impairment trajectory. Lastly, we do not know if physical activity and nutrition intervention in the peri-dialysis initiation period will have an overall impact on outcomes like mortality and functional decline after the initiation of dialysis.

**Conclusion**

CKD is a model for accelerated aging and is significantly associated with frailty, cognitive impairment, and loss of appetite. Early screening with necessary interventions, such as exercise and nutrition interventions, may help to modify the trajectory of CKD and improve physical function, cognition, and perceived health.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**Authors’ contributions**

Conceptualization: RAM, AV
Writing—original draft: RAM
Writing—review & editing: RAM, AV
All authors read and approved the final manuscript.

**ORCID**

Reshma Aziz Merchant, https://orcid.org/0000-0002-9032-0184
Anantharaman Vathsala, https://orcid.org/0000-0002-4252-8060

**References**


43. Kelly DM, Rothwell PM. Disentangling the relationship between chronic kidney disease and cognitive disorders. Front Neurol


50. Pendlebury ST, Klaus SP, Mather M, de Brito M, Wharton RM. Routine cognitive screening in older patients admitted to acute medicine: abbreviated mental test score (AMTS) and subjective memory complaint versus Montreal Cognitive Assessment and IQCODE. Age Ageing 2015;44:1000–1005.


Nutrition and quality of life in chronic kidney disease patients: a practical approach for salt restriction

Kunitoshi Iseki

1Clinical Research Support Center, Nakamura Clinic, Okinawa, Japan
2Okinawa Dialysis and Transplant Association, Okinawa, Japan
3Okinawa Heart and Renal Association, Okinawa, Japan

The clinical practice guidelines (CPGs) for nutrition in chronic kidney disease (CKD) were updated after 20 years from the previous guidelines by the Kidney Disease Outcomes Quality Initiative (KDOQI). During this period, the severity of CKD was defined by eGFR and albuminuria by the organization Kidney Disease: Improving Global Outcomes (KDIGO). Main risk factors for CKD such as hypertension, hyperlipidemia, obesity, metabolic syndrome, and diabetes mellitus are closely related to lifestyle. Nutritional management is important to prevent and retard the progression of CKD. Members of the International Society of Renal Nutrition and Metabolism (ISRNM) reviewed the KDOQI CPG draft. ISRNM is an international scientific society comprising members of multiple subspecialties. ISRNM proposed the medical term protein-energy wasting (PEW), which is a keyword in renal nutrition. The prevalence of PEW among dialysis patients is high. The success of dietary therapy depends on adherence to the diet. It has to be palatable, otherwise eating habits will not change. To prevent the development and progression of CKD and PEW, regular consultation with an expert dietitian is required, especially regarding salt and protein restriction. Our cluster-randomized trial showed that intervention by a dietitian was effective at retarding the progression of stage 3 CKD. In this review, I focus on salt (sodium) restriction and introduce tips for salt restriction and Japanese kidney-friendly recipes. Due to the lack of randomized controlled trials, nutritional management of CKD inevitably relies on expert opinion. In this regard, well-designed observational studies are needed. Too strict salt restriction may decrease quality of life and result in PEW.

**Keywords:** Chronic kidney disease, Dialysis, Hypertension, Salts, Sodium

**Introduction**

Chronic kidney disease (CKD) is increasing worldwide and is common in the elderly population [1]. It is commonly associated with lifestyle-related conditions such as diabetes mellitus (DM), hypertension, hyperlipidemia, smoking, and obesity. Information regarding lifestyle factors such as smoking, drinking alcohol, exercise, sleep, and eating habits is usually obtained during screening and daily medical practice. Correction of an unhealthy lifestyle often has favorable outcomes. For instance, recovery from metabolic syndrome was associated with a reduced risk of CKD [2]. In addition to pharmacological management, nutritional management is an important strategy in CKD patient care.
The Kidney Disease Outcomes Quality Initiative (KDOQI) clinical guidelines for nutrition in CKD [3] were updated after 20 years from the previous guidelines in 2000 [4]. Severity of CKD was determined using the “heat map” published in 2013 by Kidney Disease: Improving Global Outcomes (KDIGO) [5]. The first draft was finished by 2016 with an extensive review of related references. However, during the review process with stakeholders, there were a lot of questions, comments, and discussion and the final draft was only published four years later in 2020. In Japan, two major scientific associations are involved in CKD patient care: the Japanese Society of Nephrology (JSN) and the Japanese Society for Dialysis Therapy (JSCT). Both these associations work on early detection and prevention of the progression of CKD to end-stage kidney disease (ESKD), which requires dialysis and renal transplantation [6–8].

Salt restriction and protein restriction are two major aspects of nutritional management in CKD patients. However, dietary habits differ by culture, ethnicity, and other socioeconomic conditions as well as individually. Physicians taking care of CKD patients often do not have enough experience and knowledge regarding dietary management. Twenty-four-hour urine sodium excretion does not reflect actual intake as CKD progresses [9]. In chronic hemodialysis (HD) patients, failure of salt (and potassium) restriction is fatal. Therefore, collaboration with dieticians is needed during all stages of CKD. However, there is a paucity of strong evidence based on randomized controlled trials (RCTs) for dietary management in CKD patients, reflecting difficulty in recruiting sufficient patients and the required duration of interventions. Practical approaches may vary with country or district, cultures, stages of CKD, and socioeconomic conditions, but may provide useful knowledge for others concerning nutritional management.

Clinical manifestations of excess salt intake in CKD patients are hypertension, edema, and proteinuria. Regular checks of blood pressure, body weight, and urine tests can help detect CKD at an early stage. Follow-up intervals at the clinic or hospital vary with stage of CKD from every 2 weeks to annually. In this regard, self-check of blood pressure and body weight at home can be helpful. Information technology may help facilitate communication between CKD patients and physicians remotely. This is reflected by the clinical practice point added in the recent KDIGO guidelines of “Think Globally and Act Locally.”

Guidelines and guidance

The KDOQI guidelines recommend limiting sodium intake to less than 100 mmol/day (or <2.3 g/day) sodium or <5.8 g salt to reduce blood pressure and improve volume control in CKD 3 to 5, CKD 5D, or posttransplantation patients. Moreover, in adults with CKD 3 to 5D, restriction of dietary sodium intake has been proposed as an adjunctive lifestyle modification strategy to achieve better volume control and more desirable body weight. Recently, the KDIGO clinical practice guidelines for the management of hypertension in CKD were published [10]. In the top 10 takeaways for clinicians, sodium restriction was ranked number 7. Low sodium (<2 g/day) or salt (<5 g/day) intake and moderate-intensity physical activity (≥150 min/week) were recommended for CKD patients with high blood pressure.

KDOQI guidelines were summarized in the International Society of Renal Nutrition and Metabolism (ISRN) journal [11]. Effective medical nutritional therapy in CKD requires shared goals by all stakeholders including dietitians and other healthcare professionals. Well-designed observational studies and RCTs with nutritional and dietary interventions are needed. ISRN published the consensus statement on “Eating during Hemodialysis Treatment” in 2018 [12].

Dietary habits differ by culture, ethnicity, and other socioeconomic factors. In Japan, the JSN and JSCT have published evidence-based clinical practice guidelines and guidance for CKD patient care [6–8]. The 18th Congress of the ISRN was held in Okinawa, Japan in April 2016. Dietary management in CKD patients was one of the main topics. After this Congress, practical guidelines for salt and protein restriction to retard the progression of CKD to ESKD were summarized with the goal of promoting further collaboration between nephrologists and dietitians [13].

Practical salt restriction

Seven target interventions were identified. Cessation of smoking and maintaining normal body weight as reflected by a body mass index (BMI) of <25 kg/m² were ranked first and second, with salt restriction third [13]. For hypertensive CKD patients, we suggested a salt intake of 3 to 6 g per day. Modification of lifestyle is a difficult and time-consuming process. We recommended at least 30 minutes face-to-face
guidance sessions by a dietician, every 3 months if needed. Unless salt intake is adequately controlled, edema, heart failure, and hypertension can result. We recommended careful estimation of the daily intake of foods and additives. Salt intake may vary with cooking processes, in particular commercial processes.

For salt and protein restriction in individual patients, laboratory and medication data are required. Therefore, collaboration between physicians, nephrologists and/or general physicians, and dieticians is mandatory. After a thorough interview, we start salt and protein restriction separately. We show the participant how to roughly estimate salt content by using the amount of salt per one teaspoon. One teaspoon contains about 6 g of salt. A single-day dietary recall is used to semi-quantitatively estimate the amount of sodium intake. Urine collection for 24 hours to measure sodium excretion is not feasible for the general population. It is difficult to evaluate the amount of sodium in processed foods. When sodium content is expressed as “mg,” salt content should be calculated using the following formula: salt (g) = Na (mg) × 2.54/1,000. One gram of sodium is equal to 43.5 mEq.

Estimating salt content in processed foods is important. A rough estimation of sodium is helpful for daily life. Dietary recall is necessary and may need help from trained interviewers. There is a wide variety of “junk foods” available for purchase. Generally, restaurant food and take-out foods are salt-rich, although this may differ by restaurant or region. Tips on how to evaluate salt content are summarized in Fig. 1. Commonly ordered foods in Japan are hamburgers, curry rice, and ramen. The salt content of hamburgers and curry rice is about 1.6 g and 3.4 g, respectively. One bowl of salt ramen contains more than 10 g of salt. However, salt intake may differ by seasoning and quantity of soup. A list of high salt foods is provided in Fig. 2. Tips to estimate salt content are listed in Fig. 3. Reducing miso soup and pickle consumption is an effective way to reduce dietary salt intake [14]. Soy sauce is common in Japan but contains a lot of salt. Low-salt soy sauce is available, but potassium content is high. This is important for dialysis patients to be aware of. Dashi Wari soy sauce is tasty and has a low potassium content. Therefore, it is recommended for those who require potassium restriction. Fig. 4 summarizes the list of seasoning materials that can help reduce salt intake.

**Figure 1.** Tips for salt restriction when buying cooked foods and eating out. Modified from Iseki and Yamagata [13] according to the Creative Commons License.

1) Ask for low-salt cooking at restaurants
2) Do not drink soup
3) Use separate dishes for dressing or mayonnaise
4) Select foods that are easy to estimate salt intake
5) When eating out, restrict salt more than usual at home

**Figure 2.** List of high salt foods. Modified from Iseki and Yamagata [13] according to the Creative Commons License.

1) Fast foods: burgers, fries, chicken fingers, and pizza
2) Salty snack foods: salted pretzels, chips, salted nuts, and salted crackers
3) Frozen dinners: frozen meat dishes and frozen pizza
4) Processed meats: bacon, sausage, lunch meat, and hot dogs
5) Cheese and dairy: cheese, cottage cheese, and buttermilk
6) Sauces and condiments: soy sauce, commercial tomato sauce, and salad dressing
7) Drinks: regular vegetable juice, juice blends, and salty alcoholic beverages
8) Seasonings: salt and salt blends

**Figure 3.** Tips to estimate salt content. Modified from Iseki and Yamagata [13] according to the Creative Commons License.

1) Use a spoon to estimate the amount of added seasoning, in particular, when using common seasoning materials such as table salt, source, and miso
2) Estimate roughly as salt (grams) per teaspoon
3) Select low-salt seasoning and low salt foodstuffs (avoid too much)
4) Check the amount of salt in each food item
Japanese Kidney-Friendly Recipes and tips on salt restriction are available in the homepage of ISRNM (Patients’ Corner). Dashi (broth) and soup recipes are provided as are tips on how to reduce salt in instant noodles. The top three salted foods consumed in Japan are instant ramen, salted plums, and pickles. Instant ramen has been on the market in Japan since August 1958. It is cheap and easy to cook, but very salty. Dashi (broth) is a tasty low-sodium meal. Umami mushrooms and vegetables (especially root vegetables) are added, and spices and herbs are utilized. The YouTube site advises checking water hardness and recommends using soft water with less Ca and Mg. If needed, a water softener can be used. Use of soft water can reduce ‘nigami’ (bitter taste) and ‘egumi’ (harshness). Three keys to reducing salt in stews are 1) to combine dashi with poultry and mushrooms, 2) to add soy sauce at the end, and 3) to leave out the cooking liquid to reduce the salt even further. When preparing simmered vegetables and chicken, it is important to stick to the order of adding seasonings with sugar first and salt second. In 1971, cup noodles were invented. They are cheap and easy to cook, requiring only the addition of hot water. To reduce salt but preserve taste, remove the hot water after 1 minute and then add hot water again and wait 2 minutes, and eat it. This method can reduce the amount of salt by 50%.

**General population**

In Japan, the leading cause of ESKD since 1998 has been DM with fewer ESKD cases due to chronic glomerulonephritis. The main causes of DM are obesity [15] and metabolic syndrome. Diagnostic criteria for metabolic syndrome in Asians are different from in Western populations [16]. The cutoff waist circumference values measured at the umbilicus are 85 cm for men and 90 cm for women [17]. Metabolic syndrome is common and a predictor of both the incidence and progression of CKD in the general population [18–21].

Higher sodium intake is associated with incident CKD [22,23]. Recent meta-analysis supported that higher salt intake increased the odds of developing CKD [24]. Our group has been using the nationwide screening program of the ‘Specific Health Check-up and Guidance System (Tokutei-Kensin)’ initiated in 2008 [25,26]. The main purpose of this program is to detect metabolic syndrome and promote lifestyle modifications for people aged 40 to 74 years. In Japan, dipstick proteinuria, but not albuminuria, is used for general health screenings. Measurement of microalbuminuria is only reimbursed for early-stage diabetic kidney disease. We have shown that dipstick proteinuria is an independent predictor of death among screening participants [27]. We also found by analysis of a self-administered questionnaire on medical history and lifestyle that a 1-year change toward a healthy lifestyle was associated with a decline in proteinuria [28]. Moreover, we found that consuming fast foods is a risk factor for incident DM [29].

The effect of sodium intake on the development of CKD in a prospective cohort of people with normal renal function was investigated [30]. Sodium intake was estimated using a 24-hour dietary recall Food Frequency Questionnaire. Both individuals with low sodium intake (<2.08 g/day [5.28 g salt]) and those with high sodium intake (>4.03 g/day sodium [10.2 g salt]) were at higher risk of developing CKD in the presence of hypertension (n = 3,106) but not in the absence of hypertension (n = 4,871). In other words, the incidence of CKD was different between hypertensive and non-hypertensives. Adequate sodium intake appears to be important in individuals with hypertension as both too little and too much salt appear to be hazardous. Excess sodium restriction may activate the renin-angiotensin-aldosterone system, sympathetic nervous system, and aggravate insulin resistance [31].

---

**Figure 4. List of seasoning materials to reduce salt intake.** Modified from Iseki and Yamagata [13] according to the Creative Commons License.
The importance of lifestyle modification is not yet fully appreciated, at least among general physicians [32,33]. Other unhealthy lifestyle factors such as disturbed sleep, a sedentary lifestyle, and constipation should be taken into consideration when treating CKD patients. The prevalence of obstructive sleep apnea is high among Japanese non-dialysis CKD patients [34,35]. Nocturnal hypoxemia is a risk factor for rapid decline of kidney function [36]. We showed that treatment of sleep apnea syndrome by continuous positive airway pressure was life-saving [37]. CKD is often asymptomatic, therefore late referral to a nephrologist is not uncommon [38–40]. Nausea and vomiting are often the first presentations of CKD patients. CKD is associated with the presence of dysbiosis, which can be defined as an “imbalanced intestinal microbial community with quantitative and qualitative changes in the composition and metabolic activities of the gut microbiota” [41,42]. Constipation is common and related to CKD severity [43].

Stage 3 to 5 chronic kidney disease patients

Several studies have shown the beneficial effects of an educational program in CKD patients [44–46]. However, more collaboration with general physicians is needed. After the publication of the KDIGO guidelines [5], the term “CKD” has become more popular among nonspecialists, mass media, and laypeople. We care for CKD patients following the KDIGO guidelines [5,10,47], in particular the Japanese version [6–8]. Following these guidelines, we focus on individuals with metabolic syndrome as good targets for nutritional intervention.

We published a cluster-randomized trial on the effect of behavior modification in early to moderate stage CKD [48]. We estimated the effects of intervention by dieticians on lifestyle modification. A total of 2,379 patients (1,195 in group A that received standard interventions and 1,184 in group B who received advanced interventions), aged between 40 and 74 years, had CKD and were under management by general physicians. All general physicians belonged to local medical associations. Group B patients received three additional interventions: educational intervention for lifestyle modification (including sodium and protein restriction, if needed) and a CKD status letter to prevent their withdrawal from treatment, while group B general physicians received data sheets to facilitate reducing the gap between target and practice. For this intervention, we collaborated with registered dieticians of the Japan Dietetic Association.

The difference in cumulative incidence of a doubling of serum creatinine or 50% reduction in estimated glomerular filtration rate (eGFR) gradually increased between groups A and B over a follow-up of up to 3.5 years. We concluded that our care system achieved behavior modification of CKD patients, namely significantly fewer discontinuous clinical visits and behavior modification of both GPs and nephrologists, namely significantly higher referral and co-treatment rates, resulting in retardation of CKD progression, especially in patients with proteinuric stage 3 CKD. Registered patients received more than 10 interviews of 30 minutes in duration every 3 months during the study. Furthermore, we are analyzing the results of 10 years of observation of the initial cohort and focused the patients with advanced CKD and eGFR of <45 mL/min/1.73 m² in this cohort [49]. Also, report results using a Markov model, Okubo et al. [50] evaluated the cost-effectiveness of this intervention and found that the intervention used in this study was an efficient use of finite healthcare resources in Japan based on calculated cost per quality-adjusted life-year.

There are five basic tastes: sweet, sour, salty, umami, and bitter. In CKD, specific impairment in sour, umami, and salty tastes has been reported [51]. Proper dietary management and a healthy lifestyle are effective at reducing the incidence and progression of CKD, and therefore the incidence of ESKD requiring dialysis. Too high and too low salt intake are both dangerous. Recently, Kang et al. [52] showed that high salt intake, more than 11.3 g/day, was a risk factor for CKD progression. In a study based in an Italian nephrology clinic, salt intake of <6 g/day posed a greater risk of ESKD than salt intake of ≥6 g/day [53].

Dialysis patients

HD is a life-saving therapy for those with ESKD, yet the prognosis remains poor [54]. Unfortunately, no RCTs have reported survival benefits according to dialysis-related factors such as session time, frequency, or dialyzer membrane area [55]. There are also unfortunately no clinical practice guidelines for dialysis. At the initiation of dialysis therapy, various comorbid conditions such as stroke, cardiovascular...
disease, diabetic complications, and cancers may be present. Medical treatments such as erythropoietin stimulating agents, statins, and antihypertensives have failed to show survival benefits. Furthermore, well-designed RCTs have shown that pharmacological interventions offer no survival benefits [56–58].

The mortality rate of Japanese dialysis patients is lower than that of European and American dialysis patients [59] for reasons that are not yet clear. Consequently, careful rounds at each dialysis session and timely laboratory data are required by the physician in charge and other staff. Moreover, the number of elderly patients who require additional assistance with factors like transport, communication, and other personal issues is increasing. Decisions not to undergo dialysis or withdraw from dialysis are serious problems even in developed countries [60]. Meticulous control of known predictors of survival is important [61]. Also, the importance of nutritional management, in particular on PEW, is increasingly being recognized not only in dialysis patients but also in predialysis patients [62–64].

We previously reported that serum albumin (S-Alb) was a strong predictor of death among chronic dialysis patients [65]. At that time, we assumed that S-Alb functioned as a proxy of nutritional status as it was correlated with dialysis dose. When we extended the observation period of the previous RCT study participants to 10 years [66] and investigated the combination of S-Alb and serum phosphate (S-Pi) on survival, we found that the best survival was seen in those patients with higher S-Alb and lower S-Pi, while the worst survival was seen in those patients with lower S-Alb and lower S-Pi. In chronic HD patients, S-Pi appears to be a surrogate of protein intake [67].

**Weight change during hemodialysis**

During the introductory phase of chronic HD (within 6 months), many patients experience a large weight change; weight decreases in some patients due to mitigation of fluid overload due to edema or heart failure while weight increases in other patients due to recovery of nutritional status. It is important to differentiate between intentional weight loss (gain) in obese (skinny) patients and unintentional change. Chronic excess fluid volume is the main cause of hypertension. In chronic HD patients, seasonal changes in blood pressure and mortality have been reported. Blood pressure and mortality increase in winter. Ambient temperature and humidity may change the amount of sweating, physical activity, and other dietary factors. Previously, we observed a seasonal variation in body weight in HD patients living in Okinawa of about 0.5 kg [68]. This amount of weight change in dialysis patients should not be ignored.

There are multiple causes of cachexia in HD patients including chronic heart failure, stroke, hepatitis-C infection, and malignancy. In particular, malignancy is often detected during the initiation phase [69]. However, among long-term HD patients, these complications are uncommon, conceivably because of the intense medical surveillance these patients are under e.g., visiting medical facilities three times per week. A slight decline in dry weight (DW) could be the first sign of these complications. In addition, depression and cognitive dysfunction are common among HD patients. Loss of appetite is the first sign of these problems. In addition to an adjusted index for malnutrition and inflammation, low functional status is an important predictor of mortality in HD patients [70].

Session time varies with body size and is usually 4 to 6 hours. To comply with these conditions, incident HD patients should be well informed and educated. Salt (sodium) restriction is mandatory for chronic HD patients. To estimate salt intake and intradialytic weight loss, serum sodium levels before and after dialysis are used [71,72]. Estimated median (25th–75th percentile) salt intake was 6.4 g/day (4.6–8.3 g/day) among Japanese HD patients [73]. One-year mortality rate was highest among those with low salt intake (<6.0 g/day). Findings were similar in subgroup analysis based on nutritional parameters such as normalized protein catabolism rate, S-Alb, and BMI. Dong et al. [74] reported that peritoneal dialysis patients with low dietary sodium intake had a higher mortality risk. Their mean (SD) salt intake was lower than Japanese HD patients at 4.6 g/day (1.9–14.0 g/day). The mechanism underlying these observations remains to be clarified. Other than those complaining of anorexia and those with evidence of PEW, the lower limit of salt intake in CKD patients, including dialysis patients, has not been determined.

**Weight change as a predictor of mortality**

Optimal DW is determined using symptoms and hypoten-
sion during HD sessions as well as parameters that reflect excess fluid volume such as chest X-rays and other laboratory tests. According to the phase 4 study of the Dialysis Outcomes Practice Patterns Study (DOPPS), the practice of deciding DW differs among dialysis facilities and those patients for whom DW is frequently adjusted show better survival [75]. If the DW is achieved, then it means that no excess fluid is present after the HD session. If the amount of fluid removed by HD is too much or the fluid is removed too fast, patients become hypotensive. Post-HD weight is a proxy of DW and refers to the target bodyweight at each HD session; this is usually stable among prevalent HD patients. In patients with a thrice-weekly HD schedule, the first dialysis session of the week may need special attention as the interval from the previous HD is longer at the first session of the week, Monday or Tuesday. Accordingly, weight gain is usually largest at the first HD session of the week. A decline in post-HD weight is a significant predictor of mortality among chronic HD patients.

In a recent study of 461 chronic HD patients with a median follow-up of 10 years, 46% of patients died [67]. The main causes of death were infection (34%) and cardiovascular disease (31%). We showed that in chronic HD patients, risk factors for death differed according to short-term (≤3 years) or long-term (>3 years) observation. Sato et al. [76] showed that the DW obtained from the 1-year observation was a strong predictor of overall death. Kalantar et al. [77] investigated weight changes after initiation of dialysis and found that chronic baseline weight loss had a greater impact on mortality than acute weight loss. However, the optimal speed and amount of weight loss, as well as the optimal duration of observation required, have yet to be determined. Siga et al. [78] used a theoretical approach to determine total mortality in chronic HD patients. Further studies are necessary to define the effects of precisely categorized changes in body weight on survival. It is also important to determine if weight loss or gain is causally associated with mortality.

**Current activities in Japan**

Japan and China were known to be high salt intake countries, mainly due to the use of soy sauce and table salt [79]. However, salt intake is gradually decreasing from 2003 to 2019 in Japan according to a national survey conducted by the Ministry of Health, Labor and Welfare (Fig. 5). However, salt intake by men remains higher than that by women. This is likely because men eat out more and drink at bars where they are served finger foods. Alcohol consumption per se is a risk factor for the development [80] and progres-

---

**Figure 5. Trends in salt intake in Japan.** Data are from the National Survey of the Ministry of Health, Labor and Welfare.

---
Elderly men (≥60 years) have a higher intake of salt than younger men. This may be because they have old eating habits and it is more difficult for them to change their dietary habits than younger men. Also, a clear geographic difference in salt intake has been reported in Japan, where it is high in the Hokkaido and Nagano prefectures and lowest in Okinawa. Okinawa is a sub-tropical area; therefore, people do not eat preserved foods such as pickles. Okinawa was occupied after World War II until 1972, therefore the lifestyle is more Americanized than in other areas of Japan. Hokkaido and Nagano are cold in winter, and foods are saltier than in Okinawa. Education on salt restriction is important, in particular in young children [82,83]. Recently, school lunch regulations to reduce salt were introduced (https://www.mext.go.jp/a_menu/sports/syokuiku/1407704.htm). It is hoped that these regulations will promote healthy eating habits in Japan. According to the Ministry of Finance, the amount of salt added to foods by the food processing industry has been decreasing from 2008 to 2018. During these 10 years, the total population has also decreased by about 1.25 million. Nevertheless, salt consumption decreased more than expected. Such a trend could be explained by the efforts of multiple subspecialties other than nephrology such as hypertension [82–84], diabetology, and endocrinology [85,86] societies. In particular, the Japanese Society of Hypertension (JSH) has actively been promoting salt restriction [83]. Details of JSH salt reduction activities have been summarized recently [84]; these activities and target both children and adults, the food industry and food manufacturing companies, as well as the government.

The JSDT annual report stated that the crude annual mortality rate among prevalent HD patients had remained stable at 9% (1983) and 10% (2018), despite the large increase in total number of patients from about 53,000 (1983) to 339,000 (2018). Mean age of prevalent dialysis patients increased from 48.3 years old (1983) to 68.8 years old (2018). The percentage of DM increased from 7.4% (1983) to 39% (2018) of the prevalent dialysis population. The mean age of incident dialysis patients increased from 51.9 years old.

Figure 6. Trends in prevalence, per million population, of chronic dialysis patients in Japan. Data are from the Japanese Society for Dialysis Therapy. Modified and prepared by Iseki K.

664  www.krcp-ksn.org
The incidence of dialysis patients with DM increased from 15.6% (1983) to 42.3% (2018). The percentage of chronic glomerulonephritis cases has been declining steadily from 60.0% in 1983 to 15.6% in 2018. These trends can be explained by changes in lifestyle, advances in medical treatment, and national health care strategies. Fig. 6 shows trends in the prevalence of dialysis patients in Okinawa and Japan. Until 2008, it increased linearly in both the whole of Japan and Okinawa. Okinawa used to be the prefecture with the highest number of prevalent dialysis patients [20,87,88]. However, this appears to have stabilized at around 3,100 per million population.

Renin-angiotensin system blockers are useful for CKD patients with hypertension and proteinuria and have contributed to slowing the progression of CKD to ESKD [89,90]. Angiotensin II-receptor blockers (ARBs) have been available in Japan since July 1998. Sodium-glucose cotransporter 2 inhibitors [91,92] to treat DM were introduced in January 2014. The benefits of these drugs are weakened by high salt intake. By contrast, severe salt restriction and/or volume depletion CKD patients may have hyperkalemia. Although we do not have enough information on the use of angiotensin–converting enzyme inhibitor/ARBs in Japanese patients, their use may be higher than in the United States [93]. In addition to these drugs, collaborative efforts among public health nurses and dieticians on dietary management may, at least partly, have contributed to slowing down the rate of increase of dialysis patients. More studies are required to confirm this assumption. Maintaining a healthy lifestyle, including lower salt intake with protein restriction, plays an important role in decreasing the incidence and slowing down the progression of CKD.

Conclusions

Salt restriction with adequate protein and calorie intake is important in all stages of CKD, and in dialysis patients in particular. Recent reviews and meta-analyses support the benefits of salt reduction [94–96]. Nutritional (salt) management needs to be adjusted for individual lifestyle, dietary habits, and available food types [97], as the elderly population is increasing rapidly in both Japan and Korea. Clinical practice guidelines for CKD patients are mostly based on observational studies and expert opinion. More well-designed observational studies on nutritional management are needed. Too strict salt restriction may decrease quality of life, aggravate CKD, and eventually induce PEW. Sharing knowledge and experience may facilitate observational studies and RCTs to further improve the care of CKD patients [98,99].

Conflicts of interest

The author has no conflicts of interest to declare.

Acknowledgments

I would like to thank the organizing committee of the KSN2021 (Professor Won Kim, the Congress President; Professor Chul Woo Yang, President of the Korean Society of Nephrology; and Professor Sang-Ho Lee, the Chair Scientific Committee) and Professor Tae-Hyun Yoo MD, Ph.D., the Editor-in-Chief of Kidney Research and Clinical Practice.

ORCID

Kunitoshi Iseki, https://orcid.org/0000-0001-6624-0216

References

34. Iseki K, Tohyama K, Matsumoto T, Nakamura H. High prevalence of chronic kidney disease among patients with sleep relat-


88. Usami T, Koyama K, Takeuchi O, Morozumi K, Kimura G. Regional variations in the incidence of end-stage renal failure in


Why should we focus on high-volume hemodiafiltration?

Sug-Kyun Shin¹, Young-Il Jo²

¹Division of Nephrology, Department of Internal Medicine, NHIS Ilsan Hospital, Goyang, Republic of Korea
²Division of Nephrology, Department of Internal Medicine, Konkuk University School of Medicine, Seoul, Republic of Korea

Though noticeable technological advances related to hemodialysis (HD) have been made, unfortunately, the survival rate of dialysis patients has yet to improve significantly. However, recent research findings reveal that online hemodiafiltration (HDF) significantly improves patient survival in comparison to conventional HD. Accordingly, the number of patients receiving online HDF is increasing. Although the mechanism driving the benefit has not yet been fully elucidated, survival advantages are mainly related to the lowering of cardiovascular mortality. High cardiovascular mortality among HD patients is seemingly attributable to the cardiovascular changes that occur in response to renal dysfunction and the HD-induced myocardial stress and injury, and online HDF appears to improve such secondary cardiovascular changes. Interestingly, patient survival improves only if the convection volume is supplied sufficiently over a certain level during online HDF treatment. In other words, survival improvement from online HDF is related to convection volume. Therefore, there is a growing interest in high-volume HDF in terms of improving the survival rate. The survival improvement will require a minimum convection volume of 23 L or more per 4-hour session for postdilution HDF. To obtain an optimal high convection volume in online HDF, several factors, such as the treatment time, blood flow rate, filtration fraction, and dialyzer, need to be considered. High-volume HDF can be performed easily and safely in routine clinical practice. Therefore, when the required equipment is available, performing high-volume HDF will help to improve the survival rate of dialysis patients.

Keywords: Convective therapies, Chronic kidney failure, Hemodiafiltration, Mortality, Survival

Introduction

As underlying diseases of chronic kidney disease, such as diabetes, are surging drastically with the gradual increase in life expectancy, the number of patients with end-stage renal disease (ESRD) on dialysis is increasing explosively. According to Canaud et al.'s report [1] published in 2020, the number of patients with ESRD receiving renal replacement therapy reached 3,171,000 globally in 2017, among which those on hemodialysis (HD) accounted for 2,823,000 (89%). Further, of the 2,823,000 patients undergoing HD, 286,000 (10%) were receiving hemodiafiltration (HDF). In 2009, the number of HDF patients was 77,300, increasing by 3.7 times to 286,000 in 2017, resulting in an annual growth rate of as high as 18% [1]. With the explosive upsurge in the number of ESRD patients, significant advancements in dialysis therapy methods and technology have also occurred. However, despite such technological progress, patient survival has not improved much, and the lifespan of a dialysis patient remains shorter than that of...
As improved survival rates among dialysis patients are an important new research finding, recent studies have revealed revealing that high-volume HDF improves patient survival. In particular, high-volume HDF, should be given special attention. Hence, this review will examine, through a literature analysis, the clinical benefit of high-volume HDF, the effect of improving the survival rate and its mechanism, and the method of implementing high-volume HDF.

### Survival improvement by high-volume hemodiafiltration

Recent research findings have revealed that the survival improvement gained from online HDF is related to convection volume [6,8,10,17,18]. In other words, patient survival rates improve only if convection volume is supplied sufficiently above a certain level. CONTRAST was conducted involving patients of low-flux HD and postdilution HDF, and it reported no difference in all-cause mortality among these two groups. However, when patients were separated according to convection volume into three groups of <18.17 L, 18.17 to 21.95 L, and >21.95 L, respectively, and subsequently analyzed, the >21.95-L group showed a significant improvement in survival (hazard ratio [HR], 0.57; p < 0.02) [4]. The Turkish OL-HDF study also reported this finding. In the Turkish OL-HDF study, while there existed no significant difference in death rate between patients who received high-flux HD and those who received postdilution HDF, the separation of HDF patients, based on a convection volume of 17.4 L, and subsequent analysis demonstrated that, among the >17.4-L group, overall mortality and cardiovascular mortality rates decreased by 46% (relative risk [RR], 0.54; 95% confidence interval [CI], 0.31–0.93; p = 0.02) and 71% (RR, 0.29; 95% CI, 0.12–0.65; p = 0.003), respectively [5]. In the ESHOL study, an analysis of a limited group of high-efficiency postdilution HDF patients with convection volumes of 22.9 to 23.9 L documented an improvement in the all-cause mortality rate by 30% in comparison to HD patients (p = 0.01) [6]. Peters et al. [8] conducted a pooled IPD analysis of 2,793 patients who participated in four well-known RCTs (CONTRAST, Turkish OL-HDF study, ESHOL, and FRENCHIE [French Convective versus Hemodialysis in Elderly] study) and revealed a survival improvement attributed to high-volume HDF. In other words, their IPD analysis indicated that, among online HDF patients, the overall mortality and cardiovascular mortality rates declined by 14% and 23%, respectively. No-
tably, the analysis of three groups (<19 L, 19–23 L, and >23 L) of convection volume showed that survival remarkably improved (HR for all-cause mortality, 0.78; HR for cardiovascular mortality, 0.69) among the patients with convection volumes of >23 L (per 1.73 m² of body surface area per session) [8]. Nubé et al. [17] also reported in an IPD meta-analysis that high-volume HDF significantly reduced all-cause mortality and cardiovascular mortality; also, they found that, the higher the convection volume, the lower the risk of death. In 2019, a cohort study using data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) showed that survival was significantly higher under HDF than under HD [12].

These findings strongly imply that high-volume HDF is required to improve patient survival. Moreover, such improved survival from high-volume HDF was demonstrated not only in postdilution HDF but also in predilution HDF. In 2019, a study was conducted using data from the Japanese Society for Dialysis Therapy Renal Data Registry (JRDR) to analyze survival among HD and predilution HDF patients with 5,000 couples of a propensity-matched cohort, which produced the finding that predilution HDF led to significantly higher overall survival than HD (HR for all-cause mortality, 0.83). Notably, the patient group with a high substitution volume of ≥40 L had significantly better survival than the patient group with a volume of <40 L. In the study, the optimal substitution volume for improved survival was 50.5 L (95% CI, 39.0–63.5 L) [13]. Recently, Canaud et al. [18] reported that the convective dose for survival gain is a minimum of 75 L per week. All of these research findings point out that the most critical factor is not performing HDF but supplying enough convection volume during HDF. In short, volume is what matters.

**Survival improvement mechanism of high-volume hemodiafiltration**

Why is cardiovascular mortality high among hemodialysis patients?

Cardiovascular disease is the most common cause of death among conventional HD patients. According to the 2020 annual report of the United States Renal Data System (USRDS), cardiovascular disease accounts for 55.2% of deaths among ESRD patients receiving HD, and, in particular, cardiac arrhythmia/cardiac arrest accounts for 44.2% of all-cause mortality [2]. Such a high cardiovascular mortality rate among HD patients is seemingly attributable to secondary cardiovascular changes due to renal dysfunction and HD-induced myocardial stress and injury. In ESRD patients, the secondary cardiovascular changes are caused by the multiple factors of fluid overload, uremic cardiomyopathy, secondary hyperparathyroidism, anemia, altered lipid metabolism, and accumulation of gut microbiota-derived uremic toxins like trimethylamine N-oxidase; such cardiovascular changes contribute to a high number of deaths [19]. Nevertheless, cardiovascular mortality remains high even when these issues, such as fluid overload, hyperparathyroidism, and anemia, are dealt with, as HD itself apparently also causes myocardial stress and injury [20].

**Why do hemodiafiltration and hemodialysis differ in terms of mortality rate?**

While several studies have reported the finding that an appropriate increase in convection volume in online HDF enhances patient survival significantly, the mechanism by which high-volume HDF improves survival is still not fully understood [21]. However, considering the suggestion by previous studies that the observed survival advantages are mainly related to the reduction of cardiovascular mortality, the following potential mechanisms are suggested [22,23].

**Intradialytic hemodynamic instability**

Intradialytic hypotension (IDH) is not uncommon during intermittent HD. Locatelli et al. [24] reported that the incidence of symptomatic IDH among HD patients was 7.5% across 28,950 sessions. During dialysis, fluid removal occurs in the intravascular compartment, and removed fluid is replenished from the interstitial fluid compartment. Mismatching between the refill rate and the plasma-removal rate creates volume contraction, which, for a normal person, engages the baroreceptor-mediated reflex to function and does not cause hypotension. However, in a uremic patient, mismatching-induced volume contraction hinders the baroreceptor-mediated reflex, finally resulting in IDH. Mismatching between the refill rate and the plasma-removal rate creates volume contraction, which, for a normal person, engages the baroreceptor-mediated reflex to function and does not cause hypotension. However, in a uremic patient, mismatching-induced volume contraction hinders the baroreceptor-mediated reflex, finally resulting in IDH. Subsequently, IDH induces myocardial stress, which ultimately contributes to a high mortality rate among dialysis patients. In contrast, HDF reduces the frequency of IDH development significantly; in other words, HDF improves
intradialytic hemodynamic instability [17]. Locatelli et al. [24] reported that carrying out HDF reduced the frequency of symptomatic IDH onset by 50.9%. In the FRENCHIE study, which was conducted among elderly patients to study intradialytic treatment tolerance, the frequencies of the intradialytic symptomatic hypotension development for HD and HDF recipients were 1.73% and 1.39%, respectively, being significantly lower among HDF patients [25]. Nubé et al. [17] determined during an IPD meta-analysis using data of large-scale RCTs that the survival improvement gained from HDF is attributable to a reduction in fatal cardiac events, which is related to the improvement of intradialytic hemodynamic instability. Though administering replacement solution in large volumes may raise concerns about a potential risk of fluid overload during high-volume HDF, Chazot et al. [26] reported that there existed no significant difference in fluid overload development between HD and HDF patients. The cooling effect of replacement solution in large volumes also helps maintain hemodynamic stability [27].

**Endothelial dysfunction**

There is some evidence that HDF improves endothelial dysfunction. An RCT of 42 HD patients measured flow-mediated dilatation and carotid distensibility after carrying out HD and high-volume HDF (>22 L/session) for 4 months, which led to significant improvement only in HDF patients. Such improvement in endothelial dysfunction was associated with oxidative stress, inflammation, and nitric oxide [28]. In the HDF, heart, and height (3H) study of pediatric patients, markers of endothelial dysfunction, such as asymmetric dimethylarginine (ADMA) and symmetric dimethylarginine (SDMA), improved significantly during HDF treatment [29,30].

**Inflammation/oxidative stress**

There are several reports that suggest HDF can help to improve inflammation and oxidative stress. A follow-up study of CONTRAST traced the changes in C-reactive protein (CRP) level for 3 years and found that, despite increasing significantly among HD patients, the CRP level remained stable among HDF patients [31]. The 3H study revealed that the total antioxidant capacity improved during HDF treatment, while inflammation markers such as high-sensitivity CRP significantly decreased [30].

