ISSN 1738-5997 (Print)
ISSN 2092-9935 (Online)

Electrolyte & Blood Pressure

Vol. 21, No. 1, June 2023 Page 1–44, 2023

Electrolytes & Blood Pressure

Vol. 21, No. 1, June 2023

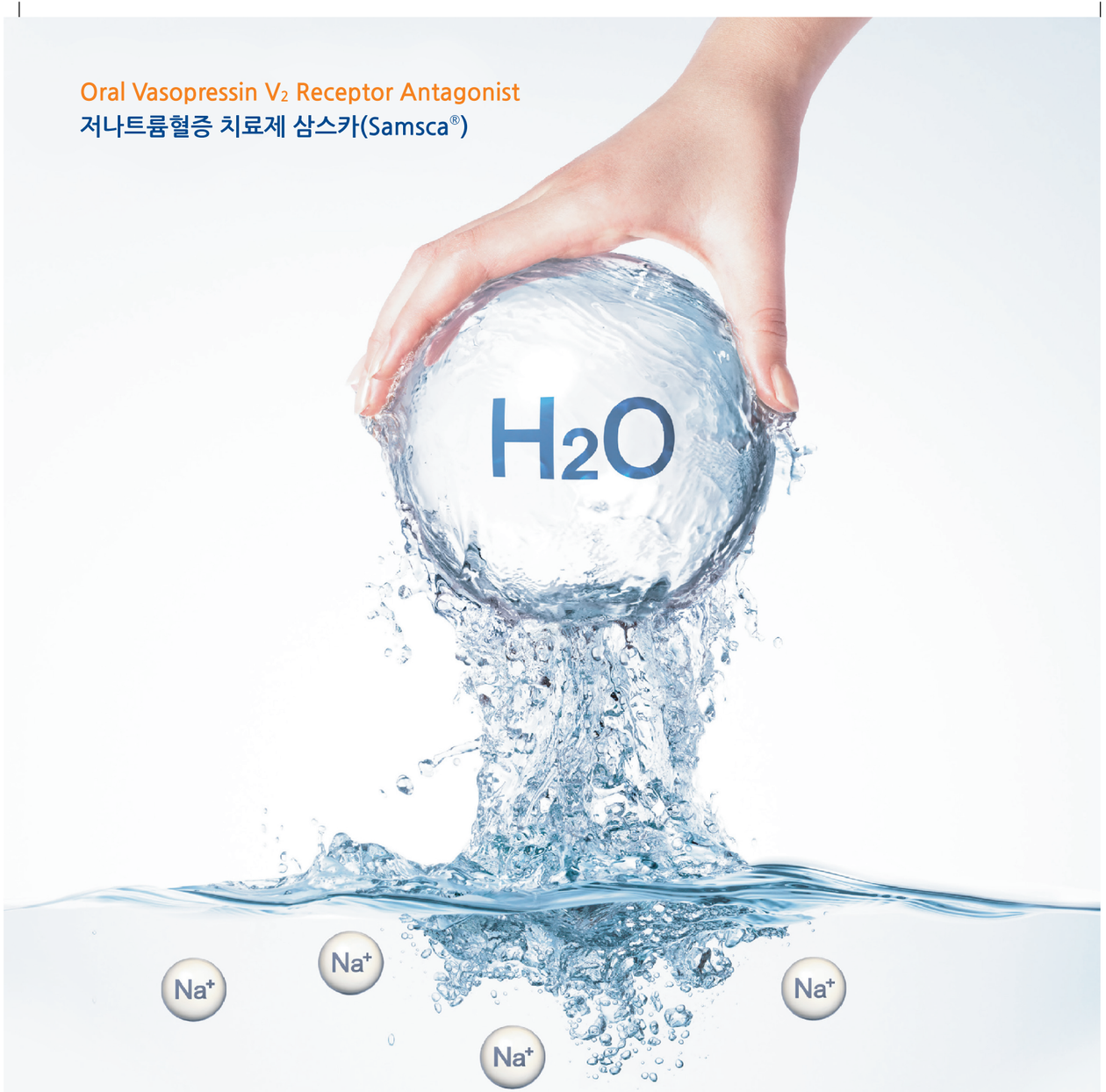
전해질고혈압연구회
E&BP
Korean Society for Electrolyte and Blood Pressure Research

전해질고혈압연구회
E&BP
Korean Society for Electrolyte and Blood Pressure Research

The Official Journal of
Korean Society for Electrolyte and Blood Pressure Research

Oral Vasopressin V_2 Receptor Antagonist

저나트륨혈증 치료제 삼스카(Samsca®)



- **Aquaretic effect** to selectively increase solute-**free water clearance** by the kidney.[1]
- In patients with **euvolemic or hypervolemic hyponatremia,** Samsca®(tolvaptan) was effective in **increasing serum sodium concentrations**.[2]

References

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

Otsuka

한국오츠카제약 Under license from Otsuka Pharmaceutical Co., Ltd

06227 서울시 강남구 역삼로 226 오츠카비전빌딩

Tel 02-3287-9000 | www.otsuka.co.kr

Samsca® (tolvaptan) 15 mg 30 mg tablets

SAM-23-006 | 20230407 approved

命稟메디칼주식회사

MYOUNG POOM MEDICAL CO. LTD

칼륨억제제 이젠 우수한 품질로 편리하게 치료합니다!

카로스현탁액

경구용 현탁액 20ml
Calcium Polystyrene Sulfonate 5g

[제품요약정보] [전문의약품] ■ **제조회사_** (주)휴온스 ■ **제품명_** 카로스현탁액 ■ **주성분·함량_** 이 약 1포 중 폴리스티렌설폰산칼슘 5g ■ **효능·효과_** 고칼륨혈증억제제
■ **용법·용량_** 성인: 폴리스티렌설폰산칼슘으로서 1일 15~30g을 2~3회 나누어 경구투여 한다. 연령증상에 따라 적절히 증감한다.
■ **금기_** 배합금기: 칼슘염과 반응하는 물질 또는 칼슘에 흡수가 저해되는 약물과의 배합은 피한다.
■ **신중투여_** 변비가 자주 발생하는 환자, 장관협착증환자, 소화관궤양환자
■ **주요이상반응_** 변비, 식용부진, 구역
■ **보험수가: 760원/포** ■ **보험코드_ 670606111** ■ **포장단위_ 90포/Box**

카슈트현탁액

경구용 현탁액 20ml
Calcium Polystyrene Sulfonate 5g

[제품요약정보] [전문의약품] ■ **제조회사_** DID바이오(주) ■ **제품명_** 카슈트현탁액 ■ **주성분·함량_** 이 약 1포 중 폴리스티렌설폰산칼슘 5g ■ **효능·효과_** 고칼륨혈증억제제
■ **용법·용량_** 성인: 폴리스티렌설폰산칼슘으로서 1일 15~30g을 2~3회 나누어 경구투여 한다. 연령증상에 따라 적절히 증감한다.
■ **금기_** 배합금기: 칼슘염과 반응하는 물질 또는 칼슘에 흡수가 저해되는 약물과의 배합은 피한다.
■ **신중투여_** 변비가 자주 발생하는 환자, 장관협착증환자, 소화관궤양환자
■ **주요이상반응_** 변비, 식용부진, 구역
■ **보험수가: 796원/포** ■ **보험코드_ 664101341** ■ **포장단위_ 100포/Box**

Electrolytes & Blood Pressure

Publisher : Soo Wan Kim, MD (President of the Korean Society for Electrolyte and Blood Pressure Research)

Editorial Correspondence : Sejoong Kim, MD, PhD

Editor-in-Chief of Electrolytes & Blood Pressure
Division of Nephrology, Department of Internal Medicine, Seoul National University Bundang Hospital, 82, Gumi-ro 173Beon-gil, Bundang-gu, Seongnam, Gyeonggi-do 13620, Korea
TEL : +82-31-787-7051 | FAX : +82-31-787-4052 | E-mail: junhaegil@gmail.com

Business Correspondence : Should be sent to the Korean Society for Electrolyte and Blood Pressure Research

Division of Nephrology, Department of Internal Medicine, Chonnam National University Hospital 42, Jebongro, Dong-gu, GwangJu 61469, Korea
TEL : +82-62-220-6499 | FAX : +82-62-225-8578
E-mail : junhaegil@gmail.com | Web : http://eng.kidneykorea.com

Printed by Medical Publishing
#601, Jangyang Building, 15 Eulji-ro 14-gil, Jung-gu, Seoul 04550, Korea
TEL : +82-2-713-2446 | FAX : +82-2-2279-3960 | E-mail : med2002@nate.com

Printed on June 29, 2023 | Published on June 30, 2023

Electrolytes & Blood Pressure has been indexed/tracked/covered in the following:

- Korea Citation Index (KCI)
- KoMCI Web
- PubMed Central
- Google Scholar
- CrossRef
- KoreaMed
- KoreaMed Synapse
- Western Pacific Region Index Medicus (WPRIM)
- SCOPUS EMBASE
- Chemical Abstracts (CA Search)

The Journal was supported by the Korean Federation of Science and Technology Societies Grant funded by the Korean Government (MEST).

Electrolytes & Blood Pressure

Vol. 21, No. 1, June 2023

CONTENTS

Review Articles

Erratum

Review Article

ISSN 1738-5997 (Print) · ISSN 2092-9935 (Online)
Electrolyte Blood Press 2023;21:1-7
https://doi.org/10.5049/EBP.2023.21.1.1

Renal Replacement Therapy For Elderly Patients with ESKD Through Shared Decision-Making

Jin Eop Kim[1*], Woo Yeong Park[2*], Hyunsuk Kim[1]

[1]*Department of Internal Medicine, Chuncheon Sacred Heart Hospital, Chuncheon, Gangwond-do, Republic of Korea;*
[2]*Department of Internal Medicine, Keimyung University Dongsan Hospital, Keimyung University School of Medicine, Daegu, Republic of Korea*
**These two authors contributed to the manuscript equally*

Received: October 24, 2022
Revised: December 2, 2022
Accepted: April 2, 2023
Corresponding Author: Hyunsuk Kim, MD, PhD
Department of Internal Medicine, Hallym University Medical Center, Chuncheon Sacred Heart Hospital, Chuncheon-si, 24253 Gangwon-do, Korea
Tel: +82-33-240-5196; Fax: +82-33-240-5498
E-mail: nephrokim@hallym.ac.kr

The incidence and prevalence of end-stage kidney disease (ESKD) in Korea are increasing, and ESKD constitutes a very important medical and social issue. Elderly dialysis patients have the highest risk of early mortality within 3 months after initiating dialysis, and geriatric syndromes such as aging, frailty, functional impairment, and cognitive impairment are crucial for the prognosis of elderly patients. Shared decision-making (SDM) is an approach through which clinicians and patients can achieve informed preferences, thereby yielding better clinical outcomes and quality of life. Through SDM-based, close consultation among patients, families, and healthcare providers, an ESKD Life-Plan for elderly patients should be established. A multidisciplinary approach led by nephrologists can help them to provide proper vascular access for dialysis at the right time, with the right evidence, and to the right patient. Strategies that can improve peritoneal dialysis in elderly patients include assisted peritoneal dialysis, homecare support programs, and automated peritoneal dialysis. In order to enhance the role of kidney transplantation in elderly patients with ESKD, it is necessary to accurately identify patients' clinical conditions before transplantation and to perform active rehabilitation activities and postoperative management to promote recovery after transplantation. With the aging population and the increase in ESKD in the elderly, clinicians must identify factors affecting the mortality and quality of life of elderly dialysis patients.

Key Words: Elderly, Renal replacement therapy, Hemodialysis, Peritoneal dialysis, Kidney transplantation, End-Stage Kidney Disease Life-Plan, Shared decision making

1. Current status of elderly ESKD

The increasing prevalence of diabetes and hypertension, in combination with population aging, has led to a drastic increase in end-stage kidney disease (ESKD). The prevalence of chronic kidney disease is 8%-11% worldwide and 10.8% in South Korea[1]. According to the 2020 United States Renal Data System, during 2008-2018, the prevalence of ESKD steadily increased among people aged 65 years or older[2]. South Korea is the country with the fourth highest ESKD prevalence rate in Asia after Taiwan, Japan, and Singapore. In 2020, the Korean Society of Nephrology reported that the prevalence of ESKD continues to increase and that the elderly (aged 65 years or older) account for 54.6% of these patients (Fig. 1). 1 The mean age of dialysis patients is 65.9 years in 2019, and the mean age of hemodialysis patients (60.5±15.0 years old) is higher than that of peritoneal dialysis patients (56.0±14.8 years old)[1].

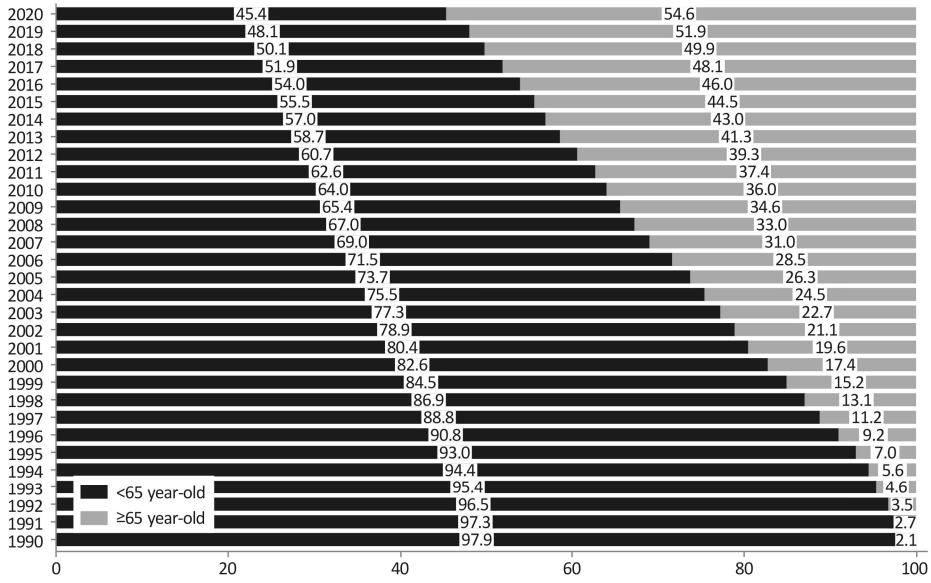


Fig. 1. The prevalence of ESKD among people aged 65 years or older in South Korea was 54.6% in 2020 and has steadily increased since the 1990s. X-axis, age; Y-axis, year (adopted from KORDS, 2020). Abbreviations: KORDS, Korean Renal Data System.

2. Considerations for dialysis in elderly patients with ESKD

All dialysis patients have the highest early mortality rate within 3 months of initiating dialysis, and elderly patients have a higher early mortality rate than others[3]. Geriatric syndromes such as aging, frailty, functional impairment, and cognitive impairment play a crucial role in the prognosis of elderly hemodialysis patients[4,5]. In addition, predicting the prognosis and likelihood of early death before and during dialysis is helpful for determining whether to perform dialysis in elderly patients. In 2018, the Act on Hospice and Palliative Care and Decisions on Life-Sustaining Treatment for Patients at the End of Life (hereinafter referred to as the Act on Decisions on Life-Sustaining Treatment) included hemodialysis as a life-sustaining treatment. Most nephrologists also have positive opinions about withholding or withdrawing dialysis of patients in end-of-life or dying process according to the Act on Decisions on Life-Sustaining Treatment and are trying to establish and apply appropriate guidelines[6].

3. Choice of renal replacement therapy for elderly patients with ESKD through shared decision-making

The first problem that elderly patients with ESKD encounter is deciding whether to undergo renal replacement therapy[7]. According to the End Stage Kidney Disease Life-Plan (ESKD Life-Plan) provision in the 2019 K/DOQI guidelines, it is necessary to establish an individualized plan considering patients' conditions, medical/living environment, and preferences (Fig. 2). Patients who choose conservative treatment require treatment of comorbidities, symptom control, and psychological support[8]. In addition, in 2020, the Korean Society of Nephrology reported that Since 2010, the mortality gap between peritoneal dialysis and hemodialysis has gradually narrowed (Fig. 3)[9] in patients aged 65 years or older[1]. Therefore, the choice of a dialysis method according to patients' characteristics and preferences became more important than the mortality rate[10]. Shared decision-making (SDM) has been defined as "an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences[11]". Increasingly many older patients face the need to decide between conservative care and dialysis as a treatment plan for advanced chronic kidney disease. SDM is recommended for preference-sensitive decisions of this type[12]. Although there is debate regarding the survival rate after dialysis, a study reported that the 1-year survival rate

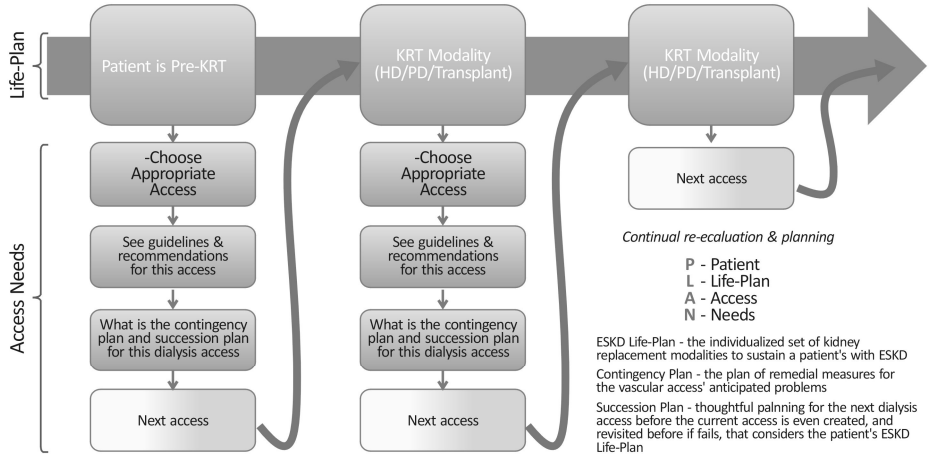


Fig. 2. ESKD Life-Plan and Associated Access Needs: What's the PLAN? (modified from the Figure 1.1 of 2019 K/DOQI guidelines Abbreviations: HD, hemodialysis: PD, peritoneal dialysis, KRT, kidney replacement therapy.

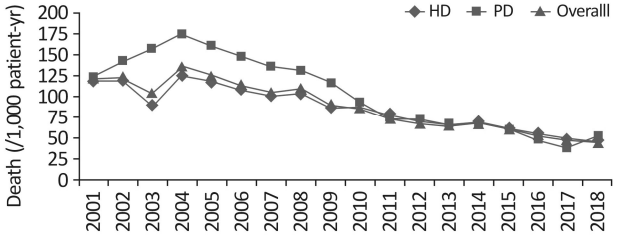


Fig. 3. Mortality rate for dialysis patients in Korea. In 2018, the unadjusted mortality rate for dialysis patients was 45.18 per 1,000 patient-years, and mortality rates by dialysis modality were 45.10 for HD patients and 51.33 for PD patients per 1,000 patient-years (adopted from KORDS, 2020). Abbreviations: HD, hemodialysis: PD, peritoneal dialysis, KORDS, Korean Renal Data System.

increased when dialysis was performed in patients aged 80 years or older[5]. Moreover, elderly patients aged 75 years or older were satisfied with life after dialysis and adapted better to dialysis than younger people[13]. Furthermore, a substantial majority of elderly patients aged 80 years or older who were undergoing dialysis recommended dialysis to others, with only 12.5% of them recommending against dialysis[14]. In order to apply the concept of the ESKD Life-Plan to elderly patients with ESKD, SDM with close consultation between patients, families, and healthcare providers is required.

1) Conservative treatment

Since the implementation of the Act on Decisions on Life-Sustaining Treatment, the number of registrants among people in their 70s has increased. Clinicians could consider conservative treatment for patients who are >75 years old, those with extensive comorbidities, or those who have poor functional status, because non-conservative treatment results in little survival benefit for these populations[15]. Although there is little consensus on conservative treatment for ESKD, this concept includes not performing renal replacement therapy in a clinical situation where renal replacement therapy would otherwise be initiated, as well as interventions to delay the progression of kidney disease, reduce complications to the extent possible, and facilitate in-depth communication. These interventions include medications to correct anemia and alleviate symptoms, consultations, blood tests, advance care planning, and psychological, environmental, and familial support[15,16]. Dialysis is a life-sustaining treatment[17] and can be withdrawn among patients in the end-of-life or dying process. However, dialysis for elderly patients is distinctive from other life-sustaining treatments due to a lack of consensus regarding whether dialysis itself is categorized as an end-of-life care, the meaning of maintenance dialysis, and whether dialysis is helpful for the survival rate or quality of life of elderly patients[8]. The consideration of symptoms, quality of life, hospital- free days, and cost-effectiveness is sometimes more important for patients and families than survival gain. Meanwhile, patient-centered and holistic care can be maximized by providing comprehensive conservative care and basing interventions on

existing evidence regarding survival, symptoms, quality of life, and experiences[15]. Before starting renal replacement therapy, careful consideration should be given to ensuring that patients understand the prognosis and the potential benefits and harms of therapy, as well as patients' values, goals, and preferences[18]. Since patients and their family members decide whether to undergo dialysis without previously experiencing it, careful SDM with healthcare providers is needed[5,10]. Moreover, using a standard definition of conservative care will help clinicians to understand conservative care and select it when appropriate for their elderly patients[18].

2) Hemodialysis

Most elderly patients with ESKD choose hemodialysis [3,19-22]. The formation, maturation, and maintenance of well-functioning vascular access, such as an arteriovenous fistula or arteriovenous graft, are very important in hemodialysis for elderly patients. Since, in particular, dialysis with a catheter can cause higher cardiovascular, infectious, or all-cause mortality in elderly patients, planned surgery for vascular access is essential as the best method that can optimize the success rate and maintain stable survival[8]. Several clinical practice guidelines recommend an arteriovenous fistula over an arteriovenous graft. However, it is unclear whether this recommendation must be applied to elderly patients because of the need to consider urgent hemodialysis, the life expectancy, and the maturation time of arteriovenous fistula in elderly patients[23]. Therefore, elderly patients with ESKD who should receive renal replacement therapy according to the new K/DOQI guidelines should also make short- and long-term life-plans and prepare vascular access accordingly[8]. A carefully prepared vascular access for dialysis should undergo minimal intervention for its maturation and maintenance. If dialysis is performed with a central venous catheter, the infection risk must be minimized. Considerations for vascular access include life expectancy and prognosis, patients' health conditions, patients' preferences, vascular condition, possibility of maturation of arteriovenous fistula, the possibility of continuing interventions, and quality of life of patients and families. Ultimately, in an ESKD Life-Plan, individualized vascular access should be planned according to the individual patient's needs[24,25]. Furthermore, it is important for healthcare providers to prepare vascular access at the right time and initiate and perform stable dialysis that can improve the survival rate and quality of life of elderly patients. This choice should be made through SDM, with appropriate consideration of the characteristics of the elderly, the speed of progression to ESKD, surgical problems, the policies of dialysis institutions, and the type of dialysis that family members want[4,8,23,26]. Moreover, The 2019 KDOQI guidelines recommend that nephrologists have extensive experience and insight in coordinating and integrating multidisciplinary vascular access teams based on the patient's ESKD Life-Plan[17].

3) Peritoneal dialysis

According to the Korean Society of Nephrology report in 2020, the number of peritoneal dialysis patients, unlike that of hemodialysis patients, continues to decrease (prevalence of peritoneal dialysis, 2015, 6%; 2016, 5%; 2017 onwards, 4%)[1]. This trend is thought to be affected by autonomy, comorbidities, and the performance status of elderly patients with ESKD, as well as economic issues, the level of resource utilization, cultural issues, patients' preferences, late referrals to nephrology, educational level, sex, living alone, and age[27,28]. The peritoneum does not significantly change due to aging, but in elderly individuals, changes in peritoneal mesothelial cells may occur and they may be vulnerable to inflammation. Diverticulosis, intestinal obstruction, and constipation are common in the elderly, and these conditions can affect the physiology of the peritoneum and worsen the function of a peritoneal catheter. In addition, patients with a history of abdominal surgery are at an elevated risk of adhesions and abdominal wall leaks[27]. Because most elderly patients with ESKD are immobile due to malnutrition or frailty and have a high risk of cardiovascular disease due to underlying diseases such as hypertension and diabetes, peritoneal dialysis as a maintenance dialysis method for elderly patients with ESKD can be used appropriately.

