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Novel therapeutic approaches in chronic kidney disease, uremia and kidney transplantation: past, present and future

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In the January 2020 issues of the Current Opinion in Nephrology and Hypertension (CONH) [1] there were several articles related to the novel therapeutic approaches to prolonged and preserve the function of native kidneys [2–11] and kidney allografts [12]. In the current 2021 issue of CONH, we extend the theme with more focus on improving kidney health and also emphasize novel management strategies for common metabolic conditions related to chronic kidney disease (CKD), end-stage kidney disease (ESKD) and kidney transplantation. Over the past century, global public health problems have evolved and shifted from communicable to noncommunicable diseases as the so-called '*epidemiological transition*' [13]. Dynamic changes of public health diseases have transiently been confounded by the current unprecedented coronavirus disease 19 (COVID-19) pandemic that has caused additional morbidity and mortality particularly among patients with kidney disease. Some dedicated articles in this issue will discuss preparedness and potential therapy for COVID-19 especially in ESKD patients and kidney transplant recipients.

In addition to several strategies to prolong kidney health and slow CKD progression, early interventions to prevent complications of CKD, particularly cardiovascular diseases (CVDs), are critical. As the leading cause of morbidity and mortality in the CKD population [14,15], CVD in CKD has long been a major challenge and a target for primary prevention. Several CVD risk prediction scores have been developed in CKD, but the validity of these scoring systems remains somewhat limited primarily from a dynamic change in characteristics of CKD over time [16]. In addition to conventional risk factors of CVD in the general population, nontraditional risk factors of CVD in CKD are proposed to be incorporated in the prediction models using large clinical database of CKD cohorts, including the U.S. veterans who have greater risks of CKD and other comorbidities, which may explain higher CVD risk in CKD compared to the general population. These CVD risk factors and prediction models are discussed in this issue.

CVD is the most common cause of morbidity and mortality in the general population worldwide [17,18], as well as in CKD and ESKD [19,20], and hypertension is one of the leading risk factors for CVDs [21]. Given the magnitude of the problem, hypertension has long been an important public health problem. Several professional societies have regularly updated guidelines for blood pressure management and recently emphasized single-pill combination of antihypertensive medications [22]. An updated pharmacologic therapy, including mineralocorticoid receptor antagonists (MRAs), MRA esaxerenone (CS-3150), MRA finerenone, angiotensin-rezeptor-neprilysin-inhibitors, and endothelin A receptor antagonist atrasentan, are discussed with outcomes from clinical trials. In addition, procedural-based interventions with renal nerve denervation for resistant hypertension are reviewed.

Nonpharmacological intervention particularly nutrition and dietary management is currently one of the critical therapeutic strategies to slow the progression of CKD [23]. There has been more recognized and growing evidence of intestinal dysbiosis as one of the important pathogeneses of several chronic diseases in humans, including CKD [24]. Compare to the imbalance among the epidemiological triad of the

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host, agent and environment [25,26], dysbiosis is an alteration of human, intestinal microbiota, and dietary intake. An overview of intestinal microbiome related to CKD and outcomes are reviewed. Dietary management to intervene intestinal dysbiosis, including plant-based (including dietary fiber and plant-sourced fat e.g. linoleic acid), low protein, supplementation with pro-, pre and syn-biotics, and constipation treatment are discussed, such as plant-dominant low protein diet, also known as PLADO diet [27]. In addition, novel diagnostic approaches to detect alteration of intestinal microbiome, including molecular identification of species in the intestinal microbiota and nanotechnology, are introduced, and these may change the paradigm to better leverage intestinal microbiome constellations from culture-based diagnosis to real-world management of CKD.

Hemodialysis remains the most common treatment modality in ESKD patients in essentially all countries throughout the world, including the United States. Several factors contribute to delivering hemodialysis care in a standardized fashion, including the efficiency of hemodialysis staff, cost and policy. However, individualized hemodialysis treatment may provide optimal care to meet physiological requirements for each ESKD patient, particularly incident ESKD patients with residual kidney function. A personalized hemodialysis treatment in the review with a proposed framework divided hemodialysis prescription into early, intermediate, advanced and terminal stage of ESKD progression, which may guide nephrologists to provide incremental or decremental hemodialysis with a shared decision from patients and their family members. However, further evidence, including from randomized control trials, is still required to address the remaining questions, particularly appropriate hemodialysis prescription, safety, benefits and risks of personalized hemodialysis therapy compared to the current standardized hemodialysis approach of thrice-weekly initiation and maintenance. A combined standardized and personalized hemodialysis approach is also discussed.