**Vascular stiffness**

Pulse-wave velocity (PWV) is a surrogate measurement that indicates vascular stiffness. Despite increasing significantly within 6 months after the initiation of HD, aortic PWV remained stable in HDF patients. Also, the diastolic relaxation area, which indicates left ventricular refilling, increased significantly among HDF patients [32]. In another RCT that followed patients for 1 year after treatment, brachial PWV increased significantly after HD onset while remaining stable among HDF patients [33].

**Cardiac remodeling**

HDF significantly reduces the levels of natriuretic peptides, such as brain natriuretic peptide (BNP), N-terminal–proBNP (NT-proBNP), and proBNP. These natriuretic peptides are significantly correlated with certain echocardiography remodeling parameters, such as left atrium diameter, left ventricular diastolic diameter, and left ventricular mass index (LVMI), and HDF reduces such a cardiac burden [34]. Another prospective crossover study also demonstrated that, while there were no significant changes in the left atrium diameter under HD, it declined significantly under HDF, which was correlated with the decrease in nitric oxide and ADMA [35]. Recently, Páll et al. [36] reported that T peak-end interval was lower under HDF than under HD and showed a significant correlation with LVMI. However, in a recently released meta-analysis, conventional HD and HDF showed no significant variations in the impact on the changes of LVMI and ejection fraction [37]. Hence, additional studies will be required to demonstrate whether HDF helps improve left ventricular hypertrophy to enhance survival.

**Sympathetic tone activity**

Chronic sympathetic overactivity is a well-known cardiovascular risk factor. In a prospective study, Park et al. [38] reported that online HDF improved autonomic nervous system dysfunction in chronic dialysis patients.

**How to perform high-volume hemodiafiltration**

**What is the optimal convection volume?**

Although the mechanism has not been fully elucidated, it is apparently obvious that high-volume HDF helps to im-
prove patient survival. Nonetheless, there still remains a question of whether any selection bias has played a role in improving the survival from high-volume HDF in previous studies [16,39]. For example, in their pooled IPD analysis, Peters et al. [8] carried out online HDF with the convective dose of 69 L per week or higher, which requires patients to have vascular access in good condition. In other words, it cannot be completely ruled out that study participants might have included only those healthy enough to endure such a high dose. Despite these limitations, however, all of these studies support the conclusion that high-volume HDF improves survival significantly in a manner largely attributable to reduced cardiovascular mortality.

There have been several rounds of discussion about how much of a convection volume is required at minimum to gain improved survival. Previous reports have indicated that the volume threshold for improved survival varied between studies, ranging from a minimum of 15 L to a maximum of 23.1 L [40]. This phenomenon is due to differing study schemes and volume definitions. Peters et al. [8] reported in their pooled IPD analysis that survival improvement required a minimum convection volume of 23 L/1.73 m² body surface area per HDF session. Previous research findings suggest that, for postdilution HDF, the survival improvement will require a minimum convection volume of ≥23 L per 4-hour session [41–44]. Based on the results of the main clinical trials, the current recommendation for high-volume HDF on a thrice-weekly treatment schedule would be a convective volume of ≥23 L/session [44]. Considering the dilution factor, a minimum convection volume of 46 L per session would be required for predilution HDF [43,45]. According to a report using data from the JRDR database, the optimal substitution volume leading to improved survival was estimated to be 50.6 L/session in patients receiving predilution HDF [13]. Therefore, more important than anything else is carrying out high-volume HDF therapy that supplies convection volume at a sufficient level of ≥23 L/session, not just carrying out HDF [8,12,13].

What are the factors for the optimal level of high convection volume?

As reviewed so far, determining how to obtain a high convection volume of ≥23 L/session is a key to conducting HDF successfully. However, there is an issue that high convection volumes may not be obtained automatically just by performing online HDF treatment. In CONTRAST, for example, only 22% of participating patients reached a target convection volume of 24 L [4], which points out that a special strategy should be deployed to achieve high convection volumes. Several factors, such as treatment time, blood flow rate, filtration fraction, and dialyzer, are required to obtain an optimal high convection volume in online HDF [40,46–48]. Below are the respective reviews of these factors.

Treatment time
Treatment time is a crucial determining factor of convection volume, and one of the surest ways to increase the convection volume is by extending the treatment time [46], which will increase the convection volume with ease. With a blood flow rate of 400 mL/min and a filtration fraction of 25% in postdilution HDF, extending the treatment time by one hour can increase the convection volume by approximately 6 L [48]. Therefore, if blood flow is insufficient, it is advisable to increase the treatment time to obtain a high convection volume. However, extending the treatment time by one hour is not an easy task in the real world. Extending the treatment time even 30 minutes, if not one hour, would help to increase the convection volume. In CONTRAST, a 30-minute extension of the treatment time increased convection volume by approximately 2.5 L [46].

Blood flow rate
Blood flow rate is also a critical determinant of convection volume, and it represents the most important limiting factor, especially in postdilution HDF [3,49,50]. In postdilution HDF, to reduce the risk of increasing viscosity and clotting complications, a dialyzer reduces the infusion flow to ≤33% of the blood pump flow rate (Qb). Therefore, it is recommended that, in postdilution HDF, the blood flow rate should be kept at 350 to 500 mL/min to obtain a sufficiently high convection volume [3,22,40,51]. If carrying out postdilution HDF is unlikely to deliver this level of blood flow rate, it may prevent the expected clinical benefits from online HDF from manifesting. If this level of blood flow rate is hard to come by, predilution HDF offers a better option [52,53]. Predilution HDF makes it possible to obtain a high convection volume with a low blood flow rate of 200 to 250
On the other hand, if a blood flow rate may not reach 350 to 500 mL/min in postdilution HDF, a high convection volume can be obtained by increasing the treatment time, adjusting the filtration fraction, and using an auto-substitution mode [47,49,54,55]. Nevertheless, the blood flow rate is still very important. Even if a recommended level of 350 to 500 mL/min is not reached, the higher the blood flow rate, the easier it gets to carry out high-volume HDF. Madison et al. [49] studied the influence of blood flow rate on convection volume by adjusting the blood flow rate to 250, 300, 350, 400, and 450 mL/min, respectively, per session in 23 patients undergoing postdilution HDF. The convection volumes in each session were 23.7 ± 2.2, 26.9 ± 3.1, 30.2 ± 2.3, 32.8 ± 3.3, and 35.2 ± 2.9 mL/min, respectively, and higher blood flow rates led to increased levels of convection volume; specifically, the convection volume increased by 8 to 12 mL/min for each surge of blood flow rate by 50 mL/min [49]. Therefore, maintaining the blood flow rate at a high level, if possible, is critical to obtaining enough convection volume.

Two key determining factors of the blood flow rate are the type of vascular access and needle size [47]. If there are no problems, such as stenosis, an arteriovenous fistula (AVF) or arteriovenous graft (AVG) may generally achieve a blood flow rate higher than that achieved with a central venous catheter (CVC). In a study conducted by Marcelli et al. [50] of 3,315 postdilution HDF patients in six European countries, the blood flow rates of AVF, AVG, and CVC were 391 ± 64, 390 ± 62, and 316 ± 50 mL/min, respectively. Considering the degree of reaching a substitution volume of ≥21 L in a multivariate logistic regression analysis, AVG was lower than AVF by 41.5% and CVC was lower than AVF by 57.8% [50]. However, having CVC does not necessarily mean there is an inability to conduct high-volume HDF [56]. In one study that analyzed CONTRAST data, which compared convection volume in patients undergoing postdilution HDF with AVF, AVG, or CVC, the convection volumes were 19.7 ± 4.4, 19.3 ± 4.4, and 21.9 ± 4.4 mL/session, respectively, with no difference between the types of vascular access [46].

For patients with AVF or AVG, needle size is important to achieve a high blood flow rate. If not for the issue of stenosis, a large needle would help to increase the blood flow rate. There is a general concern that the use of a large needle exacerbates the shunt outcome. However, according to one observational study, there existed no difference in complications between 14-, 15-, and 16-gauge needles [57]. Therefore, an insufficient level of convection volume will necessitate the use of a larger-sized needle. It is recommended to use a 16-gauge needle for a blood flow rate of 300 to 350 mL/min and a 15-gauge needle for a blood flow rate of 350 to 400 mL/min [47,58]. In a study conducted in Europe, 61.3% of the needles used were 15-gauge, and approximately 85% of patients had a blood flow rate of ≥300 mL/min [59]. Another study indicated that a needle larger than 15-gauge was not needed to carry out high-volume HDF [55]. It should be noted that an increase in the blood flow rate may lead to an increase in the recirculation rate [60], which also further increases with inappropriate arterial inflow due to lowered cardiac output or stenosis in the venous outflow. As a higher recirculation rate may hinder efforts to obtain a sufficient level of convection volume, it is necessary to monitor the recirculation rate regularly [47].

**Filtration fraction**

Filtration fraction is also an important determining factor for convection volume. In clinical practice, the filtration fraction is defined as “a ratio of the convection volume to the blood flow rate.” Accordingly, a higher filtration fraction heightens ultrafiltration, leading to an elevated convection volume. However, in postdilution HDF, replacement solution is injected after the dialyzer, increasing the hemoconcentration in the dialyzer, which causes coagulation in the dialyzer and damages it. Accordingly, the European Dialysis Working Group recommended a filtration fraction of 20% to 25% as appropriate in postdilution HDF [61]. Nevertheless, the use of a dialysis machine with an automatic pressure-control mode may extend the filtration fraction up to 30% [62]. The use of a dialysis machine with an automatic pressure-control mode can keep the transmembrane pressure within a range of 180 to 190 mmHg to prevent hemoconcentration, helping to obtain a high convection volume [49]. Meanwhile, an appropriate anticoagulation therapy is essential as a higher filtration fraction elevates blood coagulation in the dialyzer due to hemoconcentration. The convective clearance of heparin when used as an anticoagulant (unfractionated heparin or low-molecular-weight heparin) increases with the surge of the convection volume in online HDF. Therefore, the dose of heparin would be...
in HDF may be 10% higher than in HD [5].

**Dialyzer**

Online HDF necessitates a highly permeable membrane to filter water and middle-molecule solutes, and the membrane must be properly sized for the blood flow rate [51]—that is, a high-flux membrane should have an ultrafiltration coefficient (KUF) of >20 mL/hr/mmHg/m² and a sieving coefficient of >0.6 for β₂-microglobulin [43]. The membrane size should be at least 0.80 to 1.0 m² per 200 mL/min for effective extracorporeal blood flow, meaning that a 2.0-m²-sized hemodialyzer is appropriate for a blood flow rate of 400 mL/min [63].

**Strategies to obtain an optimal convection volume for high-volume hemodiafiltration in the real world**

In 2015, Chapdelaine et al. [47] suggested a method for obtaining an appropriate level of convection volume, which reported that a stepwise increase of the factors of treatment time, blood flow rate, and filtration fraction helps to increase the convection volume. In other words, for a patient with a blood flow rate of 300 mL/min, filtration fraction of 25%, and treatment time of 210 minutes, the convection volume was 15.8 L/session; with the extension of treatment time to 240 minutes, the convection volume increased to 18.0 L/session. At this time, when the blood flow rate was increased from 300 to 350 mL/min, the convection volume increased from 18.0 to 21.0 L/session. Further, an increase in the blood flow rate to 400 mL/min caused the convection volume to increase from 21.0 to 24.0 L/session. Stepwise adjustment of treatment time, blood flow rate, and filtration fraction in this patient allegedly led the convection volume to finally rise up to 29.8 L [47]. de Roij van Zuijdewijn et al. [54] conducted a prospective multicenter study to determine how many postdilution HDF patients would show a convection volume of ≥22 L would be obtainable when such a stepwise protocol is applied. This study applied the stepwise protocol in all patients to increase the treatment time to 4 hours, the blood flow rate to 400 mL/min, and the filtration fraction to 33% if possible, which produced the result that a convection volume of ≥22 L was achieved in more than 80% of patients with an average of 26 L/session. A high convection volume could be obtained by increasing the blood flow rate and filtration fraction even when the treatment time could not be extended [54].

In actual clinical practice, it is not difficult to obtain a high convection volume if the treatment time, blood flow rate, and filtration fraction were adjusted appropriately according to patient condition by referring to the above stepwise protocol suggested by Chapdelaine et al. [47]. For a low blood flow rate, the switch from postdilution HDF to predilution HDF will help to increase in convection volume. Jo et al. [64] reported that this switch could achieve a high convection volume in >90% of patients. Taking an actual example, convection volume for a female patient aged 74 years under postdilution HDF was 24.0 L, but it reached 30.2 L after applying the stepwise protocol [64] (Fig. 1). Recently, Kim et al. [65] reported in a prospective observational study that a sufficiently high convection volume could be obtained by appropriately adjusting the blood flow rate, needle size, and dialyzer surface area. In this prospective observational study, an 8-step stepwise protocol was applied to 30 patients receiving postdilution HDF. The researchers first gradually increased the blood flow rate (280→300→330 mL/ min, steps 1–3), followed by needle size (16→15 gauge, step 4), and the dialyzer surface area (1.8→2.5 m²) was increased sequentially. After changing the dialyzer surface area, the blood flow rate and needle size were increased sequentially in the same manner (steps 5–8). In step 1, 13.3% of patients reached a substitution volume of ≥21 L, while 96.7% of patients achieved a high convection volume after step 8 [65]. In conclusion, it is not difficult to obtain an appropriate level of convection volume for high-volume HDF in the real world by increasing the treatment time, blood flow rate, needle size, dialyzer surface area, and filtration fraction using a stepwise protocol. The recommended adequate prescriptions and requirements for successful high-volume HDF are summarized in Table 1 [43,51].

**Points to consider when interpreting the results of studies reported to date on hemodiafiltration**

There are discrepancies among existing studies on whether high-volume HDF reduces the risk of mortality in patients with ESRD. Furthermore, the quality of evidence derived from the RCTs reported to date is considered low due to methodological limitations—that is, most trials were not specifically designed to evaluate the effects of different
A 74-year-old female patient with a height of 164 cm and a weight of 114 kg underwent postdilution hemodiafiltration (HDF). Initially, the treatment time was 4 hours, and the blood flow rate (BFR) was 270 mL/min. An increase in the BFR to 300 mL/min led the convection volume to increase to 25.5 L. The treatment time was extended to 4 hours and 30 minutes when the target convection volume of 29 L/session was not reached, even after maximizing the filtration fraction via an auto-substitution (auto-sub) mode. However, the convection volume did not reach the target at 27.5 L. Finally, when the BFR was further increased to 320 mL/min, the convection volume reached 30.2 L.

**Figure 1.** Case of applying a stepwise protocol to obtain the convection volume in the real world. A 74-year-old female patient with a height of 164 cm and a weight of 114 kg underwent postdilution hemodiafiltration (HDF). Initially, the treatment time was 4 hours, and the blood flow rate (BFR) was 270 mL/min. An increase in the BFR to 300 mL/min led the convection volume to increase to 25.5 L. The treatment time was extended to 4 hours and 30 minutes when the target convection volume of 29 L/session was not reached, even after maximizing the filtration fraction via an auto-substitution (auto-sub) mode. However, the convection volume did not reach the target at 27.5 L. Finally, when the BFR was further increased to 320 mL/min, the convection volume reached 30.2 L.

**Table 1.** Prerequisites for successful high-volume HDF

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Equipment needed for successful high-volume HDF</strong></td>
<td></td>
</tr>
<tr>
<td>Dialysis machine</td>
<td>Certified dialysis machine for online HDF</td>
</tr>
<tr>
<td>Dialyzer</td>
<td>High-flux membrane (1.6–2.2 m²); ultrafiltration coefficient, &gt;20 mL/hr/mmHg/m²; sieving coefficient, &gt;0.6 for β₂-microglobulin, &lt;0.001 for albumin</td>
</tr>
<tr>
<td>Dialysate</td>
<td>Ultrapure dialysate</td>
</tr>
<tr>
<td>Dialysate composition</td>
<td>Adjusted according to the patients’ needs</td>
</tr>
<tr>
<td>Water treatment</td>
<td>Production of ultrapure dialysate and substitution fluid</td>
</tr>
<tr>
<td><strong>Prescriptions for successful high-volume HDF</strong></td>
<td></td>
</tr>
<tr>
<td>Mode</td>
<td>Post-, pre-, mid-, or mixed dilution</td>
</tr>
<tr>
<td>Vascular access</td>
<td>AV fistula, AV graft, or central venous catheter</td>
</tr>
<tr>
<td>Blood flow rate</td>
<td>300–450 mL/min (in post- or mid-dilution) and 200–250 mL/min (in pre-dilution)</td>
</tr>
<tr>
<td>Dialysate flow rate</td>
<td>&gt;500 mL/min</td>
</tr>
<tr>
<td>Infusion flow</td>
<td>Automatic infusion flow (&lt;33% of blood flow rate)</td>
</tr>
<tr>
<td>Treatment time</td>
<td>&gt;4 hr/session, three times per week</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>20%–25% in post-dilution HDF</td>
</tr>
<tr>
<td></td>
<td>Using a dialysis machine with automatic pressure-control mode, FF can be extended by up to 30%</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>No dose adjustment for unfractionated heparin, but dose adjustment for low-molecular-weight heparin</td>
</tr>
<tr>
<td>Convective volume</td>
<td>&gt;23 L/session or 25 L/1.73 m² for post-dilution HDF, &gt;46 L/session or 52 L/1.73 m² for pre-dilution HDF, and &gt;35 L/session or 40 L/1.73 m² for mid- or mixed dilution HDF</td>
</tr>
</tbody>
</table>

AV, arteriovenous; FF, filtration fraction; HDF, hemodiafiltration.
convective volumes. In addition, there was significant heterogeneity in dialysis interventions, including convective modalities, among trials. Therefore, caution is required when evaluating the effect of high-volume HDF on patient mortality.

In particular, the possibility that selection bias may have affected mortality in each study should be considered. High-volume postdilution HDF requires a higher blood flow rate, and high blood flow rates are better reached in patients with good vascular access, who also tend to be healthier individuals. Ultimately, this selection bias may affect patient mortality. If the patients selected for RCT were healthier than those excluded from the study, there is no doubt that the selection bias could affect study outcomes and lead to a lower all-cause mortality rate [66]. Indeed, compared to the DOPPS (Dialysis Outcomes and Practice Patterns Study) HDF population, HDF patients who participated in the three large studies (CONTRAST, Turkish OL-HDF study, and ESHOL) had well-functioning vascular access [4,5,6,16]. However, in a Japanese study using the JRDR database, blood flow rates of patients receiving predilution HDF were not higher than those with HD (p = 0.99) after propensity score matching. Nevertheless, patients undergoing high-volume predilution HDF had a significantly lower mortality rate than those receiving HD or low-volume predilution HDF [13].

Although high-volume HDF has shown several promising survival advantages over conventional HD, it remains controversial whether conclusive evidence is sufficient. Therefore, definitive studies are needed to determine whether high-volume HDF is preferred over standard high-flux HD. For this purpose, the CONVINCE (comparison of high-dose HDF with high-flux HD) study, an international, multicenter, prospective, open-label RCT, is currently in progress to compare the benefits and harms of high-volume HDF and high-flux HD [67]. It is expected that this study will provide conclusive evidence of the superiority of high-volume HDF over standard high-flux HD in terms of the impact on all-cause mortality.

**Conclusion**

Although all data to date do not yet provide an accurate account of the exact mechanism, high-volume HDF apparently does provide a significant survival benefit compared to conventional HD. On the other hand, compared to conventional HD, high-volume HDF led to almost no issues when carried out, and an appropriate level of convection volume is easily obtainable in routine clinical practice. Therefore, when the required equipment is available, performing high-volume HDF can help to improve the survival rate of dialysis patients.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**Authors’ contributions**

Conceptualization, Data curation, Visualization: YIJ
Investigation: SKS
Formal analysis, Methodology, Project administration: SKS, YIJ
Writing–original draft: SKS, YIJ
Writing–review & editing: YIJ
All authors read and approved the final manuscript.

**ORCID**

Sug-Kyun Shin, https://orcid.org/0000-0001-7866-0955
Young-Il Jo, https://orcid.org/0000-0002-6695-7062

**References**

5. Ok E, Asci G, Toz H, et al. Mortality and cardiovascular events in...


43. Schiiff H. High-volume online haemodiafiltration treatment and outcome of end-stage renal disease patients: more than one mode. *Int Urol Nephrol* 2020;52:1501–1506.


Introduction

Diabetes is a global health issue, and the prevalence of its complications has increased in the past few decades. Approximately one in 11 people in the world suffers from diabetes, and 87% to 90% of those patients have type 2 diabetes mellitus (T2DM) [1]. Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease (CKD). Approximately 40% of T2DM patients develop DKD, and about 10% of deaths from T2DM are due to kidney failure [2]. The Asian population is more vulnerable to DKD than people in Western countries [3]. A genetic component could be involved because DKD causes more end-stage kidney disease among the Asian population in China, the USA, and Eastern Europe than it does in people of other ethnicities. Different pathways have been found in the pathophysiology of DKD. Metabolic factors such as hyperglycemia and hyperalbuminuria can alter hemodynamics by increasing local angiotensin production, which leads to afferent arteriole dilatation and efferent arteriole constriction. The consequent glomerular hyperfiltration or increase in intraglomerular pressure can cause chronic kidney damage. Those metabolic factors also promote interstitial inflammation, which leads to extracellular matrix (ECM) accumulation, interstitial fibrosis, and irreversible kidney damage [2,4].

Sodium-glucose co-transporter 2 inhibitors (SGLT2is)
have their effects at the proximal convoluted tubule, where they increase glucose reabsorption, urinary glucose excretion, and natriuresis [5,6]. The unique mechanism of SGLT2is causes pleiotropic effects that reduce hyperglycemia, hemoglobin A1c (HbA1c), weight, and blood pressure [7–10]. Several studies have focused on the renal-specific outcomes of SGLT2is and found that they have renoprotective effects, largely due to their ability to reduce sodium reabsorption at the proximal tubule, which improves intraglomerular pressure and reduces hyper-perfusion [11,12]. Cardiovascular death was also reduced in CKD patients who used an SGLT2i [13]. Although SGLT2is and renin-angiotensin-aldosterone system inhibitors (RAASis) are widely combined in the nephrology community, initiation of that practice is not recommended in patients with an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m², and it should be discontinued when patients require kidney replacement therapy [14].

During the past few years, more treatment options have been investigated in conjunction with RAASi and SGLT2i treatment to slow the progression of DKD (Tables 1, 2). This review revisits conventional management strategies for DKD: lifestyle modifications, glycemic and blood pressure control, and RAASi use. The mechanisms and preclinical and major clinical studies for new treatments, specifically glucagon-like peptide-1 receptor agonists (GLP-1 RAs), nonsteroidal mineralocorticoid receptor antagonists (MRAs), and selective endothelin A receptor antagonists (ERAs) are then reviewed.

**Lifestyle modification**

Lifestyle modifications, such as exercise, smoking cessation, and diet control, are the backbone of DKD management. The DASH (Dietary Approaches to Stop Hypertension) diet, which is high in vegetables, fruit, and low-fat dairy products, improved systolic blood pressure and 24-hour blood pressure measurements in primary hypertension patients [15]. The guideline for diabetes patients with CKD published in 2020 by Kidney Disease Improving Global Outcomes (KDIGO) recommends an individualized dietary prescription made using shared decision making. A balanced healthy diet of high-fiber foods (vegetables and fruit), plant-based protein, legumes, and unsaturated fat is encouraged. The guideline recommends protein intake of 0.8 g/kg of body weight/day for DKD patients who

<table>
<thead>
<tr>
<th>Drug class</th>
<th>GLP-1 agonist</th>
<th>Selective nonsteroidal mineralocorticoid receptor antagonist</th>
<th>Selective endothelin A receptor antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example and dosage</td>
<td>Liraglutide</td>
<td>Finerenone</td>
<td>Atrasentan</td>
</tr>
<tr>
<td></td>
<td>Exenatide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dulaglutide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Semaglutide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Efpeglenatide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Binds to GLP-1 receptor to reduce blood glucose level and maintain postprandial glucose homeostasis</td>
<td>Selective blockade of mineralocorticoid receptor</td>
<td>Selective blockade of endothelin A receptor</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Subcutaneous injection (except semaglutide which is also available orally)</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Putative effect</td>
<td>1. Natriuretic and diuretic properties and alteration of intrarenal hemodynamics</td>
<td>1. Reduces expression of mineralocorticoid receptor at the protein and mRNA levels</td>
<td>1. Decreases vascular tone and systemic blood pressure</td>
</tr>
<tr>
<td></td>
<td>2. Anti-inflammatory and antifibrotic effects:</td>
<td>2. Downregulates inflammatory cells and inflammatory cytokines such as TGF-β mRNA and osteopontin mRNA</td>
<td>2. Decreases the production of inflammatory cytokines (TGF-β)</td>
</tr>
<tr>
<td></td>
<td>a. Decreases production of TGF-β</td>
<td></td>
<td>3. Decreases macrophage infiltration</td>
</tr>
<tr>
<td></td>
<td>b. Reduces macrophage infiltration</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>c. Reduces fibronectin and collagen IV production</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>Gastrointestinal tract upset</td>
<td>Hyperkalemia</td>
<td>Fluid retention</td>
</tr>
</tbody>
</table>

GLP-1, glucagon-like receptor-1; IV, intravenous; mRNA, messenger RNA; TGF-β, transforming growth factor-β.
are not on renal replacement therapy and 1 to 1.2 g/kg of body weight/day in patients treated with hemodialysis or peritoneal dialysis. Processed meat, refined carbohydrates, and sweetened beverages are not recommended. Sodium should be restricted to <2 g/day to reduce the risk of CKD progression and increased blood pressure. A regular exercise regime, with at least 150 minutes of moderate-intensity exercise per week, has also been recommended for patients with DKD [16]. Obese patients are recommended to undertake a structured program of weight reduction. Metformin, SGLT2is, and GLP-1 RAs could have additional benefits in weight loss [17]. However, clinicians are advised to be cautious with caloric restriction, especially in patients with advanced CKD, because it can lead to malnutrition and other adverse outcomes [16].

Table 2. Summary of currently available GLP-1 RAs, selective MRAs, and selective ERAs, with dosages

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route and frequency</th>
<th>Dosage</th>
<th>Recommended renal adjustment dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 RA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide Subcutaneous injection; twice daily</td>
<td>Initially, 5 μg twice daily within the 60-minute period before the morning and evening meals; can increase to 10 μg twice daily after 1 month of therapy, based on the clinical response</td>
<td>Not recommended for patients with CrCl of &lt;30 mL/min/1.73 m²; caution recommended when initiating or escalating the dose in patients with CrCl of 30–50 mL/min/1.73 m²</td>
<td></td>
</tr>
<tr>
<td>Lixisenatide Subcutaneous injection; once daily</td>
<td>Initially, 10 μg once daily within the 60-minute period before the first meal of the day; on day 15, increase to 20 μg once daily</td>
<td>Not recommended for patients with CrCl of &lt;15 mL/min/1.73 m²</td>
<td></td>
</tr>
<tr>
<td>Liraglutide Subcutaneous injection; once daily</td>
<td>Initially, 0.6 mg once at any time of day; after 1 week of the 0.6 mg dose, increase to 1.2 mg once daily; if additional glycemic control is required, can increase to 1.8 mg once daily after ≥1 week of treatment with the 1.2 mg dose</td>
<td>No dosage adjustments required</td>
<td></td>
</tr>
<tr>
<td>Exenatide XR Subcutaneous injection; once weekly</td>
<td>2 mg once weekly at any time of day</td>
<td>Not recommended for patients with an eGFR of &lt;45 mL/min/1.73 m² or with kidney failure</td>
<td></td>
</tr>
<tr>
<td>Dulaglutide Subcutaneous injection; once weekly</td>
<td>Initially, 0.75 mg once weekly at any time of day; if additional glycemic control is required, can increase to 1.5 mg once weekly</td>
<td>No dosage adjustments required</td>
<td></td>
</tr>
<tr>
<td>Semaglutide Subcutaneous injection; once weekly</td>
<td>Initially, 3 mg once daily at least 30 minutes before intake of the first food, fluid, or other oral medications of the day; to be taken with no more than 120 mL of plain water only; after 30 days on the 3 mg dose, increase to 7 mg once daily; if additional glycemic control is required, can increase to 14 mg once daily after ≥30 days of treatment with the 7 mg dose</td>
<td>No dosage adjustments required for the subcutaneous or oral dose</td>
<td></td>
</tr>
<tr>
<td>Finerenone Oral; once daily</td>
<td>20 mg daily at any time of the day</td>
<td>For CrCl of &gt;60 mL/min/1.73 m²; start at 20 mg daily</td>
<td></td>
</tr>
<tr>
<td>Atrasentan Oral; once daily</td>
<td>0.75 mg daily</td>
<td>For CrCl of &lt;60 mL/min/1.73 m²; start at 10 mg daily then increase to 20 mg daily after 4 weeks, if tolerated</td>
<td></td>
</tr>
<tr>
<td>Selective endothelin A receptor antagonist</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GLP-1 RA, glucagon-like peptide-1 receptor agonist; ERA, endothelin A receptor antagonist; MRA, mineralocorticoid receptor antagonist; XR, extended-release.
**Glycemic control**

In various clinical studies, tight glycemic control has shown benefits in reducing diabetes-related microvascular complications. The UKPDS (UK Prospective Diabetes Study) group compared patients with tight glycemic control, with an average HbA1c of 7.4%, with a control group with an HbA1c of 8%. A 32% reduction in diabetes-related endpoints and a 36% reduction in all-cause mortality during follow-up were seen in the tight control group [18], and the microvascular risk reduction persisted for 10 years, as shown by a follow-up study [19]. In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial, the intensive treatment arm, in which HbA1c was kept <6.5%, demonstrated a 21% reduction in diabetic nephropathy and albuminuria compared with the conventional group [20]. In a post-study analysis of ADVANCE data, a reduction in end-stage kidney disease was the only positive finding with statistical significance in the intensive treatment group (hazard ratio [HR], 0.54; p = 0.007), and no benefit was found in preventing renal-disease-related deaths [21]. Furthermore, in the Veterans Affairs Diabetes Trial, intensive diabetes control to an average HbA1c of 6.9% showed no significant benefit in microvascular complications [22].

The current KDIGO guideline recommends an individualized HbA1c target ranging from 6.5% to 8%, depending on the risk profile for developing hypoglycemia, whereas the Asian Pacific Society of Nephrology (APSN) guideline suggests that the target not be lower than 7% to balance the risks of micro- and macrovascular complications against the development of hypoglycemia [17]. The glycemic target should definitely be individualized based on the patient’s severity of CKD, life expectancy, comorbidities, macrovascular complications, propensity of treatment to hypoglycemia, and awareness.

**Blood pressure control**

Intensive and individualized blood pressure control is recommended not only for the management of T2DM [23], but also in DKD to prevent cardiovascular mortality, the progression of kidney disease, and albuminuria. In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) blood pressure trial, 4,733 patients with T2DM were randomized to receive intensive therapy (systolic blood pressure target of <120 mmHg) or standard therapy (systolic blood pressure of <140 mmHg). After a mean follow-up of 4.7 years, the incidence of macroalbuminuria was lower in the intensive treatment arm, but the incidence of microalbuminuria did not differ significantly [24]. A systematic review of three other randomized controlled trials also concluded that lowering the blood pressure target had benefits for patients with macroalbuminuria [25]. Similar findings were reported for Asian DKD patients with heavy proteinuria (urine protein to creatinine ratio, >1 g/gCr); a target systolic blood pressure of ≤130 mmHg offered renoprotection and cardioprotection [26].

The current APSN clinical guideline for DKD recommends that blood pressure be lowered toward 130/80 mmHg to offer stroke and cardiovascular protection and slow kidney disease progression [17]. In the 2021 Joint Association of British Clinical Diabetologists and UK Kidney Association guideline, the blood pressure target varies with the stage of CKD and degree of proteinuria. For patients with T2DM and a urine albumin to creatinine ratio (UACR) of <3 mg/mmol, the target blood pressure should be less than 140/90 mmHg. For patients with a UACR > 3 mg/mmol, the target blood pressure should be less than 130/80 mmHg. However, caution should be used if blood pressure is not measured in a standardized manner, and a less aggressive approach should be offered to patients with a short life expectancy [27].

**Renin-angiotensin-aldosterone inhibition**

RAASis—angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs)—are widely used in hypertension management. Their ability to reduce proteinuria is predominantly due to their effect on the vasodilation of the glomerulus efferent arterioles, as has been shown in various clinical trials. In the Irbesartan Diabetic Nephropathy trial, 1,715 patients with DKD were randomized to receive irbesartan, amlodipine, or placebo. The patients who received irbesartan had a lower incidence of doubling serum creatinine, amlodipine, or placebo. The patients who received irbesartan had a lower incidence of doubling serum creatinine, amlodipine, or placebo. The patients who received irbesartan had a lower incidence of doubling serum creatinine, amlodipine, or placebo. The patients who received irbesartan had a lower incidence of doubling serum creatinine, amlodipine, or placebo.
trial, 1,513 DKD patients were randomized to receive 50 mg or 100 mg of losartan daily, in addition to their conventional antihypertensive treatment. A 20% of reduction in end-stage kidney disease or renal-related death was observed. Proteinuria and the incidence of first admission of heart failure were also reduced compared with the placebo group [28–30]. A similar result was seen in the Randomized Olmesartan and Diabetes Microalbuminuria Prevention trial: patients who received olmesartan had a lower incidence of microalbuminuria than those in the placebo group. The treatment group also had a delayed onset of microalbuminuria (23% slower than the placebo group). However, major cardiovascular events were more frequent in the olmesartan arm, especially among patients with pre-existing ischemic heart disease [31].

Hyperkalemia, hypotension, and acute kidney injury were the most frequent adverse events noted in those studies. Moreover, based on the results of the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint trial, combining an ACEi and ARB is not recommended. Patients on both an ACEi and ARB did not have any additional benefit in terms of proteinuria reduction, but they did have an increased risk of adverse events [29]. To prevent adverse events, blood pressure, serum creatinine, and potassium should be monitored within 2 to 4 weeks of starting or adjusting the dosage of an ACEi or ARB. An acute (30%) rise in serum creatinine level from baseline within 4 weeks of initiating treatment or increasing the dose should lead clinicians to rule out any underlying cause, such as hypovolemia, concomitant medications, or renal artery stenosis. In addition, dietary potassium restriction should be reinforced, and concurrent drugs (e.g., an aldosterone antagonist) that can lead to hyperkalemia should be reviewed. Adding diuretics or sodium bicarbonate can ameliorate hyperkalemia [16].

Glucagon-like peptide-1 receptor agonist

GLP-1 is an incretin hormone from intestinal cells that is secreted in response to food intake. It acts with an independent pathway from insulin to lower the blood glucose level and achieve postprandial glucose homeostasis. In humans, GLP-1 receptors are found predominantly in glomerular and proximal tubular cells; the natriuretic and diuretic properties of GLP-1 can influence renal hemodynamics [32]. Moreover, the kidneys are the major site of excretion of GLP-1, glucose-dependent insulinotropic peptide (GIP), and their metabolites. Although GLP-1 and GIP levels increase in patients with renal failure, those inactive forms of incretin hormones do not have any renoprotective effects on patients [33].

In animal models, GLP-1 agonist has shown renoprotective effects by reducing inflammation and promoting antifibrosis in the renal parenchyma. Those effects are independent of its ability to lower blood glucose. Exendin-4 promotes ABCA1 expression in glomerular endothelial cells and decreases renal cholesterol accumulation, which alleviated inflammation and proteinuria in diabetic mice [34]. An injection of liraglutide into spontaneously diabetic Torii fatty rats produced food intake, weight, blood pressure, and blood glucose reductions, downregulated the renal expression of p-mTOR, and increased the expression of LC3B-II, a marker of autophagy [35]. Another study demonstrated that giving low-dose lixisenatide to early-onset diabetic rats reduced renal transforming growth factor-β1 (TGF-β1) and exhibited antioxidant effects, such as increased iNOS and COX-2 production [36]. In rat mesangial cells treated with advanced glycation end products (AGEs), a GLP-1 receptor agonist had an anti-inflammatory effect by attenuating the production of AGE-induced interleukin-6, tumor necrosis factor-α, and AGE receptors [37].

GLP-1 RA treatment reduced ECM production via different pathways (Fig. 1). For example, a GLP-1 RA reduced fibronectin and collagen IV production by glomerular mesangial cells [38]. It also inhibited the proliferation of human mesangial cells, which upregulate TGF-β1 and connective tissue growth factor, thereby reducing ECM production and preventing fibrosis in the glomerular mesangium [39]. In a streptozotocin-induced type 1 diabetes mouse model, liraglutide attenuated Wnt/β-catenin signaling proteins and reduced glomerular fibronectin, collagen type IV, and α-smooth muscle actin, which reduced glomerular ECM accumulation and renal injury [40].

A GLP-1 RA showed an immunomodulatory effect that prevented macrophage and T cell infiltration and reduced intercellular adhesion molecule-1 (ICAM-1) and type IV collagen accumulation. GLP-1 RA cleavage products also exhibited immunomodulatory effects that attenuated the renal accumulation of macrophages and T cells [41]. GLP-1 RAs can also act on GLP-1 receptors on macrophages,
monocytes, or glomerular endothelial cells to inhibit the release of pro-inflammatory cytokines from macrophages and ICAM-1 on glomerular cells [42]. A similar effect was seen in a murine model of nephrotoxic serum nephritis: a GLP-1 RA blocked the glycolysis of T cells, which decreased Glut1 messenger RNA (mRNA) expression and the proliferation of TH1 and TH17 cells [43].

The diuresis and natriuresis effects of GLP-1 RAs were seen in both experimental and human studies and occurred via renal and extra-renal mechanisms. GLP1-RAs target Na⁺/H⁺ exchanger 3 (NHE3), which is found at the proximal tubule. NHE3 was found to reabsorb filtered sodium from the glomerulus and increase the glomerular pressure through tubuloglomerular feedback, similar to that seen with the sodium-glucose co-transporter. The GLP-1 RA was observed to inactivate or induce the phosphorylation of NHE3, which increased natriuresis [44]. The extra-renal natriuresis effects of GLP-1, including cardiac and neuronal responses to GLP-1, have also been studied. Liraglutide was found to activate GLP-1 receptors at cardiac myocytes, which increased the secretion of atrial natriuretic peptide and promoted natriuresis [45].

Several early clinical studies examined the renoprotective effect of combining a GLP-1 RA with oral antidiabetic agents or insulin (Table 3). A small study that combined weekly liraglutide with a RAASi reduced albuminuria by 32% and average systolic blood pressure by 5 mmHg [46]. In a post hoc comparison of data from patients using once-weekly exenatide and those using a non-GLP-1 receptor agonist (both groups received the maximum tolerated dose of a RAASi), a 26.2% reduction in albuminuria was seen, and its effect was independent of baseline RAASi usage [47,48]. In a post hoc analysis for the data of DECREASE (Dapagliflozin Plus Exenatide on Central REgulation of Appetite in diabetes type 2) study, the combination of twice-daily exenatide and dapagliflozin was found to have a synergistic effect in reducing mean urine albuminuria compared with the use of dapagliflozin alone; –39.6% vs. –18.1% in UACR compared with baseline [49]. Another study compared exenatide plus glargine to lispro plus glargine and showed a greater UACR.

*Figure 1. The biological mechanism of GLP-1 receptor agonist.*

ANP, atrial natriuretic peptide; GLP-1, glucagon-like peptide-1; NHE3, Na⁺/H⁺ exchanger 3.
change in the exenatide group. Weight loss was observed in the exenatide group (−1.38 ± 0.63 kg), and weight gain was seen in the insulin group (+1.30 ± 0.66 kg).

In future therapeutic use, GLP-1 RAs might work in conjunction with mesenchymal stem cells to stabilize inflammation and fibrosis while the mesenchymal stem cells restructure the renal parenchyma.

In large-scale human clinical studies, GLP-1 RAs showed positive effects in slowing the progression of DKD, though the early data were mainly from cardiovascular or diabetes studies. In the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial, 9,340 patients with T2DM were recruited to receive liraglutide or placebo, and patients’ cardiovascular outcomes were investigated. DKD events were lower in the liraglutide arm than in the placebo arm (1.5 vs. 1.9 events per 100 patient-years of observation), and CKD progression was slowed in patients with eGFR of <30 mL/min/1.73 m².