Therefore, peritoneal dialysis should not be determined according to the physician's preference, and healthcare providers should provide proper and individualized information

so that patients make an unbiased decision[28]. In addition, when chronic kidney disease has progressed to a severe degree, timely dialysis education is also important because cognitive impairment or uremia can prevent patients from being able to make an appropriate choice. Although the prevalence of peritoneal dialysis is decreasing and its survival rate is slightly less favorable than that of hemodialysis, peritoneal dialysis nevertheless has advantages that distinguish it from hemodialysis. The following considerations shed light on cases where it may be preferable to perform peritoneal dialysis in elderly patients. First, if peritoneal dialysis is used as emergency dialysis[29], maintenance peritoneal dialysis becomes more likely. Second, assisted peritoneal dialysis, homecare support programs, and automated peritoneal dialysis can be used[30]. Third, in the US and Europe, insurance fees for peritoneal dialysis are cheaper than those for hemodialysis. If a separate healthcare delivery system and fee system are applied to peritoneal dialysis, the frequency of peritoneal dialysis may increase. Finally, it is important to decide whether to perform peritoneal dialysis on an individualized basis, considering elderly patients' conditions[31].

4) Kidney transplantation

Kidney transplantation is known as the best treatment for ESKD, with advantages including a prolonged life expectancy, improved quality of life, and reduced opportunity cost compared to dialysis treatment[32]. According to the Korean Society of Nephrology report in 2020, the number of patients undergoing transplantation due to ESKD reached 21,153 in South Korea. In particular, the proportion of elderly kidney transplant recipients (aged 60 years or older) increased from 7.4% in 2008 to 18.4% in 2016. According to the Korea Organ Transplantation Registry data from the Korean Society for Transplantation, the 1-year and 5-year patient and allograft survival rates in kidney transplant recipients over the age of 60 were 96.5% 90.4%, 94.8%, and 85.5%, respectively. Due to population aging, the donors and recipients of living donor kidney transplantation are also gradually becoming older. Due to the lack of donor kidneys in deceased donors, the number of patients on the waiting list for brain death donors is rapidly increasing and the waiting period is becoming longer, resulting in an increase in the recipients' ages[1].

Since elderly patients with ESKD have several conditions, such as malnutrition, chronic inflammation, chronic kidney disease - mineral bone disease, and vascular calcification, before transplantation, their circumstances should be considered when determining kidney transplantation. After transplantation, precautions are necessary to minimize the following problems: decreased muscle mass, bone density, and muscle strength in the upper and lower limbs; increased fatigue; a reduced ability to engage in aerobic activities; malnutrition; sarcopenia; cardiopulmonary dysfunction; and frailty[33,34]. Both dialysis recipients themselves and healthcare providers should solve social adaptation issues after transplantation through active rehabilitation activities for symptoms occurring post-transplantation[32,35-37]. For this, it is necessary for healthcare providers to accurately identify the clinical conditions of elderly patients before transplantation, continue active rehabilitation activities and postoperative management to promote the patients' recovery, and control medications and monitor clinical conditions after discharge[34-38].

Conclusion

With the aging population and the increase in ESKD in the elderly, clinicians must identify factors affecting the mortality and quality of life of elderly dialysis patients, and through SDM based on close consultation between patients, families, and medical staff, an ESKD Life-Plan should be established.

Acknowledgement

This research was supported by a grant from the National Research Foundation of Korea (grant number: NRF-2021R1I 1A3057140).

REFERENCES

1. Trends in epidemiologic characteristics of end-stage renal disease from 2020 KORDS (Korean Renal Data System). 2020.
2. 2020 Annual Data Report, USRDS.
3. Zhao X, Wang M, Zuo L: Early mortality risk in incident Chinese hemodialysis patients: a retrospective cohort study.

Ren Fail 2017;39(1):526-532.
4. Canaud B, Tong L, Tentori F, et al.: Clinical practices and outcomes in elderly hemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Clin J Am Soc Nephrol 2011;6(7):1651-1662.
5. Jassal SV, Watson D: Dialysis in late life: benefit or burden. Clin J Am Soc Nephrol 2009;4(12):2008-2012.
6. Hong YA, Chung S, Park WY, et al.: Nephrologists' Perspectives on Decision Making About Life-Sustaining Treatment and Palliative Care at End of Life: A Questionnaire Survey in Korea. J Palliat Med 2021;24(4):527-535.
7. Berger JR, Hedayati SS: Renal replacement therapy in the elderly population. Clin J Am Soc Nephrol 2012;7(6):1039-1046.
8. Lok CE, Huber TS, Lee T, et al.: KDOQI clinical practice guideline for vascular access: 2019 update. Am J Kidney Dis 2020;75(4):S1-S164.
9. Hong YA, Ban TH, Kang C-Y, et al.: Trends in epidemiologic characteristics of end-stage renal disease from 2019 Korean Renal Data System (KORDS). Kidney Res Clin Pract 2021;40(1):52.
10. Song Y-H, Cai G-Y, Xiao Y-F, Chen X-M: Risk factors for mortality in elderly haemodialysis patients: a systematic review and meta-analysis. BMC Nephrol 2020;21(1):1-10.
11. Elwyn G, Frosch D, Thomson R, et al.: Shared decision making: a model for clinical practice. J Gen Intern Med 2012;27(10):1361-1367.
12. Verberne WR, Stiggelbout AM, Bos WJW, van Delden JJ: Asking the right questions: towards a person-centered conception of shared decision-making regarding treatment of advanced chronic kidney disease in older patients. BMC Med Ethics 2022;23(1):1-8.
13. Lamping DL, Constantinovici N, Roderick P, et al.: Clinical outcomes, quality of life, and costs in the North Thames Dialysis Study of elderly people on dialysis: a prospective cohort study. The Lancet 2000;356(9241):1543-1550.
14. Buemi M, Lacquaniti A, Bolignano D, et al.: Dialysis and the elderly: an underestimated problem. Kidney Blood Press Res 2008;31(5):330-336.
15. Murtagh FE, Burns A, Moranne O, Morton RL, Naicker S: Supportive care: comprehensive conservative care in end-stage kidney disease. Clin J Am Soc Nephrol 2016;11(10):1909-1914.
16. Okamoto I, Tonkin-Crine S, Rayner H, et al.: Conservative care for ESRD in the United Kingdom: a national survey. Clin J Am Soc Nephrol 2015;10(1):120-126.
17. Lee HS, Kim SG: A Korean perspective on the 2019 Kidney Disease Outcomes Quality Initiative guidelines for vascular access: what has changed and what should be changed in practice? Kidney Res Clin Pract 2021;40(1):29.
18. Williams AW, Dwyer AC, Eddy AA, et al.: Critical and honest conversations: the evidence behind the "Choosing Wisely" campaign recommendations by the American Society of Nephrology. Clin J Am Soc Nephrol 2012;7(10):1664-1672.
19. Han SS, Park JY, Kang S, et al.: Dialysis modality and mortality in the elderly: a meta-analysis. Clin J Am Soc Nephrol 2015;10(6):983-993.
20. Park JY, Yoo KD, Kim YC, et al.: Early dialysis initiation does not improve clinical outcomes in elderly end-stage renal disease patients: a multicenter prospective cohort study. PloS One 2017;12(4):e0175830.
21. Kim H, An JN, Kim DK, et al.: Elderly peritoneal dialysis compared with elderly hemodialysis patients and younger peritoneal dialysis patients: Competing risk analysis of a Korean prospective cohort study. PLoS One 2015;10(6):e0131393.
22. Brown EA, Finkelstein FO, Iyasere OU, Kliger AS: Peritoneal or hemodialysis for the frail elderly patient, the choice of 2 evils? Kidney Int 2017;91(2):294-303.
23. Liu P, Pang SC, Li H, et al.: Outcomes of arteriovenous fistula in elderly patients on maintenance haemodialysis. Int Urol Nephrol 2021;53(9):1923-1931.
24. Shah S, Chan MR, Lee T: Perspectives in Individualizing Solutions for Dialysis Access. Adv Chronic Kidney Dis 2020;27(3):183-190.
25. Vachharajani TJ, Moist LM, Glickman MH, et al.: Elderly patients with CKD-dilemmas in dialysis therapy and vascular access. Nat Rev Nephrol 2014;10(2):116-122.
26. Qian JZ, McAdams-DeMarco M, Ng DK, Lau B: Arteriovenous fistula placement, maturation, and patency loss in older patients initiating hemodialysis. Am J Kidney Dis 2020;76(4):480-489. e481.
27. Brown E: Peritoneal dialysis for older people: overcoming the barriers. Kidney Int 2008;73:S68-S71.
28. Wright S, Danziger J: Peritoneal Dialysis in Elderly Patients. Am Soc Nephrol 2009.
29. Arramreddy R, Zheng S, Saxena AB, Liebman SE, Wong L: Urgent-start peritoneal dialysis: a chance for a new beginning. Am J Kidney Dis 2014;63(3):390-395.
30. Oliver M-J, Quinn R, Richardson E-P, Kiss A-J, Lamping D-L, Manns B-J: Home care assistance and the utilization of peritoneal dialysis. Kidney Int 2007;71(7):673-678.
31. Figueiredo AE, Bernardini J, Bowes E, et al.: A syllabus for teaching peritoneal dialysis to patients and caregivers. Perit Dial Int 2016;36(6):592-605.
32. Dreyer GJ, De Fijter JW: Transplanting the elderly: man-

datory age-and minimal histocompatibility matching. Front Immunol 2020;11:359.
33. Ozkayar N, Altun B, Halil M, et al.: Evaluation of sarcopenia in renal transplant recipients. Nephrourol Mon 2014;6(4).
34. So S, Au EH, Lim WH, Lee VW, Wong G: Factors Influencing Long-Term Patient and Allograft Outcomes in Elderly Kidney Transplant Recipients. Kidney Int Rep 2021;6(3):727-736.
35. Lehner L, Staeck O, Halleck F, Liefeldt L, Bamoulid J, Budde K: Need for optimized immunosuppression in elderly kidney transplant recipients. Transplant Rev 2015;29(4):237-239.
36. Korabiewska L, Lewandowska M, Juskowa J, Białoszewski D: Need for rehabilitation in renal replacement therapy involving allogeneic kidney transplantation. In: Transplant Proc: 2007: Elsevier; 2007:2776-2777.
37. Cho W, Kim H, Park U, et al.: Rehabilitation of transplantee and Transplant Games. J Korean S Transplant 2017;31(1):6-15.
38. Messias AA, Reichelt AJ, Dos Santos EF, et al.: Return to work after renal transplantation: a study of the Brazilian Public Social Security System. Transplantation 2014;98(11): 1199-1204.

Review Article

ISSN 1738-5997 (Print) · ISSN 2092-9935 (Online)
Electrolyte Blood Press 2023;21:8-17
https://doi.org/10.5049/EBP.2023.21.1.8

Management of Hypertension in Fabry Disease

Su Hyun Kim[1], Soo Jeong Choi[2]

[1]*Department of Internal Medicine, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, Republic of Korea;*
[2]*Department of Internal Medicine, Soonchunhyang University College of Medicine, Bucheon, Republic of Korea*

Received: March 31, 2023
Revised: May 5, 2023
Accepted: May 11, 2023
Corresponding Author: Soo Jeong Choi, MD, PhD
Division of Nephrology, Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, 170 Jomaru-ro, Bucheon 14584, Korea
Tel: +82-32-621-5169; Fax: +82-32-621-5016
E-mail: crystal@schmc.ac.kr

Fabry disease (FD), a rare X-linked lysosomal storage disorder that depletes alpha-galactosidase A (α-GalA), is caused by mutations in the GLA gene. Diminished α-GalA enzyme activity results in the accumulation of Gb3 and lyso-Gb3. The pathophysiology of hypertension in FD is complex and unclear. The storage of Gb3 in arterial endothelial cells and smooth muscle cells is known to produce vascular injury by increasing oxidative stress and inflammatory cytokines as a primary pathophysiological mechanism. In addition, Fabry nephropathy developed, resulting in a decrease in kidney function and contributing to hypertension.

The prevalence of hypertension in patients with FD was between 28.4% and 56%, whereas hypertension in patients with chronic kidney disease ranged between 33% and 79%. A study using 24-hour ambulatory blood pressure monitoring (ABPM) to measure blood pressure (BP) indicated a high prevalence of uncontrolled hypertension in FD. Thus, 24-hour ABPM ought to be considered for FD hypertension assessments.

Appropriate treatment of hypertension is believed to reduce mortality in patients with FD caused by kidney disease, cardiovascular disease, and cerebrovascular disease because hypertension significantly impacts organ damage. Up to 70% of FD patients have been reported to have kidney involvement, and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers prescribed for proteinuria are recommended as first-line therapy with antihypertensive drugs. In conclusion, hypertension should be controlled appropriately, given the different morbidity and mortality caused by significant organ involvement in FD patients.

Key Words: Fabry disease, Hypertension, Enzyme replacement therapy, Angiotensin-converting enzyme inhibitors, Angiotensin receptor blockers

INTRODUCTION

Fabry disease (FD) is a rare multisystemic and X-linked lysosomal storage disease. It is caused by mutations in the galactosidase alpha (GLA) gene, resulting in a deficiency of alpha-galactosidase A (α-GalA) enzyme function[1]. The reduced or absent α-GalA activity causes the progressive accumulation of glycosphingolipids, especially globotriaosylceramide (Gb3; also abbreviated as GL3) and the deacylated Gb3 (globotriaosylsphingosine [lyso-Gb3, also lyso-GL3]) in various cell types and organs, including the kidney, heart, skin, blood vessels, peripheral nerves, and central nervous system. The prevalence of FD ranges between 1:40,000 and 1:117,000[2-4], and the clinical symptoms are nonspecific and highly variable.

FD can be classified into two phenotypes: "classic" and "later-onset, also called non-classic." In the classic phenotype, affected males have a total, or almost total, absence of α-GalA activity, and the symptoms typically appear in childhood or adolescence[1]. These symptoms include peripheral neuropathic pain, hypohidrosis, cutaneous angiokeratomas, lenticular and corneal verticillata, gastrointestinal symptoms including abdominal pain and diarrhea, micro-

albuminuria, and proteinuria. As patients age, they may develop serious complications, such as chronic kidney disease, cardiomyopathy, arrhythmias, and cerebrovascular diseases, which can lead to severe morbidity and higher mortality[5-7].

Later-onset or non-classic phenotypes of Fabry patients have variable levels of residual α-GalA activity and heterogeneity in clinical presentations. Therefore, the onset of clinical symptoms is typically between the fourth and sixth decades of life; however, they may manifest in childhood with very different symptoms than the classic phenotype. They are also milder than in the case of the classic phenotype. They are frequently limited to a single organ (usually the heart or kidney)[8,9]. Adult-onset cardiac (cardiomegaly, left ventricular hypertrophy, cardiomyopathy, hypertrophic cardiomyopathy, and myocardial infarction) and renal (end-stage kidney disease) variants are more prevalent[10-12].

Similarly to other X-linked genetic disorders, hemizygous males display more severe clinical symptoms than females. In females, X-linked gene expression is mosaic due to X-chromosome inactivation, which involves the random transcriptional silencing of one X-chromosome in each cell[1]. Consequently, based on penetrance and expression, females can exhibit various symptoms ranging from mild to severe.

The primary pathophysiological mechanism of FD is the storage of Gb3 in lysosomes, which causes cellular dysfunction by inhibiting autophagy and initiating apoptosis[13]. Eliminating accumulated Gb3 using enzyme replacement therapy (ERT) was anticipated to prevent disease progression and alleviate organ damage. Despite ERT treatment, advanced FD showed progressive major organ damage. It may be related to a secondary pathway via increased oxidative stress and induce an immunological response by activating the renin-angiotensin system (RAS) through the storage of lyso-Gb3.

Since it is generally accepted that FD is associated with a low prevalence of hypertension, very few studies have been conducted on it. On the other hand, due to the recent publication of studies on hypertension, there is a growing awareness of the significance of treating hypertension. Thus, we will review the prevalence of hypertension in FD patients, its pathophysiological mechanism, the impact of hypertension on organ damage, and therapies through a review of the literature.

Blood Pressure in Fabry Disease

Patients with FD are known to have significantly lower blood pressure (BP) than the general population[14], despite the high prevalence of heart, kidney, and nervous system diseases associated with high BP. The most plausible explanation is autonomic dysfunction, which includes impaired sweating, reduced saliva and tear production, altered gastrointestinal motility, arrhythmia, and orthostatic hypotension[15,16].

Several factors have been proposed as mechanisms of autonomic dysfunction. First, there is evidence of accumulation of glycosphingolipids and lipid-stained inclusions in central autonomic nuclei and peripheral nerves[17]. And somatic epidermal and dermal autonomic nerve fiber reductions were observed in skin biopsy[18]. FD vasculopathy, including smooth muscle cell hypertrophy with stored glycolipid, also affects autonomic dysfunction by constricting small neural blood vessels[19]. Baroreflex-mediated vasoconstriction due to the dysfunction of sympathetic vasomotor fibers in patients with FD is another known mechanism, as reported by Hilz et al.[20]. In addition, an insufficient increase in heart rate despite physical activity causes exercise intolerance and orthostatic hypotension in advanced stages[21].

Considering these autonomic dysfunctions, it is controversial whether the definition of hypertension in patients with FD can be used for the general population. The autonomic nervous system primarily regulates BP variability[14]. The classification of BP and the definition of hypertension is unchanged from previous European guidelines and is defined as an office systolic BP (SBP) ≥140 mmHg and/or diastolic BP (DBP) ≥90 mmHg, which is equivalent to a 24-h ambulatory BP monitoring (ABPM) average of ≥130/80 mmHg, or a home BP monitoring average ≥135/85 mmHg[22]. Considering the characteristics of low BP in patients with FD, it has been reported that even slightly elevated SBP can be associated with organ damage even if BP does not meet the criteria for hypertension[23]. BP variability was higher in FD patients compared with controls, while there was a decrease in heart rate variability and more non-dipper in FD[14].

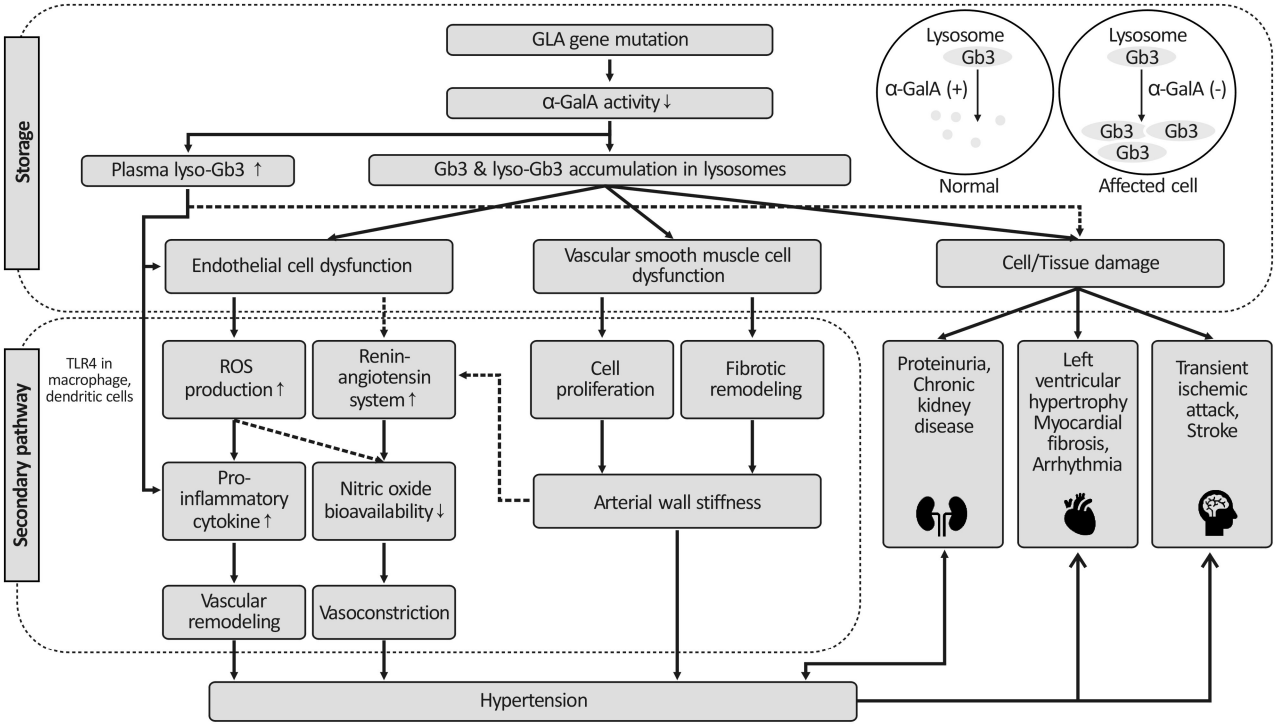


Fig. 1. The proposed pathophysiology of hypertension in Fabry disease. Mutations in the GLA gene reduced alpha-galactosidase A (α-GalA) activity, resulting in the progressive accumulation of Gb3 and lyso-Gb3 in plasma, endothelial cells, and vascular smooth muscle cells, which damages major organ damage. The cellular dysfunction produced by the storage of Gb3 in the lysosome leads to secondary injury, including immunological response through increased reactive oxygen species (ROS) and renin-angiotensin system activation. Chronic kidney disease resulting from FD nephropathy contributes to the development of hypertension. The solid line is a hypothesis based on clinical trials or basic research on Fabry disease. In contrast, the dotted lines reflect an assumed theory based on the mechanism of essential hypertension.

In a recent study by Rossi et al. on outpatient monitoring, 18.8% of 31 patients with FD had increased BP, and three had masked hypertension[24].

Pathophysiology of Hypertension

The pathophysiological mechanisms underlying hypertension in FD are poorly understood due to the limited number of clinical and basic investigations on the mechanism of hypertension in FD. The accumulation of Gb3 in arterial endothelial cells and smooth muscle cells is considered the key pathophysiologic mechanism for inducing hypertension-related vascular injury (Fig. 1)[19,25].

Essential hypertension is associated with an elevation of reactive oxygen species (ROS), which induce pro-inflammatory cytokines and vascular remodeling[26]. Gb3 loading into endothelial cells causes intracellular ROS and increases the expression of cell adhesion molecules[27]. Increased ROS production eventually triggers an increase in pro-inflammatory cytokines, resulting in vascular remodeling. In a study targeting FD cardiomyopathy, interleukin-6 (IL-6), interleukin-1 β (IL-1β), tumor necrosis factor-α (TNF-α), and monocyte chemoattractant protein-1 (MCP-1), which is the pro-inflammatory cytokine, were significantly higher than those of the control group, suggesting that pro-inflammatory cytokines affect hypertension in FD[28].

FD patients may have a potential relationship between the RAS system and hypertension, as the activation of angiotensin II can reduce the activity of endothelial nitric oxide synthase (eNOS) activity, leading to vasoconstriction and elevated BP, a mechanism also observed in the general population[29]. Additionally, research by Fujii et al. indicates that Gb3 and angiotensin-converting enzyme (ACE) are expressed in the same location in the proximal tubules, while Batista

et al. found that α-GalA infusion inhibits ACE activity, leading to a temporary reduction in BP in Fabry patients after ERT[30,31]. However, the effects were compensated with upregulated ACE activity and increased plasma angiotensin II two weeks later. Bothou et al. also found a positive correlation between elevated renin and lyso-Gb3 levels in men with FD, while Shu et al. demonstrated that aortic endothelial cells lacking α-GalA had decreased eNOS activity and nitric oxide availability[32,33]. While these findings suggest a potential role of the RAS system in hypertension development in FD patients, further research is needed to confirm this relationship.

In addition, Gb3 is known to stimulate cell proliferation and fibrosis in smooth muscle cells, leading to inflammation and elevated BP. Storage of lyso-Gb3 within the medial layer of the arteries may also promote smooth muscle cell proliferation, with the fibrotic remodeling of the arterial wall leading to arterial wall stiffness[34]. Aerts et al. report that lyso-Gb3 dramatically increased the plasma of affected FD patients and tissues of FD mice and induced smooth muscle cell proliferation in vitro[34]. Barbey et al. showed that plasma from FD could stimulate the proliferation of vascular smooth muscle cells and cardiomyocytes[35]. The resulting shear stress may increase the expression of angiotensin I and II receptors in endothelial cells, increasing ROS, and decreasing NO synthesis[19]. These factors may initiate an inflammatory cascade with pro-thrombotic and pro-inflammatory effects on endothelial cells and vascular smooth muscle cells[19,36].