Another personalized approach for advanced CKD patients is nondialysis therapy by conservative management of CKD as dialysis may neither consistently provide survival benefit nor the quality of life, particularly uremic-related symptom relief in some patients, such as the elderly with several major medical comorbidities [10]. Palliative care has emerged to become one of the most important options to ensure the expected levels of health-related quality of life mainly by mitigating symptoms and bringing the patients to goal of 'living well with kidney disease' as per the theme of the upcoming 2021 World Kidney Day campaign [28,29]. Moreover, slowing progression of CKD as the so-called preservative management should be an integral part of the conservative therapy to attenuate uremic complications [10,30]. Several nondialytic nonrenal therapies to remove fluid, electrolytes, for example potassium and uremic toxins via the intestinal route, such as induced diarrhea or modified gut microbiome and perspiration route, are discussed.

Since late 2019, emerging infectious diseases and outbreaks in particular from the COVID-19 pandemic have overshadowed the medicine, including kidney care. In early 2020, the first published COVID-19 case was reported in an ESKD patient [31] and the current COVID-19 pandemic continues as the most important and emergent public health problem of the globe, including for high-risk CKD, ESKD and kidney transplant patients. We have learned more on a daily basis from the rapid growth of information about this highly contagious and life-threatening disease that resulted from severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), and several strategies have been applied to prepare for the dynamic process of this pandemic especially in kidney transplant recipients [32]. Apart from the virulence of SARS-CoV-2 itself, other factors are related to prognosis of patients with kidney diseases and COVID-19, including host-related factors and the environmental factors. The state of immunosuppression in CKD, ESKD and kidney transplanted patients increases the risk of contracting and the severity of COVID-19 in these populations. Moreover, the use of effective medications is limited in patients with poorly functioning kidneys, and passive immunity can potentially cause allosensitization leading to barriers in finding acceptable donors. Regarding environmental factors, practicing social distancing is difficult especially in ESKD patients requiring chronic in-center hemodialysis. Several novel therapeutic approaches are discussed.

Also relevant under the COVID-19 pandemic are special circumstances for the management for patients with acute kidney injury (AKI) from COVID-19. Throughout 2020 and likely beyond, the world population has dealt with a continuous and recurrent surges of COVID-19 outbreaks. No region of the world has remained spared. SARS-CoV-2 is known to at least indirectly affect kidneys and lead to AKI requiring renal replacement therapy especially in some severe COVID-19 cases with respiratory failure needing critical/intensive care unit stay with mechanical ventilation, although the mechanisms of AKI in COVID-19 remain unrevealed [33]. Medical supplies shortage can cause a huge public health problem. Chronic renal replacement therapy (CRRT) machines and components can be

in high demand during AKI surges, including pandemic and disasters, such as major earthquakes [34]. Lack of resources was experienced at the beginning of the pandemic in early 2020 and may return in the future with recurrent pandemic surges. The proposed creative hemofiltration apparatus using basic devices adapted from conventional CRRT model is discussed.

Diabetes is another common risk factor for CVD in patients with CKD, including kidney transplant recipients. Posttransplant diabetes mellitus (PTDM) worsens short- and long-term poor kidney allograft and patient outcomes [35]; however, strong evidence related to the use of antihyperglycemic agents in kidney transplant population is lacking. The novel therapy for PTDM in this issue provides an overview of epidemiology and pathogenesis, including risk factors, definition and diagnosis. An article containing the discussion about management for PTDM, including both nonpharmacological and pharmacological aspects, provides a practical aspect for caring for kidney transplant recipients. Recent clinical trials related to PTMD are reviewed.

Hyperkalemia after successful kidney transplantation is commonly seen even in patients with a well-functioning kidney allograft. Pathogenesis of posttransplant hyperkalemia is discussed with more focus on medications routinely used for management of allograft rejection, opportunistic infection prophylaxis and hypertension. Both nonpharmacologic and pharmacologic management are reviewed in detail. Given the benefits of a potassium-rich, plant-dominant, heart-healthy diet for kidney allograft and patient outcomes, imposed dietary restrictions using a low-potassium diet that often deprives the patient of heart-healthy diets may prevent the opportunity to prolong kidney allograft survival [5,27]. Therefore, pharmacological management for chronic or recurrent hyperkalemic kidney transplant recipients becomes a crucial role to control serum potassium while allowing patients to gain benefits from consuming healthy potassium-rich foods. Two novel antihyperkelmic agents, patiromer and sodium zirconium cyclosilicate, are reviewed. Although there are no studies about these two potassium binding agents in kidney transplant recipients as much as those in the nontransplant population, evidence regarding their potential efficacy and safety in terms of drug–drug interactions with immunosuppressive medications is reviewed.