Table 3. Summary of clinical trials of GLP-1 RAs and renal outcomes

<table>
<thead>
<tr>
<th>Clinical trial* (year)</th>
<th>Agent</th>
<th>Patient characteristics</th>
<th>Cohort size</th>
<th>Duration</th>
<th>Renal outcome</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEADER (2017) [52,54]</td>
<td>Liraglutide (1.8 mg vs. placebo)</td>
<td>T2DM with high CV risk</td>
<td>9,340</td>
<td>3.84 years</td>
<td>New-onset macroalbuminuria, doubling of the serum creatinine level, ESRD, renal death</td>
<td>HR, 0.78 (95% CI, 0.67–0.92)</td>
</tr>
<tr>
<td>SUSTAIN-6 (2016) [54]</td>
<td>Semaglutide (0.3 mg, 0.1 mg vs. placebo)</td>
<td>Age &gt; 50 yr with established CVD or CKD stage 3–5</td>
<td>3,297</td>
<td>104 weeks</td>
<td>New or worsening nephropathy (persistent macroalbuminuria, doubling of the serum creatinine level, and Ccr of &lt;45 mL/min/1.73 m²)</td>
<td>HR, 0.64 (95% CI, 0.46–0.88)</td>
</tr>
<tr>
<td>AWARD-7 (2018) [58]</td>
<td>Dulaglutide (0.75 mg, 1.5 mg vs. placebo)</td>
<td>T2DM with moderate to severe CKD (stage 3–4)</td>
<td>576</td>
<td>52 weeks</td>
<td>Changes in eGFR decline and UACR from baseline</td>
<td>eGFR decline: −1.1 (1.5 mg), −1.5 (0.75 mg), −2.9 (glargine)</td>
</tr>
<tr>
<td>ELIXA (2018) [56]</td>
<td>Lixisenatide (10–20 mg vs. placebo)</td>
<td>T2DM with recent acute coronary syndrome</td>
<td>6,068</td>
<td>108 weeks</td>
<td>Percent change in UACR and eGFR from baseline</td>
<td>eGFR decline no significant differences among groups</td>
</tr>
<tr>
<td>REWIND (2019) [57]</td>
<td>Dulaglutide (1.5 mg vs. placebo)</td>
<td>T2DM with a previous CV event or CV risk factors</td>
<td>9,901</td>
<td>5.4 years</td>
<td>New onset of macroalbuminuria, sustained eGFR decline (≥30%), or RRT</td>
<td>HR, 0.85 (95% CI, 0.77–0.93)</td>
</tr>
</tbody>
</table>

CCr, creatinine clearance; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; RRT, renal replacement therapy; T2DM, type 2 diabetes mellitus; UACR, urine albumin to creatinine ratio.
>30 days or end-stage kidney disease) by 32% [55]. In an exploratory analysis of the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) study that specifically targeted renal outcomes, lixisenatide was found to reduce proteinuria in patients with different preexisting severities of proteinuria, and eGFR did not change significantly [56]. In an exploratory analysis of the REWIND (Researching Cardiovascular Events with Weekly Incretin in Diabetes) study, dulaglutides reduced the incidence of first-onset microalbuminuria in T2DM patients (HR, 0.77; 95% CI, 0.68–0.87; p < 0.0001), the rate of decline in eGFR, and the incidence of chronic renal replacement therapy initiation [57].

The AWARD-7 (Dulaglutide versus insulin glargine in patients with type 2 diabetes and CKD) study examined the renal outcomes of patients with moderate to severe DKD and demonstrated that GLP-1 RAs have a unique class effect. AWARD-7 included 576 patients with stage 3–4 DKD who all received maximum RAASi therapy, oral hypoglycemic agents, and/or insulin before randomization. Patients were randomized to receive weekly dulaglutide (0.75 mg or 1.5 mg) or glargine insulin for 52 weeks, and changes in HbA1c and UACR and the rate of decline in eGFR were examined. The study found no significant change in UACR compared with baseline, but the rate of eGFR decline was slower in the dulaglutide groups (–1.1 mL/min/1.73 m² and –1.5 mL/min/1.73 m² with 1.5 mg and 0.75 mg, respectively), and the incidence of end-stage kidney disease was also lower in the dulaglutide groups [58]. Compared with other cardiovascular event-oriented studies in which the treatment of T2DM and hypertension varied among patients, the AWARD-7 study successfully demonstrated an independent class effect for renoprotection, which can be related to the mechanism discussed.

In terms of adverse events, lixisenatide had a higher incidence of gastrointestinal adverse events than placebo (by 14%) [59]. Several cases of acute kidney injury were associated with GLP-1 RA treatment, mainly acute tubular injury [60]. Liraglutide is recommended over exenatide because exenatide is predominantly excreted via renal mechanisms, but caution should be exercised with liraglutide because it lacks adequate pharmacokinetic data [61]. None of the major clinical studies discussed above reported any significant adverse events.

In summary, GLP-1 RAs have been shown to improve weight loss, hypertension, glycemic control, and UACR. The renoprotective effect was attributed to their ability to target immunomodulatory pathways, reduce the release of inflammatory cytokines, downregulate the chemotraction of inflammatory cells, and reduce intracellular matrix deposition and subsequent interstitial fibrosis. They also increase natriuresis and diuresis, which can alter renal hemodynamics. Both RAASis and SGLT2is target glomerular hemodynamics by altering renal perfusion or tubuloglomerular feedback, but they do not alter renal interstitial inflammation. The additional natriuresis and anti-inflammatory effects of GLP-1 RAs can be another tool for managing advanced CKD. Most of the clinical evidence discussed is based on post hoc analyses of data from cardiovascular trials. The AWARD-7 study demonstrated that GLP-1 RAs have a potential class effect independent of blood pressure and glycemic control. More renal outcome-oriented studies of different GLP-1 RAs should be conducted to strengthen the evidence for that unique class effect.

**Nonsteroidal selective mineralocorticoid receptor antagonist**

Aldosterone has multiple extra-renal effects, including the induction of inflammation, increased vascular rigidity, collagen formation, and the stimulation of fibrosis. Blocking the mineralocorticoid receptor can prevent or slow the progression of heart or kidney disease [62]. Steroidal MRAs, e.g., spironolactone or eplerenone, can prolong survival in cardiac failure patients by improving hypertension and having antifibrosis and anti-inflammatory effects [63,64]. However, it is underused in CKD, even though it has been shown to improve proteinuria, because it carries a risk of hyperkalemia, as shown in a previous meta-analysis [65].

Finerenone (Fig. 2), a nonsteroidal selective MRA, was found in animal studies to have renoprotective effects and ameliorate proteinuria with few adverse events [66]. Rodent models of T1DM and T2DM show an increase in the expression of mineralocorticoid receptors at the protein and mRNA levels, apart from albuminuria and renal injury. Other factors that contribute to the activation of inflammatory cells such as TGF-β mRNA and osteopontin mRNA were also increased in those models. Those factors were downregulated with the use of an MRA, which indicates that MRAs might have a role in reducing inflammation and fibrosis [67].
Selective MRAs also show antifibrosis effects in animal cardiac models. For example, in a preclinical model with deoxycorticosterone acetate and salt-challenged rats, finerenone not only prevented kidney damage and proteinuria but also reduced cardiac damage and ventricular hypertrophy [68]. In phase 2 clinical studies, finerenone was found to ameliorate UACR after 90 days of treatment in DKD patients [69,70]. Other agents, such as aparenalone (phase II study) and examenone (phase III study), were shown to reduce proteinuria (Table 4) [71,72].

The FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) study is a major human clinical study on finerenone in which 5,734 patients with DKD stage 3b to 4 were randomized to receive finerenone or placebo with the maximum tolerated dose of a RAASi. In a median follow-up of 2.6 years, the finerenone group had fewer renal composite events (kidney failure, sustained decrease in eGFR of at least 40% from baseline, or death from renal causes) than the placebo group [73]. A subsequent study also demonstrated that finerenone treatment reduced composite kidney outcomes in patients with a history of cardiovascular disease (15.3% in finerenone group vs. 20.5% in placebo group) [74]. However, in a post hoc safety analysis, hyperkalemia was more common in the finerenone arm (21.4% with serum potassium level of >5.5 mmol/L and 4.5% with >6 mmol/L) [75].

The FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) study tested finerenone in patients with less severe CKD than those in the FIDELIO-DKD study, and its focus was on the cardiovascular outcome. Finerenone reduced the incidence of death from cardiovascular causes compared with placebo (12.4% vs. 14.2%). Kidney failure and death from renal causes were also less common in the finerenone arm (9.5% vs. 10.8%) [76].

Overall, finerenone has renoprotective effects, and evidence shows that it reduces proteinuria, likely as a result of its anti-inflammatory and antifibrotic effects. Despite a higher incidence of hyperkalemia in the finerenone arm of the FIDELIO-DKD study, the discontinuation rate was lower than in other clinical studies that combined a RAASi with a specific target and intervention for hyperkalemia during the study period [77,78]. The patients in the FIDELIO-DKD study had relatively advanced CKD, so regardless of the study result and rate of adverse events, dietary restriction of potassium and careful monitoring during treatment would be highly recommended for such patients.

**Selective endothelin A receptor antagonist**

Endothelin-1 (ET-1) can be stimulated by different factors
### Table 4. Summary of clinical trials of nonsteroidal mineralocorticoid receptor antagonists and renal outcomes

<table>
<thead>
<tr>
<th>Clinical trial (year)</th>
<th>Agent</th>
<th>Patient characteristics</th>
<th>Cohort size</th>
<th>Duration</th>
<th>Renal outcome</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase III clinical study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESAX-DN (2020) [71]</td>
<td>Esaxerenone (CS-3150) of 1.5–2.5 mg vs. placebo</td>
<td>T2DM with UACR of 45–300 mg/g</td>
<td>455</td>
<td>52 weeks</td>
<td>UACR remission (&lt;30 mg/g creatinine and ≥30% reduction from baseline on two consecutive occasions)</td>
<td>22% of patients achieved complete remission of UACR HR, 5.13 (95% CI, 3.27–8.04)</td>
</tr>
<tr>
<td>FIDELIO-DKD (2020) [73]</td>
<td>Finerenone of 20 mg vs. placebo</td>
<td>UACR of 30 to &lt;300 mg/g and eGFR of ≥25 to &lt;60 mL/min/1.73 m² or UACR of ≥300 mg/g and eGFR of ≥25 to &lt;75 mL/min/1.73 m²</td>
<td>5,734</td>
<td>2.6 years</td>
<td>Time to onset of kidney failure</td>
<td>HR, 0.82 (95% CI, 0.73–0.93; p = 0.00)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Phase II clinical study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finerenone on albuminuria in DKD (2015) [70]</td>
<td>Finerenone (1.25, 2.5, 5, 7.5, 10, 15, or 20 mg per day) vs. placebo</td>
<td>T2DM with UACR ≥ 30 mg/g and eGFR ≥ 30 mL/min/1.73 m²</td>
<td>823</td>
<td>90 days</td>
<td>Reduction of UACR from baseline at day 90</td>
<td>7.5 mg: HR, 0.79 (90% CI, 0.68–0.91; p = 0.004) 10 mg: HR, 0.76 (90% CI, 0.65–0.88; p = 0.001) 15 mg HR, 0.67 (90% CI, 0.58–0.77; p &lt; 0.001) 20 mg HR, 0.62 (90% CI, 0.54–0.72; p &lt; 0.001)</td>
</tr>
<tr>
<td>ARTS-DN (2017) [69]</td>
<td>Finerenone (1.25, 2.5, 5, 7.5, 10, 15, or 20 mg per day) vs. placebo</td>
<td>Japanese patients with T2DM, UACR ≥ 30 mg/g, and eGFR ≥ 30 mL/min/1.73 m²</td>
<td>96</td>
<td>90 days</td>
<td>Reduction of UACR from baseline at day 90</td>
<td>The least square mean ratio of UACR to baseline was reduced to 0.670 at day 90 in the 20 mg group compared with placebo and the other treatment groups</td>
</tr>
<tr>
<td>Apararenone in DKD (2021) [72]</td>
<td>Apararenone (2.5, 5, or 10 mg) vs. placebo</td>
<td>eGFR ≥ 30 mL/min/1.73 m² or UACR ≥ 50 mg/g or median UACR ≥ 50 mg/g and &lt;300 mg/g in the first morning void urine samples</td>
<td>293</td>
<td>52 weeks</td>
<td>Change of UACR at 24 weeks</td>
<td>Remission rate of UACR at 52 weeks</td>
</tr>
</tbody>
</table>

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; T2DM, type 2 diabetes mellitus; UACR, urine albumin to creatinine ratio.
in DKD, such as an increase in the insulin level, hyperglycemia, or acidemia [79]. It has multiple pathological effects, including the alteration of renal blood flow and glomerular filtration by the activation of ETA receptors in the vascular smooth muscles of the glomeruli and small vessels of the kidney. ET-1 can also cause renal inflammation by increasing the production of inflammatory cytokines and growth factors, and it promotes the chemoattraction of macrophages in the kidney and subsequently increases interstitial matrix deposition.

ERAs have been available since the early 1990s and have been used mainly to treat hypertension through their reduction of renal vascular tone (Fig. 3). Moreover, ERAs ameliorate renal interstitial inflammation and fibrosis. An early preclinical study showed that a selective ERA reduced the progression of DKD by improving vascular tone, decreasing the production of inflammatory cytokines (including TGF-β), and attenuating macrophage infiltration [80].

A human clinical study showed that an ERA improved blood pressure and the systemic vascular index [81]. Clinical studies of avosentan demonstrated improvement in UACR and dyslipidemia in DKD patients [82,83]. In those studies, fluid overload and exacerbation of cardiac failure were the most common adverse effects [84–87]. A human clinical study of atrasentan showed that it had a renoprotective effect when it was used in conjunction with a RAA-Si. In that study, 51% of the DKD patients who received 0.75 mg of atrasentan and 55% of the patients who received 1.25 mg of atrasentan had proteinuria reductions compared with the placebo group. Improvements in low-density lipoprotein cholesterol, triglycerides, and 24-hour blood pressure monitoring were also reported in that study. However, the dropout rate was relatively high among patients receiving the higher dose of atrasentan due to intolerance of weight gain and anemia [88].

A similar study was stopped early due to a high number of similar adverse events.

**Figure 3. The biomechanism of selective endothelin receptor antagonist.**

DKD, diabetic kidney disease.
<table>
<thead>
<tr>
<th>Clinical trial (year)</th>
<th>Agent</th>
<th>Subject characteristics</th>
<th>Cohort size</th>
<th>Duration</th>
<th>Renal outcome</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wenzel et al. (2009) [83]</td>
<td>Avosentan (5/10 /25/50 mg vs. placebo)</td>
<td>T2DM with eGFR of &gt;30 mL/ min and UAER of ≥0.2 and ≤5.6 mg/min</td>
<td>286</td>
<td>12 weeks</td>
<td>Change in UAER</td>
<td>Decreased mean relative UAER in avosentan group (16.3%–29.9%) compared with placebo (35.5%). 7.3% of patients had adverse events and withdrew from treatment</td>
</tr>
<tr>
<td>ASCEND (2010) [82]</td>
<td>Avosentan (25/50 mg) daily vs. placebo</td>
<td>T2DM with UACR of ≥35 mg/ mmol</td>
<td>1,392</td>
<td>4–16 months (premature termination of study)</td>
<td>Doubling Scr, ESRD, or death Change in UACR Cardiovascular outcome</td>
<td>UACR decrease by: 44.3% in 25 mg group 49.3% in 50 mg group 9.7% in placebo group Adverse events rate: 19.6% in 25 mg group 18.2% in 50 mg group 11.5% in placebo group</td>
</tr>
<tr>
<td>Atrasentan in DKD patients (2011) [91]</td>
<td>Atrasentan (0.25, 0.75, or 1.75 mg daily) vs. placebo</td>
<td>T2DM with eGFR of &gt;20 mL/ min/1.73 m² &amp; UACR of 100 to 3,000 mg/g</td>
<td>89</td>
<td>8 weeks</td>
<td>Reduction of UACR</td>
<td>UACR reduction 21% in 0.25 mg group 42% in 0.75 mg group 35% in 1.75 mg group</td>
</tr>
<tr>
<td>Rafnsson et al. (2012) [81]</td>
<td>Bosentan 125 mg BD vs. placebo</td>
<td>T2DM with urine albumin concentration of &gt;20 μg/L or &gt;30 μg per 12 hours or an albumin/creatinine ratio of &gt;3.0 mg/mmol</td>
<td>46</td>
<td>4 weeks</td>
<td>Change in UACR</td>
<td>No significant change</td>
</tr>
<tr>
<td>RADAR (2014) [88]</td>
<td>Atrasentan (0.75 or 1.25 mg) vs. placebo</td>
<td>T2DM with eGFR of 30–75 mL/min/1.73 m² and UACR of 300–3,500 mg/g</td>
<td>211</td>
<td>12 weeks</td>
<td>Reduction of UACR</td>
<td>UACR reduction 35% in 0.75 mg group (95% CI, 24–45) 38% in 1.25 mg group (95% CI, 28–47)</td>
</tr>
<tr>
<td>SONAR (2019) [89]</td>
<td>Atrasentan 0.75 mg vs. placebo</td>
<td>T2DM with eGFR of 30–75 mL/min/1.73 m² &amp; UACR of 300–5,000 mg/g</td>
<td>4,711</td>
<td>5 years</td>
<td>A composite of doubling of serum creatinine (sustained for ≥30 days) or end-stage kidney disease (eGFR of &lt;15 mL/min/1.73 m² sustained for ≥90 days, chronic dialysis for ≥90 days, kidney transplantation, or death from kidney failure)</td>
<td>6% of patients in the atrasentan group and 7.9% of the placebo group had a primary composite renal endpoint event HR, 0.65 (95% CI, 0.49–0.88); p = 0.0047</td>
</tr>
</tbody>
</table>

BD, twice daily; CI, confidence interval; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; Scr, serum creatinine; T2DM, type 2 diabetes mellitus; UACR, urine albumin to creatinine ratio; UAER, urine albumin excretion rate.
of similar adverse events. The SONAR (Study of Diabetic Nephropathy with Atrasentan) is the largest randomized controlled trial to date to investigate the efficacy of ERA. Patients had to enter a 6-week "enrichment period" in which they received 0.75 mg of atrasentan daily to monitor them for any adverse events before they were randomized for the main trial. In the main trial, 4,711 patients with stage 2 to 4 DKD and a UACR between 300 and 5,000 g/mg were randomized to continue taking atrasentan or receive placebo. A 35% to 38% reduction in proteinuria was seen in the atrasentan arm. Both studies concluded that fluid retention and exacerbation of heart failure were common side effects, but the incidence of those effects did not differ significantly from placebo [89]. A post hoc analysis of the SONAR data that compared pretrial eGFR to eGFR during the trial period found a reduction in the rate of eGFR decline in the atrasentan group compared with the placebo group [90]. Early clinical studies of ERAs demonstrated positive results for renal outcomes, such as a reduction in albuminuria (Table 5 [81–83,88–90]). However, a high rate of adverse events such as fluid overload, the exacerbation of cardiac failure, and death, outweighed those therapeutic effects, which might explain the lack of further clinical studies of ERAs. The SONAR study heralded the positive potential of ERA for managing DKD, but it seems to be suitable only for a highly selected group and requires careful clinical monitoring. Moreover, clinicians should be cautious about the adverse effects of ERAs, primarily fluid overload and the exacerbation of cardiac failure. A trial period of ERA use with close monitoring for adverse reactions could be useful. Overall, more clinical studies with different ERAs should be conducted to clarify their efficacy and adverse effects.

Conclusion

For the past 20 years, RAASis have been the only treatment with evidence to show that they reduce proteinuria and the progression of kidney disease. The advent of SGLT2is thus changed the landscape of DKD management. Despite their effectiveness, the current guidelines do not recommend that an SGLT2i be initiated in patients with an eGFR < 30 mL/min/1.73 m², and SGLT2i treatment should be stopped when a patient requires kidney replacement therapy. GLP-1 RA treatment does not require a dose adjustment according to eGFR, so it could potentially fill that treatment gap [16]. Finerenone and atrasentan might offer additional benefits when used with conventional therapy. However, more real-world data are required to demonstrate their efficacy and safety. Despite those advances, lifestyle modifications and regular DKD complication screening using the UACR in diabetes patients should be emphasized in the primary care setting to avoid missing the window of opportunity for initiating specific treatments.

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

ATPC was supported by the Croucher Senior Medical Fellowship, which was awarded to SCWT in 2019. This work is also supported by philanthropic donations from the Mr & Mrs Tam Wing Fan Edmund Renal Research Fund, Dr. Rita T Liu SBS of the L & T Charitable Foundation Ltd. & the Bingei Family of Indo Café, Mr. Winston Leung, Mr. K.K Chan of Hong Kong Concrete Co. Ltd., Ms. Lau Siu Suet, and an Endowment Fund established at the University of Hong Kong for the “Yu Professorship in Nephrology" awarded to SCWT. The funding bodies had no role in writing the manuscript.

Authors’ contributions

Writing–original draft: ATPC
Writing–review & editing: ATPC, SCWT
All authors read and approved the final manuscript.

ORCID

Anthony T.P. Chan, https://orcid.org/0000-0002-4327-4090
Sydney C.W. Tang, https://orcid.org/0000-0002-6862-1941

References

15. Moore TJ, Conlin PR, Ard J, Svetkey LP. DASH (dietary approaches to stop hypertension) diet is effective treatment for stage 1 isolated systolic hypertension. Hypertension 2001;38:155–158.
27. Kidney Disease: Improving Global Outcomes (KDIGO) Blood


51. Habib HA, Heeba GH, Khalifa M. Effect of combined therapy of
mesenchymal stem cells with GLP-1 receptor agonist, exenatide, on early-onset nephropathy induced in diabetic rats. *Eur J Pharmacol* 2021;892:173721.


77. Fried LE, Emanuele N, Zhang JH, et al. Combined angiotensin...


Background: Sodium chloride (NaCl) reabsorption in the cortical thick ascending limb (cTAL) is regulated by opposing effects. Nitric oxide (NO) inhibits NaCl reabsorption while 8-iso-prostaglandin-F2α (8-iso-PGF2α) stimulates it. Their interaction has not been evaluated in the cTAL. Because 8-iso-PGF2α has considerable stability while NO is a free radical with a short half-life, we hypothesized that, in the cTAL, the inhibition of NaCl absorption will be reversed by 8-iso-PGF2α.

Methods: Chloride absorption (J Cl) was measured in isolated perfused cTALs and whether the activation of protein kinase A (PKA) is required for this interaction. Since cyclic adenosine monophosphate (cAMP) is a major messenger for the 8-iso-PGF2α signaling cascade, and NO inhibits J Cl by decreasing cAMP bioavailability, we measured 8-iso-PGF2α-stimulated cAMP in the presence of sodium nitroprusside (SNP).

Results: The NO donor, SNP (10⁻⁶ M), decreased J Cl by 41%, while luminal 8-iso-PGF2α (100 μM) increased J Cl to 315 ± 46 pmol/min/mm (p < 0.003), reversing the effects of the NO donor. SNP inhibited J Cl, 8-iso-PGF2α failed to increase J Cl in the presence of H89. Basal cAMP was 56 ± 13 fmol/min/mm, in the presence of SNP 57 ± 6 fmol/min/mm, and 8-iso-PGF2α increased it to 92 ± 2 fmol/min/mm (p < 0.04).

Conclusion: We concluded that 1) NO-induced inhibition of J Cl in the cTAL can be reversed by 8-iso-PGF2α, 2) 8-iso-PGF2α and NO interaction requires PKA to control J Cl, and 3) in the presence of NO, 8-iso-PGF2α continues to stimulate J Cl because NO cannot reverse 8-iso-PGF2α-stimulated cAMP level.

Keywords: Hypertension, Isoprostanes, Nitric oxide, Oxidative stress

Introduction

The nephron segment, cortical thick ascending limb (cTAL) regulates sodium chloride (NaCl) reabsorption as one of the most involved segments in NaCl retention states. In normal conditions, absorption of NaCl is balanced with...
its excretion, maintaining Na balance. This homeostasis is the final result of the action of molecules increasing and decreasing transport. However, in pathologic conditions, such as congestive heart failure, chronic kidney disease, hypertension, cirrhosis, and other diseases, Na retention is greater than its excretion, leading to a positive Na imbalance. This Na overload occurs because Na retention factors overcome the actions of molecules that increase its excretion, resulting in resistance to natriuretic effects. Understanding the interaction of the autacoids at the different nephron segments, especially at the cTAL, would help to elucidate such deleterious conditions and find strategies to manage them.

Previously, we reported that 8-iso-prostaglandin-F2α (8-iso-PGF2α) increases Na⁺ and Cl⁻ reabsorption at the cTAL [1]. This effect, in vivo, would increase Na balance, inducing a blood pressure elevation that could be displayed as hypertension, congestive heart failure, cirrhosis, chronic kidney disease, or other edematous states. On the other hand, nitric oxide (NO) inhibits Na⁺ reabsorption at the cTAL, and this effect, in vivo, would induce diuresis and natriuresis, a mechanism that would decrease the described Na gain [2,3]. Despite the clear understanding of the importance of these effects, the interaction of NO and 8-iso-PGF2α in the cTAL has not been evaluated to elucidate their outcomes.

Na⁺ regulation has been previously reported at several nephron segments mediated by agents such as NO and angiotensin II in the cTAL [4,5], NO and arginine vasopressin at the cortical collecting duct level [6], and other segments [7]. The final effect of the interaction between NO and 8-iso-PGF2α is based on the intracellular activation of different regulators. Actually, whereas NO inhibits NaCl reabsorption by increasing intracellular cyclic guanosine monophosphate (cGMP) and decreasing cyclic adenosine monophosphate (cAMP) levels [7], 8-iso-PGF2α increases cAMP. The final effect will be elicited when one cyclic nucleotide preponderantly represses the other. When attempting to understand the crosstalk regulation of cyclic nucleotide concentrations, one must consider that such regulation can occur at the level of cyclic nucleotide synthesis, phosphodiesterase-mediated degradation, or even cellular efflux. Thus, we hypothesized that, in cTAL, persistent effects of 8-iso-PGF2α on Na reabsorption prevail over the shorter-acting NO effects, and protein kinase A (PKA) activation is required for such interaction.

**Methods**

**Animals**

Male New Zealand white rabbits (700–1,200 g) were housed for 3 to 7 days before the study for acclimatization. The experiments were approved by the Institutional Animal Care and Use Committee of the J. Robert Cade Foundation (No. FJRC #2009) in Córdoba, Argentina. All animals were housed and handled according to the Public Health Service Policy on Humane Care and Use of Laboratory Animals.

**Preparation and dissection of the cortical thick ascending limb of Henle**

Animals were anesthetized with sodium thiopental (30 mg/kg, intravenously) and xylazine (20 mg/kg, intramuscularly) plus ketamine (50 mg/kg, intramuscularly). The kidney was exposed and bathed in ice-cold saline and then excised and cut into coronal slices along the longitudinal axis. The slices were placed in oxygenated physiological saline in a temperature-regulated chamber at 4°C. The cTAL of Henle was dissected from the medullary ray under a stereomicroscope as previously described [6,8].

**Perfusion of thick ascending limbs**

cTALs in a temperature-regulated chamber were perfused between concentric glass pipettes at 37°C as described [6]. The basolateral bath was exchanged at a rate of 0.5 mL/min. A total of five to eight tubules were analyzed during each protocol. Time-control experiments were conducted to ensure the stability of tubular transport. Chloride absorption (Jcl) was measured as previously described [6,9]. cTALs were perfused and equilibrated for 20 minutes, and basal Cl absorption was calculated two to three times. Test ed compounds, including 8-iso-PGF2α, were either added to or removed from the lumen or bath as indicated. After a 20-minute equilibration period, tubular fluid was again collected 2 or 3 times.
Chloride concentrations in the perfusate and collected fluid

Chloride concentrations were measured by microfluorometry [10]. Because water is not reabsorbed by the thick ascending limb, \( J_{\text{Cl}} \) was calculated by the following equation:

\[
J_{\text{Cl}} = CR \times (C_{\text{Cl}}^0 - C_{\text{Cl}}^1),
\]

where \( CR = \) collection rate normalized/tubule length, \( C_{\text{Cl}}^0 = \) chloride concentration in the perfusion solution, and \( C_{\text{Cl}}^1 = \) chloride concentration in the collected fluid.

Cyclic adenosine monophosphate

cAMP was measured as previously described [1]. Briefly, tubules were isolated and incubated in 95 µL perfusion solution containing 1-mM 3-isobutyl-1-methylxanthine at 37°C for 10 minutes before adding 5-µL medium containing inhibitors or hormones. The reaction was stopped 30 minutes later with methanol (100 µL), and cAMP and cGMP levels were measured by an enzyme immunoassay (EIA; Cayman Chemical, Ann Arbor, MI, USA). The samples were centrifuged, the supernatant was transferred to another tube and dried in a Savant centrifugal vacuum concentrator, and the pellet was reconstituted in 110-µL sodium acetate buffer. The cAMP standard was treated the same way. The results were expressed as fmol/min/mm tubule length.

Statistics

Data were analyzed by paired and unpaired Student t tests and one-way analysis of variance, and results with \( p < 0.05 \) were significant. Results were expressed as mean ± standard error of the mean.

Results

Since the 8-iso-PGF2α/NO interaction in cTAL is uncertain, we chose a maximum NO bioavailability model. As described, the micro-isolated rabbit cTALs were transferred to a temperature-regulated chamber and perfused between concentric glass pipettes at 37°C [6] with the NO donor sodium nitroprusside (SNP) in a concentration that decreases transport by 40% as endogenous NO is inhibited in this nephron segment [11]. Before adding SNP to the bath, \( J_{\text{Cl}} \) was 333 ± 35 pmol/min/mm. SNP (1 mM) in the bath reduced \( J_{\text{Cl}} \) to 195 ± 26 pmol/min/mm (\( p = 0.01 \) vs. basal; \( n = 5 \)) (Fig. 1), a 41% decrease, and remained inhibited for the rest of the experiment (196 ± 22 pmol/min/mm). In vivo, this reduction in \( J_{\text{Cl}} \) should increase diuresis. In time-control experiments, \( J_{\text{Cl}} \) remained constant throughout the experimental period.

Next, we tested whether 8-iso-PGF2α stimulates \( J_{\text{Cl}} \) in the presence of SNP. Basal \( J_{\text{Cl}} \) was 330 ± 18 pmol/min/mm; when SNP (1 mM) was added to the bath, \( J_{\text{Cl}} \) decreased to 191 ± 19 pmol/min/mm. After adding 8-iso-PGF2α (100 µM) to the lumen, \( J_{\text{Cl}} \) increased to 346 ± 39 pmol/min/mm (\( p < 0.02 \) vs. NO; \( n = 5 \)) (Fig. 2). We tested this concentration since those lower did not affect \( J_{\text{Cl}} \) [1]. Next, we evaluated the effect of 8-iso-PGF2α present in the basolateral side. Basal \( J_{\text{Cl}} \) was 235 ± 38 pmol/min/mm, which decreased in the presence of SNP (1 mM) to 139.4 ± 27 pmol/min/mm and increased to 297 ± 29 pmol/min/mm in the presence of 8-iso-PGF2α (100 µM; \( p < 0.02 \) vs. NO; \( n = 5 \)) (Fig. 3). These data indicate that the maximal NO effect on cTAL is insufficient to prevent the 8-iso-PGF2α-stimulated NaCl reabsorption.

![Figure 1. SNP inhibits \( J_{\text{Cl}} \), nitric oxide decreases \( J_{\text{Cl}} \) in the cTAL. Basal \( J_{\text{Cl}} \) was 333.5 ± 35.2 pmol/min/mm and the addition of SNP (1 mM) decreased it to 195.9 ± 26.1 pmol/min/mm (*p = 0.01 vs. basal; \( n = 5 \)) (Fig. 1), a 41% decrease, and remained decreased during the experimental time (196.5 ± 22.3 pmol/min/mm). cTAL, cortical thick ascending limb; \( J_{\text{Cl}} \), chloride absorption; SNP, sodium nitroprusside.](www.krcp-ksn.org)
the effect of 8-iso-PGF2α on cAMP in the presence of a NO donor, SNP (1 mM). Basal cAMP was 56.3 ± 13.1 fmol/min/mm, while that in the presence of the NO donor was 57.8 ± 6.1 fmol/min/mm, and 8-iso-PGF2α increased it to 92.1 ± 2.9 fmol/min/mm (*p < 0.001 vs. control and vs. SNP period; n = 10, one-way analysis of variance [Tukey honestly significant difference post hoc test]). cAMP, cyclic adenosine monophosphate; JCl, chloride absorption; NO, nitric oxide; SNP, sodium nitroprusside; 8-iso-PGF2α, 8-iso-prostaglandin-F2α.

In cTAL, 8-iso-PGF2α stimulates JCl via a cAMP-dependent mechanism [1], while NO inhibits chloride reabsorption by stimulation of a cGMP-stimulated phosphodiesterase, which decreases cAMP level [12]. Thus, we evaluated the effect of 8-iso-PGF2α on cAMP in the presence of a NO donor, SNP (1 mM). Basal cAMP was 56.3 ± 13.1 fmol/min/mm, while that in the presence of the NO donor was 57.8 ± 6.1 fmol/min/mm, the addition of 8-iso-PGF2α to which increased cAMP to 92.1 ± 2.9 fmol/min/mm (*p < 0.04) (Fig. 4). Thus, 8-iso-PGF2α-stimulated NO-inhibited JCl is associated with a 60% increase in cAMP.

In the cTAL, PKA mediates the effect of 8-iso-PGF2α on JCl. Thus, we evaluated the effect of 8-iso-PGF2α on SNP-inhibited JCl in the presence of H89 (10 mM), a PKA inhibitor. Basal JCl was 249 ± 13 pmol/min/mm and decreased to 173 ± 14 pmol/min/mm when SNP (1 mM) was added to the bath. Addition of H89 to the bath did not change JCl significantly (158 ± 10 pmol/min/mm). Under these conditions, 8-iso-PGF2α could not stimulate SNP-inhibited JCl (147 ± 15 pmol/min/mm) (Fig. 5). Time control did not change during the experiment (280 ± 22 pmol/min/mm vs. 282 ± 36 pmol/min/mm). These data indicate that 8-iso-PGF2α requires PKA activity to reverse the NO-inhibited JCl.
The significance of this interaction resides not only in improving understanding of the normal physiology, but also in the prevention and treatment of many conditions such as hypertension, chronic renal failure, and cirrhosis, where isoprostanes increase and an Na retention state prevails [18].

The compound 8-iso-PGF2α binds the TXA2 receptor, a peroxidized derivative of prostaglandin-F2 localized in the basolateral and apical membrane of the thick ascending limb segment, which then activates cAMP production [14]. Following the release of 8-iso-PGF2α, sudden activation of the TXA2 receptor receptor in the thick ascending limb occurs [1], stimulating chloride reabsorption via cAMP. Simultaneously, NO inhibits 8-iso-PGF2α via cGMP generation. Therefore, the interaction between these two intracellular mechanisms could regulate sodium transport.

In the kidney, 8-iso-PGF2α induces vasoconstriction, which can modulate renal blood flow [19]. In the thick ascending limb, TXA2 receptor release stimulates PKA and induces an increase in chloride reabsorption across the Na-K-Cl cotransporter 2 (NKCC2) [20]. Increased concentrations of 8-iso-PGF2α and other isoprostanes have been observed in both the urine and plasma of hypertensive subjects. The enhanced NaCl retention in response to 8-iso-PGF2α might contribute to the pathogenesis of hypertension [20]. In the distal nephron, NO decreases cAMP, which reduces fluid absorption via PKA [21].

We further investigated whether 8-iso-PGF2α could reverse NO effects when PKA is inhibited. This experiment should establish whether the interaction between the mechanisms linking 8-iso-PGF2α and NO precedes or follows activation of PKA. In the presence of PKA inhibition, 8-iso-PGF2α did not change JCl, indicating that PKA activity is required to reverse the NO-inhibited JCl. Moreover, these results indicate that 8-iso-PGF2α reverses NO-induced inhibition of JCl via a mechanism involving activation of PKA. Since PKA is mainly activated by cAMP, we studied cAMP and found that NO was not able to reduce the cAMP level induced by 8-iso-PGF2α.

Nevertheless, the effects of 8-iso-PGF2α and NO on NaCl excretion have been shown in several models [22]. The decreased urinary Na+ excretion caused by systemic nitric oxide synthase (NOS) inhibition correlates with higher urinary 8-iso-PGF2α [23,24]. Also, the superoxide scavenger Tempol blunts these changes, suggesting that inhibition of

Discussion

To our knowledge, this is the first report showing that 8-iso-PGF2α can override NO’s diuretic effects in the cTAL, suggesting that Na+ retention will prevail over Na+ excretion in clinical conditions associated with increased 8-iso-PGF2α level. Although in the kidney, discrete 8-iso-PGF2α and NO effects have both been shown in vivo and in vitro, we designed this in vitro investigation to identify the local interaction and final effect of these two autacoids on chloride transport at the nephron segment.

Despite the well-known importance of prostaglandin in Na reabsorption, the effects of its derivatives are less clear. We evaluated the effects of 8-iso-PGF2α binding to the G-protein coupled receptor thromboxane A2 (TXA2) receptor, localized in the thick ascending limb segment [13,14]. This 8-iso-PGF2α is a modified prostaglandin produced by nonenzymatic oxidation of prostaglandin-F2α by reactive oxygen species [15,16] and induces vasoconstriction in the kidney and can impact renal blood flow [17]. Our data demonstrate that the NO donor decreases chloride reabsorption in the thick ascending limb of Henle; under these circumstances, 8-iso-PGF2α is activated by PKA and stimulates Cl− reabsorption. In vivo, this interaction results in a decrease of natriuresis and sodium increase.

Figure 5. Effect of 8-iso-PGF2α on NO-induced JCl inhibition in the presence of H89, a PKA inhibitor.

*p < 0.03 vs. control period; n = 5, one-way analysis of variance (Holm-Sidak test).

JCl, chloride absorption; NO, nitric oxide; PKA, protein kinase A; 8-iso-PGF2α, 8-iso-prostaglandin-F2α.
NO synthesis enhances endogenous superoxides, which could increase renal 8-iso-PGF2α level. These studies, however, show correlation but no direct interaction in the transport mechanisms. At any rate, 8-iso-PGF2α increases Cl− by stimulating cAMP synthesis [1].

In contrast, the effect by which NO inhibits NKCC2 activity might involve both an increase in cGMP [12,25,26] and a decrease in cAMP [27]. In our study, the NO donor did not decrease cAMP, whereas cGMP can play an essential role in the NO-inhibited JCl. This effect might involve protein trafficking, limiting the total pool of NKCC2 at the membrane level [28] since 8-iso-PGF2α’s increase of JCl is mediated by NKCC2 [1].

The mechanism(s) by which cGMP acts to regulate trafficking of the transporter might involve a decrease in insertion of the transporter into the membrane. Although evidence exists supporting the constitutive degradation of surface NKCC2, which is hypothesized to occur by decreasing NKCC2 level due to increasing NKCC2 ubiquitination and proteasomal degradation [28], it appears plausible that NO acts by increasing cGMP, which decreases cAMP [27] to lead to a reduction in exocytic insertion of NKCC2 into the apical membrane, reducing the number of transporters [19]. This process results in lower NKCC2 activity and blunted net NaCl reabsorption.

Our experiments demonstrate that interaction with 8-iso-PGF2α increases intracellular cAMP; in the presence of H89, 8-iso-PGF2α does not increase chloride reabsorption. These results show that the interaction occurs after activation of PKA since H89 prevented 8-iso-PGF2α and JCl inhibited NO and not because 8-iso-PGF2α blunts cGMP formation. Indeed, we found that NO caused no significant change in 8-iso-PGF2α-stimulated cAMP level. This indicates that NO-stimulated phosphodiesterase activity has little or no effect on 8-iso-PGF2α-stimulated cAMP level. This notion might not apply to other cellular compartments, where NO-stimulated phosphodiesterase could be activated separately from 8-iso-PGF2α-stimulated cAMP. Thus, 8-iso-PGF2α might interact with NO at the level of cAMP or cGMP.