Pinto et al. reported that an immune response causes hypertension in patients with FD, and innate immunity also plays a major role[37]. The innate immune system recognizes danger signals through pattern recognition receptors, such as toll-like receptor 4 (TLR4), expressed primarily on the surface of macrophages and dendritic cells. Glycolipids such as lyso-Gb3 can bind to TLR4 in FD, which in turn activates the NF-κB pathway to release pro-inflammatory cytokines and trigger systemic and local inflammatory responses[38,39].

As FD nephropathy advances, CKD occurs, contributing to hypertension development. Kidney involvement is already known to be extremely prevalent in FD, and Gb3 deposition in the kidney is a primary cause[40]. In addition, high BP itself contributes to kidney damage; hence, high BP and kidney damage are tightly linked. In general, untreated patients present three clinical stages of FD nephropathy, depending on their age. In the first stage (infancy and adolescence), there is glomerular hyperfiltration. In the second (adult) stage, it is kidney-related with proteinuria and lipiduria, and in the third stage, severe kidney and cardiovascular complications develop, resulting in hypertension[41].

Hypertension is a progressive disease whose prevalence increases with advancing age. It is also known that the prevalence of hypertension increases with age in FD. In particular, the prevalence of kidney and cardiovascular diseases, which are highly related to hypertension, increases with age, so this effect is thought to have an impact[42,43].

Prevalence of Hypertension in Fabry Disease

According to a meta-analysis of the general European population, the prevalence of hypertension was 44.2%[44]. In a study of patients in the United States, the prevalence of hypertension in patients with chronic kidney disease was between 80 and 85 percent[45]. The prevalence of hypertension in patients with FD has been observed to range between 28% and 63.5% (Table 1)[14,24,40,41,46-51]. In the study by Lenders, hypertension was as high as 63.5%, which is attributed to the fact that the average age was older than in earlier studies, and the group with albuminuria reached 75.0%[50].

The majority of the research that reported the prevalence of hypertension was based on cross-sectional studies, and because of this, it was not able to adequately estimate the prevalence of hypertension using information such as medical history and the use of antihypertensive medicines. Two studies found that when the BP of FD patients was measured using ABPM, the prevalence of hypertension was 31-40%[14,24]. Considering that 5% to 41% of the patients had a glomerular filtration rate of less than 60, including other cross-sectional studies, hypertension in patients with FD was lower than in the general population.

Conversely, there is evidence that patients with FD have a high prevalence of uncontrolled hypertension. Kleinert et al. reported that among 391 patients with FD, 57% of males and 47% of females had uncontrolled hypertension when hypertension was defined as SBP ≥130 mmHg and

Table 1. Prevalence of hypertension in Fabry patients

Author, year	Region	N	Male (%)	Age (year)	Diagnosis of HTN	eGFR	eGFR<60, n (%)	HTN, n (%)	HTN in CKD, n (%)	Kidney involvement, %	CNS involvement, %	Cardiac involvement, %	ERT/Chaperon therapy, %	ACEi/ARBs, %
Dincer, 2022	Turkey	30	53.3	38.1±13.4		91.7±40.8	9 (30%)	12 (40%)	5 (55.6%)	71	35.4	32.3	96.8	35.5
Ferrari, 2021	Argentina	93	44.0	32±16.6	History of HTN	-	38 (41%)	26 (28%)	-	41	-	47	100	-
Rossi, 2021	Europe	32	25.0	50.3±12.4	SBP ≥130 or DBP≥80 mmHg vis ABPM	-	6 (19%)	10 (31%)	2 (33%)	32.3	65.6	90.6	59.4	21.9
Lenders, 2020	Germany	59	53.0	49±13	History of HTN	-	1 (5%)	33 (63.5%)	-	70.8	-	68	57.6	72.1
Wang, 2020	Taiwan	22	72.7	47 (32.8–56.3]	History of HTN	83.6 (59.8–112.2)	2 (9.1%)	9 (40.9%)	-	-	-	24.7	-	-
Lidove, 2016 (FOS)	Global	2,044	56.0	≥18	History of HTN	-	-	599 (29%)	-	48.9	19.7	66.3	67.2	35.6
Schiffmann, 2009	Global	395	61.0	41.0 (5.0–77.1)	History of HTN	-	77 (19%)	221 (56%)	61 (79%)	26.3	17	58.7	100	16.7
Ortiz, 2008	Global	1,262	46.0	-	SBP ≥130 or DBP≥80 mmHg vis office BP	81/82 for male and female	255 (20%)	554 (44%)	-	-	-	-	-	-
Kleinert, 2006 (FOS)	Global	391	54.0	40 (24, 58)	SBP ≥130 or DBP≥80 mmHg vis office BP	79 (53, 109)	104 (27%)	205 (52.4%)	70 (67%)	-	-	-	-	24.9
Branton, 2002	USA	105	100.0	38±11	History of HTN	-	-	31 (30%)	-	74.3	-	-	-	19

ABPM, Ambulatory blood pressure monitoring; ACEi, Angiotensin-Converting Enzyme Inhibitors; ARBs, Angiotensin II receptor blockers; FOS, Fabry Outcome Survey registry; HTN, hypertension; CKD, chronic kidney disease

DBP ≥90 mmHg[51]. Rossi et al. demonstrated the importance of ABPM by reporting that hypertension was detected in three (9.4%) patients by normal clinic measurements, while increased BP was found in six (18.8%) patients by ambulatory monitoring, which revealed three cases of masked hypertension[24].

There may be heterogeneity in the reported data due to differences in study group age and kidney function at baseline. Hypertension prevalence increases with age in Fabry Outcome Survey (57.7% aged ≥75 years; 48.2% aged 65-74; 41.9% aged 50-64; 21.8% aged 18-49)[47]. According to Branton and colleagues, hypertension was not a prominent feature in this population, often not manifesting until patients experienced a decline in kidney function, and they proposed that hypertension is more likely to be essential or secondary to pre-existing kidney disease[46].

The incidence of hypertension in patients with FD often increases with decreased kidney function. Patients with a glomerular filtration rate of less than 60 mL/min/1.73 m^2 had higher BP, according to a study by Ortiz et al.[40]. Schiffman et al. also reported that approximately 80% of patients with CKD had hypertension, whereas about 50% had a glomerular filtration rate of ≥60 mL/min/1.73 m^2 [41]. Dincer et al. reported the 24-hour BP determined by ABPM was significantly different between GFR <60 ml/min and greater than 60, while the proportions of patients taking antihypertensive drugs were similar[14].

Many studies show gender does affect hypertension. Ortiz et al. reported no difference between genders in the eGFR <60 and ≥60 groups[40]. In the group under 40 years old, however, there was a substantially higher frequency of hypertension among males (51%) than females (35%; p= 0.0003) with CKD stages 1 or 2[40]. These results might suggest organ involvement is associated with hypertension rather than gender.

Considering that the BP of FD patients is lower than that of the general population, the prevalence of hypertension is likely to be higher than estimated; therefore, additional research is necessary. In addition, since most studies have diagnosed hypertension by taking a patient's medical history and prescribing medication, tests such as ABPM should be considered to prevent major organ damage and active treatment of hypertension in patients with FD.

Hypertension and Major Organ Damage

The major consequences of hypertension are myocardial infarction, heart failure, stroke, and kidney failure. In the general population, for every 20 mmHg increase in SBP or 10 mmHg increase in DBP, the risk of cardiovascular disease doubles[52].

Hypertension contributes to the disease burden of FD,

just as it contributes to the disease burden of many other conditions in the general population. Due to the high prevalence of kidney, cardiac, and neurological diseases in FD, hypertension has detrimental effects on disease progression and prognosis despite the low prevalence of hypertension in patients with FD compared to the general population[53].

Fabry nephropathy presents with a wide range of disease severity in males and females, proteinuria is typically a manifestation of podocyte injury, and urinary protein excretion is strongly associated with Fabry nephropathy progression[40,54]. A high prevalence of uncontrolled BP was reported in patients with FD and deteriorating CKD in the Fabry Outcome Survey Registry and the Fabry Registry[40,51]. Otiz et al. found SBP was higher with lower eGFR in Fabry patients[40]. Proteinuria in kidney disease is generally recognized as a risk factor for disease progression[40,55]. These findings suggest that hypertension may contribute to the decline of kidney function.

There is also evidence of an association between hypertension and cardiovascular disease in FD. Cardiovascular disease was the most common cause of death in both genders, accounting for 40% of men and 41.7% of women[5]. Linhart et al. evaluated the cause of death on 113 affected relatives of 714 patients with FD[56]. Cardiovascular mortality rate was most frequent in 41 female, while that was the second cause in 72 men. In a study by Patel et al., hypertension increased the odds of a cardiovascular event (myocardial infarction, heart failure, or heart-related death) by 7.8 in men and 4.5 in women[57].

Hypertension has been considered the most crucial risk factor for cerebrovascular disease (CVD) in FD[58]. At the Fabry Registry, patients with CVD were more likely than FD patients without CVD to report a history of hypertension, 52.9% versus 20.5%, respectively[59]. A greater proportion of female stroke patients reported a history of hypertension than male stroke patients (32 of 52, 61.5%).

Management of Hypertension

As described above, as few as 30% to as many as 50% or more of FD patients are accompanied by hypertension [14,24,46-49]. Appropriate treatment of such hypertension contributes to the reduction of mortality due to kidney, cardiovascular, and cerebrovascular diseases in FD patients and, consequently, may positively affect the disease progression and prognosis of FD, so active hypertension treatment is recommended[40,51].

The European Society of Hypertension-European Society of Cardiology guidelines suggest that a target BP in patients with FD with proteinuria >1 g/day should be less than 125/75 mmHg, whereas a target BP in patients with FD with proteinuria of 0.25-1 g/day should be 130/80 mmHg[60,61]. In addition to ERT, the current treatment guidelines published by Eng et al. emphasize the importance of managing hypertension in patients with kidney disease[62].

When treating hypertension in patients with FD, it may be beneficial to consider medications that offer organ-protective effects, such as for the kidney, heart, and brain. Medications for hypertension in Fabry patients may include angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), calcium channel blockers (CCBs), or beta-blockers. Additionally, sodium-glucose cotransporter 2 (SGLT2) inhibitors, which have recently emerged as a potential new antihypertensive drug, can also be considered.

ACEi/ARBs are the primary medications prescribed for hypertensive patients with FD. This is because proteinuria is very common in patients with FD, and it is the first-line treatment for proteinuria. Management of proteinuria is a critical feature in preserving kidney function in patients with FD. A consistent antiproteinuric therapy with ACEi or ARBs was shown to decrease the progression of kidney disease in FD[63,64]. Table 1 shows that ACEi/ARBs were used (16.7-71%) for organ damage in patients with FD.

Monitoring BP while using ACEi/ARBs is essential because sudden hypotension can impair kidney function. Although patients with hypertension were not targeted, Muntze's study reported that kidney function deteriorated after using ACEi/ARBs[65]. They said that migalastat was used as a treatment drug, and the left ventricular mass index significantly decreased in 14 patients while eGFR significantly deteriorated. The authors observed a significant correlation between the initiation of ACEi and SBP drop below 120, leading to a higher risk of kidney function deterioration. Hence, when BP falls below SBP 120 during the initiation of antihypertensive medications like ACEi, it is crucial to closely monitor BP to prevent any potential kidney function decline.

CCBs may be considered as a potential treatment option for hypertension in FD, but evidence for their use is lacking[66]. However, chest pain is a common symptom in FD patients, with up to 60% of hemizygous males and heterozygous females experiencing it[67]. For treating angina and left ventricular outflow tract obstruction, CCBs like verapamil and diltiazem should be considered[68].

Beta-blockers with high cardiac selectivity are recommended for patients with angina pectoris, myocardial infarction, or tachycardia[69,70]. But when prescribing beta-blockers to patients with FD, caution is necessary due to the increased risk of bradyarrhythmias and chronotropic incompetence[71]. A high prevalence of symptomatic heart failure (47 out of 116 patients, 69 classic types and 47 late-onset) was reported in FD patients by Rob et al., with beta-blockers being the most frequently used medication (51%), followed by ACEi (43%), diuretics (28%), ARBs (15%), and MRAs (8.5%)[72].

Steroidal and non-steroidal MRAs are recommended for their kidney protective effects, which include reducing proteinuria, as well as their cardioprotective effects in patients with heart failure[69,73,74]. However, it should be noted that there are risks of hyperkalemia or acute kidney injury, so caution must be taken when administering these medications as part of hypertension treatment.

SGLT2 inhibitors have demonstrated the potential to lower BP, suggesting their use as new antihypertensive drugs[75]. Even in patients with FD, SGLT2 inhibitors, similar to RAS blockade, may provide optimal kidney protection and control of systemic and intrarenal BP[76]. While recent findings suggest no risk of acute kidney injury associated with SGLT2 inhibitors, caution should still be exercised when using these drugs in patients with altered kidney function due to volume depletion[77]. Although there are no direct study results on the effect of SGLT2 inhibitors on FD, clinical studies are scheduled to be conducted and results are anticipated[78].

Since a high-sodium diet can reduce the effectiveness of ACEi/ARBs[79] and is associated with an increased risk of progression to end-stage kidney disease in patients with proteinuria[80], a low-sodium diet is strongly recommended for FD patients with proteinuria[81].

The FD-specific current treatments are ERT and chaperone therapy, which reduce intracellular Gb3 accumulation. ERT involves exogenous supplementation of α-GalA enzymes such as Fabrazyme and Replagal. Migalastat hydrochloride is an oral pharmacological chaperone that corrects the misfolded endogenous α-GalA and promotes the transport of α-GalA into lysosomes. Other future therapies, such as matrix reduction therapy, mRNA-based therapy, and gene therapy, are under development[81].

Two studies found that ERT treatment improved hypertension and decreased proteinuria[82,83]. However, it is difficult to fully explain the effect of ERT alone, given that the patients who participated in these studies were also getting ACEi or ARBs medication. ACEi and ARBs are routinely used to protect the kidneys in FD. There are reports that ERT can reduce inflammation by regulating the immune system. FD leads to the activation of the pro-inflammatory pathway associated with hypertension. ERT may modulate the immune system to reduce the level of inflammation.

In conclusion, the improved treatment of hypertension has probably contributed to the decline in kidney and cardiovascular disease-related mortality in FD patients. All Fabry patients should have adequate control over their BP. As indicated previously, because of uncontrolled hypertension, 24-hour BP measurements and oral medications such as ACEi/ARBs should be considered while monitoring BP.

Conflict of Interest

The authors have no conflicts of interest to declare

REFERENCES

1. Germain DP: Fabry disease. Orphanet J Rare Dis 2010;5:30.
2. Desnick RJ, Brady R, Barranger J, et al.: Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. Ann Intern Med 2003;138(4):338-46.
3. Linthorst GE, Hollak CE, Korevaar JC, Van Manen JG, Aerts JM, Boeschoten EW: Alpha-Galactosidase A deficiency in Dutch patients on dialysis: a critical appraisal of screening for Fabry disease. Nephrol Dial Transplant 2003;18(8):1581-4.
4. Gibas AL, Klatt R, Johnson J, Clarke JT, Katz J: Disease rarity, carrier status, and gender: a triple disadvantage for women

with Fabry disease. J Genet Couns 2008;17(6):528-37.
5. Waldek S, Patel MR, Banikazemi M, Lemay R, Lee P: Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry Registry. Genet Med 2009;11(11):790-6.
6. Nowak A, Mechtler T, Kasper DC, Desnick RJ: Correlation of Lyso-Gb3 levels in dried blood spots and sera from patients with classic and Later-Onset Fabry disease. Mol Genet Metab 2017;121(4):320-4.
7. Hoffmann B: Fabry disease: recent advances in pathology, diagnosis, treatment and monitoring. Orphanet J Rare Dis 2009;4:21.
8. Mehta A, Ricci R, Widmer U, et al.: Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur J Clin Invest 2004;34(3):236-42.
9. Yuasa T, Takenaka T, Higuchi K, et al.: Fabry disease. J Echocardiogr 2017;15(4):151-7.
10. Jaurretche S, Antongiovanni N, Perretta F: Fabry nephropathy. Role of nephrologist and clinical variables associated with the diagnosis. Nefrología (English Edition) 2019;39(3):294-300.
11. Choi JH, Lee BH, Heo SH, et al.: Clinical characteristics and mutation spectrum of GLA in Korean patients with Fabry disease by a nationwide survey: Underdiagnosis of late-onset phenotype. Medicine (Baltimore) 2017;96(29):e7387.
12. Doheny D, Srinivasan R, Pagant S, Chen B, Yasuda M, Desnick RJ: Fabry Disease: prevalence of affected males and heterozygotes with pathogenic GLA mutations identified by screening renal, cardiac and stroke clinics, 1995-2017. J Med Genet 2018;55(4):261-8.
13. Tuttolomondo A, Simonetta I, Riolo R, et al.: Pathogenesis and Molecular Mechanisms of Anderson-Fabry Disease and Possible New Molecular Addressed Therapeutic Strategies. Int J Mol Sci 2021;22(18).
14. Dincer MT, Ozcan SG, Ikitimur B, et al.: Blood Pressure Variability in Fabry Disease Patients. Nephron 2022;146(4):343-50.
15. Cable WJ, Kolodny EH, Adams RD. Fabry disease: impaired autonomic function. Neurology 1982;32(5):498-502.
16. Biegstraaten M, van Schaik IN, Wieling W, Wijburg FA, Hollak CE: Autonomic neuropathy in Fabry disease: a prospective study using the Autonomic Symptom Profile and cardiovascular autonomic function tests. BMC Neurol 2010; 10:38.
17. Kaye EM, Kolodny EH, Logigian EL, Ullman MD: Nervous system involvement in Fabry's disease: clinicopathological and biochemical correlation. Ann Neurol 1988;23(5):505-9.
18. Liguori R, Di Stasi V, Bugiardini E, et al.: Small fiber neuropathy in female patients with fabry disease. Muscle Nerve 2010;41(3):409-12.
19. Rombach SM, Twickler TB, Aerts JM, Linthorst GE, Wijburg FA, Hollak CE: Vasculopathy in patients with Fabry disease: current controversies and research directions. Mol Genet Metab 2010;99(2):99-108.
20. Hilz MJ, Marthol H, Schwab S, Kolodny EH, Brys M, Stemper B: Enzyme replacement therapy improves cardiovascular responses to orthostatic challenge in Fabry patients. J Hypertens 2010;28(7):1438-48.
21. Burlina AP, Sims KB, Politei JM, et al.: Early diagnosis of peripheral nervous system involvement in Fabry disease and treatment of neuropathic pain: the report of an expert panel. BMC Neurol 2011;11:61.
22. Williams B, Mancia G, Spiering W, et al.: 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. Blood Press 2018;27(6):314-40.
23. Fervenza FC, Torra R, Warnock DG: Safety and efficacy of enzyme replacement therapy in the nephropathy of Fabry disease. Biologics 2008;2(4):823-43.
24. Rossi F, Svarstad E, Elsaid H, et al.: Elevated Ambulatory Blood Pressure Measurements are Associated with a Progressive Form of Fabry Disease. High Blood Press Cardiovasc Prev 2021;28(3):309-19.
25. DeGraba T, Azhar S, Dignat-George F, et al.: Profile of endothelial and leukocyte activation in Fabry patients. Ann Neurol 2000;47(2):229-33.
26. Lassegue B, Griendling KK: Reactive oxygen species in hypertension; An update. Am J Hypertens 2004;17(9):852-60.
27. Shen JS, Meng XL, Moore DF, et al.: Globotriaosylceramide induces oxidative stress and up-regulates cell adhesion molecule expression in Fabry disease endothelial cells. Mol Genet Metab 2008;95(3):163-8.
28. Chen KH, Chien Y, Wang KL, et al. Evaluation of Proinflammatory Prognostic Biomarkers for Fabry Cardiomyopathy With Enzyme Replacement Therapy. Can J Cardiol 2016; 32(10):1221 e1-e9.
29. Ding J, Yu M, Jiang J, et al.: Angiotensin II Decreases Endothelial Nitric Oxide Synthase Phosphorylation via AT(1)R Nox/ROS/PP2A Pathway. Front Physiol 2020;11:566410.
30. Fujii Y, Numata S, Nakamura Y, et al.: Murine glycosyltransferases responsible for the expression of globo-series glycolipids: cDNA structures, mRNA expression, and distribution of their products. Glycobiology 2005;15(12):1257-67.
31. Batista EC, Carvalho LR, Casarini DE, et al.: ACE activity is modulated by the enzyme alpha-galactosidase A. J Mol Med (Berl) 2011;89(1):65-74.
32. Bothou C, Beuschlein F, Nowak A: Endocrine disorders in patients with Fabry disease: insights from a reference cen-

tre prospective study. Endocrine 2022;75(3):728-39.
33. Shu L, Park JL, Byun J, Pennathur S, Kollmeyer J, Shayman JA: Decreased nitric oxide bioavailability in a mouse model of Fabry disease. J Am Soc Nephrol 2009;20(9):1975-85.
34. Aerts JM, Groener JE, Kuiper S, et al.: Elevated globotriaosylsphingosine is a hallmark of Fabry disease. Proc Natl Acad Sci USA 2008;105(8):2812-7.
35. Barbey F, Brakch N, Linhart A, et al.: Cardiac and vascular hypertrophy in Fabry disease: evidence for a new mechanism independent of blood pressure and glycosphingolipid deposition. Arterioscler Thromb Vasc Biol 2006;26(4):839-44.
36. Dandona P, Dhindsa S, Ghanim H, Chaudhuri A: Angiotensin II and inflammation: the effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockade. J Hum Hypertens 2007;21(1):20-7.
37. Del Pinto R, Ferri C: The role of Immunity in Fabry Disease and Hypertension: A Review of a Novel Common Pathway. High Blood Press Cardiovasc Prev 2020;27(6):539-46.
38. Anders HJ, Banas B, Schlondorff D: Signaling danger: toll-like receptors and their potential roles in kidney disease. J Am Soc Nephrol 2004;15(4):854-67.
39. Sanchez-Nino MD, Carpio D, Sanz AB, Ruiz-Ortega M, Mezzano S, Ortiz A: Lyso-Gb3 activates Notch1 in human podocytes. Hum Mol Genet 2015;24(20):5720-32.
40. Ortiz A, Oliveira JP, Waldek S, et al.: Nephropathy in males and females with Fabry disease: cross-sectional description of patients before treatment with enzyme replacement therapy. Nephrol Dial Transplant 2008;23(5):1600-7.
41. Schiffmann R, Warnock DG, Banikazemi M, et al.: Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. Nephrol Dial Transplant 2009;24(7):2102-11.
42. Carson AP, Howard G, Burke GL, Shea S, Levitan EB, Muntner P: Ethnic differences in hypertension incidence among middle-aged and older adults: the multi-ethnic study of atherosclerosis. Hypertension 2011;57(6):1101-7.
43. Egan BM, Zhao Y, Axon RN: US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. JAMA 2010;303(20):2043-50.
44. Wolf-Maier K, Cooper RS, Banegas JR, et al.: Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA 2003;289(18):2363-9.
45. Whaley-Connell AT, Sowers JR, Stevens LA, et al.: CKD in the United States: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004. Am J Kidney Dis 2008;51(4 Suppl 2):S13-20.
46. Branton MH, Schiffmann R, Sabnis SG, et al.: Natural history of Fabry renal disease: influence of alpha-galactosidase A activity and genetic mutations on clinical course. Medicine (Baltimore) 2002;81(2):122-38.
47. Lidove O, Barbey F, Niu DM, et al.: Fabry in the older patient: Clinical consequences and possibilities for treatment. Mol Genet Metab 2016;118(4):319-25.
48. Ferrari G, Reisin R, Kisinovsky I, et al.: Major cardiovascular adverse events in Fabry disease patients receiving agalsidase alfa. Medicina (B Aires) 2021;81(2):173-9.
49. Wang WT, Sung SH, Liao JN, Hsu TR, Niu DM, Yu WC: Cardiac manifestations in patients with classical or cardiac subtype of Fabry disease. J Chin Med Assoc 2020;83(9):825-9.
50. Lenders M, Nordbeck P, Kurschat C, et al.: Treatment of Fabry's Disease With Migalastat: Outcome From a Prospective Observational Multicenter Study (FAMOUS). Clin Pharmacol Ther 2020;108(2):326-37.
51. Kleinert J, Dehout F, Schwarting A, et al.: Prevalence of uncontrolled hypertension in patients with Fabry disease. Am J Hypertens 2006;19(8):782-7.
52. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies C: Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002;360(9349):1903-13.
53. Krämer J, Bijnens B, Störk S, et al.: Left Ventricular Geometry and Blood Pressure as Predictors of Adverse Progression of Fabry Cardiomyopathy. PLoS One 2015;10(11):e0140627.
54. Wanner C, Oliveira JP, Ortiz A, et al.: Prognostic indicators of renal disease progression in adults with Fabry disease: natural history data from the Fabry Registry. Clin J Am Soc Nephrol 2010;5(12):2220-8.
55. Ruggenenti P, Perna A, Remuzzi G, Investigators GG: Retarding progression of chronic renal disease: the neglected issue of residual proteinuria. Kidney Int 2003;63(6):2254-61.
56. Linhart A, Kampmann C, Zamorano JL, et al.: Cardiac manifestations of Anderson-Fabry disease: results from the international Fabry outcome survey. Eur Heart J 2007;28(10):1228-35.
57. Patel MR, Cecchi F, Cizmarik M, et al.: Cardiovascular events in patients with fabry disease natural history data from the fabry registry. J Am Coll Cardiol 2011;57(9):1093-9.
58. Viana-Baptista M: Stroke and Fabry disease. J Neurol 2012;259(6):1019-28.
59. Sims K, Politei J, Banikazemi M, Lee P: Stroke in Fabry disease frequently occurs before diagnosis and in the absence of other clinical events: natural history data from the Fabry Registry. Stroke 2009;40(3):788-94.

