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Authors

Tantisattamo, Ekamol
Hanna, Ramy M
Kalantar-Zadeh, Kamyar

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Novel therapeutic approaches in chronic kidney disease and kidney transplantation: the draw of evolving integrated multimodal approaches in the targeted therapy era

Ekamol Tantisattamo[a,b,c], *Ramy M. Hanna*[a], *and Kamyar Kalantar-Zadeh*[a,b,d]

Management of risk factors for kidney diseases may prevent or lower the incidence of chronic kidney disease (CKD) and kidney failure, statutorily known as end-stage renal disease. However, the prevalence of CKD and kidney failure has been increasing in the form of a global CKD epidemic [1]. The goal is not only decreasing the incidence of CKD, known as primary prevention, but also alleviating CKD progression, known as secondary and tertiary prevention, that is, intervening in earlier CKD stages and in more advanced CKD to prevent or delay renal replacement therapy, respectively [2]. Preventive and therapeutic strategies should be broad but they can also be specific to the mechanism of CKD and its complications. Overall knowledge in nephrology and transplant fields has evolved; however, implementing science from bench to bedside has encountered challenges related to several factors including lack of long-term clinical studies, restrictive policies and regulations, constraints in economic aspects political views, and psycho-social factors including health literacy [3]. Therefore, novel therapies or innovative modification and creative combination of management strategies that target the pathophysiologic mechanisms of CKD should be taken into account on prevention and treatment of kidney diseases including kidney failure.

To extend our scientific evidence and authors' contributions from the previous two article collections *Novel Therapeutic Approaches in Nephrology and Hypertension* in the *Current Opinion in Nephrology and Hypertension* in January 2020 and January 2021, which focused on novel therapeutic approaches to prolong and preserve the function of native kidneys [4–15] and kidney allografts and kidney health and novel management strategies for common metabolic conditions related to CKD, end-stage kidney disease (ESKD), and kidney transplantation [16–27], respectively, the January 2022 article collection in the current issue of *Current Opinion in Nephrology and Hypertension* introduces novel and renewed multimodal approaches in the form of integrated therapeutic strategies for CKD, kidney failure, and transplantation and some practical and individualized approaches, with overarching spectureum from diet and lifestyle modification to emerging pharmacotherapy.

Being the leading cause of CKD and kidney failure as well as high morbidity and mortality [28], diabetes mellitus brings several challenges but urges clinical and public health providers to improve care for CKD patients with diabetes. Metabolic disarrangement in CKD and kidney failure patients and dialysis factors are associated with a high prevalence of dysglycemia both hypoglycemia and hyperglycemia. Pathogenesis of dysglycemia in CKD and kidney failure populations are reviewed. Epidemiology and evidence of the association between dysglycemia and main clinical outcomes including mortality and hypoglycemia-related hospitalizations were summarized. Management of glycemic derangements emphasizing multimodalities including individualized blood glucose targets,

[a]Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology, Hypertension and Kidney Transplantation, University of California Irvine School of Medicine, Orange, [b]Nephrology Section, Department of Medicine, Tibor Rubin Veterans Affairs Medical Center, Veterans Affairs Long Beach Healthcare System, Long Beach, California, [c]Multi-Organ Transplant Center, Section of Nephrology, Department of Internal Medicine, William Beaumont Hospital, Oakland University William Beaumont School of Medicine, Royal Oak, Michigan and [d]Lundquist Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California, USA

Correspondence to Ekamol Tantisattamo, MD, MPH, Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology, Hypertension and Kidney Transplantation, Department of Medicine, University of California Irvine School of Medicine, 101 The City Drive South, Orange, CA 92868, USA. Tel: +1 714 456 5142; fax: +1 714 456 6034; e-mail: etantisa@hs.uci.edu

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nonpharmacologic and pharmacologic interventions, and blood glucose monitoring were also discussed.

In addition to glycemic control for patients with CKD in diabetes, the type of diet plays a role in the slow progression of CKD with and without diabetes. A heart-healthy diet with low carbohydrate and low fat has been widely recommended for a long period; however, there is no consensus on a low-protein diet especially the amount of dietary protein intake. Low-protein with plant-focused diet as part of the multimodal intervention and medical nutrition therapy synergistically affecting current pharmacological management for example renin–angiotensin–aldosterone system blockade and sodium–glucose transport protein 2 inhibitors to slow CKD progression was comprehensively reviewed. A plant-focused low-protein diet for the nutritional management of CKD/diabetes mellitus (PLAFOND), a type of plant-dominant low-protein diets (PLADO), with lower glycemic index and somewhat lower energy intake, compared with other types of PLADO diets, was introduced and possible mechanisms of renoprotection as well as potential limitations for implementing this diet, were discussed.