The pathomechanism whereby 8-iso-PGF2α prevents NO-inhibited JCl might be observed under several conditions characterized by increased blood pressure, such as hypertension and chronic renal failure. In such conditions, urinary 8-iso-PGF2α [29] and cAMP [30] are elevated as well as other oxidative stress mediators. On the contrary, NO production is impaired in part due to limitations on substrate (L-arginine) availability and increased circulating levels of endogenous NO synthase inhibitors, in particular asymmetric dimethylarginine and reduced renal cortex abundance of the neuronal NOS [31]. This effect of NO correlates with urinary cGMP level [32]. This pathological condition is characterized by sodium retention as a consequence of enhanced sympathetic activity [33] and increase synthesis of intrarenal angiotensin II synthesis [34], endothelin-1 [35], and 8-iso-PGF2α, all of which stimulate sodium reabsorption. In contrast, the antinatriuretic effect of NO is blunted under these conditions, leading to sodium retention, hypertension, fibrosis, and end-organ damage.

The beneficial effect of 8-iso-PGF2α blockade has been observed in several animal models. Studies in diabetic animals with nephropathy showed that supplementation with vitamin E via reduced production of transforming growth factor-beta reduced urinary isoprostanate level and improved proteinuria and blood urea nitrogen level [36]. In spontaneously animal models of hypertension and angiotensin II-induced hypertension, both with elevated plasma isoprostanate level, Tempol administration decreases renal isoprostanate excretion and lowers blood pressure [4,37].

These beneficial effects observed by isoprostane blockade (and increase in NO availability) can prevent sodium overload, hypertension, chronic fibrosis, and end-organ damage. Clinical evaluations are under review to estimate the beneficial effect of isoprostane blockade (NCT03358524, NCT01125501, and NCT00552227).

Although the results of this report can explain important pathophysiological conditions, it has some limitations. One important limitation is the H89, despite being the most commonly used PKA inhibitor, might have nonspecific inhibitory effects.

In conclusion, 8-iso-PGF2α can increase JCl at the kidney cTAL via stimulation of PKA even when JCl is inhibited by NO. This increase of JCl is associated with a higher cAMP tissue concentration, which cannot be inhibited by NO, indicating the importance of 8-iso-PGF2α as a therapeutic intervention in kidney repair and functional restoration to regulate fluid and electrolyte balance.

**Conflicts of interest**

All authors have no conflicts of interest to declare.
Funding

This work was partially supported by Grant PIP 6525 from CONICET, Argentina, and by grant from the J. Robert Cade Foundation (No. L#003).

Acknowledgments

Néstor H. García acknowledges the support from the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET).

Authors’ contributions

Conceptualization, Funding acquisition: LIJ, NHG
Investigation, Investigation, Methodology: PDC, STB, GBS
Data curation, Formal analysis: GBS, LIJ, NHG
Writing–original draft: GBS, NHG
Writing–review & editing: PDC, STB, LIJ, EIOA, NHG
All authors read and approved the final manuscript.

ORCID

Pablo D. Cabral, https://orcid.org/0000-0001-5400-4291
Guillermo B. Silva, https://orcid.org/0000-0001-9168-3369
Sandra T. Baigorria, https://orcid.org/0000-0002-5447-0943
Luis I. Juncos, https://orcid.org/0000-0002-3840-0419
Ebenezer I. O. Ajayi, https://orcid.org/0000-0001-6348-5840
Néstor H. García, https://orcid.org/0000-0002-9057-9030

References


Clinical relevance of postoperative proteinuria for prediction of early renal outcomes after kidney transplantation

Junseok Jun1,* , Kyungho Park1,* , Hyun Suk Lee1, Kyo Won Lee2, Jung Eun Lee1, Jae Berm Park2, Kyunga Kim3, Woosong Huh1, Yoon-Goo Kim1, Dae Joong Kim1, Hye Ryoun Jang1

1Division of Nephrology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
2Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
3Statistics and Data Center, Research Institute for Future Medicine, Samsung Medical Center, Seoul, Republic of Korea

Background: Proteinuria is associated with poor allograft and patient survival in kidney transplant recipients. However, the clinical relevance of spot urine protein-to-creatinine ratio (PCR) or albumin-to-creatinine ratio (ACR) as predictors of renal outcomes during the early postoperative period following kidney transplantation (KT) has not been determined.

Methods: This single-center retrospective cohort study included 353 kidney transplant recipients who underwent KT between 2014 and 2017 and were followed up for more than 3 years. Among them, 186 and 167 recipients underwent living donor KT and deceased donor KT, respectively. The PCR and ACR were measured during the immediate postoperative period (within 7 days postoperatively), before discharge (2–3 weeks postoperatively), and 3–6 months postoperatively.

Results: The median age of the patients was 51 years (interquartile range, 43–59 years), and 62.9% were male. An immediate postoperative PCR of ≥1 mg/mg was associated with old age, diabetes mellitus, high systolic blood pressure, delayed graft function, and donor factors (deceased donor KT, old age, and high serum creatinine concentrations). The PCR and ACR 3 to 6 months posttransplant were inversely associated with the estimated glomerular filtration rate at 1 year posttransplant. Deceased donor KT recipients with immediate postoperative PCR of ≥3 mg/mg showed a greater incidence of delayed graft function and lower estimated glomerular filtration rate before discharge than those with immediate postoperative PCR of <3 mg/mg.

Conclusion: Early postoperative proteinuria is a useful biomarker to predict early renal outcomes after KT.

Keywords: Delayed graft function, Kidney transplantation, Proteinuria, Renal outcome, Urine protein-to-creatinine ratio

Received: October 27, 2021; Revised: April 17, 2022; Accepted: April 18, 2022

Correspondence: Hye Ryoun Jang
Division of Nephrology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea. E-mail: shinehr@skku.edu
ORCID: https://orcid.org/0000-0001-9856-6341

*Junseok Jun and Kyungho Park contributed equally to this study as co-first authors.

Copyright © 2022 by The Korean Society of Nephrology
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial and No Derivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/) which permits unrestricted non-commercial use, distribution of the material without any modifications, and reproduction in any medium, provided the original works properly cited.
Introduction

Proteinuria is a marker of kidney injury and risk factor for progression to chronic kidney disease, cardiovascular disease, and mortality [1]. Several previous studies have reported that proteinuria is associated with poor allograft and patient survival [2–4], as well as an increased risk of cardiovascular disease in kidney transplant recipients (KTRs) [2,5,6]. In these studies, the prevalence of proteinuria after kidney transplantation (KT) ranged from 7.5% to 45%, depending on its definition; most previous studies measured proteinuria between 1 month and 1 year after KT [3,4,7].

Ischemia-reperfusion injury during KT causes renal tubular injury through an inflammatory process that can subsequently result in proteinuria [8]. Further, proteinuria induces kidney injury by causing tubules to release chemokines and cytokines, leading to interstitial inflammation and fibrosis [9,10]. Therefore, early postoperative proteinuria might reflect tubular injury and be an early indicator of poor renal outcomes after KT. However, the optimal timing for measurement of proteinuria in KTRs and the associations between early postoperative proteinuria and renal outcomes have not been determined.

We hypothesized that early postoperative proteinuria might reflect early renal outcomes in KTRs and investigated the clinical relevance of postoperative proteinuria, as assessed by the spot urine protein-to-creatinine ratio (PCR) and albumin-to-creatinine ratio (ACR), as a surrogate marker to predict early renal outcomes in KTRs.

Methods

Study population and variables

This single-center retrospective cohort study screened 474 adult patients (≥18 years old) who underwent KT between January 1, 2014 and December 31, 2017, at Samsung Medical Center, Sungkyunkwan University School of Medicine. A total of 353 patients were finally included after excluding patients for whom ACR or PCR measurements within 7 days posttransplant were unavailable. Baseline characteristics, such as age, sex, renal replacement therapy (RRT) modality before KT, causes of end-stage kidney disease (ESKD), body mass index (BMI), history of diabetes mellitus or cardiovascular disease, and donor information, including age, BMI, and serum creatinine at the time of KT, were obtained from electronic medical records. All patients were followed for 3 years after KT.

The immediate postoperative period was defined as postoperative days 1 to 7 after surgery. All PCRs and ACRs were measured using spot urine samples during the immediate postoperative period, prior to discharge, and 3–6 months after KT. Immediate postoperative PCR and ACR values were defined as the first PCR and ACR assessments within the immediate postoperative period. The PCR and ACR prior to discharge were defined as the last PCR and ACR during the hospital stay, usually 2 to 3 weeks postoperatively. The PCR and ACR at 3–6 months posttransplant were defined as the median values.

To evaluate correlations between spot urine PCR or ACR and 24-hour urine protein excretion within 1 month after KT, all values measured on the same day or the median spot urine PCR/ACR values calculated within 1 month from the time of initial 24-hour urine protein measurement were compared.

Ethics statement

This study complied with internationally accepted standards for research practice and reporting. The study protocol was approved by the Institutional Review Board of Samsung Medical Center (No. 2019-08-112-002) in compliance with the Declaration of Helsinki, and the requirement for informed consent was waived.

Study outcomes

The primary outcome was early renal function as evaluated by the estimated glomerular filtration rate (eGFR) at 1 year posttransplant. The secondary outcome was delayed graft function (DGF) in deceased donor kidney transplant (DDKT) recipients. The presence of DGF was defined as an event in which RRT was required within 7 days posttransplant. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation, which uses serum creatinine concentrations [11]. The eGFR prior to discharge was defined as the last eGFR measured during the hospital stay, and the eGFR at 3 to 6 months posttransplant was defined as the median eGFR value during this
period. Moreover, eGFRs at 1, 2, and 3 years posttransplant were defined as median eGFR values for the 9 to 15, 21 to 27, and 33 to 39 months intervals after KT, respectively.

**Statistical analyses**

Baseline characteristics are presented as numbers (percentages) for categorical variables and medians (interquartile ranges) or means ± standard deviations for continuous variables, as appropriate. Differences between groups were analyzed using the Wilcoxon rank-sum test or chi-square test. Logarithmic transformation of the postoperative PCR and ACR was performed because of the skewed distribution of these ratios. Univariable analyses were performed for postoperative PCR and ACR, using the eGFR as the outcome variable. Subsequently, multivariable regression analyses of the postoperative PCR and ACR were performed using models including covariates such as age, sex, donor status, donor serum creatinine, and acute rejection during the first 6 months after KT.

Statistical significance was set at a two-tailed p-value of 0.05. All statistical analyses were performed using IBM SPSS Statistics for Windows (released 2017, version 25.0; IBM Corp., Armonk, NY, USA).

**Results**

**Baseline characteristics and renal outcome depending on the degree of proteinuria in the immediate postoperative period**

A total of 353 patients were analyzed to evaluate the degree of immediate postoperative proteinuria (Table 1). The median age of KTRs was 51 years (43–59 years), and 222 of the 353 patients (62.9%) were male. Diabetes mellitus was the most common cause of ESKD (112 of 353 KTRs, 31.7%).

We analyzed the cut-off value of the immediate postoperative PCR for predicting an eGFR of ≥60 mL/min/1.73 m² at 1 year postoperative using Youden’s index method [12]. The best cut-off PCR value was 1.26 mg/mg (sensitivity, 68.8%; specificity, 45.9%). For ease of application in clinical practice, we used a PCR of 1 mg/mg (sensitivity, 60.6%; specificity, 53.3%) as a cut-off value, and divided the KTRs into two groups: the low-PCR (PCR < 1 mg/mg) and high-PCR groups (PCR ≥ 1 mg/mg).

The low- and high-PCR groups included 195 (55.2%) and 158 KTRs (44.8%), respectively. Compared to patients in the low-PCR group, patients in the high-PCR group were older (PCR ≥ 1 mg/mg vs. PCR < 1 mg/mg, 55 years [46–61 years] vs. 48 years [41–56 years]; p < 0.001) and had a higher prevalence of diabetes mellitus (39.9% vs. 26.2%, p = 0.008), higher systolic blood pressure (145 mmHg [134–157 mmHg] vs. 138 mmHg [125–150 mmHg], p = 0.001), higher incidence of DGF (22.2% vs. 2.1%, p < 0.001), and lower eGFR at 1 year posttransplant (64.3 ± 19.0 mL/min/1.73 m² vs. 69.2 ± 17.5 mL/min/1.73 m², p = 0.01). In addition, the proportion of deceased donors was greater (74.7% vs. 25.1%; p < 0.001), the donors were older (52 years [43–64 years] vs. 48 years [37–56 years], p < 0.001), and the donors’ serum creatinine concentrations were greater (1.14 mg/dL [0.84–1.87 mg/dL] vs. 0.81 mg/dL [0.67–0.95 mg/dL], p < 0.001) in the high-PCR group than in the low-PCR group. The proportion of both sexes, BMI, and the causes of ESKD were comparable between the groups.

A lesser percentage of patients in the high-PCR group received ABO-incompatible (ABOi) grafts (17.1% vs. 33.8%, p < 0.001), but the presence of donor-specific antibodies was similar to that in the low-PCR group. Most ABOi grafts were from living donors (ABOi grafts from living donors vs. deceased donors were 80% vs. 18%, respectively). Patients in the high-PCR group received more antithymocyte globulin (ATG) monotherapy than basiliximab or ATG + rituximab as an induction therapy compared with those in the low-PCR group. Most ABOi grafts were from living donors (ABOi grafts from living donors vs. deceased donors were 80% vs. 18%, respectively). Patients in the high-PCR group received more antithymocyte globulin (ATG) monotherapy than basiliximab or ATG + rituximab as an induction therapy compared with those in the low-PCR group. Most ABOi grafts were from living donors (ABOi grafts from living donors vs. deceased donors were 80% vs. 18%, respectively). Patients in the high-PCR group tended to have a greater incidence of diabetes mellitus nephropathy and a shorter median interval to diagnosis after KT than the low-PCR group, although the difference was not statistically significant. The incidence of acute rejection or BK virus nephropathy and the diagnosis of posttransplant glomerular pathology, including recurrent or de novo glomerulonephritis, was similar between the two groups.

**Serial follow-up evaluations of postoperative proteinuria and estimated glomerular filtration rate**

The immediate postoperative PCR and ACR were much
**Table 1. Characteristics of the study population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Low-PCR group (^a)</th>
<th>High-PCR group (^b)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>353</td>
<td>195</td>
<td>158</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>51 (43–59)</td>
<td>48 (41–56)</td>
<td>55 (46–61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>222 (62.9)</td>
<td>119 (61.0)</td>
<td>103 (65.2)</td>
<td>0.44</td>
</tr>
<tr>
<td>RRT modality before KT</td>
<td></td>
<td></td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>265 (75.1)</td>
<td>139 (71.3)</td>
<td>126 (79.7)</td>
<td></td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>30 (8.5)</td>
<td>20 (10.3)</td>
<td>10 (6.3)</td>
<td></td>
</tr>
<tr>
<td>No dialysis</td>
<td>58 (16.4)</td>
<td>36 (18.5)</td>
<td>22 (13.9)</td>
<td></td>
</tr>
<tr>
<td>Cause of ESRD</td>
<td></td>
<td></td>
<td></td>
<td>0.61</td>
</tr>
<tr>
<td>GN</td>
<td>97 (27.5)</td>
<td>54 (27.7)</td>
<td>43 (27.2)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>112 (31.7)</td>
<td>50 (25.6)</td>
<td>62 (39.2)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>33 (9.3)</td>
<td>24 (12.3)</td>
<td>9 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Cystic kidney disease</td>
<td>16 (4.5)</td>
<td>9 (4.6)</td>
<td>7 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>40 (11.3)</td>
<td>25 (12.8)</td>
<td>15 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>55 (15.6)</td>
<td>33 (16.9)</td>
<td>22 (13.9)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>22.7 (20.7–25.1)</td>
<td>22.7 (20.6–25.5)</td>
<td>22.6 (20.6–24.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>114 (32.3)</td>
<td>51 (26.2)</td>
<td>63 (39.9)</td>
<td>0.008</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>27 (7.6)</td>
<td>12 (6.2)</td>
<td>15 (9.5)</td>
<td>0.314</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>141 (128–153)</td>
<td>138 (125–150)</td>
<td>145 (134–157)</td>
<td>0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>83 (74–90)</td>
<td>83 (75–90)</td>
<td>83 (74–91)</td>
<td>0.88</td>
</tr>
<tr>
<td>Donor age (yr)</td>
<td>50 (38–60)</td>
<td>48 (37–56)</td>
<td>52 (43–64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male donor</td>
<td>205 (58.1)</td>
<td>107 (54.9)</td>
<td>98 (62.0)</td>
<td>0.19</td>
</tr>
<tr>
<td>Donor height (cm)</td>
<td>167 (159–172)</td>
<td>165 (158–172)</td>
<td>167 (160–173)</td>
<td>0.26</td>
</tr>
<tr>
<td>Donor weight (kg)</td>
<td>66.0 (57.9–74.3)</td>
<td>66.2 (57.8–74.4)</td>
<td>66.0 (57.9–74.3)</td>
<td>0.90</td>
</tr>
<tr>
<td>Donor BMI (kg/m(^2))</td>
<td>24.1 (21.7–26.3)</td>
<td>24.5 (22.1–26.3)</td>
<td>23.9 (21.5–26.3)</td>
<td>0.34</td>
</tr>
<tr>
<td>Donor serum creatinine (mg/dL)</td>
<td>0.89 (0.70–1.24)</td>
<td>0.81 (0.67–0.95)</td>
<td>1.14 (0.84–1.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Donor status</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Living</td>
<td>186 (52.7)</td>
<td>146 (74.9)</td>
<td>40 (25.3)</td>
<td></td>
</tr>
<tr>
<td>Deceased</td>
<td>167 (47.3)</td>
<td>49 (25.1)</td>
<td>118 (74.7)</td>
<td></td>
</tr>
<tr>
<td>ABO incompatibility</td>
<td>93 (26.3)</td>
<td>66 (33.8)</td>
<td>27 (17.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Donor-specific antibody</td>
<td>56 (15.8)</td>
<td>26 (13.5)</td>
<td>20 (12.9)</td>
<td>0.875</td>
</tr>
<tr>
<td>Induction therapy</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No induction</td>
<td>1 (0.3)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>ATG</td>
<td>218 (61.8)</td>
<td>104 (53.3)</td>
<td>114 (72.6)</td>
<td></td>
</tr>
<tr>
<td>ATG + rituximab</td>
<td>73 (20.7)</td>
<td>50 (25.6)</td>
<td>23 (14.6)</td>
<td></td>
</tr>
<tr>
<td>Basiliximab</td>
<td>60 (17.0)</td>
<td>40 (20.5)</td>
<td>20 (12.7)</td>
<td></td>
</tr>
<tr>
<td>Basiliximab + rituximab</td>
<td>1 (0.3)</td>
<td>0 (0)</td>
<td>1 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Delayed graft function</td>
<td>39 (11.0)</td>
<td>4 (2.1)</td>
<td>35 (22.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>129 (36.5)</td>
<td>79 (40.5)</td>
<td>50 (31.6)</td>
<td>0.10</td>
</tr>
<tr>
<td>Antibody-mediated rejection</td>
<td>25 (7.1)</td>
<td>17 (8.7)</td>
<td>8 (5.1)</td>
<td>0.18</td>
</tr>
<tr>
<td>BK virus nephropathy</td>
<td>21 (5.9)</td>
<td>11 (5.6)</td>
<td>10 (6.3)</td>
<td>0.79</td>
</tr>
<tr>
<td>Post-KT glomerular pathology</td>
<td>56 (15.9)</td>
<td>26 (13.3)</td>
<td>30 (19.0)</td>
<td>0.41</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>6 (1.7)</td>
<td>3 (1.5)</td>
<td>3 (1.9)</td>
<td></td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>7 (2.0)</td>
<td>4 (2.1)</td>
<td>3 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Membranoproliferative GN</td>
<td>2 (0.6)</td>
<td>2 (1.0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>9 (2.5)</td>
<td>1 (0.5)</td>
<td>8 (5.1)</td>
<td></td>
</tr>
<tr>
<td>CNI toxicity</td>
<td>13 (3.7)</td>
<td>7 (3.6)</td>
<td>6 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>19 (5.4)</td>
<td>9 (4.6)</td>
<td>10 (6.3)</td>
<td></td>
</tr>
<tr>
<td>Interval from KT to diagnosis of glomerular pathology (day)</td>
<td>193 (145–408)</td>
<td>362 (14–414)</td>
<td>86 (15–398)</td>
<td>0.565</td>
</tr>
<tr>
<td>Treatment of ACEI/ARB within 1 year after KT</td>
<td>34 (9.6)</td>
<td>16 (8.2)</td>
<td>18 (11.4)</td>
<td>0.313</td>
</tr>
</tbody>
</table>

Data are expressed as number only, median (interquartile range), and number (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ATG, antithymocyte globulin; BMI, body mass index; CNI, calcineurin inhibitor; DBP, diastolic blood pressure; ESRD, end-stage renal disease; GN, glomerulonephritis; IgA, immunoglobulin A; KT, kidney transplantation; PCR, spot urine protein-to-creatinine ratio; RRT, renal replacement therapy; SBP, systolic blood pressure.

\(^a\)Patients with immediate postoperative PCR of <1 mg/mg. \(^b\)Patients with immediate postoperative PCR of ≥1 mg/mg.
greater than the PCR and ACR before discharge and at 3 to 6 months postoperatively. The median PCR and ACR decreased from 0.87 mg/mg (0.52–1.98 mg/mg) and 373 μg/mg (183–1,258 μg/mg) during the immediate postoperative period to 0.22 mg/mg (0.52–0.87 mg/mg) and 52 μg/mg (26–127 μg/mg) and 0.13 mg/mg (0.10–0.21 mg/mg) and 19 μg/mg (13–39 μg/mg) prior to discharge and 3 to 6 months posttransplant, respectively (Fig. 1). The median eGFR values were 73.3 mL/min/1.73 m$^2$ (55.4–89.9 mL/min/1.73 m$^2$), 61.1 mL/min/1.73 m$^2$ (50.9–71.8 mL/min/1.73 m$^2$), and 66.4 mL/min/1.73 m$^2$ (54.0–79.9 mL/min/1.73 m$^2$) prior to discharge, at 3 to 6 months posttransplant, and at 1 year posttransplant, respectively. There were no significant differences between the eGFR values 1 and 3 years after KT (Fig. 1).

**Correlations between 24-hour urine protein excretion and spot urine protein-to-creatinine ratio**

We performed correlation analyses of spot urine PCR or ACR and 24-hour urine protein excretion in 333 patients who underwent a 24-hour urine protein measurement within 1 month posttransplant. The median spot urine PCR ($R = 0.676, p < 0.001$) and ACR ($R = 0.728, p < 0.001$) showed good correlation with 24-hour urine protein excretion (Fig. 2). Spot urine PCR measured on the same day was also correlated with 24-hour urine protein excretion ($R = 0.610, p < 0.001$).

**Association between postoperative proteinuria and early renal outcome**

The univariable linear regression analyses indicated that the eGFR at 1 year posttransplant was correlated with PCR and ACR in the immediate postoperative period, ACR prior to discharge, and PCR and ACR at 3 to 6 months posttransplant. After adjusting for sex, age, donor status (living vs. deceased), donor serum creatinine concentration, and acute rejection during the first 6 months after KT, the eGFR 1 year after KT was correlated with PCR and ACR at 3 to 6 months posttransplant (PCR: adjusted $\beta$ coefficient, $-13.771$; $p = 0.04$; and ACR: adjusted $\beta$ coefficient, $-5.947$; $p = 0.002$). In a multivariable analysis, the PCR and ACR measured less than 3 months posttransplant were not correlated with the eGFR 1 year after KT (Table 2).

We analyzed the PCR cut-off value at 3 to 6 months posttransplant for prediction of an eGFR of $\geq 60$ mL/min/1.73 m$^2$ at 1 year posttransplant using Youden’s index method [12]. The best PCR cut-off value was 0.158 mg/mg (sensitivity, 71.0%; specificity, 52.5%). In addition, according to the PCR cut-off value, we divided the patients into two groups: those with PCR of $\geq 0.2$ mg/mg and <0.2 mg/mg at

---

**Figure 1.** Serial follow-up measurements of postoperative proteinuria and eGFR. (A) Serial follow-up measurements of the spot urine PCR (median and interquartile range) after KT. (B) Serial follow-up measurements of the spot urine ACR (median and interquartile range) after KT. (C) Serial follow-up measurements of eGFR (mean ± standard deviation). ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; KT, kidney transplantation; PCR, protein-to-creatinine ratio.
Table 2. Associations between postoperative proteinuria and early renal outcome (eGFR at 1 year after kidney transplantation)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β coefficient</td>
<td>p-value</td>
</tr>
<tr>
<td>PCR, immediately postoperation</td>
<td>-3.68</td>
<td>0.03</td>
</tr>
<tr>
<td>ACR, immediately postoperation</td>
<td>-3.53</td>
<td>0.01</td>
</tr>
<tr>
<td>PCR, before discharge</td>
<td>-4.73</td>
<td>0.18</td>
</tr>
<tr>
<td>ACR, before discharge</td>
<td>-4.45</td>
<td>0.02</td>
</tr>
<tr>
<td>PCR, 3–6 months posttransplant</td>
<td>-11.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACR, 3–6 months posttransplant</td>
<td>-8.62</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Log transformation was performed for PCR (mg/mg) and ACR values (µg/mg). ACR, spot urine albumin-to-creatinine ratio; PCR, protein-to-creatinine ratio.

*Each model was adjusted for sex, age, recipient’s diabetes mellitus and hypertension, donor status (living vs. deceased), donor serum creatinine concentration, delayed graft function, and acute rejection within 6 months after kidney transplantation using multivariable linear regression analyses.

3 to 6 months posttransplant, according to the definition of proteinuria in routine clinical practice. Patients with PCR of <0.2 mg/mg at 3 to 6 months posttransplant had similar eGFRs at 3 to 6 months posttransplant as those of patients with PCR of ≥0.2 mg/mg at 3 to 6 months posttransplant, but had greater eGFRs between 1 and 3 years posttransplant (p < 0.001) (Fig. 3).

Proteinuria in the immediate postoperative period as a surrogate marker for delayed graft function

We compared the incidence of DGF and the postoperative eGFR in DDKT recipients according to the degree of immediate postoperative proteinuria (Table 3). A total of 167 DDKT recipients were divided into two groups: 67 in the heavy proteinuria group (immediate postoperative PCR ≥ 3 mg/mg) and 100 in the control group (immediate postoperative PCR < 3 mg/mg). The incidence of DGF was significantly greater in the heavy proteinuria group than in the control group (control group vs. heavy proteinuria group, 12% vs. 39%; p < 0.001). After adjusting for age, sex, donor serum creatinine concentration, donor age, number of human leukocyte antigen mismatches, and presence of donor-specific antibodies, heavy proteinuria in the immediate postoperative period was still associated with DGF (adjusted odds ratio, 5.86; 95% confidence interval, 2.26–15.16; p < 0.001). The heavy proteinuria group had lower postoperative eGFR within 1 month posttransplant than the control group (64.2 mL/min/1.73 m² [49.7–85.4 mL/min/1.73 m²] vs. 49.6 mL/min/1.73 m² [35.8–66.5 mL/
min/1.73 m², p = 0.001). However, eGFR 1 year after DDKT was comparable between the groups.

The incidence of DGF and postoperative eGFR were also compared in living donor KT (LDKT) recipients according to the degree of proteinuria in the immediate postoperative period (Supplementary Table 1, available online). A total of 186 LDKT recipients were divided into two groups: 72 in the high-ACR group (immediate postoperative ACR ≥ 300 µg/mg) and 114 in the low-ACR group (immediate postoperative ACR < 300 µg/mg). The occurrence of DGF was reported in only one LDKT recipient, and no difference in postoperative eGFR between the groups was noted.

**Discussion**

In this study, proteinuria at 3 to 6 months posttransplant was identified as a surrogate marker for prediction of early renal outcomes in KTRs. Compared to those with low PCRs during the immediate postoperative period, the KTRs with high PCRs were older and had a greater prevalence of diabetes mellitus and incidence of DGF, and higher systolic blood pressure and serum creatinine concentrations than the donors of the low-PCR group. Furthermore, we found a good correlation between 24-hour urine protein excretion and spot urine PCR or ACR during the first month posttransplant. In DDKT recipients, heavy proteinuria (PCR ≥ 3 mg/mg) during the immediate postoperative period was associated with a high incidence of DGF and low eGFR within 1 month of KT.

The severity of proteinuria after KT has been shown to be inversely associated with graft survival and favorable patient outcomes [2–4,13–19]. Similarly, a recent large cohort study demonstrated that the severity of proteinuria at 3 months, 1 year, 2 years, and 6 years after KT, as well as at the time of allograft biopsy, was inversely associated with graft survival [16]. In particular, proteinuria of >1 g/day was related to transplant glomerulopathy, microcirculatory inflammation, and de novo or recurrent glomerular disease diagnosed from both indication and protocol biopsies. Although the associations between proteinuria and graft survival or renal histology in the first 3 months after KT were weaker than those thereafter, our results were consistent with previous studies showing that proteinuria at 3 months after KT is a predictor of graft outcome [14,18,19].

Previous studies have reported that diabetes mellitus, hypertension, advanced recipient age, advanced donor age, extended criteria donor, and DGF were associated with

![Figure 3. Serial follow-up measurements (for up to 3 years) of the postoperative eGFR according to the degree of proteinuria at postoperative 3 to 6 months after KT.](image)

**Table 3. Incidence of DGF and eGFR depending on the degree of immediate postoperative proteinuria in DDKT recipients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>PCR (mg/mg)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;3 (n = 100)</td>
<td>≥3 (n = 67)</td>
</tr>
<tr>
<td>DGF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR, before discharge</td>
<td>64.2 (49.7–85.4)</td>
<td>49.6 (35.8–66.5)</td>
</tr>
<tr>
<td>eGFR, postoperative 3–6 months</td>
<td>58.5 (45.5–68.2)</td>
<td>52.6 (41.5–67.7)</td>
</tr>
<tr>
<td>eGFR, postoperative 1 year</td>
<td>62.8 (48.0–74.7)</td>
<td>60.0 (46.3–73.4)</td>
</tr>
</tbody>
</table>

Data are expressed as number (%) or median (interquartile range).

DDKT, deceased donor kidney transplantation; DGF, delayed graft function; eGFR, estimated glomerular filtration rate; PCR, spot urine protein-to-creatinine ratio.
decreased allograft function [20–23]. The abovementioned factors were observed in the high-PCR group during the immediate postoperative period in our study. These results indicated that immediate postoperative PCR of ≥1 mg/mg may possibly indicate allograft damage and can be used as a surrogate marker to predict poor renal outcome after KT.

Currently, there is no consensus regarding the optimal method to assess the degree of proteinuria in KTRs [7]. Several studies have reported a high overall correlation between 24-hour urine protein or albumin excretion and spot urine PCR or ACR in KTRs (median correlation coefficient, 0.92; range, 0.772–0.998) [24–28], although one study showed only modest accuracy of spot urine PCR or ACR for prediction of 24-hour urine protein excretion despite high correlation between spot urine PCR or ACR and 24-hour urine protein excretion [29]. However, the correlation between 24-hour urine protein or albumin excretion and spot urine PCR or ACR within 1 month after surgery has not yet been reported. In the early postoperative period after KT, proteinuria from the native kidney [30], proteinuria due to tubular dysfunction as a result of ischemic-reperfusion injury, especially in the DDKT [31], and an increase in postoperative creatinine production due to high-dose corticosteroid treatment [32] may affect both the degree of proteinuria and accuracy of spot urine PCR or ACR. Our study demonstrated a good correlation between 24-hour urine protein excretion and spot urine PCR or ACR within 1 month posttransplant, and this may be valuable information for physicians and KTRs who experience difficulty in obtaining 24-hour urine collection.

In many previous KT studies, the timing of proteinuria measurement varied considerably, ranging from 1 month to 1 year after KT [3,4,7,13,14,33] and proteinuria during this period was associated with an increased risk of allograft dysfunction [4,13,14]. However, there were conflicting results regarding the prognostic value of proteinuria at 1 month after KT [4,14]. A few studies have evaluated the clinical value of proteinuria less than 1 month after transplant, and one among them showed an association between proteinuria measured 1 week posttransplant and graft function [15]; however, this study included only LDKT recipients, and proteinuria was assessed using 24-hour urine collection within 1 week posttransplant, but only by qualitative tests were used after 1 month [15]. Our study investigated the clinical value of quantitative measurement of urine protein excretion at different time points, including during the immediate postoperative period. The severity of proteinuria 3 to 6 months posttransplant was the most reliable predictive factor of eGFR 1 year posttransplant, regardless of the type of KT. Proteinuria occurring 3 to 6 months posttransplant may reflect irreversible allograft injury and can be considered a predictor of poor renal outcomes. In contrast, immediate postoperative proteinuria was not associated with allograft function at 1 year posttransplant. These results suggest that immediate postoperative proteinuria might reflect postoperative allograft injury, which is reversible in many cases and can be improved with adequate postoperative management.

Overall, DGF is the most important predictor of poor graft survival [20]. The main cause of DGF is tubular damage caused by ischemia-reperfusion injury [8]. We evaluated the potential value of proteinuria in the immediate postoperative period to predict DGF and renal function after KT, since the renal outcome may improve with an early diagnosis of DGF and appropriate therapeutic interventions. Heavy proteinuria (PCR ≥ 3 mg/mg) during the immediate postoperative period was associated with a high incidence of DGF and poor renal function within 1 month posttransplant in DDKT recipients. However, proteinuria in the immediate postoperative period was not associated with renal function as assessed 1 month posttransplant. These results suggest that immediate postoperative proteinuria may reflect tubular damage due to ischemia-reperfusion injury, which can be reversed with adequate postoperative management.

Our study had a few limitations. First, the composition of the study population might limit the generalizability of our results because this was a single-center study; however, the results are still clinically significant since we analyzed serial PCR and ACR assessments in an adequate number of both LDKT and DDKT recipients. Second, owing to the retrospective cohort study design, some unmeasured confounding factors may not have been addressed. Several key factors affecting allograft function were considered in the analyses to overcome this issue. Further multicenter prospective studies are necessary to validate our findings. Third, since we adopted renal function 1 year posttransplant as the primary outcome, long-term graft function could not be adequately evaluated. However, several studies have reported that renal function 1 year posttransplant
could reliably predict long-term graft survival [34,35]. Follow-up data spanning the interval from the immediate postoperative period to 3 years after KT were included in our study.

Despite the above limitations, we presented cut-off values for urine PCR during the immediate postoperative period and at 3 to 6 months posttransplant to predict eGFR 1 year after transplantation. These cut-off values could be very useful in identifying high-risk KTRs in clinical practice and indicate the need for more careful monitoring as well as appropriate management of renal function to improve renal outcomes in KTRs who have PCRs above the cut-off values. In addition, this study demonstrated a strong correlation between 24-hour urine protein excretion and spot urine PCR within 1 month posttransplant.

In conclusion, the degree of proteinuria 3 to 6 months posttransplant may be a good surrogate marker to predict allograft function 1 year posttransplant, and proteinuria during the immediate postoperative period may be a potential predictor of DGF in DDKT recipients. Therefore, early postoperative proteinuria can be considered as a biomarker to predict early renal outcomes in KTRs.

Conflicts of interest

All authors have no conflicts of interest to declare.

Acknowledgments

We thank all the members of the kidney transplantation team at Samsung Medical Center, Sungkyunkwan University School of Medicine.

Authors’ contributions

Conceptualization: HRJ
Data curation: JJ, KP, HSL
Formal analysis: JJ, KP, KK
Investigation: JJ, KP, JEL, KK, WH, YGK, DJK, HRJ
Methodology: JJ, HRJ
Project administration: KWL, JEL, JBP, WH, YGK, DJK
Visualization: JJ, KP
Writing—original draft: JJ, KP, HSL, KWL
Writing—review & editing: JJ, KP, HRJ, JEL, JBP, WH, YGK, DJK

All authors read and approved the final manuscript.

ORCID

Junseok Jun, https://orcid.org/0000-0003-2532-0177
Kyungho Park, https://orcid.org/0000-0002-4888-7523
Hyun Suk Lee, https://orcid.org/0000-0003-4444-0537
Kyo Won Lee, https://orcid.org/0000-0002-2722-7817
Jung Eun Lee, https://orcid.org/0000-0002-4387-5291
Jae Berm Park, https://orcid.org/0000-0001-9117-2278
Kyunga Kim, https://orcid.org/0000-0002-0865-2236
Wooseong Huh, https://orcid.org/0000-0001-8174-5028
Yoon-Goo Kim, https://orcid.org/0000-0002-8176-295X
Dae Joong Kim, https://orcid.org/0000-0001-7526-1107
Hye Ryoun Jang, https://orcid.org/0000-0001-9856-6341

References

9. Abbate M, Zoja C, Remuzzi G. How does proteinuria cause pro-


Background: Whether continuous renal replacement therapy (CRRT) should be applied to critically ill patients with both acute kidney injury (AKI) and cancer remains controversial because of poor expected outcomes. The present study determined prognostic factors for all-cause in-hospital mortality in patients with AKI and cancer undergoing CRRT.

Methods: We included 471 patients with AKI and cancer who underwent CRRT at the intensive care unit of a Korean tertiary hospital from 2013 to 2020, and classified them by malignancy type. The primary outcomes were 28-day all-cause mortality rate and prognostic factors for in-hospital mortality. The secondary outcome was renal replacement therapy (RRT) dependency at hospital discharge.

Results: The 28-day mortality rates were 58.8% and 82% in the solid and hematologic malignancy groups, respectively. Body mass index (BMI), presence of oliguria, Sequential Organ Failure Assessment (SOFA) score, and albumin level were common predictors of 28-day mortality in the solid and hematologic malignancy groups. A high heart rate and the presence of severe acidosis were prognostic factors only in the solid malignancy group. Among the survivors, the proportion with RRT dependency was 25.0% and 33.3% in the solid and hematologic malignancy groups, respectively.

Conclusion: The 28-day mortality rate of cancer patients with AKI undergoing CRRT was high in both the solid and hematologic malignancy groups. BMI, presence of oliguria, SOFA score, and albumin level were common predictors of 28-day mortality in the solid and hematologic malignancy groups, but a high heart rate and severe acidosis were prognostic factors only in the solid malignancy group.

Keywords: Acute kidney injury, Continuous renal replacement therapy, Malignancy
Introduction

Because of remarkable advances in the diagnosis and treatment of cancer, an increasing number of cancer patients are admitted to intensive care units (ICUs) [1]. A retrospective cohort study using validation of Simplified Acute Physiology Score (SAPS) 3 data from Korean ICUs reported that patients with cancer accounted for 34.8% of the total number of patients admitted [2]. Acute kidney injury (AKI) is a common and severe complication in this population. AKI has various etiologies, including cancer itself (multiple myeloma, neoplastic urinary tract obstruction, and renal malignant infiltration), cancer treatment (nephrotoxic chemotherapy and tumor lysis syndrome), sepsis, antibiotics, and iodine contrast [3]. In recent studies, up to 54% of cancer patients who are admitted to an ICU have AKI, and some of them require renal replacement therapy (RRT) [4,5].

However, whether continuous RRT (CRRT) can be applied to critically ill patients with both AKI and cancer remains controversial because of the poor expected outcomes of the dual diagnosis. In-hospital mortality rates in cancer patients who require dialysis are reported to be between 51% and 90% [6–8]. Because of geographic variations in the diagnosis of different types of cancer, domestic epidemiologic data are essential to guide the management of patients with both AKI and cancer, but few studies have reported the clinical characteristics, prognoses, and prognostic factors of such Korean patients. Therefore, the present study investigated 28-day all-cause mortality, prognostic factors of mortality, and RRT dependency at hospital discharge among patients with AKI and a solid or hematologic malignancy who received CRRT.

Methods

This study was approved by the Institutional Review Board of Pusan National University Hospital (No. 2102-022-100), which waived the requirement for informed patient consent because of the retrospective design of the study. All clinical investigations were conducted in accordance with the principles of the Declaration of Helsinki.

Study design and subjects

This was a retrospective, single-center study. Data collected from the medical records of 2,466 patients who underwent CRRT from March 2013 to December 2020 in the ICU of a single-center university-affiliated hospital were reviewed (Fig. 1). All patients were aged >18 years. After excluding patients without malignancy and with end-stage kidney disease on dialysis, 471 were eligible for inclusion in this study. Patients were grouped according to type of malignancy as solid malignancy group (n = 298) and hematologic malignancy group (n = 173).