Obesity has been one of the leading public health problems for several decades, and its prevalence continues to increase in CKD, ESKD and kidney transplant recipients [36]. Obesity in kidney transplant recipients is associated with poor patient and allograft outcomes. However, even epidemiological data are still inconclusive with mixed results. Sarcopenia referred to loss of muscle mass and strength is also common in both transplant waitlisted patients and kidney transplant recipients and may contribute to poor clinical outcomes. Sarcopenic obesity is not uncommon and may better explain some of the epidemiological findings in transplant cohorts that include obese kidney transplant recipients. Nonpharmacologic therapy and surgical interventions to achieve weight loss, including for sarcopenic obesity during pre and posttransplant periods, are reviewed.

Although kidney transplantation has long been the treatment of the choice for advanced CKD and ESKD, complications from life-long immunosuppressive medications are one of the leading causes that prevent '*One Organ for Life*' after successful kidney transplantation. Tolerance induction through chimerism has been an emerging approach to allow immunosuppression withdrawal. The fundamental concept of tolerance and chimerism is briefly discussed. Current clinical trials about tolerance induction through chimerism among four regimens are summarized with a brief discussion about the limitations of research in this field, including utility of the biomarkers of tolerance. Although successful tolerance can theoretically decrease the number of retransplantation, given limited tolerance studies pertaining to living donor kidney transplantation, tolerance induction may still not resolve the unmet need of the mismatched organ demand and supply. Other kidney replacement therapies using stem cell and organ engineering or bioartificial kidneys may be complementary or alternative to the tolerance induction.

In summary, this special issue highlights novel therapeutic approaches in nephrology and hypertension and brings experts from the field of nephrology and transplantation related to kidney health. We appreciate all authors for extending their knowledge and expertise and would also like to invite our readers to explore different aspects of the articles in this special issue. Please submit comments or suggestions regarding these articles and discussion in future issues of CONH to kkz@uci.edu or Wolters Kluwer editors.

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Conflicts of interest

KKZ has received honoraria and/or grants from Abbott, Abbvie, Alexion, Amgen, DaVita, Fresenius, Genzyme, Keryx, Otsuka, Shire, Rockwell and Vifor, the manufacturers of drugs or devices and/or providers of services for CKD patients. KKZ serves as a physician in a US Department of Veterans Affairs medical centers with part-compensation and is a part-time employee of a US Department of Veterans Affairs medical centers. Opinions expressed in this article are those of the authors and do not represent the official opinion of the US Department of Veterans Affairs.