60. Mancia G, Fagard R, Narkiewicz K, et al.: 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2013; 31(7):1281-357.
61. Schieppati A, Remuzzi G: Proteinuria and its consequences in renal disease. Acta Paediatr Suppl 2003;92(443):9-13;discussion 5.
62. Eng CM, Germain DP, Banikazemi M, et al.: Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. Genet Med 2006;8(9):539-48.
63. Warnock DG, Ortiz A, Mauer M, et al.: Renal outcomes of agalsidase beta treatment for Fabry disease: role of proteinuria and timing of treatment initiation. Nephrol Dial Transplant 2012;27(3):1042-9.
64. Warnock DG, Thomas CP, Vujkovac B, et al.: Antiproteinuric therapy and Fabry nephropathy: factors associated with preserved kidney function during agalsidase-beta therapy. J Med Genet 2015;52(12):860-6.
65. Muntze J, Gensler D, Maniuc O, et al.: Oral Chaperone Therapy Migalastat for Treating Fabry Disease: Enzymatic Response and Serum Biomarker Changes After 1 Year. Clin Pharmacol Ther 2019;105(5):1224-33.
66. Paim-Marques L, de Oliveira RJ, Appenzeller S. Multidisciplinary Management of Fabry Disease: Current Perspectives. J Multidiscip Healthc 2022;15:485-95.
67. Elliott PM, Kindler H, Shah JS, et al.: Coronary microvascular dysfunction in male patients with Anderson-Fabry disease and the effect of treatment with alpha galactosidase A. Heart 2006;92(3):357-60.
68. Azevedo O, Cordeiro F, Gago MF, et al.: Fabry Disease and the Heart: A Comprehensive Review. Int J Mol Sci 2021; 22(9).
69. Unger T, Borghi C, Charchar F, et al.: 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension 2020;75(6):1334-57.
70. Williams B, Mancia G, Spiering W, et al.: 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39(33):3021-104.
71. Hagege A, Reant P, Habib G, et al.: Fabry disease in cardiology practice: Literature review and expert point of view. Arch Cardiovasc Dis 2019;112(4):278-87.
72. Rob D, Marek J, Dostalova G, Linhart A: Heart failure in Fabry disease revisited: application of current heart failure guidelines and recommendations. ESC Heart Fail 2022;9(6): 4043-52.
73. Bakris G, Yang YF, Pitt B: Mineralocorticoid Receptor Antagonists for Hypertension Management in Advanced Chronic Kidney Disease: BLOCK-CKD Trial. Hypertension 2020;76(1): 144-9.
74. Heidenreich PA, Bozkurt B, Aguilar D, et al.: 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145(18):e895-e1032.
75. Kario K, Ferdinand KC, Vongpatanasin W: Are SGLT2 Inhibitors New Hypertension Drugs? Circulation 2021;143(18):1750-3.
76. Fioretto P, Zambon A, Rossato M, Busetto L, Vettor R: SGLT2 Inhibitors and the Diabetic Kidney. Diabetes Care 2016;39 Suppl 2:S165-71.
77. Bailey CJ, Day C, Bellary S: Renal Protection with SGLT2 Inhibitors: Effects in Acute and Chronic Kidney Disease. Curr Diab Rep 2022;22(1):39-52.
78. A N: Effects Of Sodium Glucose Cotranspoter 2 Inhibitors On Heart And Kidneys In Fabry Disease Patients. 2023. https://clinicaltrials.gov/ct2/show/NCT05710367 (accessed May, 2023.
79. De'Oliveira JM, Price DA, Fisher ND, et al.: Autonomy of the renin system in type II diabetes mellitus: dietary sodium and renal hemodynamic responses to ACE inhibition. Kidney Int 1997;52(3):771-7.
80. Vegter S, Perna A, Postma MJ, Navis G, Remuzzi G, Ruggenenti P: Sodium intake, ACE inhibition, and progression to ESRD. J Am Soc Nephrol 2012;23(1):165-73.
81. Lenders M, Brand E: Fabry Disease: The Current Treatment Landscape. Drugs 2021;81(6):635-45.
82. Whybra C, Miebach E, Mengel E, et al.: A 4-year study of the efficacy and tolerability of enzyme replacement therapy with agalsidase alfa in 36 women with Fabry disease. Genet Med 2009;11(6):441-9.
83. Mehta A, Beck M, Elliott P, et al.: Enzyme replacement therapy with agalsidase alfa in patients with Fabry's disease: an analysis of registry data. Lancet 2009;374(9706):1986-96.

Review Article

ISSN 1738-5997 (Print) · ISSN 2092-9935 (Online)
Electrolyte Blood Press 2023;21:18-23
https://doi.org/10.5049/EBP.2023.21.1.18

Post-Hypercapnic Alkalosis: A Brief Review

Yongjin Yi, MD, MPH

Division of Nephrology, Department of Internal Medicine, Dankook University Hospital, Dankook University College of Medicine, Cheonan, Republic of Korea

Received: March 31, 2023
Revised: April 17, 2023
Accepted: April 25, 2023
Corresponding Author: Yongjin Yi, MD, MPH
Department of Nephrology, Department of Internal Medicine, Dankook University College of Medicine
119, Dandae-ro, Dongnam-gu, Cheonan-si, Chungcheongnam-do 31116, Korea
Tel: +82-41-550-3066; Fax: +82-41-550-6033
E-mail: yongjin.neph@gmail.com

Metabolic alkalosis is a common acid-base imbalance frequently observed in intensive care unit (ICU) patients and is associated with increased mortality. Post-hypercarbia alkalosis (PHA) is a type of metabolic alkalosis caused by sustained high serum bicarbonate levels following a rapid resolution of hypoventilation in patients with chronic hypercapnia due to prolonged respiratory disturbance. Common causes of chronic hypercapnia include chronic obstructive pulmonary disease (COPD), central nervous system disorders, neuromuscular disorders, and narcotic abuse. Rapid correction of hypercapnia through hyperventilation leads to a swift normalization of pCO_2, which lacks renal compensation, consequently causing an increase in plasma HCO_3^- levels and severe metabolic alkalosis. Most of PHA occurs in the ICU setting requiring mechanical ventilation and can progress severe alkalemia due to secondary mineralocorticoid excess from volume depletion or decreased HCO_3^- excretion from decreased glomerular filtration rate and increased proximal tubular reabsorption. PHA is associated with increased ICU stay, ventilator dependency, and mortality. Acetazolamide, a carbonic anhydrase inhibitor, has been utilized for managing PHA by inducing alkaline diuresis and reducing tubular reabsorption of bicarbonate. While acetazolamide effectively improves alkalemia, its impact on hard outcomes may be limited by factors such as patient complexity, co-administered medications, and underlying conditions contributing to alkalosis.

Key Words: Metabolic alkalosis, Hypercapnia, Hyperventilation, Chronic obstructive pulmonary disease, Carbonic anhydrase

INTRODUCTION

Metabolic alkalosis is a prevalent acid-base imbalance frequently observed in patients admitted to intensive care unit (ICU). Severe alkalosis is related with clinical manifestations such as hypoventilation, neurological symptoms, and diminished systemic oxygenation[1]. In an observational investigation involving 409 patients, those presenting alkalemia with pH levels greater than 7.48 were identified to have a 27.9% mortality rate. Within the group, patients with a pH greater than 7.60 exhibited a significantly increased mortality rate of 48.5%[2].

In ICU patients, contraction of the extracellular fluid (ECF) due to vomiting, nasogastric suctioning or diuretic treatment can cause chloride-responsive metabolic alkalosis[3]. Besides metabolic alkalosis caused by volume depletion, post-hypercapnic alkalosis (PHA), a form of compensated metabolic alkalosis caused by chronic hypercapnia due to respiratory insufficiency, is relatively common in specific clinical situations. This review aims to offer a comprehensive overview of PHA by examining a case presentation and discussing the pathophysiology, epidemiology, and management, with a focus on the effects of acetazolamide treatment.

Case Presentation

An 84-year-old male presented to the emergency depart-

ment with a complaint of decreased consciousness that occurred 1 hour prior to his visit. He was hospitalized 4 years ago for an event of generalized tonic-clonic seizure and was also diagnosed with chronic obstructive pulmonary disease (COPD), hypertension, dilated cardiomyopathy, atrial fibrillation and was prescribed azilsartan 40 mg, amlodipine 5 mg, apixaban 2.5 mg twice daily, valproate 300 mg twice daily, levetiracetam 1,000 mg twice daily, doxofylline 400 mg twice daily, and a beclomethasone/formoterol inhaler 100/6 μg. The patient recently experienced a loss of appetite and poor adherence to his prescribed medications, including anti-epileptic drugs. A point-of-care test revealed a positive result for the COVID-19 PCR. The physical examination showed a blood pressure of 120/92 mmHg, pulse rate of 68 beats/min, respiratory rate of 19 breaths/min, temperature of 36.6°C, and a Glasgow coma scale (GCS) score of E3V4M5. Skin turgor was mildly reduced. Arterial blood gas analysis (ABGA) at admission demonstrated a pH of 7.37, pCO_2 of 51.8 mmHg, pO_2 of 52.2 mmHg, and HCO_3^- of 30.0 mmol/L. Biochemistry results included Na at 137 mmol/L, K at 5.2 mmol/L, Cl at 101 mmol/L, BUN/creatinine (Cr) at 18.0/0.87 mg/dL, N-terminal pro-B-type natriuretic peptide at 536.0 pg/mL, and C-reactive protein at 0.57 mg/dL.

The patient was treated for an acute exacerbation of COPD and congestive heart failure using 30 mg of methylprednisolone and intravenous furosemide. On the second day of hospitalization, the patient's mental status declined from confusion to drowsiness, with a GCS score of E3V3M4. ABGA at this time revealed pH 7.40, $PaCO_2$ 60 mmHg, PaO_2 101 mmHg, and HCO_3^- 37.1 mmol/L. The EEG displayed periodic spike waveforms.

On the third day of hospitalization, the patient's level of consciousness further decreased to stupor, and hypoxia worsened. Consequently, tracheal intubation and mechanical ventilation therapy were performed. The ABGA was pH 7.40, pCO_2 60 mmHg, pO_2 47 mmHg, and HCO_3^- 37.2 mmol/L. Six hours after initiating mechanical ventilation, the ABGA showed pH 7.44, pCO_2 51 mmHg, pO_2 101 mmHg, and HCO_3^- 34.6 mmol/L. Following 48 hours of continuous ventilation therapy, the ABGA indicated pH 7.60, pCO_2 28 mmHg, pO_2 105 mmHg, and HCO_3^- 27.5 mmol/L, suggesting the presence of respiratory and metabolic alkalosis. Serum biochemistry results included Na at 144 mmol/L, K at 4.7 mmol/L, Cl at 101 mmol/L, BUN/creatinine (Cr) at 26.0/0.65 mg/dL.

In the present case, the patient was referred to a nephrologist on tenth day of hospitalization, seven days after developing metabolic alkalemia. The patient's ABGA results were pH 7.55, pCO_2 28 mmHg, pO_2 123 mmHg, and HCO_3^- 24.5 mmol/L. After being diagnosed with PHA, the patient's pCO_2 was brought back toward normal range by allowing hypercapnia, and the furosemide dose was adjusted to maintain a euvolemic status. The day following PHA treatment, the ABGA results were pH 7.46, pCO_2 38 mmHg, pO_2 83 mmHg, and HCO_3^- 27.0 mmol/L.

On hospital day 13, the patient developed new-onset aspiration pneumonia and hypercapnia, which were managed by administering antibiotics and methylprednisolone at a dosage of 0.5 mg/kg/day. On day 14, the ABGA results indicated pH 7.41, pCO_2 60 mmHg, pO_2 104 mmHg, and HCO_3^- 38.0 mmol/L, with an electrolyte panel showing Na^+ 143 mmol/L, K^+ 3.5 mmol/L, Cl- 105 mmol/L, and a urine Cl level of 45 mmol/L. These findings suggested concomitant alkalosis that might occurred by secondary mineralocorticoid excess by administration of methylprednisolone and furosemide. Consequently, spironolactone was administered at a dose of 12.5 mg twice daily. The alkalosis subsequently corrected; however, the patient died due to the progression of pneumonia at hospital day 19.

Case Summary

The diagnosis of the presented case is PHA due to rapid correction of respiratory acidosis. PHA is an acid-base disturbance that occurs in patients with chronic hypercapnic respiratory failure when rapid hyperventilation (e.g., mechanical ventilation, non-invasive ventilation), results in a rapid correction of $PaCO_2$ that is not accompanied by sufficient reversal of renal HCO_3^- reabsorption, resulting in metabolic alkalosis. PHA frequently occurs in acute, intensive care settings, often accompanying rapid hyperventilation therapy. The complexity of patient's condition can lead to misidentification of other causative factors for metabolic alkalosis, resulting in delayed accurate diagnosis and appropriate management. The presented case illustrated a patient with multiple comorbidities such as epilepsy, COPD, and heart failure, experienced a prolonged mechanical ven-

tilation therapy due to the delayed identification of PHA resulting from hyperventilation.

Pathophysiology of PHA

Chronic hypercapnia due to respiratory insufficiency can be caused by various conditions, including COPD, central nervous system disorders, neuromuscular disorders, and narcotic abuse. When chronic hypercapnia and respiratory acidemia develops, patients undergo a renal compensation as bicarbonate reabsorption resulting in an increase in plasma HCO_{3-} and amelioration of the acidemia[4]. The retention of plasma sodium bicarbonate ($NaHCO_3$) increases effective arterial blood volume, leading to enhanced sodium chloride (NaCl) excretion. In this context, euvolemia is sustained by high total ECF $NaHCO_3$ and low total ECF NaCl.

Swift correction of hypercapnia subsequently results in primary metabolic alkalosis due to elevated plasma HCO_{3-} levels and normal pCO_2. The kidneys then attempt to rectify the alkalosis by excreting HCO_{3-}, accompanied by the excretion of sodium and potassium, the relative proportions of which are determined by aldosterone levels. If the patient has a low NaCl intake, which is common in this situation, bicarbonate excretion will cease, leading to a persistent metabolic alkalosis maintained by volume contraction and hypokalemia. Raising the total ECF NaCl can enhance effective arterial blood volume, rectifying metabolic alkalosis. It is crucial to consider that these patients often use diuretics, which can exacerbate volume depletion and play a role in the creation and persistence of metabolic alkalosis[1,5].

Epidemiology of PHA

COPD is known to be a common cause of chronic hypercapnia. In a study conducted by Dreher et al. that examined the prevalence of chronic hypercapnia among 231 patients diagnosed with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 3 or 4 COPD, the researchers discovered that 25% of the patients had $PaCO_2$ levels exceeding 45 mmHg, while 9% exhibited hypercapnia with levels exceeding 50 mmHg[6].

There is limited evidence regarding the frequency of PHA following hyperventilation therapy. In a study conducted by Banga et al., of 84 patients experiencing acute exacerbation of COPD with CO_2 retention, 17 patients (20%) exhibited alkalemia as confirmed by ABGA with a pH of 7.45 or higher, 72 hours after receiving mechanical ventilator therapy. The group of patients with PHA experienced longer days of ICU stay and ventilator dependency[7].

Diagnosis and Management of PHA

PHA is a potential complication from hyperventilation therapy in patients with underlying chronic hypercapnic respiratory failure. This condition can result from various underlying disorders, such as COPD, neuromuscular disorders, central nervous system depression, or chronic narcotic abuse. Patients with chronic hypercapnia, characterized by a pCO_2 greater than normal value of 40 mmHg, often maintain a normal blood pH of approximately 7.40 due to renal compensation. However, when an additional acute respiratory failure event, such as an acute infection, occurs, the pCO_2 may further increase, leading to additional acute respiratory acidosis. In these clinical situations, the correction of hypoventilation through mechanical or non-invasive ventilation can result in uncompensated metabolic alkalosis. This occurs due to the persistence of the underlying pathophysiology associated with hypercapnic metabolic alkalosis, which leads to severe alkalemia with a pH greater than 7.50-7.60. This results from the coexistence of mixed metabolic alkalosis and respiratory acidosis[8]. The primary goal in treating metabolic alkalosis is to address the underlying condition. Upon diagnosing post-hypercapnic alkalosis (PHA), the presence of various co-existing conditions can complicate the correction of metabolic alkalosis. ECF deficits induced by diuretics or gastrointestinal loss, the use of steroids with mineralocorticoid effects, and electrolyte imbalances such as potassium and magnesium also can contribute to alkalosis, potentially delaying the diagnosis of PHA and impeding effective treatment[3,9].

Carbonic anhydrase inhibitor is a class of medications that impede bicarbonate reabsorption in the proximal tubule by inhibiting the activity of the enzyme carbonic anhydrase. Acetazolamide has been used in the management of metabolic alkalosis, by inducing alkaline diuresis

Table 1. A summary of studies on acetazolamide treatment in patients with respiratory failure and metabolic alkalosis

Author (year)	Study design	Target group	Intervention	Study participants	Major outcomes	Results
Faisy et al. (2016)[11]	Randomized, double blind, placebo controlled, multicenter trial	Patients with COPD requires IMV less than 24 h with MA, defined as a pH ≥7.35 and HCO_3^- >26 mmol/L	ACET 500 or 1,000 mg (in case with furosemide) twice daily or placebo	ACET group, N=187 Placebo group, N=193	Duration of IMV Duration of ICU stay ICU Mortality Change of HCO_3^-	Median 136.5 vs 163 h, difference -16.0 h (95% CI, -36.5, 4.0) Median 10 vs 10 d Difference -2.1 d (95% CI, -6.1, 1.9) 11.7% vs 13.4% (p-value, 0.61) Median -0.3 vs 0.3 meq/L Difference -0.8 meq/L (95% CI, -1.2, -0.5)
Rialp et al. (2017)[12]	Randomized, double blind, placebo controlled, multicenter trial	Patients with COPD or OHS on IMV during less than 72 h with MA, defined as a pH > 7.35 and HCO_3^- >28 mmol/L	ACET 500 mg once daily or placebo when 7 AM HCO_3^- >26 mmol/L	ACET group, N=24 Placebo group N=23	Duration of IMV Duration of ICU stay Hospital mortality HCO_3^- at day 3	Median 4.9 vs 7.2 d (p-value, 0.30) Median 8.5 vs 11 d (p-value, 0.19) 16% vs 9% (p-value, 0.41) Median 30 vs 34 meq/L (p-value <0.001)
Gulsvik et al. (2013)[13]	Randomized, double blind, placebo-controlled trial	Patients with respiratory failure by pulmonary disease (PaO_2 ≤8 kPa and/or $PaCO_2$ ≥ 7 kPa) with BE of 8 meq/L	ACET 250 mg three times daily or placebo for 5 days	ACET group, N=35 Placebo group, N=35	Change of pO_2 Change of pCO_2 Change of pH Change of HCO_3^-	Mean 1.41 vs 0.81 kPa, difference 0.55 kPa (95% CI, -0.03, 1.06) Mean -0.29 vs -0.45 kPa, difference 0.19 kPa (95%CI, -0.25, 0.64) Mean -0.087 vs -0.084, difference -0.084 (95% CI, -0.102, -0.067) Mean -8.62 vs -2.16 meq/L, difference -6.31 meq/L (95% CI, -7.77, -4.86)
Vos et al. (1994)[14]	Randomized, double blind, placebo-controlled trial	Patients with COPD and hypoxemia of pO_2 ≤8.5 kPa	ACET 250 mg twice daily or placebo for 2 days with O_2 therapy via nasal cannula	ACET group, N=17 Placebo group, N=18	Change of pO_2 Change of pCO_2 Change of pH Change of HCO_3^-	Mean 1.9 vs 0.4 kPa (p-value <0.05) Mean -0.5 vs 0.3 kPa (p-value <0.05) Mean -0.07 vs -0.01 (p-value <0.05) Mean -6.7 vs 0.3 meq/L (p-value <0.05)

COPD, chronic obstructive pulmonary disease; IMV, invasive mechanical ventilation; MA, metabolic alkalosis; ACET, acetazolamide; BE, base excess.

by reducing tubular reabsorption of bicarbonate and inhibiting distal tubule secretion of hydrogen ions. After hours of acetazolamide administration, urinary bicarbonate loss occurs, leading to a decrease in serum bicarbonate levels. This reduction is typically a 4-6 mM decrease within 24 hours, accompanied by a fall in arterial pH of approximately 0.05-0.1 units. If there were no mechanical limitation to the increase of lung ventilation, the pCO_2 would decrease by approximately 5-6 mmHg due to the respiratory response[10].

Several clinical trials have investigated the use of acetazolamide for the reversal of alkalosis in patients with prolonged PHA. While some studies have focused on comparing changes in pH and HCO_3^-, a biochemical marker related to alkalosis, others, such as the study conducted by Faisy et al. and the study by Rialp et al., have examined outcome as duration of mechanical ventilation, and mortality in larger number of patient cohorts through randomized, placebo-controlled trials[11-14].

Based on the results of the studies reviewed, 250 to 500 mg PO or IV acetazolamide would be appropriate as first-line treatment in patients with PHA. The dose of acetazolamide should be adjusted, ranging from 250 to 500 mg once or twice daily, depending on response to therapy. However, dose adjustments are required when there is renal function impairment, as the drug is eliminated by the kidneys. Pharmacokinetic studies of acetazolamide have shown that serum acetazolamide concentrations are elevated in patients with decreased renal function or dialysis[15-17]. In patients with decreased renal function, CNS toxicity or acidosis may occur due to the accumulation of acetazolamide, and aplastic anemia, agranulocytosis or anaphylaxis may occur in a non-dose-dependent manner[18-20]. In these patients, a dose of 125 mg to 250 mg of acetazolamide would be appropriate.

Table 1 provides an overview of the clinical trials conducted on PHA patients. In all studies, acetazolamide demonstrated a significant improvement in base excess. In the largest study involving 380 COPD patients received mechanical ventilation therapy, acetazolamide administration resulted in a 16-hour decrease in the duration of mechanical ventilation compared to placebo. However, the difference did not reach statistical significance (95% CI, -36.5 to 4.0 h; p=0.17). Furthermore, acetazolamide therapy did not significantly reduce the duration of hospital stay or decrease mortality[11]. Rialp et al. compared the effectiveness of ace-

tazolamide 500 mg once daily versus placebo in patients with obesity hypoventilation syndrome (OHS) and COPD undergoing invasive mechanical ventilation therapy. In the randomized controlled trial, which included a total of 47 patients, acetazolamide did not reduce the duration of ventilator therapy or ICU stay and showed no effect on mortality[12]. Two other smaller studies examined changes in blood gas analysis profiles between acetazolamide and placebo in patients with COPD and chronic respiratory failure. In both studies, the results showed that acetazolamide improved alkalemia[13,14].