Clinical data collection and laboratory measurements

The following demographic and clinical data including age, sex, body mass index (BMI), cause of AKI, and comorbidities at the time of CRRT initiation were reviewed. The following clinical data were collected from the patients’ medical records: presence, type (solid or hematologic malignancy), site (breast, lung, digestive tract, prostate/bladder/kidney, and others), extent (localized to the primary tumor site or distant metastasis to other sites), status (diagnosis, induction, remission [complete or partial], stabilization,

Figure 1. Flowchart of the patient selection process.
CRRT, continuous renal replacement therapy; ESKD, end-stage kidney disease.
tion, or progression) [9], and treatment history (adjuvant or palliative chemotherapy, radiotherapy, concurrent chemoradiation therapy, and steroids) of malignancy, as well as AKI etiology (sepsis, ischemia/shock, drugs, tumor lysis syndrome, urinary tract obstruction, and others, which included multiple myeloma, postoperation, and hepatorenal syndrome). Laboratory test results of complete blood counts and albumin, potassium, bicarbonate, serum blood urea nitrogen, creatinine, and phosphorus levels were collected. The Sequential Organ Failure Assessment (SOFA) score was calculated to assess disease severity [10].

Continuous renal replacement therapy protocol

Among critically ill patients with AKI, those with sustained oliguria (urine output of <0.3 mL/kg/hr for ≥24 hours), uncontrolled volume overload (as evidenced by edema or pleural effusion despite maximal medical care), intractable hyperkalemia (serum potassium of >6.0 mmol/L despite maximal medical care), severe acidosis (arterial pH of <7.2 despite maximal medical care), or other conditions such as uremic encephalopathy received CRRT at the discretion of their physicians. All CRRT patients received continuous venovenous hemodiafiltration through the internal jugular or femoral vein. A Prismaflex (Gambror Lundia AB, Lund, Sweden) CRRT machine and AN 69 ST 100 filter set (1.0 m²; Gambro Lundia AB) were used. The initial effluent flow rates were between 35 and 40 mL/kg/hr, and additional adjustments were made according to the patient’s catabolic state or the presence of hyperkalemia and acidosis. The actual delivered dose was calculated as the mean effluent volume divided by the weight of the patient during the entire CRRT period. The downtime was calculated by adding all the times (hours) of CRRT interruption during the treatment. Patients’ body weights were measured continuously during the CRRT period. The blood flow rate was started at 150 mL/min and adjusted according to patients’ metabolic demands and hemodynamic instabilities. Heparin-free, heparin, and nafamostat mesylate were used to maintain the patency of the extracorporeal circuit while minimizing patient complications according to individual bleeding risk.

Outcomes

Patients were observed until the time of hospital discharge. The primary outcomes of the present study were 28-day all-cause mortality during the follow-up period and the prognostic factors for in-hospital mortality. The secondary outcome was RRT dependency at the time of hospital discharge. Outcomes were investigated separately in the solid and hematologic malignancy groups.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median (interquartile range [IQR]), and categorical variables are expressed as number (percentage). Comparisons between the two groups were performed using Student t test or Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Cox proportional hazards models and logistic regression models were used in univariable and multivariable analyses to determine the hazard ratios (HRs) of variables related to in-hospital mortality and RRT dependency. Variables were selected for multivariate analysis according to study aim and were adjusted. The results are reported as HR and 95% confidence interval (CI). We conducted a receiver operating characteristic (ROC) analysis to confirm the predictive accuracy of the prognostic factors for all-cause in-hospital mortality and calculated the area under the curve (AUC). All probabilities were two-tailed, and the level of statistical significance was defined as p < 0.05. All statistical analyses were performed using IBM SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline clinical characteristics of patients

The baseline clinical characteristics of the patients are presented in Table 1 according to type of malignancy. Of the 471 patients, 298 (63.3%) had a solid malignancy, and 173 (36.7%) had a hematologic malignancy. In patients with a solid malignancy, the median age was 70 years (IQR, 62–77 years) and 212 (71.1%) were male. The extent of cancer was mostly localized (79.2%), and the digestive tract was the most common site of cancer (57.0%). About half of the patients were in remission (53.4%), and 52 (17.4%) patients had a history of chemotherapy before ICU admission, and the purpose of most of that chemotherapy was palliative.
Table 1. Baseline clinical characteristics of study patients according to type of malignancy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Solid malignancy</th>
<th>Hematologic malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>298</td>
<td>173</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>70 (62–77)</td>
<td>65 (52–73)</td>
</tr>
<tr>
<td>Male sex</td>
<td>212 (71.1)</td>
<td>99 (57.2)</td>
</tr>
<tr>
<td>Solid tumor, localized/distant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>16 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>35 (11.7)</td>
<td></td>
</tr>
<tr>
<td>Digestive tract</td>
<td>170 (57.0)</td>
<td></td>
</tr>
<tr>
<td>Prostate/bladder/kidney</td>
<td>35 (11.7)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>42 (14.1)</td>
<td></td>
</tr>
<tr>
<td>Hematologic malignancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>-</td>
<td>84 (48.6)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>-</td>
<td>58 (33.5)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>-</td>
<td>23 (13.3)</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>-</td>
<td>7 (4.0)</td>
</tr>
<tr>
<td>Cancer status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>37 (12.4)</td>
<td>15 (8.7)</td>
</tr>
<tr>
<td>Induction</td>
<td>0 (0)</td>
<td>49 (28.3)</td>
</tr>
<tr>
<td>Remission</td>
<td>159 (53.4)</td>
<td>53 (30.6)</td>
</tr>
<tr>
<td>Stabilization</td>
<td>33 (11.1)</td>
<td>25 (14.5)</td>
</tr>
<tr>
<td>Progression</td>
<td>63 (21.1)</td>
<td>31 (17.9)</td>
</tr>
<tr>
<td>Underlying disease, overlapped</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>131 (44.0)</td>
<td>53 (30.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>127 (42.6)</td>
<td>45 (26.0)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>81 (27.2)</td>
<td>33 (19.1)</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>19 (6.4)</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>50 (16.8)</td>
<td>7 (4.0)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>63 (21.1)</td>
<td>14 (8.1)</td>
</tr>
<tr>
<td>Treatment history before ICU admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>52 (17.4)</td>
<td>145 (83.8)</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>18 (34.6)</td>
<td></td>
</tr>
<tr>
<td>Palliative</td>
<td>34 (65.4)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>9 (3.0)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Concurrent chemoradiation therapy</td>
<td>27 (9.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Steroid</td>
<td>0 (0)</td>
<td>5 (2.9)</td>
</tr>
<tr>
<td>Bone marrow transplantation</td>
<td>-</td>
<td>33 (19.1)</td>
</tr>
<tr>
<td>Admission (day)</td>
<td>15 (5–32)</td>
<td>26 (14–45)</td>
</tr>
<tr>
<td>ICU admission (day)</td>
<td>6 (3–14)</td>
<td>6 (3–12)</td>
</tr>
<tr>
<td>ICU admission to CRRT start (day)</td>
<td>0 (0–1)</td>
<td>1 (0–3)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.6 (19.8–25.3)</td>
<td>23.2 (20.9–26.1)</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>75 (67–89)</td>
<td>77 (68–85)</td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
<td>104 ± 24</td>
<td>115 ± 25</td>
</tr>
<tr>
<td>ICU risk factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventilator use</td>
<td>180 (60.4)</td>
<td>112 (64.7)</td>
</tr>
<tr>
<td>Vasopressor use</td>
<td>212 (71.1)</td>
<td>123 (71.1)</td>
</tr>
<tr>
<td>SOFA score</td>
<td>11 (8–13)</td>
<td>13 (10–16)</td>
</tr>
<tr>
<td>6-Hr urine output before CRRT (mL)</td>
<td>95 (20–255)</td>
<td>160 (50–380)</td>
</tr>
</tbody>
</table>

(Continued to the next page)
### Table 1. Continued

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Solid malignancy</th>
<th>Hematologic malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>110 (36.9)</td>
<td>100 (57.8)</td>
</tr>
<tr>
<td>Trauma</td>
<td>6 (2.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Surgery</td>
<td>71 (23.8)</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Cause of ICU admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>117 (39.3)</td>
<td>54 (31.2)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>56 (18.8)</td>
<td>48 (27.7)</td>
</tr>
<tr>
<td>Shock</td>
<td>125 (41.9)</td>
<td>71 (41.0)</td>
</tr>
<tr>
<td>Acute kidney injury etiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>146 (49.0)</td>
<td>123 (71.1)</td>
</tr>
<tr>
<td>Ischemia/shock</td>
<td>84 (28.2)</td>
<td>11 (6.4)</td>
</tr>
<tr>
<td>Drugs</td>
<td>21 (7.0)</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Tumor lysis syndrome</td>
<td>2 (0.7)</td>
<td>22 (12.7)</td>
</tr>
<tr>
<td>Urinary tract obstruction</td>
<td>13 (4.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Others</td>
<td>32 (10.7)</td>
<td>14 (8.1)</td>
</tr>
<tr>
<td>CRRT indication, overlapped</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained oliguria</td>
<td>163 (54.7)</td>
<td>83 (48.0)</td>
</tr>
<tr>
<td>Uncontrolled volume overload</td>
<td>154 (51.7)</td>
<td>102 (59.0)</td>
</tr>
<tr>
<td>Intractable hyperkalemia</td>
<td>25 (8.4)</td>
<td>9 (5.2)</td>
</tr>
<tr>
<td>Severe acidosis</td>
<td>94 (31.5)</td>
<td>49 (28.3)</td>
</tr>
<tr>
<td>Others</td>
<td>122 (40.9)</td>
<td>81 (46.8)</td>
</tr>
<tr>
<td>CRRT duration (hr)</td>
<td>37 (14–74)</td>
<td>47 (15–107)</td>
</tr>
<tr>
<td>Downtime (hr)</td>
<td>1 (0–5)</td>
<td>1 (0–4)</td>
</tr>
<tr>
<td>CRRT prescription</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescribed dose (mL/kg/hr)</td>
<td>38.1 (35.3–41.1)</td>
<td>38.5 (35.1–42.9)</td>
</tr>
<tr>
<td>Delivered CRRT dose (mL/kg/hr)</td>
<td>33.2 (30.1–36.6)</td>
<td>34.7 (31.6–38.7)</td>
</tr>
<tr>
<td>Laboratory finding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell (×10^3)/μL</td>
<td>12.8 (8.0–19.4)</td>
<td>3.9 (0.4–13.9)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>9.9 (8.5–11.5)</td>
<td>8.8 (7.9–10.0)</td>
</tr>
<tr>
<td>RDW-CV (%)</td>
<td>15.5 (14.2–17.0)</td>
<td>16.3 (15.2–17.9)</td>
</tr>
<tr>
<td>Platelet (×10^9)/μL</td>
<td>139 (80–209)</td>
<td>38 (20–61)</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.9 (2.5–3.2)</td>
<td>2.7 (2.3–3.2)</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>5.1 (3.8–7.2)</td>
<td>4.3 (3.8–4.9)</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.29 (7.19–7.38)</td>
<td>7.30 (7.19–7.39)</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>15.8 (11.4–20.7)</td>
<td>18.1 (14.4–22.5)</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>52.2 (28.6–73.5)</td>
<td>58.6 (38.4–84.4)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>2.53 (1.65–4.02)</td>
<td>2.40 (1.76–3.49)</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>7.5 (5.5–10.3)</td>
<td>6.9 (4.9–9.5)</td>
</tr>
<tr>
<td>Corrected calcium (mg/dL)^a</td>
<td>8.8 (8.4–9.4)</td>
<td>8.8 (8.0–9.4)</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>5.1 (3.8–7.2)</td>
<td>4.8 (3.3–7.1)</td>
</tr>
<tr>
<td>Lactic acid (mmol/L)</td>
<td>4.4 (1.9–9.0)</td>
<td>3.7 (2.1–8.4)</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>287 (195–717)</td>
<td>737 (279–1,796)</td>
</tr>
<tr>
<td>Pro-BNP (pg/mL)</td>
<td>2,411 (655–8,680)</td>
<td>4,906 (1,155–17,139)</td>
</tr>
</tbody>
</table>

Data are expressed as number only, number (%), median (interquartile range), or mean ± standard deviation.

BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; ICU, intensive care unit; RDW-CV, red cell distribution width-coefficient of variation; SOFA, Sequential Organ Failure Assessment.

^a Corrected calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 × [4–measured serum albumin (g/dL)].
The median SOFA score was 11 (IQR, 8–13), and the median 6-hour urine output before the start of CRRT was 95 mL (IQR, 20–255 mL). The most common reason for ICU admission was shock (41.9%), and the most common cause of AKI was sepsis (49.0%). Sustained oliguria was a major indication for CRRT (54.7%). In terms of initial laboratory findings at ICU admission, the median albumin level was 2.9 g/dL (IQR, 2.5–3.2 g/dL), and the median creatinine level was 2.53 mg/dL (IQR, 1.65–4.02 mg/dL).

In patients with hematologic malignancy, the median age was 65 years (IQR, 52–73 years) and 99 (57.2%) were male. Leukemia was the most common subtype (48.6%), and about one-third of patients were in remission (30.6%). Most of the patients had a history of chemotherapy before ICU admission (83.8%). The median SOFA score was 13 (IQR, 10–16), and the median 6-hour urine output before the start of CRRT was 160 mL (IQR, 50–380 mL). The most common reason for ICU admission was shock (41.0%), and the most common cause of AKI was sepsis (71.1%). Uncontrolled volume overload was a major indication for CRRT (59.0%). In terms of initial laboratory findings at ICU admission, the median albumin level was 2.7 g/dL (IQR, 2.3–3.2 g/dL), and the median creatinine level was 2.40 mg/dL (IQR, 1.76–3.49 mg/dL).

### Primary outcome

Table 2 shows the all-cause mortality of the study patients according to type of malignancy. The median follow-up duration was 15 days (IQR, 5–32 days) in the solid malignancy group and 26 days (IQR, 14–45 days) in the hematologic malignancy group. In the solid malignancy group, 175 patients (58.7%) died during the 28-day hospitalization, as did 142 of the patients (82.1%) in the hematologic malignancy group. The baseline clinical characteristics of non-survivors and survivors are presented in Supplemental Table 1 and 2 (available online) for patients in the solid and hematologic malignancy groups, respectively.

The results of the Cox regression univariable and multivariable analyses for 28-day all-cause mortality according to the baseline clinical parameters in the solid and hematologic malignancy groups are presented in Table 3 and 4, respectively. In the solid malignancy group, BMI (HR, 0.96 [95% CI, 0.93–0.98]; p = 0.001), presence of oliguria (HR, 1.82 [95% CI, 1.24–2.66]; p = 0.002), severe acidosis (HR, 1.71 [95% CI, 1.18–2.45]; p = 0.004), heart rate (HR, 1.01 [95% CI, 1.01–1.02]; p = 0.02), SOFA score (HR, 1.09 [95% CI, 1.04–1.15]; p = 0.001), and albumin level (HR, 0.74 [95% CI, 0.55–0.99]; p = 0.04) were associated with 28-day all-cause mortality. In the hematologic malignancy group, BMI (HR, 0.96 [95% CI, 0.92–0.99]; p = 0.03), presence of oliguria (HR, 1.49 [95% CI, 1.03–2.16]; p = 0.04), SOFA score (HR, 1.11 [95% CI, 1.05–1.17]; p < 0.001), and albumin level (HR, 0.69 [95% CI, 0.49–0.96]; p = 0.03) were associated with 28-day all-cause mortality. A high heart rate and presence of severe acidosis were specific prognostic factors for 28-day mortality only in patients with solid malignancy.

The ROC curves constructed using the prognostic factors predicting 28-day all-cause mortality are plotted in Fig. 2. The AUC of the variables in the solid malignancy group (BMI, oliguria, severe acidosis, heart rate, SOFA score, and albumin level) was 0.831 (p < 0.001), with a positive predictive value of 78.16% and a negative predictive value of 74.87%. The AUC of the variables in the hematologic malignancy group (BMI, oliguria, SOFA score, and albumin level) was 0.802 (p < 0.001), with a positive predictive value of 84.71% and a negative predictive value of 62.73%.

### Secondary outcome

Table 2 shows the RRT dependency of the survivors according to type of malignancy. At the time of hospital discharge,

### Table 2. All-cause mortality and RRT dependency in patients with cancer according to type of malignancy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Solid malignancy (n = 298)</th>
<th>Hematologic malignancy (n = 173)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>190 (63.8)</td>
<td>146 (84.4)</td>
</tr>
<tr>
<td>Intensive care unit death</td>
<td>183 (61.4)</td>
<td>146 (84.4)</td>
</tr>
<tr>
<td>28-Day death</td>
<td>175 (58.7)</td>
<td>142 (82.1)</td>
</tr>
<tr>
<td>RRT dependency among survivors</td>
<td>27/108 (25.0)</td>
<td>9/27 (33.3)</td>
</tr>
</tbody>
</table>

Data are expressed as number (%). RRT, renal replacement therapy.
25.0% of the patients in the solid malignancy group and 33.3% of the patients in the hematologic malignancy group were RRT dependent. The results of multivariate logistic regression analysis of prognostic factors for RRT dependency are shown in Supplementary Table 3 (available online). In the solid malignancy group, only underlying chronic kidney disease was related to RRT dependency (HR, 3.95 [95% CI, 1.69–9.24]; p = 0.001). In the hematologic malignancy group, the presence of oliguria as a CRRT indication (HR, 60.38 [95% CI, 1.02–3,576.82]; p = 0.049) and serum creatinine level at CRRT initiation (HR, 8.29 [95% CI, 1.07–64.23]; p = 0.04) were related to RRT dependency.

Discussion

This retrospective study investigated in-hospital mortality and prognostic factors for in-hospital mortality among critically ill Korean patients with both AKI and cancer who received CRRT. As expected, the 28-day all-cause mortality rates were high, 58.8% in the solid malignancy group and 82.0% in the hematologic malignancy group. Low BMI, presence of oliguria, high SOFA score, and low serum albumin level were common prognostic factors for 28-day mortality in patients with solid and hematologic malignancies, whereas a high heart rate and presence of severe acidosis were predictive only for patients with a solid malignancy. The proportion of patients who survived to hospital discharge with RRT dependency was 25.0% in the solid malignancy group and 33.3% in the hematologic malignancy group.

CRRT is an indispensable treatment modality for AKI in critically ill patients, and its overall use among patients un-
dergoing acute RRT is increasing [11,12]. In recent studies, CRRT greatly improved the rates of all-cause mortality and survival [11,12]. Because of remarkable advances in both cancer treatment and ICU treatment, patients with cancer now account for 13.5% to 34.8% of all patients admitted to ICUs [2,13–16]. Several studies have reported the outcomes of patients with both AKI and cancer who underwent RRT (Table 5) [7,16–26]. The differences in the proportions of solid and hematologic malignancies and indications for RRT among those studies make it difficult to directly compare their results. The in-hospital mortality rate ranged from 50% to 86% in patients with solid malignancy and from 72% to 86% in patients with hematologic malignancy. In this study, the prognoses for those patients were comparable to those from other studies.

The reported prognostic factors for in-hospital mortality vary among studies and include number of organ failures, SOFA score or SAPS, and serum albumin level [5,16,18,19,21,23]. BMI reflects nutrition status, and both undernutrition (BMI of <18.5 kg/m²) and overweight/obesity (BMI of ≥25 kg/m²) carry a negative prognosis in cancer [27,28]. Because hypoalbuminemia is associated with several pathologic conditions, such as nutritional deficiency and chronic inflammation [29], a low BMI might reflect poor nutritional status and contribute as a prognostic factor for all-cause mortality in both malignancy groups.

In a systematic review of studies evaluating prognostic indices including SOFA, SAPS [30], and acute physiology and chronic health evaluations [31], all of the indices effectively predicted the outcomes of general medical or surgical ICU patients [32]. Among cancer patients, several studies, including this one, have confirmed that the indices that

Table 4. Prognostic factors for 28-day all-cause mortality in hematologic malignancy patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1 HR (95% CI)</th>
<th>Model 1 p-value</th>
<th>Model 2 HR (95% CI)</th>
<th>Model 2 p-value</th>
<th>Model 3 HR (95% CI)</th>
<th>Model 3 p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.01 (0.99–1.02)</td>
<td>0.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>0.96 (0.69–1.34)</td>
<td>0.81</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.97 (0.95–1.01)</td>
<td>0.05</td>
<td>0.97 (0.93–1.01)</td>
<td>0.08</td>
<td>0.96 (0.92–0.99)</td>
<td>0.03</td>
</tr>
<tr>
<td>Cancer status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>1.06 (0.56–1.99)</td>
<td>0.86</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction</td>
<td>1.26 (0.83–1.91)</td>
<td>0.29</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stabilization</td>
<td>0.77 (0.44–1.32)</td>
<td>0.77</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progression</td>
<td>0.96 (0.59–1.58)</td>
<td>0.96</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>1.32 (0.94–1.84)</td>
<td>0.11</td>
<td>1.03 (0.67–1.58)</td>
<td>0.89</td>
<td>0.94 (0.60–1.46)</td>
<td>0.77</td>
</tr>
<tr>
<td>Oliguria</td>
<td>1.85 (1.33–2.59)</td>
<td>&lt;0.001</td>
<td>1.72 (1.21–2.45)</td>
<td>0.002</td>
<td>1.49 (1.03–2.16)</td>
<td>0.04</td>
</tr>
<tr>
<td>Severe acidosis</td>
<td>1.83 (1.28–2.62)</td>
<td>0.001</td>
<td>1.33 (0.91–1.94)</td>
<td>0.14</td>
<td>1.18 (0.80–1.75)</td>
<td>0.40</td>
</tr>
<tr>
<td>Admission cause</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>1.89 (1.21–2.96)</td>
<td>0.005</td>
<td>1.68 (1.05–2.69)</td>
<td>0.03</td>
<td>1.28 (0.76–2.17)</td>
<td>0.36</td>
</tr>
<tr>
<td>Shock</td>
<td>2.01 (1.33–3.06)</td>
<td>0.001</td>
<td>1.44 (0.86–2.39)</td>
<td>0.17</td>
<td>1.04 (0.59–1.84)</td>
<td>0.89</td>
</tr>
<tr>
<td>Heart rate</td>
<td>1.01 (1.00–1.02)</td>
<td>0.007</td>
<td>1.01 (0.99–1.01)</td>
<td>0.11</td>
<td>1.01 (0.99–1.01)</td>
<td>0.14</td>
</tr>
<tr>
<td>SOFA</td>
<td>1.13 (1.08–1.18)</td>
<td>&lt;0.001</td>
<td>1.11 (1.05–1.17)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell</td>
<td>0.99 (0.98–1.00)</td>
<td>0.04</td>
<td>0.99 (0.98–1.01)</td>
<td>0.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>0.58 (0.43–0.78)</td>
<td>&lt;0.001</td>
<td>0.69 (0.49–0.96)</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uric acid</td>
<td>0.96 (0.92–0.99)</td>
<td>0.03</td>
<td>0.99 (0.95–1.04)</td>
<td>0.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrected calcium</td>
<td>1.03 (0.92–1.16)</td>
<td>0.61</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT INR</td>
<td>1.17 (0.96–1.42)</td>
<td>0.13</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


BMI, body mass index; CI, confidence interval; HR, hazard ratio; PT INR, prothrombin time international normalized ratio; SOFA, Sequential Organ Failure Assessment.

*Corrected calcium (mg/dL) = measured total Ca (mg/dL) + 0.8 × [4 – measured serum albumin (g/dL)].
reflect a patient’s acute physiological status predict their prognosis. Consistent with the results of previous studies, cancer characteristics (cancer status, site of solid malignancy or subtype of hematologic malignancy, and treatment history) were not predictors of in-hospital mortality in the present study [9,20]. Although it was not investigated in this study, previous studies found that cancer variables influenced survival after hospital discharge, whereas acute physiologic changes were associated with in-hospital mortality [9,13,33]. The presence of oliguria was previously reported to be a prognostic variable in AKI patients admitted to the ICU [34], and our results are similar.

Patients with AKI commonly have metabolic acidosis, which is an independent predictor of unfavorable outcomes [35–37]. However, in the results of this study, the presence of severe and intractable acidosis (arterial pH of <7.2 despite maximal medical care) was a prognostic factor for all-cause in-hospital mortality only in patients with a solid malignancy. Because of the retrospective design of the study, the maximal medical care used to correct acidosis was not unified among the patients. A high heart rate was also a prognostic factor of 28-day all-cause mortality only in the solid malignancy group. It is well known that the heart rate fluctuates during the day, and the presence of combined arrhythmia was not investigated. The mortality rate in patients with hematologic malignancy was extremely high, which might explain why heart rate and severe acidosis were not meaningful as prognostic factors, unlike solid malignancy. Those results from this study need to be validated in a randomized controlled study.

In our study, the proportion of patients discharged alive from the hospital with RRT dependency was 25.0% in the solid malignancy group and 33.3% in the hematologic malignancy group. That was slightly higher than the results from other studies, which reported a range between 14% and 24% [7,23,25], and did not differ from the rates in general ICU populations [38,39]. In general ICU populations treated with RRT for AKI, age, diabetes, chronic kidney disease, and oliguria at the time of RRT initiation are associated with RRT dependency [39]. Our study showed similar results, though they differed according to type of malignancy.

This study has several strengths. Unlike previous studies,
Table 5. Summary of publications on RRT in critically ill patients with AKI and cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country and date of study</th>
<th>Study design</th>
<th>Proportions of cancer subtypes</th>
<th>No. of patients</th>
<th>RRT</th>
<th>Disease severity</th>
<th>Mortality</th>
<th>Prognostic factors for hospital mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanore et al. [21]</td>
<td>1991</td>
<td>France; May 1983–November 1989</td>
<td>Retrospective single center</td>
<td>Hemato: 100% BMT: 11%</td>
<td>43</td>
<td>-</td>
<td>SAPS II</td>
<td>ICU: 72%</td>
<td>AKI secondary to sepsis, SAPS score, mechanical ventilation support</td>
</tr>
<tr>
<td>Létourneau et al. [22]</td>
<td>2002</td>
<td>Canada; January 1994–December 1998</td>
<td>Retrospective single center</td>
<td>Hemato: 100% BMT: 100%</td>
<td>14</td>
<td>IRRT</td>
<td>CVVHDF</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Benoit et al. [18]</td>
<td>2005</td>
<td>Belgium; January 1997–June 2002</td>
<td>Retrospective single center</td>
<td>Hemato: 100% BMT: 22.4%</td>
<td>50</td>
<td>IRRT</td>
<td>CRRT</td>
<td>ICU: 79.6%</td>
<td>Hospital: 83.7%</td>
</tr>
<tr>
<td>Soares et al. [25]</td>
<td>2006</td>
<td>Brazil; May 2000–December 2004</td>
<td>Prospective single center</td>
<td>Solid: 75% Hemato: 25%</td>
<td>98</td>
<td>IRRT conventional extended</td>
<td>APACHE II</td>
<td>ICU: 43.6%</td>
<td>LOD score, late RRT (&gt;24 hr after ICU admission)</td>
</tr>
<tr>
<td>Maccariello et al. [23]</td>
<td>2011</td>
<td>Brazil; December 2004–July 2008</td>
<td>Prospective three centers</td>
<td>Solid: 73%</td>
<td>118</td>
<td>IRRT daily conventional extended</td>
<td>CRRT</td>
<td>ICU: 77%</td>
<td>Modified SOFA score</td>
</tr>
<tr>
<td>Salahudeen et al. [26]</td>
<td>2009</td>
<td>USA; January 2006–June 2007</td>
<td>Retrospective single center</td>
<td>Solid: 38% Hemato: 62% BMT: 18%</td>
<td>199</td>
<td>C-SLED</td>
<td>SOFA</td>
<td>Day 30: 65%</td>
<td>-</td>
</tr>
</tbody>
</table>
this study analyzed in-hospital mortality and prognostic factors by dividing cancer patients into solid and hematologic malignancy groups. Our finding of different prognostic factors between the malignancy groups indicates that patient prognosis should be predicted without merging those groups under a cancer diagnosis. Moreover, the ability of the combined prognostic factors to predict in-hospital mortality, as shown by the high AUCs, is notable and worth validating in future studies. This study included critically ill cancer patients with AKI undergoing CRRT from 2013 to 2020, so our data are more recent than the data used in previous studies. The results of this study thus reflect the effects of rapidly developing treatments for cancer and ICU patients, but the mortality and RRT dependency were similar to those in previous studies. This study also has several limitations. Although the analyses were performed with appropriate adjustments, the possibility of residual confounders cannot be excluded because of the retrospective nature of the study. Most of the patients were Korean, which limits the generalizability of the findings to other races. Additionally, data evaluation and comparison of medium- and long-term survival rates and renal function were not performed.

In conclusion, the 28-day mortality rate was very high in patients with AKI undergoing CRRT, reaching 58.8% in the solid malignancy group and 82.0% in the hematologic malignancy group. BMI, presence of oliguria, SOFA score, and serum albumin level were common predictors of in-hospital mortality in patients with all malignancies. These results could be helpful in establishing a therapeutic plan for CRRT in critically ill patients with cancer and AKI because the mortality rates and prognostic factors differed according to type of malignancy.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**Funding**

This work was supported by a clinical research grant from Pusan National University Hospital in 2021.
Authors’ contributions

Conceptualization: EYS, SHS
Data curation: GSJ, KSJ, HR
Formal analysis: DWK
Investigation: HJJ, HJK
Project administration: SHS
Writing-Original Draft: DWK
Writing-Review & Editing: All authors
All authors read and approved the final manuscript.

ORCID

Da Woon Kim, https://orcid.org/0000-0002-9471-5976
Geum Suk Jang, https://orcid.org/0000-0003-2061-9305
Kyoung Suk Jung, https://orcid.org/0000-0001-9215-7678
Hyuk Jae Jung, https://orcid.org/0000-0003-3407-5855
Hyo Jin Kim, https://orcid.org/0000-0001-9289-9073
Harin Rhee, https://orcid.org/0000-0001-6257-8551
Eun Young Seong, https://orcid.org/0000-0002-6006-0051
Sang Heon Song, https://orcid.org/0000-0002-8218-6974

References


Background: Autosomal dominant polycystic kidney disease (ADPKD), one of the most common human monogenic diseases, is characterized by the presence of numerous fluid-filled renal cysts and is a leading cause of end-stage renal disease (ESRD). Urinary biomarkers may be useful for predicting the variable course of ADPKD progression from cyst growth to ESRD.

Methods: To identify candidate urinary biomarkers of ADPKD progression, we used CRISPR/Cas9 genome editing to generate porcine fibroblasts with mono- and biallelic ADPKD gene knockout (PKD2+/– and PKD2–/–, respectively). We then performed RNA-sequencing analysis on these cells.

Results: Levels of osteopontin (OPN), which is expressed by renal epithelial tubular cells and excreted into urine, were reduced in PKD2–/– cells but not in PKD2+/– cells. OPN levels were also reduced in the renal cyst cells of ADPKD patients. Next, we investigated whether OPN excretion was decreased in patients with ADPKD via enzyme-linked immunosorbent assay. OPN levels excreted into renal cyst cell culture media and urine from ADPKD patients were decreased. To investigate whether OPN can predict the rate of ADPKD progression, we compared urinary excretion of OPN in ADPKD patients with slow progression and those with rapid progression. Those with rapid progression had an estimated glomerular filtration rate of >60 mL/min/1.73 m². Urinary OPN excretion levels were lower in rapid progressors than in slow progressors.

Conclusion: These findings suggest that OPN is a useful urinary biomarker for predicting ADPKD progression.

Keywords: Autosomal dominant polycystic kidney disease, Biomarkers, Clustered regularly interspaced short palindromic repeats/Cas9, Osteopontin
Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disease caused by mutations in the PKD1 and PKD2 genes. Among genetic diseases, ADPKD has a high incidence and a long disease progression course. Cysts, a typical symptom of this disease, occur in both kidneys and sometimes in the liver or other organs. The number and size of these cysts gradually increase. When patients reach their 40s and 50s, kidney function deteriorates, eventually progressing to end-stage renal disease (ESRD) [1–5].

Currently, ADPKD is diagnosed by direct PKD1 and PKD2 gene sequencing analyses. However, these techniques are associated with difficulties due to the size and complexity of these genes. Although gene variants can be detected by direct sequencing of the PKD1 and PKD2 genes, distinguishing between gene polymorphisms and pathogenic missense mutations in the absence of family history is difficult [6–9]. Therefore, in addition to direct sequencing of the PKD1 and PKD2 genes, radiologic analysis of renal cysts is performed for the diagnosis of ADPKD [10–12]. Kidney cysts begin in childhood, but the size and number of cysts must be sufficient to be detected in radiographic images. Therefore, radiologic diagnosis may be difficult in the early stages of adolescence. In addition to radiologic evaluation, monitoring of renal function is also used to determine the progression of ADPKD [13,14]. However, decreases in renal function are not completely consistent with increases in the size and number of cysts. Since decreased renal function is observed when total kidney volume (TKV) has increased to some extent, determining progression of ADPKD by measuring levels of creatinine as an indicator of renal function, especially in the early stages of disease, is difficult. Therefore, a new biomarker, preferably one detectable in the urine, is needed for predicting ADPKD progression before renal function deteriorates. Pigs in which only one allele of PKD1 has been mutated exhibit a phenotype similar to human ADPKD [15]. Compared with mice, which exhibit the ADPKD phenotype only after biallelic knockout, pigs are more similar to humans and are good animal models for the study of disease mechanisms and biomarkers. Porcine fibroblasts with biallelic knockout of the ADPKD-related gene PKD2 are similar to human renal cyst cells that display a recessive mechanism but dominant inheritance, and genes that exhibit changes in expression in these cells could be potential biomarkers.

In the current study, genes that could affect the number and size of cysts via mutation were selected. Osteopontin (OPN) is an acidic glycoprotein that has been identified as a soluble cytokine in both urine and plasma. OPN is composed of 314 amino acids, and its structure includes an N-terminal fragment that contains an integrin-binding site and a C-terminal fragment that binds two heparin molecules and CD44 variants [16–18]. OPN is a member of the small integrin-binding ligand N-linked glycoprotein (SIBLING) family of proteins and is involved in bone remodeling, cell survival, inflammation, and kidney damage [19]. According to the results of several studies, the expression levels of OPN were increased in animals with kidney diseases. These diseases included glomerulonephritis, stone formation, acute ischemic renal injury, tubulointerstitial nephritis, hydronephrosis, chronic cyclosporine-induced nephropathy, interstitial inflammation and fibrosis, and lupus nephritis [16].

In this study, we investigated OPN as a potential urinary biomarker for predicting ADPKD severity or progression.

Methods

Study subjects

The subjects enrolled in the HOPE-PKD cohort (the cohort for genotype-PhenotypE correlation in ADPKD) between 2009 and 2017 were screened [20]. All methods were conducted in accordance with relevant guidelines and regulations. The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (No. 1205-112-411). The informed consent was obtained from all subjects before performing study. Subjects who were aged over 18 years with compatible imaging findings using the unified criteria, with or without a family history of disease, were enrolled in the HOPE-PKD cohort.

Cell lines and culture

For the immortalization of porcine fibroblasts, primary cultured porcine fibroblasts from White Yucatan miniature pigs were transfected with human telomerase reverse transcriptase (hTERT) via Lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA). After transfection, the cells were
selected with 1-mg/mL G418 for two passages and then maintained in medium supplemented with 0.5-mg/mL G418. Immortalized porcine fibroblasts were cultured in Dulbecco’s Modified Eagle’s Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and minimum essential media nonessential amino acid solution (Thermo Fisher Scientific, Waltham, MA, USA) at 37°C in 5% CO₂.

To achieve PKD2 gene knockout in porcine fibroblasts by CRISPR/Cas9 genome editing, a single-guide RNA targeting PKD2 (5′-GCA TCC GGC AGG CGG CCG CG-3′) was inserted into the CRISPR/Cas9 plasmid pSpCas9-2A-Puro version 2.0 (Addgene, Watertown, MA, USA). The resulting plasmid was transfected into immortalized porcine fibroblasts using Lipofectamine 2000. After transfection, the cells were selected with 1-µg/mL puromycin for two passages.

To culture renal cyst cells, kidney tissues from the subjects in the HOPE-PKD cohort were obtained. The hTERT-immortalized renal cyst cells from ADPKD patients were derived from proximal tubular epithelial cells and cultured in DMEM supplemented with 10% FBS at 37°C in 5% CO₂ as previously described [21]. Human renal proximal tubular epithelial cells (RPTECs) were cultured in American Type Culture Collection (ATCC)-formulated DMEM/F12 supplemented with an hTERT RPTEC Growth Kit (ATCC, Manassas, VA, USA) as previously described [21].

RNA preparation and RNA-sequencing analysis

Total RNA was isolated from PKD2+/+, PKD2+/-, and PKD2−/− porcine fibroblasts using the TRIzol method according to the manufacturer’s protocol (Qiagen, Hilden, Germany). RNA-sequencing analysis was performed by MacroGen, Inc. (www.macrogen.com) with the Illumina HiSequation 2000 platform (Illumina, San Diego, CA, USA).

Real-time polymerase chain reaction

Total RNA isolated from individual porcine fibroblasts or RPTECs and from renal cyst cells was used for real-time polymerase chain reaction (RT-PCR) assays to quantify OPN and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) messenger RNA (mRNA) expression. First, we synthesized first-strand complementary DNA (cDNA) from total RNA using a PrimeScript RT-PCR Kit (Takara Bio, Shiga, Japan). Then, the first-strand cDNA was subjected to RT-PCR using Power SYBR Green PCR Master Mix (Thermo Fisher Scientific) and a QuantStudio 3 Real-Time PCR system (Thermo Fisher Scientific) according to the manufacturer’s protocols. PCR was conducted in triplicate with 40 cycles of 95°C for 15 seconds, 61°C for 30 seconds, and 58°C for 30 seconds. The threshold cycle (Cₜ) value was measured to determine the starting copy numbers of the target genes using the standard curve. The primers used to amplify porcine and human OPN and GAPDH were: sense porcine OPN: 5′-GGG CTT CGC CTC TGC CCT TC-3′ and antisense porcine OPN: 5′-GTC GGT TGC TGG GGT GTC GG-3′; sense human OPN: 5′-CCC ACG GAC CTG CCA GCA AC-3′ and antisense human OPN: 5′-TCC TTC CCA CGG CTG TCC CA-3′; sense porcine GAPDH: 5′-TCG CCA TCA ATG ACC CCT TCA-3′ and antisense porcine GAPDH: 5′-CAC CCC ATT TGA TGT TGG C-3′; and sense human GAPDH: 5′-TTG CCA TCA ATG ACC CCT TCA-3′ and antisense human GAPDH: 5′-CGC CCC ACT TGA TTT TGG A-3′.

Western blotting analysis

RPTECs and renal cyst cells from patients with ADPKD were lysed with RIPA buffer (Thermo Fisher Scientific). The protein lysates were separated by 12% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to polyvinylidene difluoride (PVDF) membranes. The membranes were incubated in blocking buffer (3% nonfat dry milk in Tris-buffered saline and 0.1% Tween 20 [TBST]) for 1 hour and then probed with primary antibodies overnight at 4°C. We used anti-PC2 (Baltimore PKD Center), anti-OPN (Proteintech, Rosemont, IL, USA), and anti-β-actin (Sigma-Aldrich, Burlington, MA, USA) primary antibodies for Western blotting analysis. After washing 3 times with TBST, the blots were incubated with a peroxidase-labeled secondary antibody for 1 hour. The blots were then washed 3 times with TBST, and the target proteins were detected using an enhanced chemiluminescence detection system (GE Healthcare, Chicago, IL, USA).

Quantitative analysis of the osteopontin levels in cell culture supernatants and urine

Supernatants from RPTEC and human renal cyst cell cultures and urine from normal individuals and ADPKD
patients were collected. We used a Human Osteopontin Quantikine enzyme-linked immunosorbent assay (ELISA) Kit (R&D Systems, Minneapolis, MN, USA) to quantify the OPN levels in the cell culture supernatants and urine. Urine samples from the HOPE-PKD cohort ADPKD patients were obtained. The levels of OPN in urine were corrected by the creatinine levels that were measured with a QuantiChrom Creatinine Assay Kit (BioAssay Systems, Hayward, CA, USA). The assay was performed according to the manufacturer’s protocol.