REFERENCES

1. Tantisattamo E, Kalantar-Zadeh K. Editorial: Novel therapeutic approaches in chronic kidney disease and uremia management. Curr Opin Nephrol Hypertens 2020; 29:1–3.
2. Palmer BE, Clegg DJ. Fluid overload as a therapeutic target for the preservative management of chronic kidney disease. Curr Opin Nephrol Hypertens 2020; 29:22–28.
3. Clegg DJ, Palmer BF. Potassium binding for conservative and preservative management of chronic kidney disease. Curr Opin Nephrol Hypertens 2020; 29:29–38.
4. Goraya N, Wesson DE. Novel dietary and pharmacologic approaches for acid-base modulation to preserve kidney function and manage uremia. Curr Opin Nephrol Hypertens 2020; 29:39–48.
5. Joshi S, Hashmi S, Shah S, Kalantar-Zadeh K. Plant-based diets for prevention and management of chronic kidney disease. Curr Opin Nephrol Hypertens 2020; 29:16–21.
6. Caggiano G, Cosola C, Di Leo V, *et al.* Microbiome modulation to correct uremic toxins and to preserve kidney functions. Curr Opin Nephrol Hypertens 2020; 29:49–56.
7. Puri I, Shirazi NM, Yap E, Saggi SJ. Intestinal dialysis for conservative management of Uremia. Curr Opin Nephrol Hypertens 2020; 29:64–70.
8. Cupisti A, Piccoli GB, Gallieni M. Charcoal for the management of pruritus and uremic toxins in patients with chronic kidney disease. Curr Opin Nephrol Hypertens 2020; 29:71–79.
9. Haarhaus M, Gilham D, Kulikowski E, *et al.* Pharmacologic epigenetic modulators of alkaline phosphatase in chronic kidney disease. Curr Opin Nephrol Hypertens 2020; 29:4–15.
10. Rhee CM, Nguyen DV, Nguyen A, Kalantar-Zadeh K. Conservative vs. preservative management of chronic kidney disease: similarities and distinctions. Curr Opin Nephrol Hypertens 2020; 29:92–102.
11. Keller RW, Jr, Kopple JD, Kalantar-Zadeh K. Perspiration interventions for conservative management of kidney disease and uremia. Curr Opin Nephrol Hypertens 2020; 29:57–63.
12. Tantisattamo E, Hanna RM, Reddy UG. Novel options for failing allograft in kidney transplanted patients to avoid or defer dialysis therapy. Curr Opin Nephrol Hypertens 2020; 29:80–91.
13. Wahdan MH. The epidemiological transition. East Mediterr Health J 1996; 2:8–20; https://apps.who.int/iris/handle/10665/118829. [Accessed 28 October 2020]
14. Global Burden of Disease Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2020; 395:709–733.
15. Carney EF. The impact of chronic kidney disease on global health. Nat Rev Nephrol 2020; 16:251.
16. Matsushita K, Ballew SH, Coresh J. Cardiovascular risk prediction in people with chronic kidney disease. Curr Opin Nephrol Hypertens 2016; 25:518–523.
17. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388:1459–1544.
18. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388:1603–1658.
19. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998; 32(5 Suppl 3):S112–S119.
20. Saran R, Robinson B, Abbott KC, *et al.* US Renal Data System 2016 Annual Data Report: epidemiology of kidney disease in the United States. Am J Kidney Dis 2017; 69(3 Suppl 1):A7–A8.
21. Fuchs FD, Whelton PK. High blood pressure and cardiovascular disease. Hypertension 2020; 75:285–292.
22. Unger T, Borghi C, Charchar F, *et al.* 2020 International Society of hypertension global hypertension practice guidelines. Hypertension 2020; 75: 1334–1357.
23. Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. N Engl J Med 2017; 377:1765–1776.
24. Pahl MV, Vaziri ND. The chronic kidney disease: colonic axis. Semin Dial 2015; 28:459–463.
25. Frost WH. Some conceptions of epidemics in general by Wade Hampton Frost. Am J Epidemiol 1976; 103:141–151.
26. Deputy Director for Public Health Science and Surveillance, Center for Surveillance, Epidemiology, and Laboratory Services, Division of Scientific Education and Professional Development. Centers for Disease Control and Prevention. Section 8: Concepts of Disease Occurrence. Lesson 1: Introduction to Epidemiology. Principles of Epidemiology in Public Health Practice, Third Edition An Introduction to Applied Epidemiology and Biostatistics. May 18th, 2012. https://www.cdc.gov/csels/dsepd/ss1978/lesson1/section8.html. [Accessed 28 October 2020]
27. Kalantar-Zadeh K, Joshi S, Schlueter R, *et al.* Plant-dominant low-protein diet for conservative management of chronic kidney disease. Nutrients 2020; 12:.
28. 2021 World Kidney Day Theme. Kidney Health for Everyone Everywhere – Living Well with Kidney Disease. https://www.worldkidneyday.org/2021-campaign/2021-wkd-theme/. [Accessed 28 October 2020]
29. Kalantar-Zadeh K, Li PK, Tantisattamo E, *et al.* Living well with kidney disease by patient and care-partner empowerment: kidney health for everyone everywhere. Kidney Int 2020; In press.
30. Kalantar-Zadeh K, Wightman A, Liao S. Ensuring choice for people with kidney failure: dialysis, supportive care, and hope. N Engl J Med 2020; 383:99.
31. Ferrey AJ, Choi G, Hanna RM, *et al.* A case of novel coronavirus disease 19 in a chronic hemodialysis patient presenting with gastroenteritis and developing severe pulmonary disease. Am J Nephrol 2020; 51:337–342.
32. Tantisattamo E, Ferrey AJ, Reddy UG, *et al.* Haddon matrix for kidney transplantation during COVID-19 pandemic: a problem solving framework for present and future. Transpl Infect Dis 2020; e13373.
33. Benedetti C, Waldman M, Zaza G, *et al.* COVID-19 and the kidneys: an update. Front Med (Lausanne) 2020; 7:423.
34. Neyra JA, Connor MJ Jr, Tolwani A. Preparedness of kidney replacement therapy in the critically ill during COVID-19 surge. Kidney Int Rep 2020; 5:961–964.
35. Shivaswamy V, Boerner B, Larsen J. Post-transplant diabetes mellitus: causes, treatment, and impact on outcomes. Endocr Rev 2016; 37:37–61.
36. Stenvinkel P, Zoccali C, Ikizler TA. Obesity in CKD: what should nephrologists know? J Am Soc Nephrol 2013; 24:1727–1736.