Although acetazolamide effectively improves alkalemia in patients with PHA, its impact on hard outcomes, such as duration of mechanical ventilation, length of stay, and mortality, may be limited by factors like patient complexity and co-administered medications. For example, loop diuretics and corticosteroids can interfere with acetazolamide's pharmacodynamics and reduce its ability of bicarbonate excretion. When these drugs are being co-administrated, a higher dose of acetazolamide (500 to 1,000 mg twice daily) may be appropriate to achieve the therapeutic effect[21]. Furthermore, diuretics contribute to chloride-responsive metabolic alkalosis via volume depletion, and mineralocorticoids result in hypokalemia and augmented ammonium excretion and bicarbonate reabsorption in the distal tubule. In such situations, acetazolamide's effectiveness in reversing alkalosis may be diminished[3].

CONCLUSION

PHA is one of the common causes of alkalosis in the process of treating respiratory failure in patients with chronic obstructive pulmonary disease. Not only PHA due to rapid correction of compensated hypercapnia, but also diuretic-induced alkalosis or mineralocorticoid excess that commonly occurring in intensive care units can be worsen severe alkalosis.

Critically ill patients with PHA are at increased risk for delayed weaning from mechanical ventilation and mortality. Therefore, prevention, monitoring, and appropriate treatment of alkalosis are essential in acutely deteriorated patients with chronic hypercapnia due to respiratory diseases.

REFERENCES

1. Galla JH: Metabolic alkalosis. J Am Soc Nephrol 2000;11(2): 369-375.
2. Anderson LE, Henrich WL: Alkalemia-associated morbidity and mortality in medical and surgical patients. South Med J 1987;80(6):729-733.
3. Webster NR, Kulkarni V: Metabolic alkalosis in the critically ill. Crit Rev Clin Lab Sci 1999;36(5):497-510.
4. Cogan MG: Chronic hypercapnia stimulates proximal bicarbonate reabsorption in the rat. J Clin Invest 1984;74(6): 1942-1947.
5. Peixoto AJ, Alpern RJ: Treatment of severe metabolic alkalosis in a patient with congestive heart failure. Am J Kidney Dis Off J Natl Kidney Found 2013;61(5):822-827.
6. Dreher M, Neuzeret PC, Windisch W, et al.: Prevalence Of Chronic Hypercapnia In Severe Chronic Obstructive Pulmonary Disease: Data From The HOmeVent Registry. Int J Chron Obstruct Pulmon Dis 2019;14:2377-2384.
7. Banga A, Khilnani GC: Post-hypercapnic alkalosis is associated with ventilator dependence and increased ICU stay. COPD 2009;6(6):437-440.
8. Riccio JF, Irani FA: Posthypercapnic metabolic alkalosis: common and neglected cause. South Med J 1979;72(7):886-887.
9. Bahloul M, Ammar R, Bouattour A, et al.: Effects of early administration of acetazolamide on the duration of mechanical ventilation in patients with chronic obstructive pulmonary disease: still far from the truth? J Thorac Dis 2017; 9(6):1393-1395.
10. Swenson E: Carbonic anhydrase inhibitors and ventilation: a complex interplay of stimulation and suppression. Eur Respir J 1998;12(6):1242-1247.
11. Faisy C, Meziani F, Planquette B, et al.: Effect of Acetazolamide vs Placebo on Duration of Invasive Mechanical Ventilation Among Patients With Chronic Obstructive Pulmonary Disease: A Randomized Clinical Trial. JAMA 2016;315(5):480-488.
12. Cervera GR, Puigdevall JR, Chorro IM, et al.: Effects of early administration of acetazolamide on the duration of mechanical ventilation in patients with chronic obstructive pulmonary disease or obesity-hypoventilation syndrome with metabolic alkalosis. A randomized trial. Pulm Pharmacol Ther 2017;44:30-37.
13. Gulsvik R, Skjørten I, Undhjem K, et al.: Acetazolamide improves oxygenation in patients with respiratory failure and metabolic alkalosis. Clin Respir J 2013;7(4):390-396.
14. Vos P, Folgering H, de Boo TM, Lemmens W, van Herwaarden

C: Effects of chlormadinone acetate, acetazolamide and oxygen on awake and asleep gas exchange in patients with chronic obstructive pulmonary disease (COPD). Eur Respir J 1994;7(5):850-855.
15. Yano I, Takayama A, Takano M, et al.: Pharmacokinetics and pharmacodynamics of acetazolamide in patients with transient intraocular pressure elevation. Eur J Clin Pharmacol 1998;54(1):63-68.
16. Schwenk MH, St Peter WL, Meese MG, Singhal PC: Acetazolamide toxicity and pharmacokinetics in patients receiving hemodialysis. Pharmacotherapy 1995;15(4):522-527.
17. Schwenk MH, Blaustein DA, Wagner JD: The pharmacokinetics of acetazolamide during CAPD. Adv Perit Dial Conf Perit Dial 1994;10:44-46.
18. Mogk LG, Cyrlin MN: Blood dyscrasias and carbonic anhydrase inhibitors. Ophthalmology 1988;95(6):768-771.
19. Newton PN, Thai LH, Tip NQ, et al.: A randomized, double-blind, placebo-controlled trial of acetazolamide for the treatment of elevated intracranial pressure in cryptococcal meningitis. Clin Infect Dis Off Publ Infect Dis Soc Am 2002;35(6):769-772.
20. Schmickl CN, Owens RL, Orr JE, Edwards BA, Malhotra A: Side effects of acetazolamide: a systematic review and meta-analysis assessing overall risk and dose dependence. BMJ Open Respir Res 2020;7(1):e000557.
21. Heming N, Faisy C, Urien S: Population pharmacodynamic model of bicarbonate response to acetazolamide in mechanically ventilated chronic obstructive pulmonary disease patients. Crit Care 2011;15(5):R213.

Review Article

ISSN 1738-5997 (Print) · ISSN 2092-9935 (Online)
Electrolyte Blood Press 2023;21:24-33
https://doi.org/10.5049/EBP.2023.21.1.24

Understanding and Treatment Strategies of Hypertension and Hyperkalemia in Chronic Kidney Disease

Sang Min Jo

Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Received: November 17, 2022
Revised: June 10, 2023
Accepted: June 12, 2023
Corresponding Author: Sang Min Jo, MD
Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29 Saemunan-ro, Jongno-gu, Seoul, Korea
Tel: +82-2-2001-2599; Fax: +82-2-2001-2601
E-mail: goodfamily888888@gmail.com

Hypertension and potassium imbalance are commonly observed in chronic kidney disease (CKD) patients. The development of hypertension would be related to several mechanisms. Hypertension is related to body mass index, dietary salt intake, and volume overload and is treated with antihypertensives. In CKD patients, managing hypertension can provide important effects that can slow the progression of CKD or reduce complications associated with reduced glomerular filtration rate. The prevalence of hyperkalemia and hypokalemia in CKD patients was similar at 15-20% and 15-18%, respectively, but more attention needs to be paid to treating and preventing hyperkalemia, which is related to a higher mortality rate, than hypokalemia. Hyperkalemia is prevalent in CKD due to impaired potassium excretion. Serum potassium level is affected by renin-angiotensin-aldosterone system inhibitors and diuretics and dietary potassium intake and can be managed by potassium restriction dietary, optimized renin-angiotensin-aldosterone system inhibitor, sodium polystyrene sulfonate, patiromer, and hemodialysis. This review discussed strategies to mitigate and care for the risk of hypertension and hyperkalemia in CKD patients.

Key Words: Chronic kidney disease, Hypertension, Hyperkalemia, Renin-angiotensin-aldosterone system

INTRODUCTION

Hypertension is commonly observed in patients with chronic kidney disease (CKD)[1], and its prevalence varies from 60% to 90%, depending on the stage and cause of CKD[2]. In CKD, the hypertension mechanisms include sympathetic overactivity, volume overload, endothelial dysfunction, salt retention, and changes in the hormonal system (e.g., increased activity renin-angiotensin-aldosterone system [RAAS]) regulating blood pressure (BP)[2,3].

In addition, serum potassium abnormalities are also commonly observed in CKD patients. In CKD, the severity of CKD, excessive dietary potassium intake, and the use of drugs such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, non-steroidal anti-inflammatory drugs, and potassium-sparing diuretics intake affect serum potassium concentration[4,5,6]. Increased renal and colonic excretion balance potassium until the very late stage of CKD, although hyperkalemia may also occur in the early stage of CKD in patients with hyporeninemia and hypoaldosteronism.

Proper management of hypertension and hyperkalemia in CKD patients may deliver important points for the prognostic management of patients. This article reviews the management strategies to mitigate the risk of hypertension and hyperkalemia for CKD patients.

Controversies of the proper target of blood pressure in CKD management

Up to now, the optimal BP level for hypertension in CKD is still controversial[7-11] since several reasons exist, such as various targets in each guideline, changing targets, and in-

Table 1. Recommended guidelines of blood pressure target for patients with diabetic chronic kidney disease (CKD) and non-diabetic CKD

		KDIGO (2012)[94]	AHA/ACG (2017)[7]	ESH/ESC (2018)[8]	KSH (2018)[95]	KSH (2022)[96]
Non-diabetic CKD	No albuminuria	<140/90	<130/80	130-139/70-79	<140/90	<140/90 (I/A)
	Albuminuria*	<130/80	<130/80	130-139/70-79	<130/80	<130/80 (IIa/B)
Diabetic CKD	No albuminuria	<140/90	<130/80	130-139/70-79	<140/90	<130/80 (IIb/C)
	Albuminuria*	<130/80	<130/80	130-139/70-79	<130/80	
Class/level of recommendation		IB/IID for the presence/absence of albuminuria	IB for the SBP and IC for the DBP target	1A/IIaB for the SBP/DBP target	-	Expert opinion considering the condition of each patient

CKD, chronic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; KDIGO, Kidney Disease Improving Global Outcomes; AHA/ACG, American Heart Association/American College of Cardiology; ESH/ESC, European Society of Hypertension/European Society of Cardiology; KSH, Korean Society of Hypertension.
*Albuminuria indicates urinary albumin excretion ≥30 mg/24h or equivalent[9].

sufficient evidence in CKD patients (Table 1).

The Kidney Disease Improving Global Outcomes guidelines recommended a target of 130/80 mmHg only for patients with albuminuric CKD in 2012, whereas the 2013 European Society of Hypertension/European Society of Cardiology (ESH/ESC) recommended a BP target of 140/90 mmHg for CKD, regardless of albuminuria. In 2015, the Systolic Blood Pressure Intervention Trial (SPRINT) was prematurely discontinued due to the interim analysis results showing that the group with a target of 120 mmHg systolic BPs had a 25% lower risk of cardiovascular disease and a 27% lower risk of all-cause mortality than those of 140 mmHg. Subsequently, the American College of Cardiology/American Heart Association guidelines committee selected the systolic BP target as 130 mmHg, an intensive target in the SPRINT rather than 120 mmHg[12,13]. This selected systolic BP target included concerns about SPRINT application to a broader population and considerations related to SPRINT's highly automated BP measurements, which on average, may be lower than routine clinic measurements. In 2018, for CKD patients, the ESH/ESC guidelines recommended a systolic blood pressure of 130 to 139 mmHg and diastolic blood pressure of 70 to 79 mmHg[8]. A previous study using the data from the Irbesartan in Diabetic Nephropathy Trial indicated decreasing cardiovascular mortality and heart failure with progressively lower achieved systolic BPs to 120 mmHg[14]. Another study involving over 70,000 veterans with eGFR <60 ml/min/m^2 and uncontrolled hypertension demonstrated a mortality hazard ratio was about 1.7 between the veteran groups with systolic BPs less than 120 mmHg and 120 to 139 mmHg[15]. Although these results show lower risks of death and cardiovascular events in people with lower than higher systolic BPs, it will be cautioned that these situations do not necessarily indicate the treatment of hypertension to the same values reduces risks proportionately.

Strategic approaches to hypertension management in CKD

Control of obesity

Obesity is a risk factor for hypertension and the progression of CKD[16-18]. Obesity increases arterial blood pressure by causing excessive renal sodium reabsorption, renal pressure natriuresis, and extracellular fluid volume expansion[19,20]. Increased blood pressure and GFR offset increased renal sodium reabsorption, maintaining sodium balance despite high arterial pressure and renal pressure natriuresis. However, chronically elevated blood pressure, renal vasodilation, and glomerular hyperfiltration may affect renal damage. These phenomena further impair renal pressure

natriuresis and exacerbate hypertension and renal impairment[21].

The results that weight gain increases blood pressure in the relationship between hypertension and obesity are supported by various studies. Population studies have shown that blood pressure is strongly related to anthropometric indicators of obesity, such as waist circumference, waist-to-hip ratio, or body mass index (BMI)[22,23]. A strong relationship between overweight and hypertension has been observed in diverse populations worldwide[23,24]. Thus, excess weight gain is a good predictor of future hypertension development. In a previous study[25], 63 patients with biopsy-proven, obesity-related glomerulopathy participated weight loss program, including diet and exercise. After two years, these patients resulted in a reduction in blood pressure and dyslipidemia, 51% of proteinuria, and 9.2% of BMI. Moreover, a systematic review showed that nonsurgical weight reduction interventions in a small, short-term study of CKD patients reduced proteinuria and BP and seemed to prevent further decline in renal function[26]. The results among three studies with 66 patients also indicated that nonsurgical interventions significantly decreased systolic BP at the end of the study period (95% CI 14.23 to 3.74; p <0.001)[27-29]. In a previous study of 112 obese patients (mean eGFR of 32 ml/min/1.73m^2) with CKD, 22% or more of the participants lost 10% or more of their body weights within 24 months, and systolic BP was also significantly reduced[30]. However, even the researchers of the previous study indicated a limitation in generalizing the results because more than half of the subjects were dialysis patients and were in a specific situation where they could receive medical advice or checkups on regular weight control. Several results have shown a positive effect of weight reduction, but data on weight loss intervention and effects on BP and renal function in CKD patients are still limited. Therefore, it is necessary to proceed with more research efforts on CKD patients' safety and prognosis through appropriate weight reduction.

Dietary salt intake reduction

In a previous study, the interaction between dietary salt intake and RAAS blockade was evaluated in CKD patients, and the effect of dietary sodium intake was also assessed through 24-hour urine sodium excretion[31]. The results of dietary sodium intake showed an apparent decrease in 24-hour urine albumin to creatinine ratio, and systolic BP was most significant in those with the lowest baseline urinary sodium to creatinine ratio.

Reduction of excessive body water

Volume overload accompanying salt retention in CKD patients is a significant cause of hypertension, and body composition can be measured using bioimpedance spectroscopy (BIS) to evaluate the volume status of dialysis patients[32,33]. Mitsides et al. assessed fluid status in CKD patients to evaluate the accuracies of BIS outputs, which may vary with changing tissue ionic sodium concentration (Na^+)[34]. Ten healthy control and 20 CKD patients participated, and the extracellular and intracellular resistance, tissue capacitance, extracellular and total body water were measured using BIS. BIS-derived volumes were 0.4±0.9 L (control group) and 0.5±1.9 L (CKD group) without significance (p=0.13). However, the CKD group showed significantly higher Na^+ (25.3±7.4 mmol/L) than the control group (21.2±3.0 mmol/L, p=0.04). The extracellular resistance in the CKD group (609±74.3 Ohms) was significantly lower than the control group (693±93.6 Ohms, p=0.01), and intracellular resistance and capacitance did not vary. Moreover, Na^+ showed a significant inverse linear relationship to extracellular resistance (r=-0.598, p<0.01), and tissue Na^+ concentration has a significant inverse linear relationship to extracellular resistance. Khan et al. performed a prospective observational study to assess the relationship between fluid overload and hypertension using diuretic therapy with BIS[35]. 312 CKD patients were enrolled and categorized in five different parts of hydration reference plot (HRP) generated by BIS (5.1% [normal BP and fluid status], 20.5% [hypertensive with severe fluid overload], 29.5% [hypertensive with mild fluid overload], 22% [hypertensive with normohydration], 10.2% [underhydration with normal/low BP] and 12.5% [normal BP with severe fluid overload]). Diuretics were administered to 46% of all patients due to BP and edema and were prescribed to most patients with [hypertensive with severe fluid overload] and [hypertensive with mild fluid overload]. The results showed that the BIS

helps classify CKS patients according to body fluid status and to manage hypertensive CKD patients. Verdalles et al. performed an evaluation study using BIS[36]. They divided patients with the dilatation of extracellular volume (ECV) measured by BIS into two groups as follows; the patients with ECV dilatation injected with a diuretic (n=30) and those without ECV dilation injected with an additional antihypertensive (n=20). After six months of follow-up, it was confirmed that the systolic BP decreased more in the patients with the ECV dilation group compared with those without ECV dilatation (21 mmHg vs. 9 mmHg, respectively; $p < 0.01$). In addition, nine patients in the ECV dilatation group and two in the other group reached a target BP of less than 140/90 mmHg. Although the BIS can be used as an effective approach for evaluating volume status, the BIS still needs further study in larger cohorts before it can become a generalized method.

Antihypertensives

Antihypertensives are often used in CKD and hypertension patients to achieve target BP. The selective renin inhibitor Aliskiren[37,38] and the selective endothelial antagonist Sitaxentan[39] have been shown to affect BP. In addition, a 36-week randomized clinical trial using Aldactone, a steroid mineralocorticoid receptor antagonist, showed well tolerated in early stage 3 CKD patients with fewer than 1% episodes of hyperkalemia ($K^+ \geq 6$ mmol/l)[40]. However, these antihypertensive trials and the accurate results are not yet widely adopted in CKD patients. Although Aliskiren has antihypertensive properties, large randomized trials of Aliskiren in combination with ACEi or ARB therapy in diabetes or heart failure found no renal benefit, with the adverse event for the combination, such as hyperkalemia[41,42]. Aldactone is also used for treatment-resistance and control of hypertension, but caution is needed in CKD patients because of hyperkalemia risk[43]. Therefore, additional researches on antihypertensives based on key factors that can achieve the goal of BP control, renal protection, and slowing the progression of CKD need to be studied to improve treatment strategies.

Hyperkalemia in CKD

Hyperkalemia, commonly defined as plasma potassium greater than 5.5 mEq/L[44], is associated with a higher mortality rate, contributing to 1.9%-5% of deaths in patients with ESRD[45,46]. Hyperkalemia is strongly associated with impaired renal potassium excretion and not a redistribution of potassium[45]. Since the kidney in a normal condition can excrete a large amount of potassium, even if 400 mEq of KCl is consumed daily, several times higher than usual, plasma potassium will increase to less than 1 mEq/L on average if normal renal function and potassium excretion mechanism are ensured[46]. Therefore, hyperkalemia may indicate a fundamental impairment in renal potassium excretion[47]. These phenomena are possibly due to progressive CKD reducing the number of nephron units available for potassium secretion or impairing the rate of collecting duct potassium secretion. In addition, hypoaldosteronism can lead to decreased renal potassium excretion and acidosis, especially in metabolic acidosis, which may affect hyperkalemia by intracellular potassium exchanging for extracellular hydrogen[45,48]. In CKD, particularly in stages 4 or 5, potassium can be excreted extrarenal from sites such as the colon[45,49]. This phenomenon can be detected when GFR decreases to 1/3 and accounts for potassium elimination of 10-20 mEq/day[50]. Moreover, a normal person eliminates 5-10% of their intake, but patients with uremia may remove up to 25% of their daily potassium excretion from the body inappropriately through the gastrointestinal tract[51].

Hyperkalemia-inducible drugs

Beta-blockers such as propranolol increase potassium uptake, which is β2-receptor-specific, including cyclic adenosine monophosphate stimulation and Na^+-k^+ ATPase activation[45]. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists reduce the aldosterone-mediated effect on renal potassium excretion, induce hyperkalemia, and the resulting adrenal release from aldosterone depends on the adrenal-renal angiotensin system[52,53]. Non-steroidal anti-inflammatory drugs (NSAIDs) cause hyperkalemia by decreasing distal delivery and flow rate of Na+ and reducing the flow-related component of potassium excretion[45,54]. Cyclooxygenase-2 inhibitors that induce sodium retention and decreased GFR can also lead to hyperkalemia[55,56]. Potassium-sparing diuretics, such as triamterene and amiloride, cause hyperkalemia by in-

hibiting apical epithelial sodium channel activity in the cortical collecting duct[57,58]. Digoxin may induce hyperkalemia due to impaired renal excretion and impaired intracellular potassium absorption[59]. In addition, cyclosporine (cyclosporine A) and tacrolimus are known to induce hyperkalemia[60,61].

Strategic approaches to potassium management in CKD

Management of dietary intake

Potassium and sodium intakes need to be considered simultaneously. High dietary K^+ intake blunts diseases associated with an excessive sodium diet, such as hypertension and cardiovascular disease, whereas low dietary potassium increases the outcome of more dietary sodium[62]. In this regard, many previous studies have reported that higher dietary sodium and lower potassium could have detrimental effects on the progression of CKD, hypertension, and diabetes[62,63]. Moreover, Korean and American diets lack potassium and are acid-producing due to the meat-based diets[64]. A meat-based diet that does not involve an intake of fruits and vegetables is related to high net endogenous acid production known to contribute to CKD progression. Therefore, proper intake of dietary fruits and vegetables and administration of endogenous alkalis may not only reduce net endogenous acid production rather, it slows the progression of CKD[65]. However, restricting dietary K^+ is not the only correct method for all CKD patients. For example, a fruit and vegetable diet is recommended for patients with early-stage CKD with clinical hypokalemia or patients with borderline hypokalemia. Therefore, dietary K^+ restriction must be cautiously applied in patients with more advanced CKD and documented hyperkalemia. A low-potassium diet is recommended for patients with advanced CKD and hyperkalemia. Clinical guidelines recommend that patients receive regular advice, such as an individualized diet and nutritionist counseling, when limiting potassium intake[66,67]. In a comprehensive review paper[68], Kalantar-Zadeh and Fouque suggested an intake of 4.7 g/day in the early stages of CKD patients but a dietary potassium restriction of less than 3 g per day in CKD patients who tend to develop hyperkalemia. Ogata et al. found significant but relatively weak associations between serum potassium and dietary potassium intake estimated by urine collections in CKD patients (unadjusted R2 values were 0.08, 0.14, and 0.18 for CKD stages 3, 4, and 5, respectively)[69]. Similarly, Noori et al. also showed a weak association (r=0.14) between dietary potassium and serum potassium among 224 patients[70]. In addition, a low potassium diet may also result in folic acid deficiency in advanced CKD patients. A previous study reported that the incidence of folic acid deficiency in patients with CKD stage 3-4 on a potassium-restricted diet was three times higher than in patients with CKD stage 1-2 on an unrestricted potassium diet[71]. Moreover, severe folic acid deficiency may increase the risk of cancers, cardiovascular disease, and neurological disorders[71].

Renin-angiotensin-aldosterone system inhibitor

Hyperkalemia in CKD patients can be managed by optimized RAAS inhibitor therapy or by limiting K^+ dietary[72,73]. The RAAS inhibitor therapy, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, slows the progression of CKD and improves the prognosis in concomitant diseases such as hypertension and diabetes. Moreover, RAAS inhibitor therapy has advantages in patients with CKD early stage for reducing hypertension and glomerulosclerosis, and patients with CKD late stage and hemodialysis for maintaining residual renal funtional[74]. On the other hand, RAAS inhibitors may also increase the risk of hyperkalemia[75]. It should be cautioned that when RAAS inhibitors are used in patients with reduced renal function, the risk of hyperkalemia may be increased, as aldosterone modulates potassium excretion by the kidneys[76]. Previous studies reported that hyperkalemia related to RAAS inhibitor takes occurrence 5% to 10% in CKD patients, whereas patients without CKD have less than 2% occurrence[77,78]. Therefore, using RAAS inhibitors requires attention and the most optimal dosage considering the patient's benefit. Furthermore, multiple researchers are also studying to verify using new K^+ binding agents such as sodium zirconium cyclosilicate (SZC) and Partiromer that maintains optimal RAAS inhibitor therapy and decreases serum K^+ (More detailed information on newer K^+ binding agents is explained following sections). Note that continuous further studies should accompany long-term clinical studies for evaluating

new K^+ binding agents, although the benefits of these new K^+ binding agents are being reported.