All human-derived materials containing urine were processed in accordance with relevant guidelines and regulations. This study was approved by the Institutional Review Board of Seoul National University Hospital (No. 1205-112-411).

Results

Establishment of porcine fibroblasts with CRISPR/Cas9-mediated targeted PKD2 gene knockout

PKD2-knockout porcine fibroblasts were generated to establish a porcine model of ADPKD that is more similar to human ADPKD disease than mouse models of ADPKD. PKD2-knockout porcine fibroblasts are additionally helpful to study ADPKD because renal fibrosis is the main reason for kidney function deterioration among ADPKD patients. We then investigated the gene expression profiles of these PKD2-knockout porcine fibroblasts through RNA-sequencing analysis to identify biomarker candidates for the prediction of ADPKD progression. We established porcine fibroblast cells in which PKD2, the ADPKD-related gene, was knocked out using CRISPR/Cas9 genome editing. First, porcine fibroblasts were immortalized with hTERT rather than simian virus 40 (SV40). SV40 induced aneuploidy and altered some signaling pathways, and induction of a PKD2 mono-allelic mutation with CRISPR/Cas9 requires no abnormalities in the number or structure of chromosomes. Since SV40 caused changes in the number and structure of chromosomes, we evaluated whether hTERT also causes these changes by karyotype analysis. We confirmed that there were no abnormalities in the number and structure of chromosomes in the karyotype of porcine fibroblasts immortalized with hTERT (Fig. 1A). Then, we used CRISPR/Cas9 to establish an ADPKD disease model in vitro in which a C nucleotide insertion mutation occurred in exon 1 of PKD2 (Fig. 1B). The protein expression levels in porcine fibroblasts were assessed to confirm whether the gene knockout was successfully achieved with the CRISPR/Cas9 system (Fig. 1C).

Messenger RNA expression of osteopontin was reduced in PKD2<sup>−/−</sup> porcine fibroblasts but not in PKD2<sup>+/−</sup> porcine fibroblasts

Porcine fibroblasts with PKD2 mono- and biallelic knockout (PKD2<sup>−/−</sup> and PKD2<sup>+/−</sup> cells, respectively) were prepared using the CRISPR/Cas9 system, and the gene expression profiles of these cells were determined through RNA-sequencing (Fig. 2A). Although ADPKD exhibits dominant inheritance, actual cyst formation is inherited in a recessive manner. PKD2<sup>−/−</sup> cells were considered to be cyst cells, and genes whose expression levels were increased or decreased in these cells were considered to be genes with altered expression in the actual renal cysts of ADPKD patients. Changes in the expression of these genes affect the number and extent of cysts and could be predictive indicators. Therefore, genes with altered expression in PKD2<sup>−/−</sup> cells but not in PKD2<sup>+/−</sup> cells were selected as potential biomarkers. Among the genes with increased or decreased expression only in PKD2<sup>−/−</sup> cells as determined by RNA-sequencing analysis, the genes with the highest expression changes and expressed in renal epithelial tubules were subsequently selected. Among these genes, genes that encode secreted proteins that can be detected in urine were selected (Fig. 2B). One such gene was OPN, and mRNA expression level of this gene was assessed by RT-PCR and agarose gel electrophoresis (Fig. 2C).

Expression of osteopontin was reduced in renal cysts of patients with autosomal dominant polycystic kidney disease

To confirm whether the mRNA expression level of OPN is decreased in the renal cysts of ADPKD patients, similar to the observations in PKD2<sup>−/−</sup> porcine fibroblasts, the mRNA expression levels of OPN in renal cyst cells were analyzed by RT-PCR. The results revealed that the OPN mRNA expression levels were significantly reduced in renal cyst cells (Fig. 3A). To determine whether these reductions also affected protein expression, the OPN protein expression lev-
els were assessed by Western blotting analysis. This analysis confirmed that the OPN protein levels were significantly reduced in renal cyst cells (Fig. 3B). Since OPN is a secreted protein, we measured the OPN levels in the supernatants of renal cyst cell cultures and confirmed that these levels were significantly reduced (Fig. 3C).

Osteopontin levels in urine from autosomal dominant polycystic kidney disease patients were significantly decreased and further decreased with increasing disease severity.

Since the expression of OPN in the renal cyst cells of AD-
PKD patients and the level of extracellular OPN secretion were decreased, the levels of OPN in urine were tested by ELISA. The levels of OPN were significantly lower in the urine of ADPKD patients than in that of normal individuals, demonstrating the potential for the use of OPN as a biomarker for the diagnosis of ADPKD (Fig. 4A).

In addition, we selected only subjects with estimated glomerular filtration rates (eGFRs) of >60 mL/min/1.73 m² to determine the ability of using OPN level to diagnose disease progression in early stages. Patients with ADPKD were divided into two groups according to the Mayo classification (class 1A-1E): a rapid progressor group (n = 11) in which disease was classified as class 1C-1E and a slow progressor group (n = 11) in which disease was classified as class 1A-1B [22] (Table 1). The protein levels of OPN in the urine were significantly lower in the rapid progressor group than in the slow progressor group (mean ± standard deviation, 0.1217 ± 0.06629 μg/mg creatinine; p = 0.03) (Fig. 4B). This demonstrates the potential for the use of OPN as a urinary biomarker to predict the severity of ADPKD progression.

**Discussion**

The diagnosis of ADPKD and the prediction of its progression remain difficult. Identification of biomarkers that
Figure 3. Expression and secretion of OPN were reduced in renal cyst cells from patients with ADPKD. (A) mRNA expression analysis of RPTECs and two different renal cyst cells from ADPKD patients by real-time polymerase chain reaction. The relative expression of OPN in RPTECs and renal cyst cells was normalized to the expression of GAPDH. (B) OPN protein expression in RPTECs and renal cyst cells. Beta-actin was used as a control for Western blotting. (C) The level of OPN secreted from RPTECs and renal cyst cells was measured by ELISA.

ADPKD, autosomal dominant polycystic kidney disease; ELISA, enzyme-linked immunosorbent assay; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; mRNA, messenger RNA; OPN, osteopontin; RPTEC, renal proximal tubular epithelial cell.

*p < 0.05, ***p < 0.001.

Figure 4. OPN in urine measured by enzyme-linked immunosorbent assay. (A) Urinary OPN levels from three different normal individuals and ADPKD patients corrected according to creatine levels. (B) Urinary OPN levels were measured in ADPKD patients in the slow progressor group (n = 11) and the rapid progressor group (n = 11).

ADPKD, autosomal dominant polycystic kidney disease; Cr, creatinine; OPN, osteopontin.

*p < 0.05.
can predict the progression of ADPKD is particularly challenging. To date, many variables, such as the glomerular filtration rate (GFR), TKV, and ADPKD genotype, have been used to predict ADPKD progression [22–26]. The GFR is an indicator of changes in kidney function, and TKV is an indicator of the number and size of renal cysts in patients with ADPKD. The GFR and TKV alone, however, are ineffective as biomarkers in the early stages of ADPKD; and, when linked to genotype analysis, these are expensive and have limitations for each individual patient. The predicting renal outcomes in ADPKD (PROPKD) score, which combines various factors such as sex, ADPKD genotype, and the presence of hypertension before the age of 35 years, also has limitations; this score can be applied only to patients older than 35 years of age and patients with the necessary clinical information available [26]. Identification of a meaningful biomarker in urine that can directly indicate the status of the kidneys in ADPKD patients would be superior to a blood biomarker. Measuring the urinary excretion of β2-microglobulin (β2MG) and monocyte chemotactic protein 1 (MCP-1) is more effective for predicting the rapid progression of ADPKD than measuring TKV and assessing genotype [27]. However, since β2MG and MCP-1 are factors that indicate tubular damage, their levels are also increased in patients with kidney diseases other than ADPKD, such as chronic kidney disease (CKD) and diabetic kidney disease. Therefore, although easy and inexpensive to measure, these urinary biomarkers do not predict ADPKD alone or distinguish ADPKD from other kidney diseases. For this reason, among the numerous proteins that are related to ADPKD, we focused on biomarkers found in urine. In addition, biomarkers in urine can predict not only a patient’s current condition but also the future progression of the disease. To examine possible biomarkers, we genetically targeted \( \text{PKD2} \), the pathogenic gene of ADPKD, using the CRISPR/Cas9 genome editing method to create a cyst-like \( \text{PKD2} \)-knockout cell model. We selected kidney-expressed, urine-excreted gene products whose expression was altered in these porcine fibroblasts as being candidate urinary biomarkers of ADPKD. The expression of these genes was verified by various methods, such as RT-PCR and ELISA.

In this study, we found that the OPN levels were reduced in both \( \text{PKD2} \) biallelic knockout porcine fibroblasts and renal cyst cells from ADPKD cohort patients. In addition, we confirmed that the urinary OPN levels of ADPKD patients were lower than those of normal controls. OPN is suggested to be an early biomarker of the renal progression of ADPKD given that, among ADPKD patients with eGFRs of 60 mL/min/1.73 m\(^2\) or higher, the OPN levels were lower in

| Table 1. Baseline characteristics between rapid progressor and slow progressor group patients |
|-----------------------------------------------|-----------------|-----------------|---------------|
| Characteristic                              | Rapid progressor group | Slow progressor group | p-value* |
| No. of patients                             | 11               | 11               | 0.48         |
| Male sex                                    | 8 (72.7)         | 6 (54.5)         | 0.12         |
| Age (yr)                                    | 34 (20–46)       | 45 (37–50)       | <0.001       |
| htTKV (mL/m)                                 | 783 (650–1,103)  | 367 (214–475)    | <0.001       |
| Mayo classification                         | A               | 3               | <0.001       |
|                                            | B               | 8               |              |
|                                            | C               | 3               |              |
|                                            | D               | 4               |              |
|                                            | E               | 4               |              |
| Genotype                                    | PKD1 PT         | 11              |              |
|                                            | PKD1 NT         | -               | 4            |
|                                            | PKD2            | -               | 7            |
| eGFR (mL/min/1.73 m\(^2\))                 | 84 (70–99)      | 101 (80–112)    | 0.19         |

Data are expressed as number only, number (%), or median (interquartile range).

eGFR, estimated glomerular filtration rate; htTKV, height-adjusted total kidney volume; NT, nontruncating; PT, protein-truncating.

*Mann-Whitney tests were performed.
rapid progressors. Although the average urinary OPN levels between slow progressors and rapid progressors differed, most of the values overlapped between these groups. This may be because the patient group was divided simply according to the Mayo classification. This suggests the need for further research on additional subgroups considering various factors, such as age and patient genotypes, in the future.

OPN is a secreted phosphorylated glycoprotein that is expressed in multiple cells, such as osteoblasts, natural killer cells, smooth muscle, activated T cells, macrophages, epithelial cells, endothelial cells, neurons, adipocytes, bone cells, kidney cells, and inflammatory cells. OPN plays a multifunctional role as a cytokine and adhesion protein and contains an integrin-binding sequence and an adhesive protein-binding sequence. OPN has been implicated in physiological and pathological processes such as bone remodeling, cellular immunity, and tissue injury. OPN activates intracellular signaling pathways and regulates gene expression through its interactions with various receptors [16,28].

In humans, OPN is expressed in the kidneys and secreted into urine and is associated with several renal diseases. Several studies have shown that OPN can be used as a biomarker of kidney diseases. OPN expression is increased in renal diseases, such as kidney cancer, immunoglobulin A nephropathy, minimal change disease, and diabetic nephropathy [16]. These studies suggested that OPN expression is closely related to the pathogenesis of renal failure and can be used as an indicator of kidney damage. In particular, previous studies have demonstrated that the levels of OPN in the urine of patients with CKD are elevated [19]. However, in the present study, we found that OPN levels were significantly reduced in PKD2-knockout porcine fibroblasts and in the renal cyst cells and urine of ADPKD patients. This OPN expression pattern is the opposite of that seen in CKD patients. The expression of OPN is reduced in osteoblasts in which PKD1 expression was silenced by short hairpin RNA (shRNA) as well as in PKD1-knockout mice [29,30]. Polycystin-1, a PKD1-encoded protein, activates the Akt/glycogen synthase kinase 3β (GSK-3β)/β-catenin pathway, resulting in the expression of Runt-related transcription factor 2 (RUNX2), an activator of OPN. In the context of PKD1 deficiency, phospho-Akt and phospho-GSK-3β levels are reduced; and decreases in the levels of active β-catenin in the nucleus result in decreased OPN levels [29]. In a mouse model in which the osteoblast-specific PKD2 gene is deleted, the RUNX2 levels and OPN levels are reduced [31]. Thus, under conditions of PKD1 or PKD2 deficiency, similar to observations in renal cysts, the expression levels of OPN in the kidneys may be reduced. Unlike patients with CKD, ADPKD patients exhibit decreased expression and urinary secretion of OPN. Therefore, OPN is potentially a good urinary biomarker for the differential diagnosis of ADPKD from CKD and for the prediction of the severity of ADPKD in patients. Further studies on whether renal damage, such as fibrosis and inflammation, in patients with ADPKD affects the urinary or plasma levels of OPN and the role of OPN gene polymorphisms are needed. These studies should include assessment of the expression of both full- and N-half-length OPN.

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

This work was carried out with the support of the Cooperative Research Program for Agriculture Science & Technology Development (Project No. PJ016222), Rural Development Administration, Republic of Korea.

Authors’ contributions

Conceptualization: Hyunho Kim
Formal analysis: Hyunsuk Kim, JS, JYB, PL, Hyunho Kim
Investigation: Hyunsuk Kim, JS
Methodology: Hyunho Kim, YKO
Resources: Hyunho Kim, YKO
Writing–original draft: Hyunsuk Kim, YKO, Hyunho Kim
Writing–review & editing: Hyunsuk Kim, YKO, Hyunho Kim
All of the authors read and approved the final manuscript.

ORCID

Hyunsuk Kim, https://orcid.org/0000-0003-1889-253X
Jinmo Sung, https://orcid.org/0000-0003-1628-926X
Ju Young Bae, https://orcid.org/0000-0001-8509-7099
Poongyeon Lee, https://orcid.org/0000-0003-2447-0392
Hyunho Kim, https://orcid.org/0000-0002-0804-3844

References


Association of sarcopenia and its components with clinical outcomes in patients undergoing peritoneal dialysis

Seok Hui Kang, A Young Kim, Jun Young Do

Division of Nephrology, Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Republic of Korea

Background: Further studies are needed to identify whether muscle mass, muscle strength, or sarcopenia is the best indicator of survival in patients undergoing peritoneal dialysis (PD). We aimed to compare the association of sarcopenia and its components with survival in patients undergoing PD.

Methods: We identified all patients with PD (n = 199). We routinely recommended handgrip strength (HGS) and lean mass measurements using dual energy X-ray absorptiometry in all patients with PD. Sarcopenia was defined using cutoff values from the Asian Working Group for Sarcopenia. We evaluated the patient and technique survival rates.

Results: The number of patients with low HGS was 95 (47.7%). The median follow-up interval was 17 months (interquartile range, 13–21 months). Kaplan-Meier curve analysis showed that patients with low HGS or sarcopenia had poorer patient and technique survival compared with patients with normal HGS or without sarcopenia. Cox regression analysis showed that patients with low HGS had greater hazard ratios for patient death and technique failure compared with those with normal HGS. However, patients with low muscle mass were not significantly higher hazard ratios for patient death or technique failure compared with those with normal muscle mass. Patients with sarcopenia had significantly greater hazard ratios for patient death or technique failure than those without sarcopenia only in univariate analysis.

Conclusion: The present study demonstrated that HGS may be superior to muscle mass or sarcopenia for predicting patient or technique survival in patients undergoing PD.

Keywords: Hand strength, Muscle, Peritoneal dialysis, Sarcopenia, Survival

Introduction

Chronic kidney disease is a major global health concern [1]. It can progress to end-stage renal disease requiring renal replacement therapy, such as hemodialysis, peritoneal dialysis (PD), or kidney transplantation. PD is a classically important dialysis modality despite being used in only a small proportion of patients undergoing dialysis [2,3]. The survival of patients undergoing PD has continuously improved with advances in management such as volume...
control and exit-site or peritonitis care [2,3]. However, the improvement in long-term survival in patients undergoing PD can lead to the development of chronic complications with increasing dialysis vintage. Among the various complications in patients undergoing PD, sarcopenia is an important condition associated with high rates of disability, mortality, and morbidities [4].

Sarcopenia is diagnosed on the basis of muscle mass, muscle strength, or physical performance. The evaluation and criteria for the diagnosis of sarcopenia have been defined according to studies conducted in the general or elderly population [5]. However, it may be difficult to apply the diagnostic criteria for sarcopenia used in a general population to patients undergoing dialysis. The guidelines recommend measuring muscle mass using bioimpedance analysis (BIA) or dual energy X-ray absorptiometry (DEXA); however, these methods are influenced by volume status in patients undergoing dialysis [5,6]. Muscle mass measurements using these methods in the post-dialysis period can be applicable in patients undergoing hemodialysis; however, dry-weight measurements may be more difficult in patients undergoing PD than in those undergoing hemodialysis. Some studies have evaluated the predictive ability for mortality of muscle mass, muscle strength, and sarcopenia as composite diagnostic indicators in patients undergoing dialysis [7,8]. However, most studies have not primarily focused on identifying optimal measurements through comparison among these indicators in patients undergoing PD. Therefore, further studies are needed to identify whether muscle mass, muscle strength, or sarcopenia is the best indicator of survival in patients undergoing PD. We aimed to compare the association of sarcopenia and its components with survival in patients undergoing PD.

Methods

Study population

This retrospective longitudinal study covered the period between September 2017 and November 2020. We identified all patients with PD from a tertiary medical center. We routinely recommended handgrip strength (HGS) and lean mass measurements in all patients with incident or prevalent PD between September 2017 and November 2020. This study included 214 patients who provided informed consent and underwent the two measurements. Among these patients, nine were excluded because of missing data and six were excluded because of inability to ambulate or having an amputated limb. Therefore, 199 patients undergoing PD were finally included. Baseline parameters including HGS and lean mass index were evaluated on the same day during a peritoneal membrane equilibration test. The end point of follow-up was October 2021. This study received ethical approval from the Institutional Review Board of Yeungnam University Medical Center (No. 2021-01-033) and was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki.

Baseline variables

We collected baseline data including age, sex, presence of diabetes mellitus (DM), dialysis modality (continuous ambulatory PD or automated PD), dialysis vintage (months), body mass index (kg/m²), weekly Kt/Vurea, C-reactive protein level (mg/dL), 4-hour dialysate-to-plasma creatinine ratio (DP₄Cr), urine volume (mL/day), edema index, serum calcium level (mg/dL), phosphorus level (mg/dL), sodium level (mEq/L), potassium level (mEq/L), albumin level (g/dL), normalized protein equivalent of total nitrogen appearance (nPNA, g/kg/day), and geriatric nutritional risk index (GNRI). DM was defined as a patient-reported history of DM and a DM diagnosis on medical records or use of DM medications. Weekly Kt/Vurea was calculated using 24-hour urine and dialysate collections, as previously described [9]. DP₄Cr was evaluated using a modified 4.25% peritoneal equilibration test, and the ratio was calculated by dividing the creatinine level in the drained dialysate at 4 hours after infusion by the blood creatinine level. The edema index was defined as extracellular water/total body water from BIA measurements (InBody 770; Biospace, Seoul, Korea). The nPNA and GNRI levels were evaluated using equations from previous studies [10–13]. GNRI was calculated using the equation from a previous study as follows: GNRI = [14.89 × albumin (g/dL)] + [41.7 × (body weight/ideal body weight)] [11]. Ideal body weight was calculated using the Lorentz equation derived from height [11].

Assessment of sarcopenia components and outcome

Lean mass was measured using DEXA. The measurements...
were performed after dialysate drainage, with the patients in the supine position and wearing a light gown. Images were obtained using a Discovery QDR Series bone densitometer (Hologic, Madison, WI, USA) and analyzed using the Hologic Discovery Wi software version 13.3. Appendicular lean mass (ALM) index (kg/m\(^2\)) was defined as the sum of the lean mass in the upper and lower extremities divided by height squared.

HGS was measured in all patients using a digital dynamometer (Takei 5401; Takei Scientific Instruments Co., Ltd, Niigata, Japan). Each patient performed three trials with the dominant hand. In our study, sarcopenia was defined as having both a low ALM index and low HGS. The cutoff values for a low ALM index or low HGS were defined using those from the Asian Working Group for Sarcopenia consensus [5], with low ALM defined as an ALM index of <7.0 kg/m\(^2\) for male patients and <5.4 kg/m\(^2\) for female patients, as measured using DEXA, and low HGS defined as <26 kg for male and <18 kg for female.

We evaluated patient and technique survival rates. Patient death was defined as death regardless of cause until the end point of follow-up. Data for patients with kidney transplantation, conversion to hemodialysis (for ≥90 consecutive days), cessation of dialysis owing to renal recovery, loss to follow-up, or transfer to another hospital were considered censored data. Technique failure was defined as patient death or conversion to hemodialysis for ≥90 consecutive days [14].

**Statistical analysis**

Data were analyzed using the statistical software SAS version 9.4 (SAS Institute, Cary, NC, USA). Categorical variables are expressed as counts (percentages) and were analyzed using Pearson chi-square test or Fisher exact test. Continuous variables were evaluated for distribution using the Kolmogorov-Smirnov test. These variables are presented as mean ± standard deviation for those with a normal distribution and median (interquartile range, IQR) for those with a non-normal distribution. Continuous variables with a non-normal distribution were compared using the Mann-Whitney U test and those with a normal distribution were compared using Student t test. Kaplan-Meier analysis was used to plot survival curves among the groups, and the log-rank method was used to determine statistical significance. Survival estimates were calculated using Cox regression analyses. Multivariate analyses were performed with age, sex, presence of DM, urine volume, serum albumin level, dialysis vintage, and edema index as covariates. We performed multivariate Cox regression analyses using the enter method. The proportional hazard assumption was satisfied for all variables. The area under the receiver operating characteristic curve (AUROC) was calculated to determine the ability of each indicator to predict mortality. Following the methodology of Pencina et al. [15,16], we further calculated the integrated discrimination improvement (IDI) and net reclassification improvement (NRI) values, with a category-free option among the models.

Because of differences in the baseline characteristics of the participants between the low and normal HGS groups, a propensity analysis was performed to minimize bias. To balance the baseline characteristics between low and normal HGS groups, we estimated propensity scores using logistic regression models and the following variables: age, sex, and DM. Participants in the low HGS group were matched with participants in the normal HGS group using 1:1 nearest neighbor matching without replacement and with a matching tolerance (caliper) of 0.2; the nearest neighborhood matching was based on propensity scores. Before the groups were matched, the standardized mean difference was 0.734, and after matching, the standardized mean difference was 0.105. The level of statistical significance was set at p < 0.05.

**Results**

**Participant clinical characteristics**

The number of patients with low HGS was 95 (47.7%), and the HGS in the normal and low HGS groups was 29.0 kg (IQR, 23.0–33.9 kg) and 17.2 kg (IQR, 13.9–20.8 kg), respectively. The HGS values in the normal and low HGS groups were 32.4 kg (IQR, 29.0–36.8 kg) and 21.0 kg (IQR, 18.3–23.2 kg) in male participants and 20.7 kg (IQR, 19.4–23.2 kg) and 14.1 kg (IQR, 12.8–16.5 kg) in female participants (p < 0.001 for both sexes). The mean age in the normal and low HGS groups was 52.8 ± 11.9 and 58.6 ± 11.9 years, respectively ([Table 1](#)). The male patient proportion, serum albumin level, and ALM index were greater in the normal HGS group than in the low HGS group. The edema index was greater
in the low HGS group than in the normal HGS group. No significant differences were observed in the proportion of patients with DM, use of automated PD, dialysis vintage, weekly Kt/V \text{urea}, C-reactive protein level, DP \text{4Cr}, urine volume, calcium level, phosphorus level, sodium level, potassium level, or nPNA between the two groups. The number of patients with low muscle mass was 122 (61.3%) and that of patients with sarcopenia was 64 (32.2%). The number of incident PD patients with PD durations of <3 months was eight (4.0%). We did not perform subgroup analyses with incident or prevalent PD patients due to the small number of incident PD patients.

Association between sarcopenia components and survival

The number of patient deaths and technique failures was 26 (13.1%) and 41 (20.6%), respectively. The number of patient deaths and incidence of technique failure was 4 (3.8%) and 13 (12.5%) in the normal HGS group and 22 (23.2%) and 28 (29.5%) in the low HGS group (p < 0.001 for patient deaths and p = 0.005 for technique failure). The causes of patient death were cardiovascular disease (12 patients, 46.2%), infection (10 patients, 38.5%), malignancy (two patients, 7.7%), cachexia (one patient, 3.8%), and cerebral hemorrhage (one patient, 3.8%). The reasons for technique failure were patient death (26 patients, 63.4%), PD peritonitis (nine patients, 22.0%), catheter malfunction (two patients, 4.9%), malignancy (two patients, 4.9%), tunnel infection (one patient, 2.4%), and uremic symptom (one patient, 2.4%).

The median follow-up interval was 17 months (IQR, 13–21 months). Kaplan-Meier curve analysis showed that patients with low HGS or sarcopenia had poorer patient and technique survival compared with patients with normal HGS or without sarcopenia (Fig. 1, 2). However, there were no significant differences in patient or technique survival between patients with low muscle mass and those with normal muscle mass.

Univariate Cox regression analysis showed that patients with low HGS had a hazard ratio of 7.45 (95% confidence

---

### Table 1. Participants’ clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Normal HGS group</th>
<th>Low HGS group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>199</td>
<td>104</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>55.7 ± 12.1</td>
<td>52.8 ± 11.9</td>
<td>58.6 ± 11.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Male sexa</td>
<td>113 (56.8)</td>
<td>68 (65.4)</td>
<td>45 (47.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes mellitusb</td>
<td>98 (49.2)</td>
<td>45 (43.3)</td>
<td>53 (55.8)</td>
<td>0.08</td>
</tr>
<tr>
<td>Automated peritoneal dialysisb</td>
<td>57 (28.6)</td>
<td>34 (32.7)</td>
<td>23 (24.2)</td>
<td>0.19</td>
</tr>
<tr>
<td>Dialysis vintage (mo)b</td>
<td>50 (25–88)</td>
<td>46 (25–88)</td>
<td>64 (27–91)</td>
<td>0.18</td>
</tr>
<tr>
<td>Body mass index (kg/m²)b</td>
<td>24.2 (21.9–26.4)</td>
<td>24.5 (22.4–26.6)</td>
<td>23.9 (21.6–26.2)</td>
<td>0.47</td>
</tr>
<tr>
<td>Weekly Kt/V_urea b</td>
<td>1.84 (1.62–2.10)</td>
<td>1.80 (1.60–2.03)</td>
<td>1.89 (1.63–2.14)</td>
<td>0.20</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)b</td>
<td>0.17 (0.06–0.45)</td>
<td>0.18 (0.05–0.39)</td>
<td>0.16 (0.07–0.46)</td>
<td>0.87</td>
</tr>
<tr>
<td>DP_4Cr</td>
<td>0.66 ± 0.13</td>
<td>0.65 ± 0.11</td>
<td>0.67 ± 0.15</td>
<td>0.51</td>
</tr>
<tr>
<td>Urine volume (mL/day)b</td>
<td>50 (0–580)</td>
<td>200 (0–844)</td>
<td>0 (0–375)</td>
<td>0.09</td>
</tr>
<tr>
<td>Edema index</td>
<td>0.400 ± 0.012</td>
<td>0.394 ± 0.012</td>
<td>0.406 ± 0.011</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum calcium (mg/dL)b</td>
<td>8.3 (7.7–8.8)</td>
<td>8.5 (7.8–8.9)</td>
<td>8.2 (7.5–8.6)</td>
<td>0.095</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dL)</td>
<td>4.9 ± 1.4</td>
<td>5.1 ± 1.4</td>
<td>4.7 ± 1.4</td>
<td>0.08</td>
</tr>
<tr>
<td>Serum sodium (mEq/L)b</td>
<td>137 (134–139)</td>
<td>137 (134–139)</td>
<td>136 (133–139)</td>
<td>0.69</td>
</tr>
<tr>
<td>Serum potassium (mEq/L)</td>
<td>4.6 ± 0.7</td>
<td>4.6 ± 0.6</td>
<td>4.5 ± 0.7</td>
<td>0.20</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>3.6 ± 0.5</td>
<td>3.7 ± 0.4</td>
<td>3.4 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>nPNA (g/kg/day)</td>
<td>0.83 ± 0.19</td>
<td>0.84 ± 0.21</td>
<td>0.83 ± 0.21</td>
<td>0.74</td>
</tr>
<tr>
<td>ALM index (kg/m²)b</td>
<td>6.05 (5.24–6.71)</td>
<td>6.28 (5.59–6.97)</td>
<td>5.79 (5.03–6.42)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as number only, mean ± standard deviation, a number (%), or b median (interquartile range).

The p-values were tested between the normal and low HGS groups and analyzed using Student t test for continuous variables with normal distributions and the Mann-Whitney U test for those without normal distributions. Categorical data were compared using Pearson chi-square test or Fisher exact tests.

ALM, appendicular lean mass; DP_4Cr, 4-hour dialysate-to-plasma creatinine concentration ratio; HGS, handgrip strength; nPNA, normalized protein equivalent of total nitrogen appearance.
interval [CI], 2.55–21.73; p < 0.001) for patient death compared with those with normal HGS (Table 2). Multivariate analyses showed the same trends as univariate analysis, and technique failure showed similar trends to patient death. However, patients with low muscle mass did not show significant hazard ratios for patient death or technique failure compared with those with normal muscle mass on univariate and multivariate analyses. Patients with sarcopenia had significantly greater hazard ratios for patient death or technique failure than those without sarcopenia only in univariate analysis.

Cox regression analyses by sex (Supplementary Table 1, available online) showed that patient survival was associated with low HGS in male patients and low HGS and sarcopenia in female patients. Technique survival was associated with low HGS in women. However, multivariate analyses did not show statistical significance between patient or technique survival rates and the three indicators in either sex.

In addition, we performed survival analysis with propensity score matching. There were no significant differences in age, sex, or presence of DM (Supplementary Table 2,
available online). Kaplan-Meier curves also showed that patients with normal HGS had better patient and technique survival rates compared to those with low HGS (Supplementary Fig. 1, available online). Furthermore, we performed Cox regression analysis using a propensity score-matched cohort (Supplementary Table 3, available online). Although statistical significance was weak compared to analysis using the total cohort, the trends were similar.

Comparison of other indices for outcomes

In male patients, the AUROC of the indicators for patient death at the end point of follow-up was 0.61 (95% CI, 0.52–0.70) for the ALM index, 0.62 (95% CI, 0.53–0.71) for GNRI, and 0.71 (95% CI, 0.62–0.79) for HGS (Fig. 3). In female patients, the AUROC was 0.59 (95% CI, 0.48–0.70) for the ALM index, 0.70 (95% CI, 0.59–0.79) for GNRI, and 0.89 (95% CI, 0.80–0.95) for HGS. No significant differences in AUROC were found among the three indicators in male patients; however, HGS was superior to the ALM index and GNRI in female patients (in male: ALM index vs. GNRI, p = 0.05; ALM index vs. HGS, p = 0.29; GNRI vs. HGS, p = 0.23; in female: ALM index vs. GNRI, p = 0.69; ALM index vs. HGS, p = 0.03; GNRI vs. HGS, p = 0.002).

In order to estimate the incremental value of low HGS in terms of its association with patient death or technique failure, the probability of events and non-events in models using relative IDI and category-free NRI values was compared (Supplementary Table 4, available online). For patient deaths, the AUROCs in the models without or with low HGS were 0.811 and 0.836, respectively. The difference between AUROCs was 0.025 and were the greatest among those with low HGS, low muscle mass, and sarcopenia. The relative IDI and category-free NRI values were 0.176 and 0.776, respectively, and statistical significance was observed between the two models. The models revealed that the addition of low HGS in the multivariate model was associated with greater predictability of patient death than models excluding low HGS. In terms of technique failure, the statistical significance in the difference between the AUROCs was weak, but the trend was similar to that of patient death.

Discussion

Our study included patients with prevalent or incident PD. We evaluated two indicators of sarcopenia (HGS as an indicator of muscle strength and muscle mass index measured using DEXA) and assessed the patient and technique sur-
vival rates according to muscle mass, HGS, or sarcopenia. We performed Kaplan-Meier curve, univariate and multivariate Cox regression, and AUROC analyses. The results of our analyses mostly showed that HGS was a better predictor of patient or technique survival than low muscle mass or sarcopenia.

Previous studies have evaluated the association between sarcopenia and its components and mortality in patients undergoing PD or patients with other comorbidities. Kim et al. [8] enrolled 131 patients undergoing PD and showed that low HGS had lower predictive ability for mortality than change in the lean or fat tissue index. However, they evaluated muscle mass using BIA and multivariate analysis included coronary artery disease and peripheral artery disease as covariates. The proportions of these problems were very small, which may have led to statistical bias. Isoyama et al. [7] enrolled 330 patients undergoing dialysis and showed that low HGS was more strongly associated with mortality than low muscle mass. However, their study did not include data on dialysis modality. Some studies have

Figure 3. Receiver operating characteristic curves of indicators used to predict patient death or technique failure at the end point of follow-up. Curves of indicators for predicting patient death in male (A) and female patients (B). Curves of indicators for predicting technique failure in male (C) and female patients (D). ALM, appendicular lean mass; GNRI, geriatric nutritional risk index; HGS, handgrip strength.
evaluated various indices of muscle mass and showed the association between these indices and mortality in patients undergoing PD; however, they did not include data on HGS [17–22]. Kamijo et al. [23] evaluated sarcopenia using muscle mass and strength and showed a positive association between the presence of sarcopenia and mortality, but did not perform analyses of sarcopenia components. Vogt et al. [24] enrolled 265 patients undergoing dialysis and showed the association between HGS and mortality; however, their study did not include data on muscle mass. Other studies enrolled patients with chronic liver disease, reduced ejection fraction heart failure, or older age and showed that low HGS was superior in predicting mortality [25–27]. Previous studies evaluated the association between sarcopenia or its components and mortality in various populations. However, few studies have compared sarcopenia components in terms of predicting mortality in patients undergoing PD. Moreover, muscle measurements using DEXA can also be considered a strength of this study compared with previous studies.

The difference between HGS and muscle mass in statistical significance may be related to two issues. First, inaccuracy in muscle mass measurements may be associated with this discrepancy in patients undergoing PD. Although muscle mass measurements using DEXA are recommended in patients undergoing PD, the measurements can be influenced by volume overload [6], which results in overestimation of muscle mass and thereby underestimation of the proportion of patients with low muscle mass [28]. Furthermore, HGS was superior to sarcopenia in predicting mortality in our study. Muscle mass in patients with low HGS may be overestimated in the presence of volume overload, which can lead to misdiagnosis in patients with sarcopenia. Second, patients undergoing dialysis are prone to insulin resistance, potentially leading to fatty infiltration within muscles [4]. Fatty infiltration in muscle in patients undergoing PD compared with the general population can result in overestimation of the functional units of muscle mass.

A sex difference in mortality prediction was an important finding of our study. Our results showed a clearer superiority of HGS in predicting mortality in female patients than in male patients. Female patients have relatively low muscle mass, and muscle strength can be more greatly influenced by neural activation or muscle architecture than muscle mass [29,30]. Therefore, the decline in muscle mass is limited in female patients compared with male patients, and factors other than muscle mass may lead to decline in strength. Consequently, HGS per se and these causal factors together may lead to high mortality.

In our study, sarcopenia was defined using the Asian Working Group for Sarcopenia consensus. Most of the diagnostic measurements and cutoff values for diagnosis of sarcopenia were derived from the general population. These guidelines suggest the use of muscle mass measurements using DEXA or BIA; however, muscle mass measurements using these are not accurate in dialysis patients [5,31–33]. Previous studies showed that these two measurements were influenced by volume status; thus, it would be difficult to apply the diagnostic criteria from the general population [28,34]. Nevertheless, there are no specific diagnostic criteria for sarcopenia in dialysis patients. Previous studies have defined sarcopenia according to diagnostic criteria from the general population and showed a positive association between clinical outcomes and sarcopenia, despite limitations in muscle mass measurements [35]. Furthermore, the guidelines from the Asian Working Group for Sarcopenia, which were derived from Asian populations, may be better criteria regarding the ethnic characteristics of Asian dialysis patients [5].

In the general population, DEXA is the gold standard for the estimation of muscle mass. Validation studies showed that BIA is an alternative method with considerable agreement compared to DEXA. However, volume overload is associated with overestimation of muscle mass measurements. Measurement during dry weight would attenuate overestimation of muscle mass measurements. Recent Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines noted that body composition measurements using BIA can be applicable in hemodialysis patients at the time of dry weight after hemodialysis [6]. In addition, Raimann et al. [36] evaluated the accuracies of extracellular and intracellular water using BIA compared to gold standard methods such as the dilution method in hemodialysis patients. Their study showed that errors in accuracy exist but are comparable in magnitude to the errors found in measurements using dilution methods. The accuracy of BIA in the volume assessment of PD patients would be similar to that for hemodialysis patients. However, the guidelines did not suggest the use of BIA for body composition measurements in PD patients. Regression equations for the
estimation of muscle mass are derived from the general population, and muscle mass measurements using these equations would be not accurate, despite accurate volume estimations. The KDOQI guidelines suggest that DEXA is a reasonable method for assessing body composition, as the method is the gold standard for measuring body composition, despite being influenced by volume [6]. Therefore, muscle mass index was estimated using DEXA in our study.

In our study, Fig. 3 shows the AUROCs for predicting patient death or technique failure according to ALM index, HGS, and nutritional indicator values. We used the GNRI as the nutritional index. The GNRI originated from the nutritional risk index, which includes serum albumin and weight loss values as opposed to body weight values [11]. However, it is difficult to measure usual body weight in geriatric patients. Weight changes were replaced by changes in ideal body weight that were derived from height. Rather than single markers such as albumin or body mass index, composite nutritional indices using various indicators would be better for predicting nutritional status or clinical outcomes [6]. Many composite nutritional indices have been introduced, and indices using three or more indicators may be better at predicting nutritional status or clinical outcomes than those using only one or two indicators. The KDOQI guidelines recommend the use of subjective global assessment (SGA) values or malnutrition inflammation scores (MIS) among many composite nutritional indices in chronic kidney disease patients [6]. SGA and MIS include 7 and 10 components, respectively, and many studies have proven their validity and reliability [6]. However, the GNRI includes only two components and has not been validated as thoroughly as the other two indices.

In our center, composite nutritional indices were not routinely evaluated. In addition, our study was a retrospective study. Therefore, our study did not include data for SGA or MIS as well-validated methods. Although the use of the GNRI was not strongly recommended in the KDOQI guidelines, GNRI values can be calculated using three variables, including participants’ current serum albumin, body weight, and height. Furthermore, GNRI values may be better indicators in patients with volume overload compared to serum albumin levels alone [37,38]. Volume overloading can lead to underestimation of serum albumin levels; however, underestimation of serum albumin levels by volume may be attenuated due to overestimation of actual body weight. Although there were insufficient data regarding the changes in GNRI values by volume overload, previous studies have shown that the GNRI is a prognostic and nutritional indicator in dialysis patients [12,13]. On the other hand, the GNRI was originally developed for geriatric participants aged ≥65 years [11]. However, some studies have evaluated the clinical usefulness of the GNRI in dialysis patients aged <65 years. Park et al. [39] enrolled hemodialysis patients with a mean age of 56.2 years, and two studies enrolled PD patients with mean ages of 52.5 and 50.2 years [13,40]. All three studies showed an association between GNRI values and mortality.

In our center, both body composition measurements and HGS were annually evaluated. As the KDOQI guidelines point out, HGS is useful for identifying protein energy wasting and functional status [6]. Muscle mass measurements using DEXA or BIA are influenced by volume status, and changes in muscle strength may develop before changes in muscle mass occur. Therefore, if muscle mass measurements are evaluated exclusively, patients with early changes in muscle composition or with volume overloading would be misdiagnosed as normal. In our center, if patients exhibit decreasing trends in HGS compared to baseline, clinicians advise them of the clinical importance of low HGS and recommend nutritional support and exercise. Furthermore, our clinicians evaluate whether there are other possible etiologies responsible for decreasing HGS, such as infection.