Potassium-lowering drugs

Sodium Polystyrene Sulfonate (SPS) is an insoluble polymeric cation exchange resin applied in oral formulation or by the rectal route to exchange sodium for potassium ions. Potassium binds to SPS and moves through the gastrointestinal tract before being eliminated in the feces[79,80]. SPS acts within 2 to 24 hours after administration and continues for 4 to 6 hours before being eliminated from the body[81]. The exchange capacity of SPS is about 33% or 1 mEq of potassium per gram of resin. SPS is not selective for potassium in the body, such as being able to bind with calcium or magnesium, so the exchange capacity of the resin is not constant and may reduce. A previous study for a randomized controlled trial evaluated the effect of SPS in CKD patients with 5.0 to 5.9 mEq/L serum K^+ concentrations (double-blind test with two groups; with oral sorbitol-free SPS and placebo[82]. The results demonstrated that the SPS group showed an apparent effect in reducing serum K^+ with significance compared to the placebo group. However, caution is needed in using SPS as studies report concerns about poor tolerability and serious gastrointestinal side effects.

SZC is a non-polymeric compound that exchanges K^+ for sodium and hydrogen ions in the gastrointestinal tract, clears bound K^+ via the feces, and is used for the management of hyperkalemia[83]. Previous studies have reported that SZC helps correct hyperkalemia and maintain normokalemia in CKD patients. Roger et al., in a long-term study of 751 outpatients with hyperkalemia, showed that serum K+ levels normalized after initiation of SZC, and normokalemia was maintained for up to 12 months[84]. Ash et al. also showed that SZC significantly reduced serum K^+ levels in a randomized, double-blind, placebo-controlled study of 90 patients with hyperkalemia and stage 3 CKD (eGFR 30-60 mL/min/1.73 m^2)[85]. It has been reported that SZC administration is beneficial for managing serum K^+ concentration in patients with hyperkalemia, while another study reported that caution should be taken for dose-related mild to moderate edema due to reductions of dosage[86,87].

Patiromer and the SZC mentioned above is a new K^+ binding drug that effectively reduces serum K^+ concentrations in CKD patients with hyperkalemia. Patiomer is a spherical and nonabsorbable polymer with higher potassium binding capacity than polystyrene sulfonate polymers[88,89]. It is characterized by low water absorption and includes calcium rather than sodium in the exchange cation[90]. Moreover, patiomer is fully ionized at the physiological pH of the colon for optimal ion exchange with the highest potassium concentration in the gastrointestinal tract[88]. Various studies have shown that in CKD patients receiving RAAS inhibitor therapy, patiromer significantly reduces serum K^+ concentration and positively affects the continuation of RAAS inhibitor therapy[91,92]. However, despite the pharmacological properties and potassium-lowering effect of patiomer, as shown in the previous study and meta-analyses[93], it needs caution for adverse events such as nausea, constipation, and diarrhea.

Future consideration

By monitoring the effects, treatment, and favorable prognosis of hypertension and potassium metabolisms in patients with CKD, medical staff must try to balance the expected benefits and adverse effects caused by potassium restriction and RAAS inhibitors. In the hypertension domain, there is a need to expand attention not only to the use of antihypertensives but also to improving patients' lifestyles, such as sodium intake and obesity control. Moreover, while potassium-lowering therapies with patiromer or SZC have been beneficial in effectively and safely correcting hyperkalemia in patients, it should be noted that research is still ongoing to overcome some concerns about continued efficacy and safety. Thus, developing and continuously researching drugs that can effectively control the potassium level without worrying about adverse effects and a diet for controlling potassium are necessary.

REFERENCES

1. Jung HH: Hypertension Management in Patients with Chronic Kidney Disease in the Post-SPRINT Era. Electrolyte Blood Press 2021;19:19-28.
2. Ravarotto V, Bertoldi G, Stefanelli LF, Nalesso F, Calò LA:

Pathomechanism of oxidative stress in cardiovascular-renal remodeling and therapeutic strategies. Kidney Res Clin Pract 2022;41:533-544.
3. Rabbani R, Noel E, Boyle S et al.: Role of Anti-hypertensives in End-Stage Renal Disease: A Systematic Review. Cureus 2022;14:e27058.
4. Gilligan S, Raphael KL: Hyperkalemia and Hypokalemia in CKD: Prevalence, Risk Factors, and Clinical Outcomes. Adv Chronic Kidney Dis 2017;24:315-318.
5. Preston RA, Afshartous D, Garg D, Medrano S, Alonso AB, Rodriguez R: Mechanisms of impaired potassium handling with dual renin-angiotensin-aldosterone blockade in chronic kidney disease. Hypertension 2009;53:754-760.
6. Bianchi S, Aucella F, De Nicola L, Genovesi S, Paoletti E, Regolisti G: Management of hyperkalemia in patients with kidney disease: a position paper endorsed by the Italian Society of Nephrology. J Nephrol 2019;32:499-516.
7. Whelton PK, Carey RM, Aronow WS, et al.: 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018;71:1269-1324.
8. Williams B, Mancia G, Spiering W, et al.: 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021-3104.
9. Georgianos PI, Agarwal R: Hypertension in Chronic Kidney Disease (CKD): Diagnosis, Classification, and Therapeutic Targets. Am J Hypertens 2021;34:318-326.
10. Chang AR, Lóser M, Malhotra R, Appel LJ: Blood pressure goals in patients with CKD: a review of evidence and guidelines. Clin J Am Soc Nephrol 2019;14:161-169.
11. Modi GK, Agarwal R: What are optimal blood pressure targets for patients with hypertension and chronic kidney disease? Curr Cardiol Rep 2015;17:101.
12. Wright JT Jr., Williamson JD, Whelton PK, et el.: SPRINT Research Group: A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103-2116.
13. Whelton PK, Carey RM, Aronow WS, et al.: 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension 2018;71:1269-1324.
14. Berl T, Hunsicker LG, Lewis JB, et al.: Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial. J Am Soc Nephrol 2005;16:2170-2179.
15. Kovesdy CP, Lu JL, Molnar MZ, et al.: Observational modeling of strict vs conventional blood pressure control in patients with chronic kidney disease. JAMA Intern Med 2014;174:1442-1449.
16. Wilson PWF, D'Agostino RB, Sullivan L, Parise H, Kannel WB: Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. Arch Intern Med 2002;162:1867-1872.
17. Gelber RP, Kurth T, Kausz AT, et al.: Association between body mass index and CKD in apparently healthy men. Am J Kidney Dis 2005;46:871-880.
18. Iseki K, Ikemiya Y, Kinjo K, Inoue T, Iseki C, Takishita S: Body mass index and the risk of development of end-stage renal disease in a screened cohort. Kidney Int 2004;65:1870-1876.
19. Hall JE, Crook ED, Jones DW, Wofford MR, Dubbert PM: Mechanisms of obesity-associated cardiovascular and renal disease. Am J Med Sci 2002;324:127-137.
20. Hall JE, da Silva AA, do Carmo JM, et al.: Obesity-induced hypertension: role of sympathetic nervous system, leptin, and melanocortins. J Biol Chem 2010;285:17271-17276.
21. Hall ME, do Carmo JM, da Silva AA, Juncos LA, Wang Z, Hall JE: Obesity, hypertension, and chronic kidney disease. Int J Nephrol Renovasc Dis 2014;18:75-88.
22. Alexander J, Dustan HP, Sims EAH: Report of the Hypertension Task Force. Department of Health Education and Welfare publication no (DHEW) 70-1631. Washington, DC: US Department of Health, Education, and Welfare 1979:61-77.
23. Jones DW, Kim JS, Andrew ME, Kim SJ, Hong YP: Body mass index and blood pressures in Korean men and women: the Korean National Blood Pressure Survey. J Hypertens 1994;12:1433-1437.
24. Cooper RS, Rotimi CN, Ward R: The puzzle of hypertension in African-Americans. Sci Am 1999;280:56-63.
25. Shen WW, Chen HM, Chen H, Xu F, Li LS, Liu ZH: Obesity-related glomerulopathy: body mass index and proteinuria. Clin J Am Soc Nephrol 2010;5:1401-1409.
26. Navaneethan SD, Yehnert H, Moustarah F, Schreiber MJ, Schauer PR, Beddhu S: Weight loss interventions in chronic kidney disease: A systematic review and meta-analysis. Clin J Am Soc Nephrol 2009;4:1565-1574.
27. Morales E, Valero MA, León M, Hernández E, Praga M: Beneficial effects of weight loss in overweight patients with chronic proteinuric nephropathies. Am J Kidney Dis 2003;41:319-327.

28. Saiki A, Nagayama D, Ohhira M, et al.: Effect of weight loss using formula diet on renal function in obese patients with diabetic nephropathy. Int J Obes (Lond) 2005;29:1115-1120.
29. Solerte SB, Fioravanti M, Schifino N, Ferrari E: Effects of diet-therapy on urinary protein excretion albuminuria and renal haemodynamic function in obese diabetic patients with overt nephropathy. Int J Obes 1989;13:203-211.
30. MacLaughlin HL, Cook SA, Kariyawasam D, Roseke M, van Niekerk M, Macdougall IC: Nonrandomized trial of weight loss with orlistat, nutrition education, diet, and exercise in obese patients with CKD: 2-year follow-up. Am J Kidney Dis 2010;55:69-76.
31. Heerspink HJL, Holtkamp FA, Parving HH, et al.: Moderation of dietary sodium potentiates the renal and cardiovascular protective effects of angiotensin receptor blockers. Kidney Int 2012;82:330-337.
32. Garimella PS, Uhlig K: Current issues in the management and monitoring of hypertension in chronic kidney disease. Curr Opin Nephrol Hypertens 2013;22:599-606.
33. Crepaldi C, Soni S, Chionh CY, Wabel P, Cruz DN, Ronco C: Application of body composition monitoring to peritoneal dialysis patients. Contrib Nephrol 2009;163:1-6.
34. Mitsides N, McHugh D, Swiecicka A, et al.: Extracellular resistance is sensitive to tissue sodium status; implications for bioimpedance-derived fluid volume parameters in chronic kidney disease. J Nephrol 2020;33:119-127.
35. Khan YH, Sarriff A, Adnan AS, Khan AH, Mallhi TH: Diuretics prescribing in chronic kidney disease patients: physician assessment versus bioimpedence spectroscopy. Clin Exp Nephrol 2017;21:488-496.
36. Verdalles U, de Vinuesa SG, Goicoechea M, et al.: Utility of bioimpedance spectroscopy (BIS) in the management of refractory hypertension in patients with chronic kidney disease (CKD). Nephrol Dial Transplant 2012;27(Suppl 4):iv31-iv35.
37. Sakai Y, Otsuka T, Ohno D, Murasawa T, Sato N, Mizuno K: Efficacy of aliskiren in Japanese chronic kidney disease patients with hypertension. Ren Fail 2012;34:442-447.
38. Siddiqi L, Oey PL, Blankestijn PJ: Aliskiren reduces sympathetic nerve activity and blood pressure in chronic kidney disease patients. Nephrol Dial Transplant 2011;26:2930-2934.
39. Dhaun N, MacIntyre IM, Kerr D, et al.: Selective endothelin-A receptor antagonism reduces proteinuria, blood pressure, and arterial stiffness in chronic proteinuric kidney disease. Hypertension 2011;57:772-779.
40. Edwards NC, Steeds RP, Chue CD, Stewart PM, Ferro CJ, Townend JN: The safety and tolerability of spironolactone in patients with mild to moderate chronic kidney disease. Br J Clin Pharmacol 2012;73:447-454.
41. Parving HH, Brenner BM, McMurray JJ, et al.: ALTITUDE Investigators. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med 2012;367:2204-2213.
42. McMurray JJ, Krum H, Abraham WT, et al.: ATMOSPHERE Committees Investigators. Aliskiren, Enalapril, or Aliskiren and Enalapril in Heart Failure. N Engl J Med 2016;374:1521-1532.
43. Bakris G, Yang YF, Pitt B: Mineralocorticoid Receptor Antagonists for Hypertension Management in Advanced Chronic Kidney Disease: BLOCK-CKD Trial. Hypertension 2020;76:144-149.
44. Dépret F, Peacock WF, Liu KD, Rafique Z, Rossignol P, Legrand M: Management of hyperkalemia in the acutely ill patient. Ann Intensive Care 2019;9:32.
45. Han SW: Hyperkalemia in Chronic Kidney Disease. Electrolyte Blood Press 2005;3:71-78.
46. Mount DB, Zandi-Nejad K: Disorders of Potassium Balance. In: Brenner & Rector's the Kidney, 7th ed., edited by Brenner BM, Philadelphia, WB Saunders Company, 2004, p997-1040.
47. Weiner ID, Linas SL, Wingo CS: Disorders of potassium metabolism. In: Clinical Comprehensive Nephrology, 2nd ed., edited by Johnson RJ, Feehally J, Philadelphia, Mosby, 2003, p109-121.
48. Schambelan M, Sebastian A, Biglieri EG: Prevalence, pathogenesis, and functional significance of aldosterone deficiency in hyperkalemic patients with chronic renal insufficiency. Kidney Int 1980;17:89-101.
49. Watanabe R: Hyperkalemia in chronic kidney disease. Rev Assoc Med Bras 2020;66(Suppl 1):S31-S36.
50. Panese S, Martin RS, Virginillo M, et al.: Mechanism of enhanced transcellular potassium-secretion in man with chronic renal failure. Kidney Int 1987;31:1377-1382.
51. Martin RS, Panese S, Virginillo M, et al.: Increased secretion of potassium in the rectum of man with chronic renal failure. Am J Kidney Dis 1986;8:105-110.
52. Bakris GL, Siomos M, Richardson D, et al.: ACE inhibition or angiotensin receptor blockade: Impact on potassium in renal failure. VAL-K Study Group. Kidney Int 2000;58:2084-2092.
53. Hilbers U, Peters J, Bornstein SR, et al.: Local renin- angiotensin system is involved in K+-induced aldosterone secretion from human adrenocortical NCI-H295 cells. Hypertension 1999;33:1025-1030.
54. Woda CB, Bragin A, Kleyman TR, Satlin LM: Flow-dependent K+ secretion in the cortical collecting duct is mediated by a maxi-K channel. Am J Physiol Renal Physiol 2001;280:F786-F793.

55. Roig F, Llinas MT, Lopez R, Salazar FJ: Role of cyclooxygenase-2 in the prolonged regulation of renal function. Hypertension 2002;40:721-728.
56. Harris RC, Breyer MD: Update on cyclooxygenase-2 inhibitors. Clin J Am Soc Nephrol 2006;1:236-245.
57. Cohen AB: Hyperkalemic effects of triamterene. Ann Intern Med 1966;65:521-527.
58. Rossier BC: Epithelial sodium channel (ENaC) and the control of blood pressure. Curr Opin Pharmacol 2014;15:33-46.
59. Eichhorn EJ, Gheorghiade M: Digoxin. Prog Cardiovasc Dis 2002;44:251-266.
60. Perazella MA: Drug-induced hyperkalemia: Old culprits and new offenders. Am J Med 2000;109:307-314.
61. Oishi M, Yagi T, Urushihara N, et al.: A case of hyperkalemic distal renal tubular acidosis secondary to tacrolimus in living donor liver transplantation. Transplant Proc 2000;32:2225-2226.
62. DuBose TD Jr.: Inadequate Dietary Potassium and Progression of CKD. Clin J Am Soc Nephrol 2019;14:319-320.
63. Sebastian A, Cordain L, Frassetto L, Banerjee T, Morris RC Jr.: Postulating the major environmental condition resulting in the expression of essential hypertension and its associated cardiovascular diseases: Dietary imprudence in daily selection of foods in respect of their potassium and sodium content resulting in oxidative stress-induced dysfunction of the vascular endothelium, vascular smooth muscle, and perivascular tissues. Med Hypotheses 2018;119:110-119.
64. Kim HW, Park JT, Yoo TH, et al.: KNOW-CKD Study Investigators. Clin J Am Soc Nephrol 2019;14:330-340.
65. Goraya N, Simoni J, Jo CH, Wesson DE: Treatment of metabolic acidosis in patients with stage 3 chronic kidney disease with fruits and vegetables or oral bicarbonate reduces urine angiotensinogen and preserves glomerular filtration rate. Kidney Int 2014;86:1031-1038.
66. KDIGO: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:S1-S150.
67. KDOQI. Chronic kidney disease: major recommendations. https://www.andeal.org/vault/pqnew95.pdf.
68. Kalantar-Zadeh K, Fouque D: Nutritional Management of Chronic Kidney Disease. N Engl J Med 2017;377:1765-1776.
69. Ogata S, Akashi Y, Kato S, et al.: Association Between Dietary Potassium Intake Estimated from Multiple 24-Hour Urine Collections and Serum Potassium in Patients With CKD. Kidney Int Rep 2022;8:584-595.
70. Noori N, Kalantar-Zadeh K, Kovesdy CP, et al.: Dietary potassium intake and mortality in long-term hemodialysis patients. Am J Kidney Dis 2010;56:338-347.
71. Hassan K: Association of low potassium diet and folic acid deficiency in patients with CKD. Ther Clin Risk Manag 2015;11:821-827.
72. Chang AR, Sang Y, Leddy J, et al.: Anti-hypertensive medications and the prevalence of hyperkalemia in a large health system. Hypertension 2016;67:1181-1188.
73. Palmer BF, Clegg DJ: Achieving the benefits of a highpotassium, paleolithic diet, without the toxicity. Mayo Clin Proc 2016;91:496-508.
74. Zhang F, Liu H, Liu D, et al.: Effects of RAAS inhibitors in patients with kidney disease. Curr Hypertens Rep 2017;19:72.
75. Packham DK, Rasmussen HS, Lavin PT, et al.: Sodium zirconium cyclosilicate in hyperkalemia. N Engl J Med 2015;372:222-231.
76. Bandak G, Sang Y, Gasparini A, et al.: Hyperkalemia after initiating renin-angiotensin system blockade: the Stockholm Creatinine Measurements (SCREAM) project. J Am Heart Assoc 2017;6:e005428.
77. Kosiborod M, Rasmussen HS, Lavin P, et al.: Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. JAMA 2014;312:2223-2233.
78. Dunn JD, Benton WW, Orozco-Torrentera E, Adamson RT: The burden of hyperkalemia in patients with cardiovascular and renal disease. Am J Manag Care 2015;21(15, suppl):s307-s315.
79. Gruy-Kapral C, Emmett M, Santa Ana CA, Porter JL, Fordtran JS, Fine KD: Effect of single dose resin-cathartic therapy on serum potassium concentration in patients with end-stage renal disease. J Am Soc Nephrol 1998;9:1924-1930.
80. Sterns RH, Rojas M, Bernstein P, Chennupati S: Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective? J Am Soc Nephrol 2010;21:733-735.
81. Kessler C, Ng J, Valdez K, Xie H, Geiger B: The use of sodium polystyrene sulfonate in the inpatient management of hyperkalemia. J Hosp Med 2011;6:136-140.
82. Lepage L, Dufour AC, Doiron J, et al.: Randomized clinical trial of sodium polystyrene sulfonate for the treatment of mild hyperkalemia in CKD. Clin J Am Soc Nephrol 2015;10:2136-2142.
83. Hoy SM: Sodium zirconium cyclosilicate: a review in hyperkalaemia. Drugs 2018;78:1605-1613.
84. Roger SD, Lavin PT, Lerma EV, et al.: Long-term safety and efficacy of sodium zirconium cyclosilicate for hyperkalaemia in patients with mild/moderate versus severe/end-stage chronic kidney disease: comparative results from an open-label, Phase 3 study. Nephrol Dial Transplant 2021;36:137-150.
85. Ash SR, Singh B, Lavin PT, Stavros F, Rasmussen HS: A phase

2 study on the treatment of hyperkalemia in patients with chronic kidney disease suggests that the selective potassium trap, ZS-9, is safe and efficient. Kidney Int 2015;88: 404-411.
86. Lokelma [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP;2018.
87. Palmer BF: Potassium Binders for Hyperkalemia in Chronic Kidney Disease-Diet, Renin-Angiotensin-Aldosterone System Inhibitor Therapy, and Hemodialysis. Mayo Clin Proc 2020; 95:339-354.
88. Li L, Harrison SD, Cope MJ, et al.: Mechanism of Action and Pharmacology of Patiromer, a Nonabsorbed Cross-Linked Polymer That Lowers Serum Potassium Concentra- tion in Patients With Hyperkalemia. J Cardiovasc Pharmacol Ther 2016;21:456-465.
89. Rosano GMC, Spoletini I, Agewall S: Pharmacology of new treatments for hyperkalaemia: patiromer and sodium zirconium cyclosilicate. Eur Heart J Suppl 2019;21(Suppl A):A28-A33.
90. Montaperto AG, Gandhi MA, Gashlin LZ, Symoniak MR: Patiromer: a clinical review. Curr Med Res Opin 2016;32: 155-164.
91. Pitt B, Anker SD, Bushinsky DA, et al.: Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. Eur Heart J 2011;32:820-828.
92. Weir MR, Bakris GL, Bushinsky DA, et al.: Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med 2015;372:211-221.
93. Meaney CJ, Beccari MV, Yang Y, Zhao J: Systematic Review and Meta-Analysis of Patiromer and Sodium Zirconium Cyclosilicate: A New Armamentarium for the Treatment of Hyperkalemia. Pharmacotherapy 2017;37:401-411.
94. Becker GJ, Wheeler DC, De Zeeuw D, et al.: Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group: KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int Suppl 2012;2:337-414.
95. Lee HY, Shin J, Kim GH, et al.: 2018 Korean Society of Hypertension Guidelines for the management of hypertension: part II-diagnosis and treatment of hypertension. Clin Hypertens 2019;25:20.
96. The Korean Society of Hypertension. 2022 Hypertension treatment guideline. https://www.koreanhypertension.org/reference/guide?mode=read&idno=10081.

Review Article

ISSN 1738-5997 (Print) · ISSN 2092-9935 (Online)
Electrolyte Blood Press 2023;21:34-43
https://doi.org/10.5049/EBP.2023.21.1.34

Hidden Acid Retention with Normal Serum Bicarbonate Level in Chronic Kidney Disease

Eun Sil Koh

Division of Nephrology, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Received: April 5, 2023
Revised: April 6, 2023
Accepted: April 16, 2023
Corresponding Author: Eun Sil Koh, MD, PhD
Division of Nephrology, Department of Internal Medicine, College of Medicine, Yeouido St. Mary's Hospital, The Catholic University of Korea, 10, 63-ro Yeongdeungpo-gu, Seoul 07345, Korea
Tel: +82-2-3779-2412; Fax: +82-2-3779-1364
E-mail: fiji79@catholic.ac.kr

Management of metabolic acidosis is crucial for preserving bone, muscle, and renal health, as evidenced by the results of several interventional studies conducted on patients with chronic kidney disease (CKD). Considering the continuity of CKD progression over time, it is reasonable to deduce that a subclinical form of metabolic acidosis may exist prior to the manifestation of overt metabolic acidosis. Covert H^+ retention with normal serum bicarbonate level in patients with CKD may result in maladaptive responses that contribute to kidney function deterioration, even in the early stages of the disease. The loss of adaptive compensatory mechanisms of urinary acid excretion may be a key factor in this process. Early modulation of these responses could be an important therapeutic strategy in preventing CKD progression. However, to date, the optimal approach for alkali therapy in subclinical metabolic acidosis in CKD remains uncertain. There is a lack of established guidelines on when to initiate alkali therapy, potential side effects of alkali agents, and the optimal blood bicarbonate levels based on evidence-based practices. Therefore, further research is necessary to address these concerns and establish more robust guidelines for the use of alkali therapy in patients with CKD. Herein, we provide an overview of recent developments on this subject and examine the potential therapeutic approaches that interventional treatments may present for patients with hidden H^+ retention, exhibiting normal serum bicarbonate levels - commonly described as subclinical or eubicarbonatemic metabolic acidosis in patients with CKD.

Key Words: Metabolic acidosis, Chronic kidney disease, Serum bicarbonate, Total carbon dioxide

INTRODUCTION

Chronic kidney disease (CKD) is characterized as a set of sustained changes in the structure or function of the kidneys, which have consequences for the overall health of the affected individual[1]. The prevalence of CKD, at all stages, displays regional differences with a range of 7-12%, across various parts of the world. CKD imposes a significant burden of national healthcare costs, especially in treating patients who require renal replacement therapy. Chronic metabolic acidosis is a prevalent condition among individuals diagnosed with CKD, resulting form a primary disruption in the regulation of acid-base equilibrium[2]. As renal function deteriorates, there is a clinical presentation where hyperchloremic acidosis transitions to high anion gap acidosis. The pathogenesis is attributed to inadequate filtration and reabsorption of organic anions. With the progression of renal disease, the amount of functional nephrons eventually becomes inadequate to effectively manage the net production of acids. Therefore, the prevalence and severity of metabolic acidosis in CKD patients progressively rises

as glomerular filtration rate (GFR) falls.

The Kidneys initially make adaptations to excrete acid, which helps prevent a decrease in the concentration of bicarbonate in the blood. In addition, despite significant retention of acid, the serum bicarbonate level does not decrease further, indicating participation of buffers outside the extracellular compartment. In CKD, acid retention occurs, which is buffered by alkali salts derived from bone. Consequently, the reduction of bone calcium carbonate due to chronic acidosis causes an increase in urinary calcium excretion, which is proportional to the accumulated acid secretion. However, as the GFR continues to decrease below 40 ml/min per 1.73 m^2, this protective mechanism becomes less effective. Chronic metabolic acidosis is also associated with increased protein catabolism, muscle wasting, impaired cardiac function, CKD progression, and increased mortality[1-4]. The connection between declining serum bicarbonate levels and worsening clinical outcomes has sparked numerous studies where addressing metabolic acidosis has slowed the progression of CKD[5-7]. Consequently, we can infer that managing metabolic acidosis through alkali replacement might be a potential therapeutic approach for improving the previously mentioned health conditions. As one might expect, in the past 20 years, a wealth of research has explored the impact of oral alkali therapy on CKD progression for stage 3-5 patients with reduced serum bicarbonate levels[3]. Although there is evidence of low-to-moderate certainty indicating that oral alkali supplementation or a decrease in dietary acid consumption may decelerate the decline of kidney function in individuals with CKD and metabolic acidosis[8].

The idea that treatment of acidosis could be beneficial in preserving kidney function was first proposed by Richard Bright, followed by Arthur Osman and Lyon et al. who conducted a crossover study showing that supplementation with bicarbonate might help preserve kidney function[5,9,10]. Mathur et al. conducted a randomized trial and showed that correction of metabolic acidosis significantly attenuates the rise in blood urea in patients with mild to moderate CKD. There were no significant differences in baseline characteristics between the bicarbonate and placebo groups[4]. A significant study demonstrating the benefits of alkali administration in patients with CKD and metabolic acidosis was conducted by Brito-Ashurst and his colleagues[6]. They revealed that, over a 2-year period, oral sodium bicarbonate supplementation delayed CKD progression and improved nutritional status, demonstrating its potential benefits for 134 CKD patients with baseline HCO_3 level 16 to 20 mEq/L.

Drawing upon this evidence, the KDIGO 2012 Clinical Practice Guideline recommend normalizing serum bicarbonate levels using alkali therapy when levels fall below 22 mEq/L, provided there are no specific contraindications[11]. It is worth noting that the research underpinning these recommendations has focused solely on hypobicarbonatemic CKD patients or animal models. However, several experimental studies and clinical trial results have suggested that H^+ retention may be present even when serum bicarbonate levels are within the normal range[12-14]. Considering the continuity of CKD progression over time, it is reasonable to infer that a subclinical form of metabolic acidosis may exist prior to the manifestation of overt metabolic acidosis. However, to date, there has been limited in-depth research regarding the clinical significance and importance of such subclinical forms of metabolic acidosis. In this review, we provide an overview of recent developments on this subject and examine the potential therapeutic approaches that interventional treatments may present for patients with hidden H^+ retention, exhibiting normal serum bicarbonate levels - commonly described as subclinical or eubicarbonatemic metabolic acidosis.

Prevalence and Clinical Course of Subclinical Metabolic Acidosis

Since we do not routinely and accurately assess covert H^+ retention in patients with CKD, the actual prevalence of subclinical metabolic acidosis is unknown, but it is likely to be higher than expected. In one study, it has been reported that approximately 85% of non-dialysis patients were found to have normal serum bicarbonate levels[15]. It is unclear what proportion of these individuals exhibit H^+ retention, which would consequently classify them as having subclinical metabolic acidosis. In two recent studies, nearly every eubicarbonatemic patient with stage 2 CKD assessed at baseline exhibited an estimated H^+ retention greater than 0 mEq[16,17]. Therefore, by embracing the broader definition of the condition, metabolic acidosis can be considered an

early complication of CKD. Nonetheless, the sample size of the tested population is limited, necessitating further research in this area. It can be hypothesized that estimated H^+ retention would be greater and virtually ubiquitous in eubicarbonatemic patients with CKD stages 3 and 4. While the exact prevalence is yet to be established, subclinical metabolic acidosis is probably prevalent in the majority of CKD stage 2-4 patients who follow a typical Western diet.

In actual clinical outpatient settings, we can recognize metabolic acidosis using serum total CO_2 (tCO_2) concentration obtained from venous samples, a surrogate for arterial [HCO_3^-]. Venous tCO_2 levels are higher than arterial [HCO_3^-] levels due to elevated levels of venous PCO_2. Under stable clinical conditions, the difference between venous tCO_2 and arterial [HCO_3^-] levels is usually no greater than 2-4 mEq/L. This difference is mainly attributed to the dissimilarities between venous and arterial blood and the buffering effect of hemoglobin on CO_2-mediated H^+ buffering, with a negligible contribution from erythrocyte carbamino-CO_2[18]. Not all cases with low tCO_2 are indicative of metabolic acidosis, as serum HCO_3^- levels can also decrease in respiratory alkalosis[19]. Consequently, it is not easy to determine the presence or absence of metabolic acidosis in CKD patients with respiratory alkalosis based solely on tCO_2 measurements. Such considerations make it challenging to diagnose metabolic acidosis based on tCO_2 alone, even in cases of simple acid-base disturbances. This difficulty becomes even more pronounced and complex in the context of mixed acid-base disorders. For an accurate diagnosis, recent data published by a Japanese research team recommends incorporating venous sample pH measurements into the interpretation, emphasizing the necessity of such tests[20]. The researchers conducted a retrospective study analyzing 1,058 Japanese patients with an eGFR below 60 ml/min per 1.73 m^2. This study evaluated the impact of venous blood pH measurements on the relationship between hypobicarbonatemia and incident ESKD. In their study cohort, approximately three-fourths of the patients had normal serum bicarbonate levels. In contrast, they found that nearly 40% of patients with CKD with hypobicarbonatemia did not have associated acidemia (pH <7.32). While it is possible that not all of these individuals had eubicarbonatemic metabolic acidosis, the findings highlight the importance of considering venous pH samples alongside serum bicarbonate analysis. In addition, even the concentration of tCO_2 varies in terms of normal range, as demonstrated by data from the United States, which shows differing reference values across 64 institutions, 2 large commercial clinical laboratories, and the major textbook of clinical chemistry[21]. The reported limits of serum tCO_2 values by clinical laboratories are frequently excessively broad and do not consistent with the range of expected in healthy individuals at sea level. Consequently, it is advisable to narrow the normal range for serum tCO_2 at sea level to 23-30 mEq/L to accurately identify most cases of covert subclinical metabolic acidosis[22].

It is biologically plausible that a subset of CKD patients with normal tCO_2 may experience acid-induced organ damage, which could also contribute to poor kidney outcomes. In the African American Study of Kidney Disease and Hypertension study, as well as in groups of United States veterans and Cleveland Clinic Foundation patients with CKD, individuals with low-normal levels of tCO_2 were found to have a higher risk of either mortality or decline in GFR compared to those with high-normal levels of tCO_2[2,7,8,23]. It is possible that individuals with low-normal levels of tCO_2 are at a higher risk of experiencing adverse outcomes because they require a greater compensatory response in order to maintain normal tCO_2 levels, which may result in more acid-mediated injury to their organs compared to those with high-normal levels of tCO_2[2].

Pathophysiologic Aspect of Subclinical Metabolic Acidosis

As previously mentioned, acid accumulation during the early stages of CKD may not be enough to decrease serum bicarbonate below the normal range, yet it can still instigate adverse effects, including bone loss, and muscle protein degradation[9]. Additionally, chronic metabolic acidosis in CKD can induce kidney injury and accelerate CKD progression. In CKD, H^+ retention reduces the pH of the interstitial and intracellular compartments within the kidney. This triggers a cascade of reactions, including the stimulation of ammoniagenesis in the remaining nephrons, increased production of proinflammatory cytokines, and elevated levels of angiotensin II, aldosterone and endothelin-1 (ET-1) in the kidneys[24].

Elevated net endogenous acid production from dietary

sources can increase H^+ retention in the body. In rats exhibiting normal kidney function or a decrease in nephron mass, the consumption of dietary acid resulted in higher levels of acid in both blood and kidney cortex, along with a rise in net acid excretion in urine, all without causing a discernible drop in plasma pH or bicarbonate concentration[25-27]. In addition, in hypertensive patients with eubicarbonatemia, albuminuria, and stage 2 CKD, who were consuming an acid-promoting Western diet, acid retention was observed along with increased plasma and urine levels of ET-1 and aldosterone, compared to individuals with stage 1 CKD following the same diet[13]. Conversely, reducing net endogenous acid production through dietary modifications or administering alkaline compounds can help alleviate H^+ retention. A single oral dose of $NaHCO_3$ led to a smaller reduction in urinary net acid excretion in patients with stage 2 CKD compared to those with stage 1, which aligns with increased acid retention in stage 2 CKD patients. After 30 days of oral $NaHCO_3$ administration, both plasma and urine levels of ET-1 and aldosterone decreased in patients with stage 2 CKD. The compensatory responses observed in response to nonvolatile acids suggest that even in cases of subclinical metabolic acidosis, patients with CKD may be retaining excessive amounts of acid, which could contribute to kidney damage. As CKD progresses continuously, it is important to correct acidosis at an early stage to prevent further deterioration of the kidney's adaptive response.

Diagnosis of Subclincal Metabolic Acidosis

As eubicarbonatemic metabolic acidosis may be involved in the progression of CKD, additional urinary markers are being investigated to aid in the evaluation of the risk of progression to end stage kidney disease (ESKD) and mortality in CKD patients without apparent acidosis.

Urine ammonium

Urinary acid excretion measurements may identify patients with CKD with eubicarbonatemic metabolic acidosis. Thus, metabolic acidosis is distinguished by a decreased rate of both the production and excretion of NH_4^+. Measuring urinary ammonia was useful in identifying increased dietary H^+ and assessing potential renal acid load in the early stages of CKD[28]. In response to metabolic acidosis, the renal proximal tubule undergoes changes in its metabolism and transport properties. The tubule increases the uptake and breakdown of glutamine and citrate, while reducing the recovery of phosphate from the ultrafiltrate. The increased breakdown of glutamine leads to greater ammoniagenesis and gluconeogenesis, with the excretion of ammonium ions helping to eliminate acid. These processes also generate HCO_3^- that are added to the plasma, partially restoring acid-base balance[29]. However, in CKD, the development of metabolic acidosis is often accompanied by a decrease in urine ammonium excretion[30]. In a study with the African American Study of Kidney Disease and Hypertension database, it was found that urine ammonium excretion decreased as measured GFR decreased. The finding that lower urine ammonium excretion is associated with higher mortality or ESKD suggests that early markers of kidney failure affecting acid-base balance may be useful in identifying individuals at risk of these outcomes, even if they have normal serum bicarbonate levels[31]. These studies indicate that acid accumulation can occur in early CKD and may not be reflected by serum acid-base parameters typically used to diagnose metabolic acidosis.

Urine citrate collection

Patients with CKD tend to have lower levels of acid excretion through ammonium as well as lower levels of base excretion through citrate and other organic anions compared to individuals without CKD. This may be a compensatory mechanism to maintain acid-base balance. As CKD progresses, acid excretion decreases even further while base excretion, such as citrate, increases in response to alkali. Therefore, evaluating urine citrate levels can serve as an early and reliable indicator of impaired acid-base balance in these patients[32].

Recent research provides evidence that measuring urinary citrate excretion, which is the most prevalent organic base in the urine that can be converted to bicarbonate, is a valuable method for detecting acid retention in CKD patients who have normal serum bicarbonate levels. Furthermore, it can also be used to evaluate the effectiveness

of alkali therapy in these patients[16,17]. Patients with CKD stage 2 showed higher baseline acid retention compared to those with CKD stage 1, and had lower urinary excretion of citrate. After consuming base-producing fruits and vegetables for 30 days, acid retention decreased in CKD stage 2 patients but not in CKD stage 1 patients. However, the overall acid retention remained higher and urinary citrate excretion remained lower in CKD stage 2 patients compared to CKD stage 1 patients, supporting the potential utility of low urinary citrate excretion in identifying acid retention in eubicarbonatemic CKD patients.

As a regular process, the body tends to excrete base by means of citraturia in response to fluctuating dietary base loads. The primary mechanism for controlling urinary citrate excretion is the reabsorption that occurs in the proximal tubule[29]. Over the past two decades, extensive studies have investigated the cellular mechanisms of how the proximal tubule handles citrate in response to acid loading. When the body is subjected to systemic acid loading or the proximal tubule cell is intracellularly acidified, a series of coordinated processes are triggered, such as increased luminal citrate uptake, cytoplasmic metabolism, and citrate entry and metabolism by the mitochondria. These processes work together to reduce citrate in the urine as a general response to acid. Therefore, measuring urinary citrate excretion is a more appropriate way to assess acid loading in the body compared to measuring plasma bicarbonate levels. A recent study found that in patients with CKD who are at risk for H^+ retention, lower levels of urinary citrate were more effective in detecting eubicarbonatemic acidosis compared to levels of urinary ammonium[17]. However, it is important to note that neither of these tests could accurately diagnose subclinical metabolic acidosis, and there is still no common consensus on such diagnostic methods. This strongly indicates that there is a pressing need for additional research to be conducted in order to develop a more reliable and effective clinical test for this condition.

Intervention of Subclinical Metabolic Acidosis

Chronic metabolic acidosis is a frequently observed condition in patients with CKD. the KDIGO 2012 Clinical Practice Guideline recommend administering alkali therapy to maintain serum bicarbonate levels above 22 mEq/L in order to prevent the deleterious effects of acid load on bone mineral density and protein catabolism[11]. The results of small-scale intervention studies conducted thus far provide evidence that correcting chronic metabolic acidosis in patients with CKD by correcting acid load can delay the progression of the disease[4,6]. Thus, the initial studies looked into how taking alkali supplements could affect the progression of CKD in participants with overt metabolic acidosis. Subsequent studies focused on the potential benefits of alkali supplements in participants with reduced eGFR but who were at an earlier stage of acid stress with eubicarbonatemia (Table 1). Mahajan et al. investigated the efficacy of sodium-based alkali for reducing acid retention in early-stage CKD patients consuming diets high in acid-producing foods, with reduced but relatively preserved eGFR and eubicarbonatemia. Their findings revealed a significant reduction in the rate of eGFR decline in patients treated with oral $NaHCO_3$ compared to those receiving sodium chloride or placebo[12]. In addition, given that alkali therapy in CKD animal models has demonstrated a reduction in kidney angiotensin II, which mediates GFR decline in partial nephrectomy models of CKD, and that metabolic acidosis may increase kidney angiotensin II in animals, it is hypothesized that alkali treatment for metabolic acidosis in eubicarbonatemic patients with plasma tCO_2 levels over 22 mEq/L may preserve GFR[14]. Goraya et al. randomized 108 patients with stage 3 CKD and plasma tCO_2 levels of 22-24 mEq/L to either usual care or interventions designed to reduce dietary acid by 50% using sodium bicarbonate or base-producing fruits and vegetables[33]. Plasma tCO_2 level decreased in the usual care group but increased in the bicarbonate or fruits and vegetables group. Furthermore, urine excretion of angiotensinogen, an index of kidney angiotensin II, increased in the usual care group but decreased with bicarbonate or fruits and vegetables. Although all groups experienced a decrease in eGFR calculated by creatinine and cystatin C, the loss was less at 3 years with bicarbonate or fruits and vegetables than in the usual care group. Therefore, they concluded that dietary alkali treatment for metabolic acidosis in eubicarbonatemic patients with plasma tCO_2 levels over 22 mEq/L reduces kidney angiotensin II activity and preserves eGFR[33].

Table 1. Recent studies with alkali treatment in chronic kidney disease within normal range of serum HCO_3

Study	Year	Study Designs	Study Subjects (n)	Baseline eGFR (ml/min per 1.73 m^2)	Baseline serum HCO_3 (mEq/L)	Interventions	Follow up duration (months)	Findings in renal outcomes
Mahajan A, et al.[12]	2010	Prospective, randomized, placebo-controlled, blinded	120	75	26 (tCO_2)	Placebo, NaCl, $NaHCO_3$	60	Renal benefit of $NaHCO_3$ in hypertensive nephropathy (↓eGFR decline, ↓blood pressure)
Goraya N, et al.[33]	2014	Single center, randomized, open label	108	30-59	22-24 (tCO_2)	Usual care, F+V, $NaHCO_3$	36	Renal benefit of F+V and $NaHCO_3$ (↓urine angiotensinogen and preserves GFR)
Melamed ML, et al.[34]	2020	Multicenter, randomized, double-blind, placebo controlled	149	36±11	24±2.2	Placebo, $NaHCO_3$	24	No difference of eGFR between study groups
Raphael KL, et al.[36]	2020	Multicenter, randomized, double-blind, placebo controlled	74	51±18	24±2 (tCO_2)	Placebo, $NaHCO_3$	6	No difference of kidney injury markers in diabetic kidney disease
Raphael KL, et al.[35]	2020	Multicenter, randomized, double-blind, placebo controlled	192	36±9	24±2	Placebo, $NaHCO_3$	7	No significant difference in the eGFR

eGFR, estimated glomerular filtration rate; $NaHCO_3$, sodium bicarbonate; NaCl, sodium chloride, F+V, fruits and vegetables; tCO_2, venous total CO_2 level

Nonetheless, recent studies have not reached a consensus on this matter. Melamed and his colleagues randomly divided 149 patients with CKD stages 3-4 into two groups and administered either 0.4 mg/kg body weight of $NaHCO_3$ or placebo, following them up for two years[34]. The baseline eGFR of study population was 36.3±11.2 ml/min per 1.73 m^2 with mean serum HCO_3, 24.0±2.2 mEq/L. After two years, there were significant differences in serum bicarbonate and potassium levels between the two groups, but there were no differences in renal outcomes or bone mineral densities[34]. The researchers speculated that the differences between their results and previous reports may be attributed to differences in study design, such as randomization. Furthermore, the Base Pilot trial conducted across multiple centers, evaluated the safety, tolerability, adherence, and pharmacodynamics of two doses of $NaHCO_3$ over a period of 28 weeks in adults with eGFR levels between 20-44 or 45-59 ml/min per 1.73 m^2 and urinary albumin/creatinine levels above 50 mg/g, and serum bicarbonate levels between 20-28 mEq/L[35]. The researchers concluded that a high dose of 0.8 mEq/kg of lean body weight daily $NaHCO_3$ was also safe and reasonable for future related studies, as no additional side effects were observed. However, the observation period was short, there was no improvement in eGFR in the high-dose $NaHCO_3$ treatment group; on the contrary, there was an increase in albuminuria. The study group assumed that the reasons for the slightly increased albuminuria is related to the effect of urinary pH on urinary protease activity, which warrants further investigation. In addition, Raphael and his colleagues conducted a study that investigated the effects of $NaHCO_3$ on renal fibrosis and injury markers in patients with diabetic nephropathy with eubicarbonatemia[36]. This was a randomized, double-blind, placebo-controlled trial that included 74 participants with type 1 or 2 diabetes, eGFR of 15-89 ml/min per 1.73 m^2, and albuminuria, with a tCO_2 concentration ranging from 22-28 mEq/L. Participants received either oral $NaHCO_3$ or placebo for six months. The primary outcomes were changes in urinary TGF-β1, renal injury markers including kidney injury molecule-1 (KIM-1), fibronectin, neutrophil gelatinase-associated lipocalin (NGAL), and albuminuria from baseline to 3 and 6 months. Sodium bicarbonate therapy increased the mean blood tCO_2 level by 1.2 mEq/L, elevated urine pH, and decreased urinary ammonium excretion. However, it did not significantly reduce TGF-β_1, KIM-1, fibronectin, NGAL, or amount of albuminuria[36]. These findings are in

contrast to a previous pilot study in patients with hypertensive CKD and normal blood tCO_2 levels, where sodium bicarbonate was shown to decrease urinary TGF-β1 levels and preserve renal function in the early stages of the disease[12,33]. The observed disparities in the study outcomes could be due to differences in the design of the studies or variations in the progression of metabolic acidosis, which maybe influenced by the underlying etiology of CKD. As such, further investigation is necessary to shed light on this matter.

It is crucial to take into account the safety concerns related to long-term $NaHCO_3$ supplementation. This matter involves the potential for sodium-mediated fluid retention, which can lead to complications such as elevated blood pressure, pulmonary edema, and heart failure. Nonetheless, the 28-week study revealed no noteworthy disparities in total body weight among the three groups, and the frequency of escalating diuretic therapy was also similar[35]. However, given that a large CKD cohort demonstrated a higher risk of heart failure events and mortality with persistent serum bicarbonate levels exceeding 26 mEq/L, caution must be exercised when considering $NaHCO_3$ supplementation therapy in patients with underlying conditions associated with severe Na^+ retention[37,38]. In addition, there may be potential side effects that have not been thoroughly investigated, such as the impact of correcting metabolic acidosis on vascular calcification in CKD. De Solis et al. found that uremic animals treated with intraperitoneal sodium bicarbonate exhibited substantially greater vascular calcification[39]. Notably, the bicarbonate concentration in these animals was similar to that in healthy animals, whereas uremic animals with untreated metabolic acidosis had lower bicarbonate concentrations and similar levels of vascular calcifitcation compared to healthy animals. These results suggested that correcting metabolic acidosis may promote vascular calcification in CKD, and that metabolic acidosis may a protective role against renal calcification and loss of GFR in uremic animals on a high-phosphate diet[40,41]. Therefore, it may be prudent to withhold alkaline therapy in patients with hyperphosphatemia. These findings highlight the need for large-scale clinical trials with long-term follow-up to assess the safety and efficacy of alkaline therapy in humans, given the potential for severe complications[42].

Veverimer, previously known as TRC101, is a new type of non-absorbable polymer that attaches to hydrogen cations and chloride anions in the gastrointestinal tract and is then eliminated through feces. This results in an increase in serum bicarbonate levels without the need for sodium supplementation[43,44]. There are still uncertainties surrounding the mechanism of action, electrolyte profile, potential interaction with colonic bacterial flora, and optimal usage of veverimer[45,46]. We are eagerly anticipating the outcomes of the ongoing research investigating the impact of veverimer on the progression of CKD. In the absence of any significant long-term safety issues, veverimer has the potential to become a valuable addition to our existing treatment arsenal. It is imperative to compare the efficacy of veverimer to that of sodium bicarbonate for treating eubicarbonatemic metabolic acidosis in CKD patients.

Adequate consumption of fruits and vegetables is an important and traditional alkaline supplementation approach. Kelly et al. conducted a meta-analysis of 104 studies with 2,755,719 participants, which revealed that higher intake of potassium and vegetables was associated with reduced odds of CKD, while higher salt intake was linked to increased odds of CKD[47]. The study supports previous findings from Bach et al.'s meta-analysis, which demonstrated that a healthy diet with higher intake of fruits, vegetables, low-fat dairy, whole grains, and fiber, combined with lower intake of sodium is associated with a 30% reduction in kidney damage and improved overall health, including high BP, metabolic acidosis, phosphorus, gut microbiome, and lower glycated hemoglobin[48]. Plant-based diets, which were usually avoided due to concerns of hyperkalemia in CKD patients, have also been shown to provide benefits even for those with ESKD[49]. Additionally, a 24-month study of 47 patients with stage 3 or 4 CKD demonstrated that a dietary potassium-restricted group had only a slightly lower serum K^+ concentration compared to the control group, suggesting that plant-based diets may still be an appropriate alkali option for CKD patients[50].