There is no agreement on a uniform definition of technique failure in PD patients. Technique failure can be defined as conversion to hemodialysis alone or a composite of patient death (regardless of cause) and conversion to hemodialysis [14]. In our study, technique failure was defined as the composite of patient death or conversion to hemodialysis. Lan et al. [14] commented that censoring for patient death can lead to overestimation of risk event estimates and suggested the use of technique failure defined as a composite of patient death or conversion to hemodialysis. However, patient death-censored technique failure should also be reported separately. Our study did not present results for patient death-censored technique failure. Kaplan-Meier curves using patient death-censored technique failure might not completely coincide with those from patient death or technique failure based on our definition. However, considering the similar trends in patient
survival curves and technique survival curves obtained with our definition, the patient death-censored technique failure curve would likely show a similar trend.

Our study had inherent limitations, including its single-center and retrospective nature. Muscle mass measurement using DEXA can be influenced by volume status despite being a gold standard method, and our data did not include information on muscle architecture or neural factors associated with strength. In addition, we did not collect data on repeated or longitudinal measurements and the follow-up interval was relatively short. Furthermore, our study did not include physical performance parameters such as gait speed. Weak statistical significance in some analyses, such as Cox regression analyses by sex, also limited the strength of our study. Despite favorable trends in low HGS, statistical non-significance could be associated with a small sample size. Analyses using a larger sample size may be useful to identify statistically significant indicators in multivariate analyses. A prospective longitudinal study including volume-independent muscle measurement, repeated measurements, or physical performance data and with a larger number of patients is warranted to overcome these limitations.

The present study demonstrated that HGS may be superior to muscle mass and sarcopenia in predicting patient or technique survival in patients undergoing PD. The routine evaluation of HGS may allow clinicians to identify risk of sarcopenia and provide patients with proper intervention before progression to severe sarcopenia.

Conflicts of interest

The authors have no competing interests to declare.

Funding

This work was supported by a 2020 Yeungnam University Research Grant (220A480015). The funder had no role in the study design; collection, analysis, and interpretation of data; writing of the report; or the decision to submit the article for publication.

Authors’ contributions

Conceptualization: SHK, JYD

Formal analysis: SHK
Methodology: SHK, AYK
Project administration: SHK, JYD
Writing—original draft: SHK, AYK
Writing—review & editing: SHK, AYK
All authors read and approved the final manuscript.

ORCID

Seok Hui Kang, https://orcid.org/0000-0003-1023-0195
A Young Kim, https://orcid.org/0000-0002-2679-5038
Jun Young Do, https://orcid.org/0000-0002-6360-9310

References


Associations among Alzheimer disease, depressive disorder, and risk of end-stage kidney disease in elderly people

Shin Chan Kang1, Hee Byung Koh2, Hyung Woo Kim3, Young Su Joo1, Seung Hyeok Han1, Tae-Hyun Yoo1, Shin-Wook Kang1, Jung Tak Park1

1Department of Internal Medicine and Institute of Kidney Disease, Yonsei University College of Medicine, Seoul, Republic of Korea
2Division of Nephrology, Department of Internal Medicine, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Republic of Korea

Background: Alzheimer disease (AD) and depressive disorder (DD) are prevalent among elderly end-stage kidney disease (ESKD) patients. However, whether preexisting mental health disorders increase the risk of ESKD is not well understood. The risk of incident ESKD in patients with or without underlying AD or DD was evaluated in a nationwide cohort of elderly people in Republic of Korea.

Methods: This study used data from the National Health Insurance Service-Senior cohort in Republic of Korea. Among the 558,147 total subjects, 49,634 and 54,231 were diagnosed with AD (AD group) or DD (DD group), respectively, during the follow-up period. Propensity score matching was conducted to create non-AD and non-DD groups of subjects. AD and DD diagnoses were analyzed as time-varying exposures, and the study outcome was development of ESKD.

Results: The incidence rates of ESKD were 0.36 and 1.17 per 1,000 person-years in the non-AD and AD groups, respectively. After adjustment for clinical variables and competing risks of death, the risk of incident ESKD was higher in the AD group than in the non-AD group (hazard ratio [HR], 1.67; 95% confidence interval [CI], 1.34–2.08). The incidence rates of ESKD in the non-DD and DD groups were 0.36 and 0.91 per 1,000 person-years, respectively. The risk of ESKD development was also higher in the DD group than the non-DD group (HR, 1.44; 95% CI, 1.19–1.76).

Conclusion: The risk of ESKD development was higher in subjects diagnosed with AD or DD, suggesting that central nervous system diseases can adversely affect kidney function in elderly people.

Keywords: Alzheimer disease, Depressive disorder, Elderly, End-stage kidney disease

Introduction

Between 2015 and 2050, the proportion of the elderly population is estimated to double from 12% to 22% worldwide [1]. At the same time, the prevalence of mental health disorders among elderly people is growing rapidly. More than 20% of adults aged 60 and older suffer from mental health disorders [2]. The most common mental health disorders...
in this age group are dementia and depressive disorder (DD), which are reported to affect approximately 5% and 17% of the elderly population, respectively [3,4]. Mental health has been found to be closely related to the prevalence of kidney disease. Cognitive impairment is found in 30% to 60% of patients undergoing hemodialysis, which is at least twice the value observed in age-matched controls [5]. In addition, in a cohort of 3,349 participants, those with moderate kidney failure were associated with a 37% increased risk of dementia, showing that the link between cognitive impairment and kidney disease is not limited to patients with advanced kidney failure [6]. Similarly, DD was found in about 20% of patients with severe chronic kidney disease (CKD) and 40% of patients on dialysis [7].

The pathophysiology underlying the relationship between mental health disorders and kidney disease is not fully understood. However, the concept of brain–kidney crosstalk has been raised recently, suggesting that diseases in the kidney can affect brain function, and vice versa [8]. Retention of uremic toxins that results from reduced kidney function has been proposed as a factor that affects the central nervous system (CNS) and could initiate mental health disorders [9]. Observational studies showing an increased risk of incident dementia and DD among CKD patients suggest the presence of such kidney to brain crosstalk [5,7]. On the other hand, CNS dysfunction can induce neurohumoral changes, hormonal disturbances, and immunologic responses that could affect kidney function [10]. Nonetheless, clinical findings supporting brain to kidney crosstalk are lacking.

To assess whether mental health disorders affect kidney function, the risk of incident end-stage kidney disease (ESKD) development was compared in patients with or without Alzheimer disease (AD) or DD by evaluating claims information from a nationwide health insurance database in Republic of Korea.

Methods

Data source

Data were retrieved from the National Health Insurance Service (NHIS)-Senior cohort database. More than 98% of the Korean population is enrolled in the mandatory NHIS program, and the remaining people, who are in the lowest income bracket, receive government benefits. The NHIS-Senior cohort, composed of 558,147 people, is constructed as a 10% representative sample of 5.5 million beneficiaries aged >60 years in 2002. The cohort was followed from January 1, 2002, through December 31, 2015, or until eligibility disqualification due to death or emigration. Further details regarding the cohort have been published previously [11]. The data can be accessed on the National Health Insurance Data Sharing Service homepage of the NHIS (http://nhiss.nhiscor.kr) after approval by the National Health Information data request review committee. The NHIS-Senior cohort provides medical claims data that have been deidentified at the individual level.

This study was conducted in accordance with the principles of the Declaration of Helsinki and the protocol was approved by the Institutional Review Board of Yonsei University Health System Clinical Trial Center (No. 4-2020-1382). The informed consent requirement was waived because this was a retrospective analysis.

Study population

Of the 558,147 subjects in NHIS-Senior cohort, those who were younger than 65 years or older than 90 years at baseline (n = 130,149) and those who were followed for less than 1 year (n = 14,469) were excluded. A 3-year washout period was applied from January 1, 2002, to December 31, 2004. The participants were divided into AD and DD evaluation cohorts. Those diagnosed with AD or ESKD during the washout period (n = 3,805) were excluded from the AD evaluation cohort. Those diagnosed with DD or ESKD during the washout period (n = 18,447) were excluded from the DD evaluation cohort (Fig. 1). The index date for all participants was January 1, 2005 (Fig. 2).

Data collection

Baseline medical histories, including comorbidities and medications, were acquired for the washout period. Baseline demographic data of age, sex, urban residence, and income were acquired as of 2005. Diagnoses and medical services were defined based on International Classification of Diseases, 10th revision (ICD-10) codes and claim records. Diagnoses of AD and DD were defined using ICD-10 codes (F00 or G30 for AD; F32, F33, F34, or F38 for DD)
Figure 1. Flow diagram of the study.
NHIS, National Health Insurance Service; AD, Alzheimer disease; DD, depressive disorder; ESKD, end-stage kidney disease.

Figure 2. Schematic depiction of the study design.
AD, Alzheimer disease; DD, depressive disorder; ESKD, end-stage kidney disease; ICD-10, International Classification of Diseases, 10th revision; KOSIS, Korean Statistical Information Service. NHIS-Senior, National Health Insurance Service-Senior.
and a concurrent prescription record for dementia- or DD-related treatment for at least 30 days during the follow-up period. Donepezil, rivastigmine, galantamine, and memantine were considered to be dementia-related treatments, and tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and atypical antidepressants were DD-related treatments. Further details regarding the ICD-10 codes and medications used to define the covariates are presented in Supplementary Table 1 (available online). Subjects were considered to have comorbidities when the condition was a discharge diagnosis after hospitalization or was documented as a diagnosis more than once in an outpatient setting. Residential area was defined using 17 district codes, and income was determined according to participant health insurance premium in 2005.

**Exposure and outcomes**

Diagnoses of AD or DD were analyzed as time-varying exposures. Those newly diagnosed with AD or DD during the follow-up period were assigned to the AD or DD group, respectively (Fig. 2). Subjects diagnosed with AD or DD after development of ESKD were treated as exposure unaffected. The study outcome was development of ESKD, defined using ICD-10 codes (Z49.1, Z49.2, Z94.0, Z99.2, or T86.1) or dialysis treatment-related claim codes that were repeated for at least 90 days during follow-up.

**Statistical analysis**

The normality of the parameter distribution was tested graphically using histograms. All continuous variables are expressed as median and interquartile range (IQR). To account for possible differences in baseline characteristics between the affected and non-affected groups, 1:1 propensity score matching was performed using the greedy (nearest neighbor) method. The propensity score was estimated as the probability of being diagnosed with AD or DD using a logistic regression based on demographic and medical data. Standardized mean differences were determined to confirm the balance between the groups. Variables were considered well balanced when the standardized mean difference was less than 0.10. All of the covariates used for estimating the propensity score were included in the adjusted models [12]. The subdistribution hazard ratio (sHR) was assessed with all-cause death as a competing risk to evaluate the association between AD or DD and ESKD incidence using the Fine and Gray method [13]. The index date of the subdistribution hazard model was January 1, 2005, and the subjects were followed to the censoring point, defined as development of ESKD or eligibility disqualification (Fig. 2). The proportional hazard assumption was tested based on Schoenfeld residuals [14]. Sensitivity analyses were performed to confirm the main findings. First, considering the possibility of selection bias inherent in the matching procedure, evaluations were performed using the propensity scores as weights to account for selection assignment differences [15]. The top and bottom one percentiles of the weight were eliminated to reduce the effect of extremely small or large weights. Second, subgroup analyses were performed according to sex, residential area, and disease onset. Median age at AD or DD diagnosis was determined from the entire cohort, and early onset was defined as a diagnosis before the median age for that disease. Third, to consider the possibility that CKD could have a causal effect on AD or DD development, analyses were conducted after excluding participants diagnosed with CKD of <180 days prior to AD or DD diagnosis. For all analyses, a p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using Stata for Windows version 15.0 (StataCorp LLC, College Station, TX, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

**Results**

**Baseline characteristics**

The baseline characteristics of the participants before propensity score matching are shown in Supplementary Table 2 (available online). In the AD evaluation cohort, 360,090 and 49,634 participants were allocated to the non-AD and AD groups, respectively. The median age of the patients in the AD group was 74 years (69–78 years), and 30.1% were male. Compared with the non-AD group, those in the AD group were older, more likely to be female, and had lower prevalence of hypertension (HTN) and peripheral arterial disease. In the DD evaluation cohort, the non-DD and DD groups contained 340,851 and 54,231 people, respectively. In the DD group, the median age of patients was 70 years.
(67–75 years), and 34.8% were male. Those in the DD group were younger and more likely to be female than subjects in the non-DD group. Patients in the AD and DD groups were subjected to 1:1 propensity score matching within the AD evaluation cohort and DD evaluation cohort, respectively. After propensity score matching, baseline characteristics were well balanced (Table 1).

### Incidence of end-stage kidney disease

In the AD evaluation cohort, during a median (IQR) follow-up of 10 years (9–10 years), 297 and 168 cases of incident ESKD occurred in the non-AD and AD groups, respectively. Per 1,000 person-years, the incidence rate of ESKD was 0.36 in the non-AD group and 1.17 in the AD group (Table 2). During a median (IQR) follow-up duration of 10 years (10–10 years) in the DD evaluation cohort, 309 and 216 cases of incident ESKD occurred in the non-DD and DD groups, respectively. The corresponding incidence rates per 1,000 person-years were 0.36 in the non-DD group and 0.91 in the DD group (Table 2).

### Effect of Alzheimer disease or depressive disorder on end-stage kidney disease development

When subdistribution hazard models were constructed

---

### Table 1. Baseline characteristics of the subjects after propensity score matching

<table>
<thead>
<tr>
<th>Variable</th>
<th>AD evaluation cohort</th>
<th>DD evaluation cohort</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-AD(n = 49,634)</td>
<td>AD(n = 49,634)</td>
<td>SMD</td>
</tr>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>74 (69–78)</td>
<td>74 (69–78)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age at AD/DD diagnosis (yr)*</td>
<td>80 (76–85)</td>
<td>76 (73–80)</td>
<td></td>
</tr>
<tr>
<td>Age at ESKD diagnosis (yr)*</td>
<td>78 (74–82)</td>
<td>79.5 (76–83)</td>
<td></td>
</tr>
<tr>
<td>Time from AD/DD to ESKD (mo)*</td>
<td>21.0 (8.7–39.9)</td>
<td>31.8 (9.5–51.4)</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>14,799 (29.8)</td>
<td>14,924 (30.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Follow-up duration (yr)</td>
<td>10 (9–10)</td>
<td>10 (9–10)</td>
<td>0.02</td>
</tr>
<tr>
<td>Urban residence</td>
<td>25,423 (51.2)</td>
<td>25,720 (51.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Income, highest tertile</td>
<td>14,503 (29.2)</td>
<td>14,866 (30.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>16,730 (33.7)</td>
<td>17,182 (34.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5,062 (10.2)</td>
<td>5,447 (11.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>4,183 (8.4)</td>
<td>4,533 (9.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>305 (0.6)</td>
<td>301 (0.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>662 (1.3)</td>
<td>774 (1.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>2,495 (5.0)</td>
<td>2,773 (5.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>915 (1.8)</td>
<td>896 (1.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>2,876 (5.8)</td>
<td>2,968 (6.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1,576 (3.2)</td>
<td>1,618 (3.3)</td>
<td>0.004</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>2,429 (4.9)</td>
<td>2,518 (5.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>COPD</td>
<td>5,695 (11.5)</td>
<td>6,012 (12.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>7,003 (14.1)</td>
<td>7,160 (14.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Medication history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAAS blocker</td>
<td>9,853 (19.9)</td>
<td>10,337 (20.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>DHP-CCB</td>
<td>12,827 (25.8)</td>
<td>12,975 (26.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Statin</td>
<td>3,749 (7.6)</td>
<td>4,047 (8.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diuretics</td>
<td>4,067 (8.2)</td>
<td>4,322 (8.7)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data are expressed as median (interquartile range) or number (%). AD, Alzheimer disease; COPD, chronic obstructive pulmonary disease; DD, depressive disorder; DHP-CCB, dihydropyridine calcium channel blocker; ESKD, end-stage kidney disease; RAAS, renin-angiotensin aldosterone system; SMD, standardized mean difference.

*These variables were not included in estimating the propensity scores.
with death as a competing risk for incident ESKD, the risk of ESKD development was significantly higher in the AD group than the non-AD group (sHR, 1.86; 95% CI, 1.50–2.30) in the AD evaluation cohort. This risk was attenuated but still statistically significant after adjusting for additional confounding variables (sHR, 1.67; 95% CI, 1.34–2.08). In the DD evaluation cohort, the risk of ESKD was higher in the DD group than the non-DD group (sHR, 1.75; 95% CI, 1.43–2.13), and that relationship was maintained after adjusting for additional confounding demographic and clinical variables (sHR, 1.44; 95% CI, 1.19–1.76) (Table 2). The cumulative incidence curves constructed for participants in the AD evaluation cohort show that the time to development of incident ESKD was significantly longer in the non-AD group than the AD group (p < 0.001) (Fig. 3A). Similarly, the time to incident ESKD development in the DD evaluation cohort was significantly longer in the non-DD group than the DD group (p < 0.001) (Fig. 3B).

When subgroup analyses were performed according to sex, residential area, and AD or DD onset, no significant interactions were found between the subgroups, suggesting that the associations found in the main analysis would be significant regardless of subgroup (Table 3).

**Sensitivity analyses**

To further account for possible selection bias, evaluations were made after propensity score weighting. In the AD evaluation cohort, the risk for ESKD development was higher in the AD group than in the non-AD group (adjusted

---

### Table 2. Comparison of end-stage kidney disease risk according to incident AD or DD using competing risk regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Event rate per 1,000 person-years</th>
<th>Crude HR, sHR (95% CI)</th>
<th>p-value</th>
<th>Adjusted HR(^a), sHR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AD evaluation cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-AD</td>
<td>0.36</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>1.17</td>
<td>1.86 (1.50–2.30)</td>
<td>&lt;0.001</td>
<td>1.67 (1.34–2.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>DD evaluation cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-DD</td>
<td>0.36</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>DD</td>
<td>0.91</td>
<td>1.75 (1.43–2.13)</td>
<td>&lt;0.001</td>
<td>1.44 (1.19–1.76)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AD, Alzheimer disease; CI, confidence interval; DD, depressive disorder; HR, hazard ratio; sHR, subdistribution HR.

\(^a\)Adjusted for clinical variables used to estimate propensity scores (listed in Table 1).

---

**Figure 3.** Cumulative incidence curves of incident end-stage kidney disease in propensity score-matched subjects diagnosed with AD (A) or DD (B). Adjusted for clinical variables used to estimate propensity scores (listed in Table 1) and competing risk of all-cause death.

AD, Alzheimer disease; DD, depressive disorder; CI, confidence interval; sHR, subdistribution hazard ratio.
sHR, 1.51; 95% CI, 1.27–1.79). In the DD evaluation cohort, ESKD development risk was higher in the DD group than the non-DD group (adjusted sHR, 1.18; 95% CI, 1.02–1.37) after adjusting for confounding factors (Supplementary Table 3, available online). To minimize possible causal effects of CKD on development of AD or DD, evaluations were conducted after excluding those diagnosed with CKD prior to diagnosis of AD or DD. The baseline characteristics

### Table 3. Subgroup analyses of end-stage kidney disease risk in subjects diagnosed with AD or DD

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of patients</th>
<th>Crude HR, sHR (95% CI)</th>
<th>p-value</th>
<th>Adjusted HR*, sHR (95% CI)</th>
<th>p-value</th>
<th>p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AD evaluation cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29,723</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.71</td>
</tr>
<tr>
<td>Non-AD</td>
<td>14,799</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>14,924</td>
<td>1.63 (1.20–2.23)</td>
<td>0.002</td>
<td>1.56 (1.14–2.14)</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>69,545</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-AD</td>
<td>34,835</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>34,710</td>
<td>2.09 (1.55–2.81)</td>
<td>&lt;0.001</td>
<td>2.07 (1.54–2.80)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Residential area</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>Urban residence</td>
<td>51,143</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-AD</td>
<td>25,423</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>25,720</td>
<td>1.85 (1.42–2.42)</td>
<td>&lt;0.001</td>
<td>1.82 (1.39–2.38)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Rural residence</td>
<td>48,125</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-AD</td>
<td>24,121</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>23,914</td>
<td>1.82 (1.27–2.61)</td>
<td>0.001</td>
<td>1.92 (1.33–2.76)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Disease onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td>Non-AD</td>
<td>49,634</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early onset AD\textsuperscript{b}</td>
<td>25,967</td>
<td>1.92 (1.52–2.43)</td>
<td>&lt;0.001</td>
<td>1.68 (1.32–2.12)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Late onset AD\textsuperscript{b}</td>
<td>23,667</td>
<td>1.07 (0.79–1.46)</td>
<td>0.65</td>
<td>1.87 (1.31–2.67)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td><strong>DD evaluation cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>Male</td>
<td>37,172</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-DD</td>
<td>18,319</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD</td>
<td>18,853</td>
<td>1.86 (1.42–2.45)</td>
<td>&lt;0.001</td>
<td>1.67 (1.27–2.19)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>71,290</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-DD</td>
<td>35,912</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD</td>
<td>35,378</td>
<td>1.62 (1.20–2.18)</td>
<td>0.002</td>
<td>1.53 (1.15–2.05)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Residential area</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>Urban residence</td>
<td>59,036</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-DD</td>
<td>29,526</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD</td>
<td>29,510</td>
<td>1.52 (1.18–1.96)</td>
<td>0.001</td>
<td>1.43 (1.11–1.84)</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Rural residence</td>
<td>49,426</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-DD</td>
<td>24,705</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DD</td>
<td>24,721</td>
<td>2.22 (1.61–3.07)</td>
<td>&lt;0.001</td>
<td>1.99 (1.40–2.76)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Disease onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.84</td>
</tr>
<tr>
<td>Non-AD</td>
<td>54,231</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early onset DD\textsuperscript{b}</td>
<td>28,786</td>
<td>1.58 (1.27–1.96)</td>
<td>&lt;0.001</td>
<td>1.52 (1.22–1.89)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Late onset DD\textsuperscript{b}</td>
<td>25,445</td>
<td>1.27 (1.14–1.80)</td>
<td>0.03</td>
<td>1.43 (1.05–1.95)</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

AD, Alzheimer disease; CI, confidence interval; DD, depressive disorder; HR, hazard ratio; sHR, subdistribution HR.

\textsuperscript{a}Adjusted for clinical variables used to estimate propensity scores (listed in Table 1) and competing risk of all-cause death. \textsuperscript{b}Early and late onset were defined based on the median age of AD or DD diagnosis.
Discussion

This study evaluated the risk of ESKD development among patients diagnosed with AD or DD using data from a nationwide representative elderly population cohort in Republic of Korea. The incidence rate of ESKD was higher among those with AD or DD than in people without AD or DD, respectively. In addition, those with AD or DD were at a higher risk for developing ESKD. This association was significant even after adjusting for confounding factors, including underlying CKD. Moreover, the significance of the relationship was maintained in sensitivity analyses using propensity score weighting. These findings suggest that preceding mental health conditions such as AD and DD affect kidney function, increasing the risk of ESKD.

Connectivity between the kidney and the CNS is suggested as one cause of the high prevalence of CNS disorders in patients with kidney disease. The possibility that underlying kidney disease could give rise to neurologic complications through cytokine-induced damage, oxidative stress, and accumulation of neurotoxic metabolites has been demonstrated in clinical and animal studies [8,16,17]. Recently, in addition to that kidney to brain crosstalk, the possibility of brain to kidney crosstalk has been proposed on the basis of several clinical phenomena. Acute kidney injury is a common accompaniment of traumatic brain injury and ischemic stroke, with reports that up to 23% of traumatic brain injury patients develop acute kidney injury [18–20]. In addition, hemodynamic and neurohormonal changes and induction of inflammatory responses upon brain death are implicated as key factors that cause acute rejection after kidney allograft transplantation [10]. However, those findings mainly involve acute disease states, and whether CNS disorders chronically affect kidney function is not well known. The results of this study, which show that the risk of ESKD is significantly higher in AD or DD patients than in people without those underlying mental health problems, suggest that brain to kidney crosstalk could chronically affect kidney function. These results are supported by a recent study conducted in China that showed that severity of depressive symptoms correlated with rapid kidney function decline [21].

Several steps of this study aimed to increase the likelihood that the assessed risk would be determined by AD or DD and not by other confounding factors. HTN and diabetes mellitus (DM) are underlying conditions well known to affect kidney function. The prevalence of patients with DM did not differ between those with or without AD or DD even before propensity score matching. Although patients with HTN were more prevalent in the non-AD group than the AD group, the difference was not large and was well balanced after propensity score matching, lowering the chances that underlying comorbidities played a role in the elevated ESKD risk reported here. In addition, the association between incident ESKD and AD or DD was maintained following additional confounding factor adjustments and propensity score matching. Moreover, when propensity score weighting was used to balance the baseline characteristics between groups with or without AD or DD, the significance of risk increase was maintained, which further reduced the possibility that confounding factors affected the reported risk of ESKD development.

Underlying CKD is another potential factor that can affect ESKD risk, with the rate of kidney function decline being aggravated in patients with CKD [22]. However, the prevalence of CKD at baseline did not differ between the groups with or without AD or DD. In addition, further adjustments for prevalent CKD after propensity score matching did not compromise the association between incident ESKD risk and AD or DD. Moreover, in the sensitivity analysis that excluded patients diagnosed with CKD before AD or DD diagnosis, the incident ESKD risk increase in patients with AD or DD was maintained, suggesting that this association is independent of underlying CKD. Nonetheless, the possibility that other factors not included in the analyses affect the risk of ESKD development cannot be ignored, and evaluations that include more variables are required to confirm the findings of this study.

Several mechanisms could explain the increased risk of ESKD in patients with AD or DD. An increase in sympathetic nervous system activity can alter kidney blood flow...
and glomerular filtration, leading to accelerated kidney function decline [10]. The dysregulation in sympathetic tone that results from an acute brain injury is suspected to be one reason that traumatic brain injury patients often develop acute kidney injury [23]. Reports showing that sympathetic nervous system activity is elevated in patients with AD or DD further support that possibility [24,25]. Alterations in the cerebral renin-angiotensin system (RAS) might also contribute to the brain to kidney crosstalk observed in this study [26]. An animal study in rats revealed that the cerebral RAS affects kidney function in DM [27]. Changes in cerebral RAS have also been implicated in patients with DD [28,29]. In addition, upregulation of the brain RAS has been closely linked to the pathogenesis of AD [29,30]. Systemic inflammation caused by CNS disorders might also affect kidney function. Microglial cells in AD have been reported to release inflammatory cytokines, including interferon-γ and interleukin (IL)-1β [31–33]. In DD patients, serum levels of IL-6 and tumor necrosis factors have been found to be increased [34]. Considering that chronic systemic inflammation is a well-known risk factor for kidney disease, the inflammatory milieu accompanying AD and DD could increase the risk of ESKD in such patients [35].

Kidney function is a known risk factor for mental health disorders [7,36,37]. Although kidney function could not be accurately determined because of the inevitable limitations of analyzing a large health insurance claims database, several actions were taken to reduce the chances of underlying kidney disease affecting the onset of ESKD. First, propensity score matching was conducted between the groups with or without AD or DD for underlying CKD. In addition, matching was performed for major CKD risk factors such as HTN, DM, and heart failure. Second, to further reduce the possibility of bias, additional adjustments were made in assessing the sHR, including CKD and CKD risk factors as covariates. Third, a sensitivity analysis excluding those diagnosed with CKD at baseline was performed to lower the chances that underlying CKD played a role. Nonetheless, completely eliminating the probability that undetermined underlying CKD had an effect on the outcome was not possible with this dataset. Therefore, the suggestive findings of this study need to be evaluated in further investigations that include data on kidney function.

This study has several limitations. First, the limitations related to the observational nature of this study should be addressed. Although actions to evaluate the risk of ESKD after onset of AD or DD have been applied, no causal relationship can be ascertained due to the retrospective design of this study. Further prospective investigations are needed to confirm the findings of this study. Second, because the evaluation used information from a NHIS claims database, the possibility of misclassified comorbidities should be considered. In addition, diagnosis codes for a particular comorbid condition might have been omitted if the patient was not being actively treated for that comorbidity. Nonetheless, the accuracy of AD classification through ICD-10 codes has been validated for the NHIS database [38]. In addition, concurrent use of AD- and DD-related medications was considered to improve diagnostic precision. Because all dialysis patients in the Republic of Korea are supported by a copayment assistance policy through the NHIS, ESKD outcomes are accurately identifiable. Third, laboratory data and detailed demographic data were not available. Although CKD was considered as a comorbidity based on diagnosis codes, it was not possible to account for relative kidney function. In addition, factors that could have affected DD, such as family history or occupational status, could not be included in the analyses.

In conclusion, the risk of ESKD development was higher in elderly patients diagnosed with AD or DD than in those who did not have those disorders. These results suggest that preceding mental health disorders could play a role in subsequent development of kidney disease. However, further detailed prospective investigations are needed for confirmation.

**Conflicts of interest**

Tae-Hyun Yoo is the Editor-in-Chief of *Kidney Research and Clinical Practice* and was not involved in the review process of this article. All authors have no other conflicts of interest to declare.

**Acknowledgments**

The National Health Information Database was provided by the National Health Insurance Service of Korea. We thank the National Health Insurance Service for its cooperation.
Authors’ contributions

Conceptualization, Project administration, Resources, Software: SCK, JTP
Data curation: SCK, HBK, HWK, YSJ, JTP
Formal analysis: SCK, HBK, JTP
Investigation, Methodology: SCK, HBK, HWK, JTP
Supervision: SHH, THY, SWK
Visualization: SCK, JTP
Writing–original draft: SCK, JTP
Writing–review & editing: SCK, JTP
All authors read and approved the final manuscript.

ORCID
Shin Chan Kang, https://orcid.org/0000-0002-6507-2676
Hee Byung Koh, https://orcid.org/0000-0002-4510-2823
Hyung Woo Kim, https://orcid.org/0000-0002-6305-452X
Young Su Joo, https://orcid.org/0000-0002-7890-0928
Seung Hyeok Han, https://orcid.org/0000-0002-6305-452X
Tae-Hyun Yoo, https://orcid.org/0000-0002-9183-4507
Shin-Wook Kang, https://orcid.org/0000-0001-7923-5635
Jung Tak Park, https://orcid.org/0000-0002-2325-8982

References


Successful provision of hemodialysis to patients with confirmed COVID-19 in Korea: the role of a cooperative network between public and private medical systems

Ji-Young Choi1*, Jeong-Hoon Lim1*, Seungyeup Han2, Seung-Chan Park3, Hee-Yeon Jung1, Jang-Hee Cho1, Chan-Duck Kim1, Yong-Lim Kim1, Sun-Hee Park1

1Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, Republic of Korea
2Department of Internal Medicine, Keimyung University College of Medicine, Daegu, Republic of Korea
3Department of Internal Medicine, Daegu Veterans Hospital, Daegu, Republic of Korea

Background

Since the outbreak of coronavirus disease 2019 (COVID-19) in February 2020, hospitalizations and deaths have increased in end-stage kidney disease (ESKD) patients in Korea. The first cases of infection with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) variant B.1.1.529 (omicron), which had replaced delta as the dominant variant, were reported in December 2021 in Korea [1]. Although the vaccination rate in ESKD patients was higher than in the general population (>61.4% vs. 36.0% as of December 31, 2021), due to the efforts of the Korean Society of Nephrology (KSN) for priority distribution of vaccines [2,3], the higher transmissibility of the omicron variant remained a threat to ESKD patients, who must undergo hemodialysis (HD) in a confined space.

According to the Korean clinical practice guidelines for preventing transmission of COVID-19 in HD facilities, a patient with confirmed COVID-19 should be transferred to a healthcare facility with an isolation room and a portable dialysis machine. In addition, a management plan including transportation should be established in consultation with the public health center and infection control division of the hospital [4]. However, with the exponential increase in the number of patients with confirmed COVID-19, the workload of public health centers has reached its limit across Korea. In fact, in Daegu Metropolitan City, the daily number of confirmed cases of SARS-CoV-2 infection increased from 125 cases on January 1, 2022, to 1,256 cases on February 3, 2022, and peaked at 24,115 cases on March 16, 2022 [5].

Establishment of a public-private cooperative network for confirmed COVID-19 in patients undergoing hemodialysis

Overloaded working conditions in public health centers have resulted in delayed connections or transfers of pa-
Choi, et al. HD in COVID-19: public-private cooperation

Patients to receive HD in isolation. Since the medical resources and situations at each hospital are different, it was not easy to establish a common and consistent public-private cooperative system.

Thus, HD-specialist members of the KSN in the Daegu-Gyeongbuk provinces established a public-private cooperation network with health policy managers from Public Health Department in Daegu Metropolitan City to ensure that patients undergoing HD could be promptly transferred to facilities with the capacity to provide HD in isolation (Fig. 1). First, they designated dedicated medical institutions to serve as inpatient as well as outpatient isolated HD facilities. Patients who showed impaired consciousness or dyspnea and maintained a fever of 38.0°C or higher for more than three days that was not controlled by antipyretics were indicated for hospitalization according to the COVID-19 response guidelines [6,7]. Second, they secured HD specialists and expanded isolation beds, including intensive care units for admitted severe dialysis patients. Third, they shared information with an established real-time hotline connecting HD units. If a patient who had been cared for in a private HD unit was confirmed to have COVID-19, the HD specialist in charge of the patient sent a message to the real-time hotline that included the patient’s age, sex, date of COVID-19 diagnosis, last dialysis date, basic dialysis information, vital signs, symptoms, availability for outpatient dialysis, and whether or not oxygen was used. Then, the health policy managers in Daegu Metropolitan City checked the messages, monitored available beds for inpatients or outpatients, and matched the COVID-19 patient to an appropriate institution to receive isolated HD. Patients with high fever or who required oxygen were mainly admitted to Kyungpook National University Chilgok Hospital or Kyungpook National University Hospital. Patients who showed no or only mild symptoms (such as rhinorrhea and a sore throat) received isolated outpatient HD at Keimyung University Daegu Dongsan Hospital, from which they were transported using their own car or a quarantine taxi provided by Daegu Metropolitan City. If a patient who received outpatient HD developed aggravating symptoms or showed a poor general condition, they could also be admitted to an isolated bed through the hotline. Due to the established real-time hotline, the patients and dialysis specialists in private HD units no longer had to struggle to personally find isolated HD facilities. In addition, this connection system between the community of HD specialists and public health managers opened a path for HD patients to receive dialysis in a timely and safe manner, as well as to overcome staff work overloads at public health centers and medical dialysis institutions.

**Patient outcomes**

Among 641,322 patients in Daegu, Korea, who were newly diagnosed with COVID-19 from January 1 to April 18, 2022, 862 were on maintenance dialysis (Fig. 2). Of these, seven patients were on peritoneal dialysis. Among 852 total COVID-19 patients on HD, 425 were classified into the at-home treatment group and underwent outpatient HD; the remaining 420 patients were hospitalized and received inpatient HD. The mean age was 63.7 ± 13.8 years, and 60.2% were male. The average age of the inpatient HD group was older than that of the outpatient HD group (66.8 ± 13.7 years vs. 60.9 ± 13.3 years). In the outpatient group, 16 pa-
Patients (3.7%) were hospitalized due to a worsening clinical course. Finally, 428 patients (98.4%) recovered, and seven patients (1.6%) died. Among the inpatient group, a total of 380 patients (90.5%) recovered, while 40 patients (9.5%) died.

**Summary**

In the event of an outbreak of an infectious disease, fast and clear communication among a unit’s healthcare personnel at primary, secondary, and tertiary medical institutions; the medical director of the city’s public health department; and the national quarantine system is vital in managing patients and preventing the transmission of infections, especially for HD patients who require regular visits to medical institutions for dialysis. This establishment of a real-time network for medical delivery was centered on HD specialists, who play an important role in responding to crises of infectious diseases, such as COVID-19.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**Funding**

This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HR22C1832).

**Data sharing statement**

The data presented in this study are available on request from the corresponding author.
Acknowledgments

We would like to thank Shin Ae Choi, Manager of the Public Health Services Bureau, Medical and Health Policy Division in Daegu Metropolitan City, and two nephrologists (Jimin Lim, M.D. and Hayeon Park, M.D.) at Keimyung University Daegu Dongsan Hospital. We appreciate the cooperation of the members of the Korean Society of Nephrology in the Daegu-Gyeongbuk provinces with the Public Health Department regarding HD patients. We also thank the doctors and nurses who worked hard to manage patients in dedicated HD facilities (Kyungpook National University Chilgok Hospital, Kyungpook National University Hospital, Keimyung University Daegu Dongsan Hospital, and Daegu Veterans’ Hospital).

Authors’ contributions

Conceptualization, Funding acquisition: JYC, JHL, SH, SHP
Data curation: all authors
Writing—original first draft: JYC, JHL
Writing—review & editing: all authors
All authors read and approved the final manuscript.

ORCID

Ji-Young Choi, https://orcid.org/0000-0002-9774-3665
Jeong-Hoon Lim, https://orcid.org/0000-0001-5517-9886
Seungyeup Han, https://orcid.org/0000-0002-7561-6534
Seung-Chan Park, https://orcid.org/0000-0002-8736-6528
Hee-Yeon Jung, https://orcid.org/0000-0003-0232-7202
Jang-Hee Cho, https://orcid.org/0000-0002-7031-5214
Chan-Duck Kim, https://orcid.org/0000-0002-4648-0324
Yong-Lim Kim, https://orcid.org/0000-0002-1344-3455
Sun-Hee Park, https://orcid.org/0000-0002-0953-3343

References

Coronavirus disease 2019 (COVID-19) has had a major impact on global communities and healthcare. Paxlovid (nirmatrelvir/ritonavir) is an oral drug for the treatment of COVID-19 that has been approved by the U.S. Food and Drug Administration. In Korea, Paxlovid is the first-line drug for patients who are >60 years old or using immunosuppressants, or those who are >40 years old with chronic diseases such as obesity, diabetes, chronic kidney disease, or hypertension. One caveat of Paxlovid treatment is the potential risk of drug interaction as it is a strong cytochrome P450 (CYP) 3A and P-glycoprotein inhibitor. Tacrolimus is the key immunosuppressant used in kidney transplant (KT) recipients; however, it is metabolized by CYP 3A enzyme, which is strongly affected by Paxlovid. Here, we introduce a case of successful management of severe acute kidney injury (AKI) in a KT patient resulting from tacrolimus overdosage after Paxlovid; AKI was successfully reversed by phenytoin administration to induce CYP3A enzyme.

A 65-year-old man presented to the emergency room with headache, nausea, abdominal pain, and peripheral neuropathy after taking Paxlovid for 3 days. He received a living donor KT 2 years prior from his wife due to focal segmental glomerulosclerosis. Maintenance immunosuppressants were tacrolimus of 4.5 mg twice a day, mycophenolate mofetil of 360 mg twice a day, and prednisone of 5 mg once a day. After 3 days of Paxlovid treatment, which was prescribed at a local clinic after diagnosis of COVID-19, the patient questioned us through his wife about how to take Paxlovid and immunosuppressants during quarantine. Considering tacrolimus toxicity, we recommended discontinuing tacrolimus immediately while completing 5 days of Paxlovid treatment. On the 3rd day after tacrolimus discontinuation and on the 1st day after completing Paxlovid treatment, the patient visited the emergency room. Trough concentration of tacrolimus was >30 ng/mL, creatinine was 9.57 mg/dL, aspartate transaminase/alanine transaminase 19/9 IU/L, and urine dipstick value was 1+. In the previous 3 months, his average tacrolimus trough level was 8.13 ng/
mL and creatinine was 1.4 mg/dL. The symptoms were suspected to be due to tacrolimus-related neurotoxicity and nephrotoxicity, and we administered phenytoin to rapidly decrease the concentration of tacrolimus by inducing the CYP3A enzyme. The patient took phenytoin for 3 days (day 1, 200 mg three times; day 2, 200–100 mg twice; day 3, 100 mg once) (Fig. 1). Phenytoin trough level was evaluated one day after the first dose at 7 AM, measuring 3.73, 4.26, 2.29, and <0.5 µg/mL on the 2nd, 3rd, 4th, and 5th days of administration, respectively. Phenytoin treatment led to a reduction in tacrolimus trough levels from >30 ng/mL to 16.6, 8.2, and 3.5 ng/mL on 1st, 2nd, and 3rd days after admission, and creatinine decreased to 1.92 mg/dL. Headache, gastrointestinal symptoms, tingling sensation, and kidney function improved 1 day after taking phenytoin and resolved by day 3. The patient restarted tacrolimus at 90% of the baseline daily dose 1 day after discontinuing phenytoin. His tacrolimus trough level was 8.2 ng/mL and creatinine concentration was 1.52 mg/dL at discharge.