CONCLUSIONS

CKD patients with hidden H^+ retention with normal bicarbonate levels may exhibit maladaptive responses that lead

to deterioration of kidney function due to the loss of adaptive compensatory mechanisms of urinary acid excretion. Modulating these responses early on may be a crucial therapeutic strategy in preventing CKD progression. However, to date, the optimal approach for alkali therapy in subclinical metabolic acidosis in CKD remains uncertain. There is a lack of established guidelines on when to initiate alkali therapy, potential side effects of alkali agents, and the optimal blood bicarbonate levels based on evidence-based practices. Addressing these knowledge gaps is likely to have significant clinical implications. Therefore, further research is necessary to address these concerns and establish more robust guidelines for the use of alkali therapy in CKD patients.

Declaration of Interest

The authors have no financial conflict of interest to declare.

Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2022R1F1A1071491).

REFERENCES

1. Romagnani P, Remuzzi G, Glassock R, et al.: Chronic kidney disease. Nat Rev Dis Primers 2017;3:17088.
2. Raphael KL: Metabolic Acidosis and Subclinical Metabolic Acidosis in CKD. J Am Soc Nephrol 2018;29(2):376-82.
3. Kraut JA, Madias NE: Metabolic Acidosis of CKD: An Update. Am J Kidney Dis 2016;67(2):307-317.
4. Mathur RP, Dash SC, Gupta N, Prakash S, Saxena S, Bhowmik D: Effects of correction of metabolic acidosis on blood urea and bone metabolism in patients with mild to moderate chronic kidney disease: a prospective randomized single blind controlled trial. Ren Fail 2006;28(1):1-5.
5. Lyon DM, Dunlop DM, Stewart CP: The alkaline treatment of chronic nephritis. The Lancet 1931;218(5645):1009-1013.
6. de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM: Bicarbonate supplementation slows progression of CKD and improves nutritional status. J Am Soc Nephrol 2009;20(9): 2075-2084.
7. Kovesdy CP: Metabolic acidosis and kidney disease: does bicarbonate therapy slow the progression of CKD? Nephrol Dial Transplant 2012;27(8):3056-3062.
8. Navaneethan SD, Shao J, Buysse J, Bushinsky DA: Effects of Treatment of Metabolic Acidosis in CKD: A Systematic Review and Meta-Analysis. Clin J Am Soc Nephrol 2019;14(7): 1011-1020.
9. Dr. Bright's Reports of Medical Cases, Illustrating the Symptoms and Cure of Diseases: Last Article. Med Chir Rev 1832;16(32): 321-356.
10. Osman AA: Effect of large doses of alkali on kidney function. Lancet 1946;1(6387):143.
11. Chapter 3: Management of progression and complications of CKD. Kidney Int Suppl (2011) 2013;3(1):73-90.
12. Mahajan A, Simoni J, Sheather SJ, Broglio KR, Rajab MH, Wesson DE: Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. Kidney Int 2010;78(3):303-309.
13. Wesson DE, Simoni J, Broglio K, Sheather S: Acid retention accompanies reduced GFR in humans and increases plasma levels of endothelin and aldosterone. Am J Physiol Renal Physiol 2011;300(4):F830-F837.
14. Wesson DE, Simoni J: Acid retention during kidney failure induces endothelin and aldosterone production which lead to progressive GFR decline, a situation ameliorated by alkali diet. Kidney Int 2010;78(11):1128-35.
15. Moranne O, Froissart M, Rossert J, et al.: Timing of onset of CKD-related metabolic complications. J Am Soc Nephrol 2009;20(1):164-171.
16. Goraya N, Simoni J, Sager LN, Mamun A, Madias NE, Wesson DE: Urine citrate excretion identifies changes in acid retention as eGFR declines in patients with chronic kidney disease. Am J Physiol Renal Physiol 2019;317(2):F502-F511.
17. Goraya N, Simoni J, Sager LN, Madias NE, Wesson DE: Urine citrate excretion as a marker of acid retention in patients with chronic kidney disease without overt metabolic acidosis. Kidney Int 2019;95(5):1190-1196.
18. Yee J, Frinak S, Mohiuddin N, Uduman J: Fundamentals of Arterial Blood Gas Interpretation. Kidney360 2022;3(8): 1458-1466.
19. Batlle D, Chin-Theodorou J, Tucker BM: Metabolic Acidosis or Respiratory Alkalosis? Evaluation of a Low Plasma Bicarbonate Using the Urine Anion Gap. Am J Kidney Dis 2017; 70(3):440-444.
20. Kajimoto S, Sakaguchi Y, Asahina Y, Kaimori JY, Isaka Y: Modulation of the Association of Hypobicarbonatemia and Incident Kidney Failure With Replacement Therapy by Venous pH: A Cohort Study. Am J Kidney Dis 2021;77(1):35-43.
21. Kraut JA, Madias NE: Re-Evaluation of the Normal Range

of Serum Total CO(2) Concentration. Clin J Am Soc Nephrol 2018;13(2):343-347.
22. Adamczak M, Surma S: Metabolic Acidosis in Patients with CKD: Epidemiology, Pathogenesis, and Treatment. Kidney Dis (Basel) 2021;7(6):452-467.
23. Raphael KL, Wei G, Baird BC, Greene T, Beddhu S: Higher serum bicarbonate levels within the normal range are associated with better survival and renal outcomes in African Americans. Kidney Int 2011;79(3):356-562.
24. Wesson DE, Buysse JM, Bushinsky DA: Mechanisms of Metabolic Acidosis-Induced Kidney Injury in Chronic Kidney Disease. J Am Soc Nephrol 2020;31(3):469-482.
25. Wesson DE: Endogenous endothelins mediate increased distal tubule acidification induced by dietary acid in rats. J Clin Invest 1997;99(9):2203-2211.
26. Wesson DE: Dietary acid increases blood and renal cortical acid content in rats. Am J Physiol 1998;274(1):F97-F103.
27. Wesson DE, Simoni J: Increased tissue acid mediates a progressive decline in the glomerular filtration rate of animals with reduced nephron mass. Kidney Int 2009;75(9):929-35.
28. Goraya N, Madias NE, Mamun A, Simoni J, Wesson DE: Biomarkers of Covert Acid Stress in Patients with Chronic Kidney Disease: A Cross-Sectional Study. Am J Nephrol 2022; 53(11-12):794-805.
29. Curthoys NP, Moe OW: Proximal tubule function and response to acidosis. Clin J Am Soc Nephrol 2014;9(9):1627-38.
30. Vallet M, Metzger M, Haymann JP, et al.: Urinary ammonia and long-term outcomes in chronic kidney disease. Kidney Int 2015;88(1):137-145.
31. Raphael KL, Carroll DJ, Murray J, Greene T, Beddhu S: Urine Ammonium Predicts Clinical Outcomes in Hypertensive Kidney Disease. J Am Soc Nephrol 2017;28(8):2483-2490.
32. Tyson CC, Luciano A, Modliszewski JL, et al.: Effect of Bicarbonate on Net Acid Excretion, Blood Pressure, and Metabolism in Patients With and Without CKD: The Acid Base Compensation in CKD Study. Am J Kidney Dis 2021;78(1): 38-47.
33. Goraya N, Simoni J, Jo CH, Wesson DE: Treatment of metabolic acidosis in patients with stage 3 chronic kidney disease with fruits and vegetables or oral bicarbonate reduces urine angiotensinogen and preserves glomerular filtration rate. Kidney Int 2014;86(5):1031-1038.
34. Melamed ML, Horwitz EJ, Dobre MA, et al.: Effects of Sodium Bicarbonate in CKD Stages 3 and 4: A Randomized, Placebo-Controlled, Multicenter Clinical Trial. Am J Kidney Dis 2020; 75(2):225-234.
35. Raphael KL, Isakova T, Ix JH, et al.: A Randomized Trial Comparing the Safety, Adherence, and Pharmacodynamics Profiles of Two Doses of Sodium Bicarbonate in CKD: the BASE Pilot Trial. J Am Soc Nephrol 2020;31(1):161-174.
36. Raphael KL, Greene T, Wei G, et al.: Sodium Bicarbonate Supplementation and Urinary TGF-β1 in Nonacidotic Diabetic Kidney Disease: A Randomized, Controlled Trial. Clin J Am Soc Nephrol 2020;15(2):200-208.
37. Dobre M, Yang W, Pan Q, et al: Persistent high serum bicarbonate and the risk of heart failure in patients with chronic kidney disease (CKD): A report from the Chronic Renal Insufficiency Cohort (CRIC) study. J Am Heart Assoc 2015;4(4).
38. Clinical and cost-effectiveness of oral sodium bicarbonate therapy for older patients with chronic kidney disease and low-grade acidosis (BiCARB): a pragmatic randomised, double-blind, placebo-controlled trial. BMC Med 2020;18(1):91.
39. de Solis AJ, González-Pacheco FR, Deudero JJ, et al: Alkalinization potentiates vascular calcium deposition in an uremic milieu. J Nephrol 2009;22(5):647-653.
40. Jara A, Felsenfeld AJ, Bover J, Kleeman CR: Chronic metabolic acidosis in azotemic rats on a high-phosphate diet halts the progression of renal disease. Kidney Int 2000;58(3): 1023-1032.
41. Jara A, Chacón C, Ibaceta M, Valdivieso A, Felsenfeld AJ: Effect of ammonium chloride and dietary phosphorus in the azotaemic rat. Part II--Kidney hypertrophy and calcium deposition. Nephrol Dial Transplant 2004;19(8):1993-1998.
42. Goraya N, Narayanan M, Wesson DE: Management of Metabolic Acidosis in Chronic Kidney Disease: Past, Present, and Future Direction. Adv Chronic Kidney Dis 2022;29(4): 416-423.
43. Bushinsky DA, Hostetter T, Klaerner G, et al.: Randomized, Controlled Trial of TRC101 to Increase Serum Bicarbonate in Patients with CKD. Clin J Am Soc Nephrol 2018;13(1): 26-35.
44. Wesson DE, Mathur V, Tangri N, et al.: Long-term safety and efficacy of veverimer in patients with metabolic acidosis in chronic kidney disease: a multicentre, randomised, blinded, placebo-controlled, 40-week extension. Lancet 2019; 394(10196):396-406.
45. Adrogué HJ, Madias NE: Veverimer: An Emerging Potential Treatment Option for Managing the Metabolic Acidosis of CKD. Am J Kidney Dis 2020;76(6):861-867.
46. Mathur VS, Li E, Wesson DE: Effects of veverimer on serum bicarbonate and physical function in diabetic patients with chronic kidney disease and metabolic acidosis: subgroup analysis from a randomized, controlled trial. Nephrol Dial Transplant 2022;37(7):1302-1309.
47. Kelly JT, Su G, Zhang L, et al.: Modifiable Lifestyle Factors for Primary Prevention of CKD: A Systematic Review and

Meta-Analysis. J Am Soc Nephrol 2021;32(1):239-253.
48. Bach KE, Kelly JT, Palmer SC, Khalesi S, Strippoli GFM, Campbell KL: Healthy Dietary Patterns and Incidence of CKD: A Meta-Analysis of Cohort Studies. Clin J Am Soc Nephrol 2019;14(10):1441-1449.
49. Joshi S, McMacken M, Kalantar-Zadeh K: Plant-Based Diets for Kidney Disease: A Guide for Clinicians. Am J Kidney Dis 2021;77(2):287-296.
50. Arnold R, Pianta TJ, Pussell BA, et al.: Randomized, Controlled Trial of the Effect of Dietary Potassium Restriction on Nerve Function in CKD. Clin J Am Soc Nephrol 2017;12(10):1569-1577.

Erratum

ISSN 1738-5997 (Print) · ISSN 2092-9935 (Online)
Electrolyte Blood Press 2023;21:44-44
https://doi.org/10.5049/EBP.2023.21.1.44

Management for Electrolytes Disturbances during Continuous Renal Replacement Therapy

Song In Baeg[1*], Kyungho Lee[2*], Junseok Jeon[2], Hye Ryoun Jang[2]

[1]Division of Nephrology, Department of Internal Medicine, Myongji Hospital, Hanyang University Medical Center, Goyang;
[2]Division of Nephrology, Department of Medicine, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea

Received: October 31, 2022
Revised: December 18, 2022
Accepted: December 19, 2022
**These two authors contributed equally as co-first authors.*
Corresponding Author: Hye Ryoun Jang, MD, PhD
Division of Nephrology, Department of Medicine, Sungkyunkwan University School of Medicine, Samsung Medical Center, Irwon-ro 81, Gangnam- gu, 06351 Seoul, Korea
Tel: +82-2-3410-0782; Fax: +82-2-3410-0064
E-mail: shinehr@skku.edu

The above article (doi: 10.5049/EBP.2022.20.2.64) contains errors.

*Song In Baeg and *Kyungho Lee equally contributed as co-first authors.

Table 1. should be corrected [from Hemosol B0 (Fresenius) to Hemosol B0 (Baxter)] as following page.

The authors would like to apologize for any inconvenience this has caused.

Table 1. Compositions of commercially available CRRT solutions in Korea

Composition (mmol/L)	Solutions*						
	MultiBic 0K (Fresenius)	MultiBic 2K (Fresenius)	MultiBic 4K (Fresenius)	Hemosol B0 (Baxter)	Prismasol 2K (Baxter)	Prismasol 4K (Baxter)	Phoxilium (Baxter)
Na^+	140.0	140.0	140.0	140.0	140.0	140.0	140.0
K^+	0	2.0	4.0	0	2.0	4.0	4.0
Ca^{2+}	1.5	1.5	1.5	1.8	1.75	1.75	1.3
Mg^{2+}	0.5	0.5	0.5	0.5	0.5	0.5	0.6
Cl^-	109.0	111.0	113.0	109.5	111.5	113.5	116.0
HCO^{3-}	35.0	35.0	35.0	32.0	32.0	32.0	30.0
Lactate	0	0	0	3.0	3.0	3.0	0
Glucose	5.55	5.55	5.55	0	6.10	6.10	0
$HPO4^{2-}$	0	0	0	0	0	0	1.2

* Availability and trade names of the solutions may differ according to countries.

전해질고혈압연구회
ℰ&BP
Korean Society for Electrolyte and Blood Pressure Research

Guidelines for Authors

Aim & Scope

Electrolytes & Blood Pressure (ISSN 1738-5997) is the official journal of the Korean Society for Electrolyte and Blood Pressure Research.

It was launched in 2003 and has been an international, peer-reviewed journal published in English since 2005. Its ISO abbreviation is Electrolyte Blood Press.

The journal mainly considers articles on electrolyte metabolism and blood pressure regulation as well as clinical practices for electrolyte disorders and hypertension.

Major article types considered for publication include original research, eccentric case reports and reviews on current topics of interest.

Accepted manuscripts are granted free online open-access immediately after publication, which permits its users to read, download, copy, distribute, print, search, or link to the full texts of its articles to facilitate access to a broad readership.

Circulation number of print copies is 500. The journal is semiannually published and indexed in SCOPUS, PubMed Central (PMC), KoreaMed, KoMCI, EMBASE, and Chemical Abstracts (CAS).

Instruction for Authors

This journal is also published online at http://enbp.org

▷ General Information

Editorial Correspondence

The Korean Society for Electrolyte and Blood Pressure Research, Dept. of Internal Medicine, Chonnam national university medical school, 42 Jebong-ro, Dong-gu, Gwangju 61469, Republic of Korea

Tel: +82-62-220-6503, Fax: +82-62-225-8578

E-mail: junhaejil@gmail.com

Conditions

EBP will not publish articles which have been previously reported at any length or articles being considered for publication elsewhere.

The authors must include a statement to this effect in their cover letter.

If publication of the data in any form has occurred or is being contemplated, a copy of such publication should be included with the submitted manuscript.

Submission of an article for publication implies the transfer of the copyright the author to the Korean Society for Electrolyte and Blood Pressure Research (KSEBPR) upon acceptance.

It is the author's responsibility to obtain permission to reproduce illustrations, tables, etc. from other publications.

The manuscript should be written in English and the editors reserve the right to make appropriate corrections in grammar and style.

Accepted papers become the permanent property of the 'Electrolyte & Blood Pressure', the official Journal of KSEBPR and may not be reproduced by any means, in whole or in part, without the written consent of the KSEBPR.

Information concerning financial disclosures (i.e.grants, funding, support, etc.) should be placed at the foot of the title page.

Author's Check List

Complete the following checklists: Corresponding author name, address, phone, fax and e-mail address appear on title page.

Abstract does not exceed 250 words (Case Reports or Clinical Discussion less than 250 words).

Key words locate at the bottom of abstract page.

Nonstandard abbreviations are spelled out on first use. References are in correct format.

Copyright transfer agreement form with the signatures of corresponding author should be included.

Review Process

Authors will receive within a week an acknowledgment that their manuscript has been forwarded to the editorial correspondence.

Manuscripts that fail to satisfy technical requirements may

be promptly returned to the authors without further review.

All Manuscripts are peer-reviewed by at least 2 anonymous reviewers selected by the editor.

Authors are encouraged to keep copies of submitted manuscripts, including figures; EBP accepts no responsibility for manuscript files that are lost or destroyed through electronic or computer problems.

Copyright

The copyright of published manuscripts is held by KSEBPR, which must receive the agreement of copyright transfer with the original manuscript submission. A submission form signed by a corresponding author should be submitted E-mail: junhaejil@gmail.com or faxed to +82-62-225-8578.

A copy of the form is available at http://enbp.org

Ethics

When reporting experiments on human subjects, indicate whether the procedures were in accordance with the ethical standards of the appropriate institutional review board or with the Helsinki Declaration of 1975 (and as revised in 1983).

When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

Page Charges

Minimum publication charges and a fee for reprints exceeding 50 copies will be made for every manuscript.

Color Illustrations

Color illustrations are reproduced at the authors' expense.

Proofs

Unless indicated otherwise, proofs are sent to the corresponding author and should be returned with the least possible delay.

Alterations made in proofs, other than the correction of printer's errors, are charged to the author.

Reprints

Rates are indicated on the order form, which must be returned with the proofs.

▷ Preparation of Manuscripts

Types of Articles Four types of articles will be accepted:

(a) Original Articles

Scientific reports of the results of original research. The text is limited to 4,000 words with an abstract, up to 50 references, acknowledgments, tables and figure legends.

(b) Reviews

Covering a timely topic by experts. The text is limited to 6,000 words with an abstract, up to 100 references, tables and figure legends.

(c) Case Reports

Clinical cases (individual or a series) on the field of electrolytes & blood pressure. The text is limited to 2,000 words with an abstract, up to 20 references, tables and figure legends.

(d) Clinical Discussions

Clinical case and questions following answers. The text is limited to 2,000 words with an abstract (case and questions), up to 30 references, tables and figure legends.

▷ Format of Manuscripts

The manuscript should be typed in English and double-spaced using 12-pt. font (preferably Times New Roman) and unjustified margins. All manuscript pages must be numbered.

1) Original Articles

Title Page

- Title
- Authors' full names
- Affiliations
- Running title: If more than 12 words in title
- Stating the material is not published previously, and will not be submitted for publication elsewhere.
- Word count (exclude title page, references, tables, figures and legends)
- Corresponding author's name, address, phone, Fax and E-mail

Abstract and Keywords

- Abstract should not exceed 300 words in original and review (250 words in Case Report and Clinical Discussions). It must be written for easy reading with no abbreviations. The abstract of the original article sho-

uld be divided into four subsections: Background, Methods, Results, and Conclusion. Four to six keywords should be listed alphabetically below the abstract.

Text

- Introduction
- Methods
- Results
- Discussion
- Acknowledgements
- References (less than 50)

Tables and Figures

- Figures and Legends (all cited)
- Tables and Figures
- Placing tables at the end of the text file
- Storing figures as separate files
- Both numbered in Arabic numerals
- Being prepared on separate pages
- Color illustrations: A final resolution of 300 dpi after scaling
- Line drawings: 800-1,200 dpi
- Figure format: preferably in JPEG or EPS format
- Size of photography: Preferably 8×8 cm, 15 cm in width× 21 cm in length is also acceptable.
- Explain all abbreviations.
- For footnotes use the following symbols, in sequence. : *, †, ‡, §, ||, ¶, **, ††, ‡‡, §§

References

- Consecutive number in parenthesis
- A limit of 50 references per manuscript
- List all authors up to 6, if more than 6, list the first 3 followed by "et al."
- B Abbreviate journal names according to the Index Medicus system

Examples

(a) Papers published in periodicals:

1. Ma SK, Bae EH, Lee JU, et al.: Altered regulation of type 3 Na^+/H^+ exchanger, type 1 Na^+/HCO_3^- cotransporter, and Na^+, K^+-AT_{Pase} in the kidney of rats with experimental rhabdomyolysis. Electrolyte Blood Press 2007; 5:55-61.

(b) Papers published in supplements:

2. Kim GH, Han JS: Therapeutic approach to hypokalemia. Nephron 2002;92(Suppl 1):28-32.

(c) Books:

3. Halperin ML, Goldstein MB: Sodium and water physiology. In: Fluid, electrolyte, and acid-base physiology: a problem-based approach. 3rd ed., Philadelphia, WB Saunders, 1999, p227-282.

(d) Chapters in edited book:

4. Textor SC, Pohl MA: Renovascular hypertension. In: Comprehensive clinical nephrology, 3rd ed., edited by Feehally J, Floege J, Johnson RJ, Philadelphia, Mosby, 2007, p429-441.

2) Reviews

Manuscripts are to be organized in the following format with all pages, including the title page, numbered consecutively. The text is written in free style.

- Title page
- Abstract: Less than 300 words, one paragraph
- Key words: 4-6 words
- Text
- Acknowledgements
- References: Limit these to 100.
- Tables, figures and legends

3) Case Reports

Manuscripts are to be organized in the following format with all pages, including the title page, numbered consecutively.

- Title page
- Abstract: Less than 250 words, one paragraph
- Key words: 4-6 words
- Introduction
- Case report: Brief medical history of patient(s), data of physical and laboratory examinations
- Discussion: Focus on the specific area which the case emphasizes.
- Acknowledgements
- References: Limit these to 20.
- Tables, figures and legends

4) Clinical Discussions

Manuscripts are to be organized in the following format with all pages, including the title page, numbered consecu-

tively.

- Title page
- Abstract: clinical case and questions less than 250 words
- Key words: 4-6 words
- Discussion: Detail answers to the questions of the case
- Acknowledgements
- References: Limit these to 30.
- Tables, figures, and legends

전해질고혈압연구회
E&BP
Korean Society for Electrolyte and Blood Pressure Research

Copyright Transfer Agreement

Title: _____

_____

Authors: _____

_____

Check Lists

- □ Corresponding author name, address, phone, fax, and E-mail address appear on title page
- □ Abstract does not exceed 250 words (case reports less than 200 words)
- □ Key words at bottom of abstract page (use MeSH in Index Medicus)
- □ Nonstandard abbreviations are spelled out on first use
- □ References are in correct format

Copyright Transfer Agreement

The Korean Society for Electrolyte and Blood Pressure Research (KSEBPR), located at Hanyang University Medical Center, 211-1 Wangsimni-ro, Seongdong-gu, Seoul 04763, Republic of Korea, and author hereby agree as follows:

1. You warrant to KSEBPR that
   (1) no part of the Article is copied from any other work,
   (2) you have obtained ALL the permissions required for any material you have used from other copyrighted publications in the Article;
   and (3) you have exercised reasonable care to ensure that the Article is accurate and does not contain anything which infringes on anyone's copyright or other rights.
2. You confirm to KSEBPR that the Article
   (1) is your original work;
   (2) has not previously been published;
   (3) will not be submitted for publication to any other journal following acceptance in Electrolytes & Blood Pressure (EBP).
3. You authorize us to act on your behalf to defend the copyright in the Article if anyone should infringe it.
4. You hereby grant to KSEBPR an exclusive license for the full period of copyright:
   to publish the final version of the Article in EBP, and to communicate it to the public, either within EBP, on its own, or with other related material, in printed, electronic or any other format or medium;
   to authorize or grant licenses to third parties to do any of the above;
   to deposit copies of the Article in online archives maintained by KSEBPR or by third parties authorized by KSEBPR.
5. All accepted works become the property of the KSEBPR and may not be published elsewhere without prior written permission from the KSEBPR.
6. In the case of a multi-authored article, you confirm that you are authorized by your co-authors to enter this form on their behalf.

Corresponding Author

Printed name	Orchid number	Signature	Date