In KT patients, a combination of three immunosuppressants is mainly used, of which calcineurin inhibitors (CNI) are metabolized by CYP3A [1]. In Korea, oral antiviral medication for COVID-19 is prescribed at a designated local clinic if there are no contraindications according to Ministry of Health and Welfare guidelines. Although not a contraindicated drug, CNI concentration increases in serum with Paxlovid treatment.

In a previous study, tacrolimus and mammalian target of rapamycin (mTOR) inhibitors were stopped and cyclosporine was reduced by 80% empirically when starting Paxlovid. CNI doses were reassessed on day 3 and day 6–7 when beginning Paxlovid. Next, immunosuppressants were resumed by serum concentration. Guidelines recommend that recent transplant patients or those who have experienced rejection try to avoid a subtherapeutic level of immunosuppressant [2,3]. However, during the pandemic, it was difficult to measure CNI level over a short period and reset the concentration to resume accordingly. Some authors recommended skipping or reducing tacrolimus in solid organ transplant recipients receiving Paxlovid;
however, there have been no reports on the rapid reversal of Paxlovid-induced nephrotoxicity after tacrolimus overdosage in a real-world setting. One case reported a gradual reduction in tacrolimus level over 8–10 days [4–6].

This patient experienced undesirable systemic tacrolimus toxicity from Paxlovid. After taking phenytoin, systemic symptoms of tacrolimus toxicity resolved and the trough level of tacrolimus decreased to nontoxic range within 3 days. Phenytoin drug level was undetectable after a 1-day withdrawal, and there were no observed side effects (hypotension, arrhythmia) from phenytoin. There was no rebound tacrolimus trough level spike after tacrolimus re-administration.

Physicians should be cautious when prescribing Paxlovid to KT recipients due to potential drug interactions with CNIs. Phenytoin, a CYP3A inducer, can be used to rapidly resolve tacrolimus overdosage.

This report was approved by the Institutional Review Board of Seoul National University Bundang Hospital (No. B-2210-785-701).

Conflicts of interest

All authors have no conflicts of interest to declare.

Authors’ contributions

Conceptualization, Investigation, Methodology: KEJ, JCJ
Data curation: KEJ, GAY, SP, SK, DWC, JCJ
Visualization: KEJ, GAY, JCJ
Writing—original draft: KEJ, JCJ
Writing—review & editing: KEJ, SP, SK, DWC, HSP, TL, JCJ
All authors read and approved the final manuscript.

References


ORCID

Eun-Jeong Kwon, https://orcid.org/0000-0003-4225-0270
Gi-Ae Yun, https://orcid.org/0000-0003-3712-9011
Seokwoo Park, https://orcid.org/0000-0003-2758-1362
Sejoong Kim, https://orcid.org/0000-0002-7238-9962
Dong-Wan Chae, https://orcid.org/0000-0001-9401-892X
Hyung Sub Park, https://orcid.org/0000-0001-8748-5925
Taeseung Lee, https://orcid.org/0000-0001-6425-5924
Jong Cheol Jeong, https://orcid.org/0000-0003-0301-7644
INSTRUCTIONS FOR AUTHORS

1. Manuscript Submission

Manuscripts for *Kidney Research and Clinical Practice* (KRCP) should be submitted online at https://www.editorialmanager.com/krcp. All submissions to KRCP must conform to the International Committee of Medical Journal Editors (ICMJE) uniform requirements for manuscripts submitted to biomedical journals. Our requirements reflect those of the ICMJE, although we also have specific requirements for different types of article. For editorial questions, please contact us via e-mail (registry@ksn.or.kr), telephone (+82-2-3486-8736), or fax (+82-2-3486-8737).

Important information

Articles should be prepared in the simplest form and submitted in the format of Microsoft Word (*.doc or *.docx). Manuscripts must be typed in English and double-spaced. All pages must be numbered consecutively starting from the title page. You may use automatic page numbering, but do NOT use other kinds of automatic formatting such as footnotes. Place text, references, tables and legends in one file with each table on a new page.

Please ensure that the following submission documents are also included, where applicable:

1. A cover letter. It must include your name, address, telephone and fax numbers, e-mail address, and state that all authors have contributed to the paper and have never submitted the manuscript, in whole or in part, to other journals.
2. A conflict of interest disclosure statement (see relevant section 4.2 below).
3. All studies involving human subjects, human data or any material derived from human must be approved by the relevant review or ethics committee. Articles must include a statement on ethics approval, the name of the relevant committee that approved the study and the committee’s approval number. Manuscripts may be rejected at any time if the authors of the research fail to provide the approval number validated by the relevant committee (see relevant section 4.1 below).
4. Articles covering the use of animals in experiments must be approved by the relevant authorities.
5. Articles where human subjects can be identified in descriptions, photographs or pedigrees must be accompanied by a signed statement of informed consent to publish (in print and online) the descriptions, photographs and pedigrees from each subject who can be identified.
6. The terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors) should be correctly used. The sex and/or gender of study participants, the sex of animals or cells should be reported, and the methods used to determine sex and gender should be described. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., ovarian cancer).
7. Clinical trials should be registered at a primary national clinical trial registration site such as www.clinicaltrials.gov, https://cris.nih.go.kr/cris/index.jsp, or other sites accredited by the World Health Organization or the International Committee of Medical Journal Editors.
8. Where material has been reproduced from other copyrighted sources, letter(s) of permission from the copyright holder(s) to use the copyrighted sources must be supplied.
9. Articles should be written in English (using American English spelling) and meet the following basic criteria: the material is original; the information is important; the writing is clear, concise and grammatically correct; the study methods are appropriate; the data are valid; and the conclusions are reasonable and supported by the data. The articles should be readable to native English users, and we recommend using professional language editing service (e.g., American Journal Experts) prior to submission to avoid delays with the review processes.
10. All authors must register and update information about academic degree, affiliation, and position when they register or submit a journal online at https://www.editorialmanager.com/krcp.
11. The copyright transfer agreement has been incorporated into KRCP submission system to collect digital signatures from each author. Upon submission of a manuscript, an email will be sent to each author for electronic signature prior to starting review process. The manuscript will not be reviewed as planned until all signatures are received. The paper submitted without the signatures of all authors on all statements will be finally removed from the system without further notice.

2. Types of Articles

2.1. Original Articles

These are expected to present major advances and important
new research results. Section headings should include Abstract, Introduction, Methods, Results, Discussion, Conflicts of interest, Acknowledgments (if applicable), and References. The text should be limited to 4,000 words (excluding tables, figures and references) and 40 references.

2.2. Review Articles
These describe new developments of significance in the field of nephrology and highlight unresolved questions and future directions. Most reviews are solicited by the editors, but unsolicited submissions may also be considered for publication. Review articles should include Abstract, Introduction, brief main headings, and References. The text should be limited to 5,000 words (excluding tables, figures and references) and 100 references.

2.3. Special Articles
Articles in this section should provide insightful analysis and commentary about any important topic in medicine, research, ethics, or health policy. They may also address consensus statements, guidelines, statements from task forces, or recommendations. Most reviews are solicited by the editors, but unsolicited submissions may also be considered for publication. The text should be limited to 5,000 words (excluding tables, figures and references) and 50 references.

2.4. Correspondence
Correspondence generally takes one of the following forms: (1) Reader’s comment on an article previously published in KRCP and/or a reply from the authors; (2) An article that may not fit to the format of original or review article but suggest creative perspectives for medical issues; (3) A brief report of any kind that presents important research findings adequate for the journal’s scope and of particular interest to the readers. The submitted manuscript includes title page, main text, conflict of interest, acknowledgments (if applicable) and references. No abstract is included, and the text should be limited to 800 words (excluding tables, figures and references) and 8 references. A maximum of 2 figures or tables may be included.

2.5. Editorials
These are manuscripts that are related to materials within the current issue; they raise challenging questions or explore controversies. The editor solicits such opinion pieces. The order of the submitted manuscript includes title page, integrated discussion, conflict of interest, acknowledgments (if applicable) and references. The text should be limited to 1,500 words and 10 references. A maximum of 2 figures or tables may be included.

2.6. Images in Practice
These present classic or unique images of common medical conditions in clinical nephrology. Images are an important part of much of what we do and learn in clinical practice. The text should be limited to 400 words. There should be no more than two figures. No tables or references are included.

3. Manuscript Preparation

3.1. Title Page
The title page should include article title, each author’s first and last names, positions (associate professor, fellow, student, etc.), and ORCID identifiers, and the institutions with which they are affiliated, short running title not exceeding 50 characters, separate word count for abstract and text, and details of the corresponding author (name, address, phone, and e-mail information). Funding sources should be included, and the individual contribution of each co-author must also be detailed (see relevant section 4.3 below).

3.2. Abstract and Keywords
Abstract should not exceed 250 words in original, review or special articles. It must be written for easy reading with no abbreviations. The abstract of the original article should be divided into four subsections: Background, Methods, Results, and Conclusion. Four to six keywords should be listed alphabetically below the abstract. For selecting keywords, refer to the Index Medicus Medical Subject Headings (available from: http://www.ncbi.nlm.nih.gov/mesh).

3.3. Main Text
The text for original articles, for example, should include the following sections: Introduction, Methods, Results, and Discussion. The Introduction should be as concise as possible, without subheadings. The Methods section should be sufficiently detailed. Subheadings may be used to organize the Results and Discussion. Each section should begin on a new page.

3.4. Acknowledgments
General acknowledgments for consultations, statistical analysis and so on should be listed after main body of text, before the References section, including the names of the individuals involved. All financial and material support for the research
and the work should be stated here clearly and explicitly.

3.5. References
References should be cited with Arabic numerals in square brackets. References are numbered consecutively in order of appearance in text. References are limited to those cited in text and listed in numerical order. List all authors if there are less than or equal to six authors. List the first three authors followed by “et al” if there are more than six authors. If an article has been published online but has not yet been given an issue or pages, the digital object identifier (DOI) should be supplied. Journal titles should be abbreviated in the style used in Index Medicus. Other types of references not described below should follow The NLM Style Guide for Authors, Editors, and Publishers (https://www.ncbi.nlm.nih.gov/books/NBK7256/). The authors may format the citations and references using the KRCP EndNote style file, but we generally recommend the authors to type the citation numbers and references manually.

**Journal articles:**

**Online publication but not yet in print:**

**Entire Book:**

**Book chapter:**

**Website:**

3.6. Tables
Tables are numbered consecutively using Arabic numerals in the order of their citation in text. Table titles should be short and descriptive (e.g. Table 1. Demographic characteristics of patients). If numerical measurements are given, the unit of measurement should be included in the column heading. The statistical significance of observed differences in the data should be indicated by the appropriate statistical analysis. All nonstandard abbreviations should be defined in footnotes. Lower case letters in superscripts (a, b, c,...) should be used for special remarks.

3.7. Figures
Figure legends should be submitted for all figures. They should be brief and specific, and placed on a separate sheet after the References section. Figures are numbered consecutively using Arabic numerals in the order of their citation in the text. Figures should be uploaded as separate files, not embedded in the manuscript file. Figures that are line drawing or photographs must be submitted separately in high-resolution EPS or TIF format (or alternatively in high-resolution JPEG format). Only high-resolution figure files (preferably 300 dpi for color figures and 1,200 dpi for line art and graphs) should be submitted. The files are to be named according to the figure number and format (e.g., Fig1.tif). Figures that are reproduced from other published sources require written permission from the authors and copyright holders.

3.8. Supplementary Digital Contents
Authors can submit supplementary digital contents to supplement the information provided in the print version of the manuscript. Supplementary materials will be published online-only. When uploading supplementary files through the online system, please use the “supplemental” file designation. Supplementary materials must be cited consecutively in the main body of the submitted manuscript and include the type of material submitted (e.g., “Supplementary Table 1”; “Supplementary Fig. 1”).
4. Ethical Considerations

4.1. Ethical Approval of Studies
For human or animal experimental investigations, appropriate institutional review board or ethics committee approval is required. Such approval and the approval number should be stated in the Methods section of the manuscript. For those investigators who do not have formal ethics review committees, the principles outlined in the Declaration of Helsinki as revised in 2013 should be followed (World Medical Association. Declaration of Helsinki: Ethical principles for medical research involving human subjects. Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). For all relevant clinical transplant articles, KRCP requires authors state in the Methods section their adherence to the Declaration of Istanbul (Available at: http://www.declarationofistanbul.org/). Copies of written informed consent and Institutional Review Board (IRB) approval for clinical research should be kept. If necessary, the editor or reviewers may request copies of these documents to resolve questions about IRB approval and study conduct.

4.2. Conflicts of Interest
The corresponding author must inform the editor of any potential conflicts of interest that could influence the authors’ interpretation of the data. Examples of potential conflicts of interest include financial support from or connections to pharmaceutical companies, political pressure from interest groups, and academically related issues. Conflict of interest statements will be published at the end of the text of the article, before the References section. Please consult the Committee on Publishing Ethics guidelines (http://www.publicationethics.org/) on conflict of interest. All sources of financial support for the study should be stated in Acknowledgments (see relevant section 3.4 above).

4.3. Authorship
Authorship credit should be based on 1) conception or design, or analysis and interpretation of data; 2) drafting the article or revising it; 3) providing intellectual content of critical importance to the work described; and 4) final approval of the version to be published. Authors should meet above four conditions. The title page should include a list of each author’s role for the submitted paper.

4.4. Redundant Publication or Duplicate Submission
Submitted manuscripts are considered with the understanding that they have not been published previously in print or electronic format (except in abstract or poster form) and are not under consideration in totality or in part by another publication or electronic medium. Authors must state that neither the manuscript nor any significant part of it is under consideration for publication elsewhere or has appeared elsewhere in a manner that could be construed as a prior or duplicate publication of the same, or very similar, work. When malpractices are found in an article submitted to KRCP, we will follow the flowchart by the Committee on Publication Ethics (COPE, https://publicationethics.org/resources/flowcharts) for settlement of any misconduct. Although the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with KRCP, its editors, or the Korean Society of Nephrology.

5. Review Process
All submissions are sent to peer reviewers. Authors will usually be notified within 4 weeks by e-mail of whether the submitted article is accepted for publication, rejected, or subject to revision before publication. Revised manuscripts must be submitted online by the corresponding author. Failure to resubmit the revised manuscript within 3 months of the editorial decision is regarded as a withdrawal.

6. Visual Abstract Guidelines
Visual Abstracts are brief graphical summaries of Original Articles published online. They serve to summarize the work for readers and may be used in social media postings. Authors do not need to include a Visual Abstract with their initial submission but will be required to submit one at the revision stage for all original research articles. The submitted visual abstract will be reviewed along with the revised manuscript. If the submission of visual abstract is delayed, there is inevitable delay in publication. Please submit it within the specified time.

6.1. Creating Your Visual Abstract
Select one of the visual abstract templates provided (https://www.krcp-ksn.org/file/KRCP_Visual_Abstracts_v1.0.pptx). There are multiple layouts to accommodate author preferences as well as graphical constraints. The visual abstract should...
include a title, methods, outcome and a concluding sentence. Please fill in the template as it's laid out and do not alter the basic components of the template.

Keep in mind the following:
• Avoid excessive detail and clutter and keep text to a minimum.
• Any descriptive text should be at least 12 pt font size.
• The visual abstract should be saved as an editable PowerPoint file as staff will add the article DOI and may edit the text for clarity.

6.2. Adding Visual Details

It is critical that you only use images for which you have permissions or rights. To avoid any potential problems, either use the copyright filter during an image search online or subscribe to an icon image bank. There are many image banks on the internet, which are free to use. The images used for visual abstract is recommended only open source, and the author is responsible for copyright issues of visual abstract. Researchers who frequently prepare visual abstracts may benefit from purchasing a subscription to access higher quality icons (e.g. Shutterstock, Getty Images, iStock, etc.).

Guiding principles:
• Select bold, solid color icons
• Avoid highly detailed icons as the intricacy may be lost in the small format
• Exclude trade names, logos, or images of trademarked items.
• Graphics should be 440 pixels wide by 350-365 pixels tall.

7. Peer Review

This journal operates blind review processes. All contributions will be initially assessed by the editor for suitability for the journal. Papers deemed suitable are then sent to a minimum of two independent expert reviewers to assess the scientific quality of the paper. The Editor is responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. For more information, please refer to Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (Available at: http://www.icmje.org/icmje-recommendations.pdf).

8. Copyright

KRCP is the official peer-reviewed publication of the Korean Society of Nephrology. Manuscripts published in the Journal become the permanent property the Korean Society of Nephrology. All articles published in the Journal are protected by copyright, which covers the exclusive rights to reproduce and distribute the article, as well as translation rights. No KRCP article, in part or whole, cannot be reproduced, stored, or transmitted for commercial purposes, without prior written permission from the Korean Society of Nephrology.

9. Similarity Check

Similarity Check is a multi-publisher initiative to screen published and submitted content for originality. To find out more about Similarity Check, visit http://www.crossref.org/crosscheck/index.html. All manuscripts submitted to KRCP may be screened, using the iThenticate tool, for textual similarity to other previously published works.

10. Open Access Policy

Every peer-reviewed research article in this journal is freely available via our website (https://www.krcp-ksn.org). Articles published in KRCP are distributed under the terms of the Creative Commons Attribution Non-Commercial and No Derivatives License (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits unrestricted non-commercial use, distribution of the material without any modifications, and reproduction in any medium, provided the original works properly cited. ANY USE of the open access version of this Journal in whole or in part must include the customary bibliographic citation, including author and publisher attribution, date, article title, Kidney Research and Clinical Practice (Kidney Res Clin Pract), and the URL https://www.krcp-ksn.org and MUST include a copy of the copyright notice. If an original work is subsequently reproduced or disseminated not in its entirety but only in part or as a derivative work this must be clearly indicated. For any commercial use of material from the open access version of the journal, permission MUST be obtained from KRCP. If necessary, please contact the Editorial Board through our editorial office (registry@ksn.or.kr). Proprietary rights notice for KRCP online were available at: https://www.krcp-ksn.org/authors/permission.php
11. Data Sharing Policy

For clarification on data accuracy and reproducibility of the results, raw data or analysis data will be deposited to a public repository, for example, Harvard Dataverse (https://dataverse.harvard.edu/) after acceptance of the manuscript. Therefore, submission of the raw data or analysis data is mandatory when requested by reviewers. If the data is already a public one, its URL site or sources should be disclosed. If data cannot be publicized, it can be negotiated with the editor. If there are any inquiries on depositing data, authors should contact the editorial office.

12. After acceptance

12.1. Article-in-press publication

After the manuscript is finally accepted, it will be published online in PDF format through the English editing, author proofing and final editorial correction process. The corresponding author should promptly and appropriately respond to this editing process. Online publication will take place within several weeks depending on the proof process. A Digital Object Identifier (DOI) is allocated, making it fully citable and searchable by title, author name(s), and the full text. Since our journal is officially published every 3 months interval, the volume, issue, and page will be finally allocated sequentially according to the order of accepted articles.

12.2. Publication charges

In order to cover the costs of reviewing, copy editing, layout, and online hosting and archiving, KRCP charges an article processing fee upon acceptance of submitted papers as follows:

- Original Article, Review Article, Special Article, and Study Protocol: KRW 1,000,000 (Korea) / USD 1,000 (rest of world)
- Correspondence, Image in Practice: KRW 300,000 (Korea) / USD 300 (rest of word).

There are no additional charges based on color, length, figures or other elements. The publication costs for invited papers such as editorials, some reviews and special articles are covered by the Korean Society of Nephrology. Payments are processed by a department unconnected to KRCP’s editorial board.

• Publication charge waiver policy

Our mission is to share the achievements in the nephrology field with researchers worldwide including the scientists in the low-income countries. We continue to apply the publication charge waiver policy to encourage the academic activity and support the limited funding for their research. To request a publication charge waiver, please send an application to registry@ksn.or.kr. Corresponding author from low-income countries could be waived. Waiver application must contain the manuscript number and country of corresponding author.
INDICATIONS
1. Renal anemia
2. Chemotherapy-induced anemia in solid cancer patients

DOSEAGE AND ADMINISTRATION
<Adolescents/patients>
Initial dose
The usual dose of NESP in adult patients is 20 μg, to be administered as a single intravenous injection once weekly.

Initial dose at the switching from epoetin-alfa preparations: See Precautions related to Dosage and Administration

Maintenance dose
When correction of anemia is achieved, the usual dose of NESP in adult patients is 15-40 μg as darbepoetin alfa (commercial name), or 200 μg as NESP, administered as a single intravenous injection once weekly. If stabilization of anemia is maintained by once every two weeks injection, the frequency of administration can be changed to once every four weeks, with a maintenance dose set to be two-fold of the dose in the once every two weeks injection. In this case, the usual dose in adult patients is 50-100 μg administered as a single injection once every four weeks, respectively. In cases where the dose should be adjusted in some degree of anemia symptoms and the patients' age, and should not exceed 100 μg as a single injection. The target of anemia correction is around 11 g/l of hemoglobin level.

<Precautions related to Dosage and Administration>
1. Initial dose at the switching from an epoetin-alfa preparation.
   When NESP is started substitution for an epoetin-alfa preparation, the dose and the frequency of administration should be determined on the basis of the dosing schedule of the epoetin-alfa preparation that has been used. See the table (package insert).

2. Patients who have been treated with an epoetin-alfa preparation twice or three times weekly. Calculate the total dose of the epoetin-alfa preparation administered during the week before the switching, and then determine the initial dose of NESP according to the table below. The treatment should be started on once weekly basis.

3. Patients who have been treated with an epoetin-alfa preparation once weekly or every two weeks. Calculate the total dose of the epoetin-alfa preparation administered during the two weeks before the switching, and then determine the initial dose of NESP according to the table below. The treatment should be started on once every two weeks basis.

STORAGE
Store in a tight light-resistant container at 2-8 °C and avoid freezing.

PACKAGING
1 syringe, 10 syringes

MANUFACTURED BY:
Takyo Pharmaceutical Co., Ltd.
1042-22, Matsuzaki, Takamatsu-shi, Ehime, Japan
Kyowa Hakko Kirin Co., Ltd.
100-1 Hagiwara-machi, Takasaki-cho, Gunma, Japan

IMPORTED BY:
KYOYA KIRIN
119, Aso Tower, 400, Nonhyeong-dong, Gangnam-gu, Seoul, 06223, Rep. of Korea
TEL 02-3471-4831 FAX 02-3471-4932

http://www.kyowa-kirin-korea.com
Improving lives together

Fresenius Medical Care is the world’s leading provider of dialysis products and services, offering life-sustaining care for people living with chronic kidney failure.

In Asia Pacific, we draw on our decades of experience and expertise to deliver our vision – Creating a future worth living. For patients. Worldwide. Every day.

Get in touch

Fresenius Medical Care Korea
(14/F, FKI Tower) 24 Yeoui-daero,
Yeongdeungpo-gu, Seoul, 07320, Rep. of Korea
Telephone: +822 2146 8800
Fax: +822 3453 9213
www.freseniusmedicalcare.asia
포시가®와 더지킴
만성콩팥병 환자의 신기능 악화 지연을 위해, 포시가®로 환자를 지켜주세요!

【용법·용량】
1. 제2형 당뇨병: 이 약은 제2형 당뇨병 환자의 혈당 조절을 향상시키기 위해 식사요법 및 기타 혈당 강하제와 병용하여 사용한다. 이 약의 권장 용량은 1일 1회 10mg이다.
2. 만성신장병: 만성 신장병 환자에서 추정 사구체 여과율 (estimated glomerular filtration rate, eGFR)의 지속적인 감소를 방지하기 위해 사용한다. 이 약의 권장 용량은 1일 1회 10mg이다.
3. 고령자 (≥ 65세) 및 간장애: 대여시 각 병합증의 특성을 고려하여 용량을 조절할 수 있다. 고령자에서 1일 1회 5mg를 권장하며, 내약성이 양호한 경우 이 용량은 10mg으로 증가시킬 수 있다. 간장애 환자에서는 체계적인 관리가 필요하며, 장기화된 사용은 체계적인 관리와 함께 한다.

【성분·함량】
유효성분: 다파글리플로진프로판디올수화물 (별규) 12.3mg (다파글리플로진으로서 10mg)

【효능·효과】
포시가의 주요 효능 효과는 다음과 같다.
1) 체액량 감소 및 신기능 장애가 있는 환자에서의 투여
2) 특정 환자군에서의 투여 (특수 집단)
3) 유일성 간질환 환자의 신기능 악화 지연을 위해,

【사용상 주의사항】
1. 제2형 당뇨병 환자에만 사용: 이 약은 제2형 당뇨병 환자에게만 사용할 수 있으며, 제1형 당뇨병 환자나 당뇨병이 없는 환자에게는 사용하지 않는다.
2. 당뇨 mellitus type 2 환자: 이 약은 당뇨 mellitus type 2 환자에게 사용할 수 있으며, 당뇨 mellitus type 1 환자나 당뇨 Mellitus의 다른 유형을 해명할 수 있다.
3. 만성신장병 환자: 이 약은 만성신장병 환자에만 사용할 수 있으며, 만성신장병의 다른 유형을 해명할 수 있다.
4. 간질환 환자: 이 약은 간질환 환자에만 사용할 수 있으며, 간질환의 다른 유형을 해명할 수 있다.
5. 중등도 이상의 신기능 악화, ESKD, 신장 또는 심혈관 질환으로 인한 사망위험 39% 감소 2)

【제2형 당뇨환자에 일부한도 개선 및 약효감소 이점】
포시가®의 주요 이점은 다음과 같다.
1. 체액량 감소 및 신기능 장애가 있는 환자에서의 투여
2. 특수 집단에 대한 투여
3. 유일성 간질환 환자의 신기능 악화 지연을 위해,

【용법·용량】
1. 제2형 당뇨병: 이 약은 제2형 당뇨병 환자의 혈당 조절을 향상시키기 위해 식사요법 및 기타 혈당 강하제와 병용하여 사용한다. 이 약의 권장 용량은 1일 1회 10mg이다.
2. 만성신장병: 만성 신장병 환자에서 추정 사구체 여과율 (estimated glomerular filtration rate, eGFR)의 지속적인 감소를 방지하기 위해 사용한다. 이 약의 권장 용량은 1일 1회 10mg이다.
3. 고령자 (≥ 65세) 및 간장애: 대여시 각 병합증의 특성을 고려하여 용량을 조절할 수 있다. 고령자에서 1일 1회 5mg를 권장하며, 내약성이 양호한 경우 이 용량은 10mg으로 증가시킬 수 있다. 간장애 환자에서는 체계적인 관리가 필요하며, 장기화된 사용은 체계적인 관리와 함께 한다.

【성분·함량】
유효성분: 다파글리플로진프로판디올수화물 (별규) 12.3mg (다파글리플로진으로서 10mg)

【효능·효과】
포시가의 주요 효능 효과는 다음과 같다.
1) 체액량 감소 및 신기능 장애가 있는 환자에서의 투여
2) 특정 환자군에서의 투여 (특수 집단)
3) 유일성 간질환 환자의 신기능 악화 지연을 위해,

【사용상 주의사항】
1. 제2형 당뇨병 환자에만 사용: 이 약은 제2형 당뇨병 환자에게만 사용할 수 있으며, 제1형 당뇨병 환자나 당뇨병이 없는 환자에게는 사용하지 않는다.
2. 당뇨 mellitus type 2 환자: 이 약은 당뇨 mellitus type 2 환자에게 사용할 수 있으며, 당뇨 mellitus type 1 환자나 당뇨 Mellitus의 다른 유형을 해명할 수 있다.
3. 만성신장병 환자: 이 약은 만성신장병 환자에만 사용할 수 있으며, 만성신장병의 다른 유형을 해명할 수 있다.
4. 간질환 환자: 이 약은 간질환 환자에만 사용할 수 있으며, 간질환의 다른 유형을 해명할 수 있다.
5. 중등도 이상의 신기능 악화, ESKD, 신장 또는 심혈관 질환으로 인한 사망위험 39% 감소 2)

【제2형 당뇨환자에 일부한도 개선 및 약효감소 이점】
포시가®의 주요 이점은 다음과 같다.
1. 체액량 감소 및 신기능 장애가 있는 환자에서의 투여
2. 특수 집단에 대한 투여
3. 유일성 간질환 환자의 신기능 악화 지연을 위해,
환자에 대한 주의사항

1. 경고

중대한 수막구균 감염 작용기전으로 인하여 이 약의 사용은 중대한 수막구균 감염(패혈증 및 뇌수막염)에 대한 환자의 감수성을 증가시킨다. 이 약의 투여 환자에서 치명적이고 생명을 위협하는 수막구균 감염이 발생하였다. 수막구균 감염은 어느 혈청군에 의해서도 발생할 수 있지만, 이 약의 투여 환자들은 흔하지 않은 혈청군(X 등)에 의한 질환이 발생할 수 있다. 감염의 위험성을 낮추기 위하여, 이 약의 치료가 지연됨으로 인한 위험이 수막구균 감염 발생의 위험성보다 큰 경우를 제외하고는 모든 환자들은 반드시 이 약의 투여 시작 최소한 2주 전에 수막구균 백신을 투여 받아야 한다. 만약 접종 받지 않은 환자가 긴급히 이 약의 치료를 받아야 하면, 최대한 빨리 수막구균 백신을 투여 받도록 한다. 수막구균 백신 접종 이후 2주 동안 적절한 예방적 항생요법으로 치료 받아야 한다. 흔한 병원성 수막구균 혈청군을 예방하기 위하여 가능하다면 혈청군 A, C, Y, W135, B에 대한 백신이 권장된다. 환자들은 백신 사용을 위한 최신의 백신 접종 지침(Advisory Committee on Immunization Practices(ACIP) recommendations)에 따라 백신을 접종 혹은 재접종 받아야 한다. 백신 접종은 보체를 더욱 활성화시킬 수 있다. 결과적으로, PNH, aHUS, 불응성 gMG 및 NMOSD를 포함한 보체 매개 질환을 가진 환자들은 용혈(PNH의 경우)이나 혈전성 미세혈관병증(TMA; aHUS의 경우) 또는 중증 근무력증의 악화(불응성 gMG의 경우) 또는 재발(NMOSD의 경우)과 같은 그들의 기저 질환의 징후 및 증상이 증가하는 경험을 할 수 있다. 따라서, 지침에 따른 백신 접종 이후 질환의 증상에 대해 면밀히 관찰되어야 한다. 백신 접종은 수막구균 감염 위험을 줄일 수 있지만, 완전히 없애지는 않는다. 적절한 항생제 사용에 대한 공식 지침(예: 국내 성인 세균성 수막염의 임상진료지침 권고안 등)을 고려하여야 한다. 수막구균 감염의 초기 징후나 증상이 나타나는지 면밀히 관찰하고, 감염이 의심되면 즉시 검사받아야 한다. 환자는 이러한 징후와 증상 및 즉시 치료를 받는 절차에 대해 안내 받아야 하며, 담당 의사는 반드시 환자와 이 약의 치료의 위험과 이익을 상의해야 한다. 수막구균 감염은 초기에 발견하고 치료하지 않으면 급격히 치명적이고 생명을 위협하게 될 수 있다. 중대한 수막구균 감염을 치료받는 환자는 이 약의 투여를 중지하도록 한다.

2. 다음 환자에는 투여하지 말 것

1) 이 약의 주성분, 뮤린 단백질 또는 기타 구성성분에 과민반응이 있는 환자
2) 치료되지 않은 중대한 수막구균(Neisseria meningitidis) 감염 환자
3) 수막구균(Neisseria meningitidis) 백신을 현재 접종하지 않은 환자 또는 백신 접종 이후 2주 동안 적절한 예방적 항생요법으로 치료를 받지 않은 환자(이 약의 치료를 늦추는 것이 수막구균 감염을 일으키는 것보다 중대하지 않은 경우)

3. 다음 환자에는 신중히 투여할 것

1) 기타 전신 감염: 작용기전으로 인하여 이 약의 치료는 활성 전신 감염이 있는 환자들에게 주의하여 투여하여야 한다. 이 약은 말단 보체 활성을 차단하므로 환자들은 감염, 특히 Neisseria균 및 피낭성 세균(encapsulated bacteria) 감염에 대한 감수성이 증가할 수 있다. 파종성 임균 감염을 포함하는 N. meningitidis 외의 Neisseria 종에 의한 중대한 감염이 보고되었다. 잠재적인 중대한 감염과 그 증상 및 징후에 대한 인식을 높이기 위하여 환자용 정보 안내서의 정보를 환자에게 제공해야 한다. 임질 예방에 관해 환자에게 조언해야 하고 위험성이 있는 환자는 정기적인 검사를 권고한다. 더욱이, 면역력이 약화된 환자와 호중구 감소 환자에서 아스페르길루스 감염이 발생하였다. 이 약을 투여 받는 소아는 폐렴연쇄상구균(Streptococcus pneumonia)과 인플루엔자 간균 B형(Haemophilus influenza type b(Hib))에 의해 중대한 감염을 일으킬 위험이 증가할 수 있다. 폐렴연쇄상구균(Streptococcus pneumonia)과 인플루엔자 간균 B형(Haemophilus influenza type b(Hib))에 의한 감염을 예방하기 위해 최신의 백신 접종 지침에 따라 백신 접종을 받도록 한다. 전신 감염이 있는 환자에게 이 약을 투여할 때는 주의하도록 한다. 에 kullirubin에 안정되고 유지 요법을 받는 환자에게 추가적인 백신 접종이 필요한 경우, 이 약 투여에 따른 백신 접종 시기를 신중히 고려해야 한다.

4. 약물이상반응 시

판 후 보고 및 완료된 임상시험에서 보고된 약물이상반응(발생률 1% 이상 발췌): 매우 흔하게(≥1/10) – 두통, 흔하게(≥1/100 ~ <1/10) - 폐렴, 상기도감염, 비인두염, 기관지염, 요로 감염, 구강 헤르페스, 백혈구감소증, 빈혈, 불면, 현기증, 미각이상, 고혈압, 기침, 입인두통, 설사, 구토, 구역, 복부통증, 발진, 탈모, 소양증, 관절통, 근육통, 열, 피로감, 인플루엔자 유사질환모든 임상시험에서, 가장 중대한 이상반응은 수막구균 패혈증이었고, 이는 이 약으로 치료 받은 환자에서 수막구균 감염증의 흔한 증상이었다. 수막구균 패혈증의 징후와 증상에 대해 환자에게 즉시 의료 조치 받을 것을 환자에게 권고해야 한다. Neisseria gonorrhoeae, Neisseria sicca / subflava, Neisseria spp unspecified로 인한 패혈증을 포함하여 Neisseria 종의 다른 사례들이 보고되었다.
MDS-101
Asahi Dialysis System MDS-101
Dialysis Equipment

Slim & Smart
High visibility and Simplified procedures
Secured ultrafiltration system
Easy maintenance
Boryung Renal Business Unit provides **TOTAL RENAL CARE**

| Boryung Renal Business Unit | Boryeong Building, 136 Changgyeonggung-ro, Jongno-gu, Seoul |
| Customer Service Center | Tel 080-708-8088  Fax 02-741-5291  www.boryung.co.kr |
Slow ADPKD. Preserve Hope.

Introducing Samsca — The first and only treatment proven to slow cyst progression.

Samsca® Tablet ADPKD product information summary [INDICATION] To slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1-4 at initiation of treatment with evidence of rapidly progressing disease. [DOSAGE & ADMINISTRATION] Tolvaptan must only be prescribed by physicians who have registered in Risk Management Program to the patients who have agreed and signed on conditions specified in Risk Management Program. Patient should follow this program. And, to mitigate the risk of significant and/or reversible liver injury, blood testing for hepatic transaminases and bilirubin is required prior to initiation of SAMSCA, continuing monthly for 18 months and at regular 3 monthly intervals thereafter. The initial dose is 60 mg tolvaptan per day as a split-dose regimen of 45 mg + 15 mg (45 mg taken upon waking and prior the morning meal and 15 mg taken 8 hours later). The initial dose is to be titrated upward to a split-dose regimen of 90 mg tolvaptan (60 mg + 30 mg) per day and then to a target split-dose regimen of 120 mg tolvaptan (90 mg + 30 mg) per day, if tolerated, with at least weekly intervals between titrations. Dose titration has to be performed cautiously to ensure that high doses are not poorly tolerated through overly rapid up-titration. Patients may down-titrate to lower doses based on tolerability. Patients have to be maintained on the highest tolerable tolvaptan dose. Samsca® Tablet is an indication for hyponatremia as well. For further information, please refer to the latest prescribing information at www.otsuka.co.kr.
At B. Braun, we don't just develop products. We provide solution for life.

Diacap Pro
THE TRUSTED PERFORMER

Dialog+
THE POWER OF FLEXIBILITY

B. Braun Korea | 13Fl. West Wing 440 Teheran-ro | Gangnam-gu, Seoul | Korea
Tel. 02-3459-7800 | www.bbraun.co.kr
그래 이제! 크레 메진!
크레메진은 당뇨병성 콩팥병 환자의 신장보호효과를 통한 만성신부전 진행을 억제시킵니다.

복용이 더욱 편리해진 크레메진 정 출시 예정
(21년 8월 신규허가획득)
Making adherence part of their daily lives

Effective phosphate management, simplified

- Increased Patient Satisfaction: Effective control with 3000mg/day
- Reduce Pill Burden: One tablet or powder each meal
- Well Established Safety Profile: Over 10 years of safety data


Prescribing Information: Before prescribing please consult the full Summary of Product Characteristics (SmPC) & Prescriber Information. Dosage and administration: Oral suspension containing 500 mg, 750 mg of lanthanum (as lanthanum carbonate). Oral powder containing 1000 mg of lanthanum (as lanthanum carbonate hydrate). Both the chewable tablets and the oral powder contain the active ingredient, containing lanthanum. Lanthrene is indicated in adult patients as a phosphate-binding agent for use in the control of hyperphosphatemia in chronic renal failure patients on hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). Lanthrene is also indicated in adult patients with chronic kidney disease not on dialysis with serum phosphate levels ≥ 5.5 mg/dL, in whom a low phosphate diet alone is insufficient to control serum phosphate levels. Dose and Administration: For oral use. Adults, including older people (> 65 years): Lanthrene should be taken with or immediately after food, with the daily dose divided between meals. The tablets must be chewed completely and not swallowed whole. To aid with chewing the tablets may be crushed. Lanthrene oral powder is intended to be mixed with a small quantity of soft food (e.g., apple sauce or other similar food product) and consumed immediately (within 15 minutes). The dose of Lanthrene should be titrated every 2-3 weeks until an acceptable serum phosphate level is reached. Controlled serum phosphate levels have been demonstrated at doses starting from 750mg per day. The maximum daily dose studied, in a limited number of patients, is 3750mg. Patients who require lanthanum therapy usually achieve acceptable serum phosphate levels at doses of 1500-3000mg lanthanum per day. Pediatric populations (> 18 years): The safety and efficacy of lanthanum in children and adolescents has not been established, use in children and adolescents is not recommended. Hemodialysis: The effect of hemodialysis on Fosrenol pharmacokinetics has not been assessed. Due to the mechanism of action and the lack of bone metabolism, at low in hemodialysis patients, changes in lanthanum may not be modified, but patients should be monitored regularly. Adverse Effects: Very common: Headache, abdominal pain, diarrhea, nausea, vomiting, allergic skin reactions. Common: ≥ 1/100 to < 1/10 patients: constipation, dyspepsia, flatulence, hypercalcemia. Consult SmPC for listing of less common side effects. Date of Revision: March 2018.

For further information, please refer to the latest prescribing information at www.takeda.co.kr or http://www.takeda.co.kr.
Homechoice Claria enabled by Sharesource
from pediatric to elderly population

Homechoice Claria
SIMPLE & SMART APD for your patient to maintain daily life

ON-DEMAND ACCESS to treatment data by GREAT VISIBILITY in APD

- Intuitive Triage Dashboard
- Patient Snapshot
- Treatment Summary
Initiate early with

for your Hypertension patients!

Treat your Fabry disease patients with Fabrazyme

1 mg/kg once every 2 weeks

COUNT ON FABRAZYMENOTICE