As another leading cause of kidney failure worldwide, the hypertension pandemic remains a critical public health problem [29]. Particularly, with evolving evidence of cardiovascular and mortality outcomes related to blood pressure (BP) that is lower than that of previous hypertension guidelines, the prevalence of hypertension increases. Results from the SBP Intervention Trial (SPRINT) demonstrated that an intensive BP target of less than 120 mmHg in nondiabetic patients with high cardiovascular risks lowered fatal and nonfatal major cardiovascular events and all-cause mortality compared with the target BP less than 140 mmHg. However, serious adverse events including hypotension, syncope, electrolyte abnormalities, and acute kidney injury (AKI) or failure were greater in the intensive therapy [30]. These issues can be even worse among those with CKD [31]. With great concern for the elderly especially those with CKD concomitantly with a high prevalence of frailty, their biological age may be far advanced than their biological age. Therefore, both intensive BP target and more conservative BP goal such as from the Eighth Joint National Committee, if implemented in a selected elderly population, can benefit from decreased cardiovascular outcomes while mitigating potential adverse events. Comments on SPRINT and Strategy of BP Intervention in the Elderly Hypertensive Patients trials as well as hypertension guidelines from current major scientific societies focusing on the elderly population were discussed.

The high prevalence of CKD, in turn, leads to an increased number of patients who transition to dialysis and kidney transplantation. Several efforts to mitigate poor outcomes of kidney failure requiring kidney replacement therapy have not succeeded given many barriers and limitations including the natural history of the disease itself, lack of specific therapies that can individualize some groups of kidney failure patients. The proposed term *Kidney dysfunction requiring dialysis (KDRD)* is introduced to emphasize the implication of individualized therapy for these patients by stratifying those as per pathophysiological, residual kidney function, and phenotypic standpoints to bring recognition of dialysis as one of the treatments that assist, rather than replace, the remaining kidney function in patients with KDRD. As such, another term 'kidney assistance therapy' rather than *kidney replacement therapy* is also suggested. These may improve not only clinical outcomes for individualized therapies but also guide clinical research and trials in the kidney failure population.

Over the past decades, dialysis has been the most common therapy for patients with kidney failure as a life-saving treatment. However, the intestine is an organ historically utilized for managing complications of CKD and ESKD such as reducing uremic toxins, controlling volume and electrolyte disturbances. With a close relationship between gut microbiome perturbation and CKD as well as the role of the intestine as a known uremic toxin-producing organ especially in the setting of dysbiosis, intestinal clearance of the toxin is another therapeutic option to mitigate uremia [32]. Authors summarized potential intervention to decrease uremic toxin in CKD and ESKD via intestinal route, as the so-called *intestinal dialysis*. History of intestinal dialysis and some therapeutic options including intestinal perfusion, irrigation, and cleaning (with laxative), an oral adsorbent [porous microcrystalline carbon with an oxygen complex (AST-120)] were discussed. Moreover, dysbiosis and uremia were summarized with gut microbiota modulation as therapeutic interventions including dietary intervention (plant-based diets, low-protein diets), and dietary modification (prebiotics, probiotics, and synbiotics). These interventions, although promising, are required additional studies.

Therapeutic interventions to slow the progression of CKD or adequately provide dialysis may not achieve the goal of effective management for advanced CKD and kidney failure requiring dialysis unless the patients receive general well being and quality of life. Whereas salivary biomarkers of kidney function can help better monitor kidney disease and its progression, and whereas physical

performance and assessment and monitoring can help improve physical function and overall well being of these patients; not only fluid, electrolyte, and metabolic disturbances but also symptoms resulting from complications of advanced CKD and kidney failure need to be controlled to have patients living well with kidney disease [33]. Among the CKD-associated symptoms, pruritus or CKD-associated pruritus (CKD-aP) is one of the frequently encountered symptoms which, on the other hand, is commonly overlooked. Concomitant with other symptoms from advanced CKD sharing similar pathogenesis of CKD-aP, symptom clusters are identified and open opportunities for target intervention to the cluster to improve symptoms in the same cluster. Epidemiology, pathogenesis, clinical manifestation, and impact on clinical outcomes of CKD-aP were reviewed. Symptom clusters and evidence-based therapy for CKD-aP were discussed.

With increased public attention about diet for health especially high dietary protein intake, there are many pieces of evidence both animal and clinical studies demonstrating pathophysiological changes in both renal hemodynamic and metabolic components that lead to glomerular injury and declined kidney function as long-term consequences. However, some studies showed no association between a high protein diet and kidney dysfunction. Mechanism of high dietary protein intake and glomerular damage from glomerular hyperfiltration is comprehensively reviewed and clinical consequences of high protein intake in athletes and bodybuilders are discussed. Apart from the quantity, quality of protein for example animal, plant-based, protein supplements may contribute to kidney dysfunction; although, further studies are required.

Although there is evidence supporting high dietary protein intake leading to progression of CKD, studies performed in kidney transplant recipients are scant and have revealed conflicting results. Kidney allograft hemodynamic alteration in the transplanted kidney can theoretically cause glomerular hyperfiltration, increased intraglomerular pressure, and subsequently glomerular damage in the long term [34–38]. Since the long-term kidney allograft outcomes have not changed over the decades and nonimmunological factors play an important role in kidney allograft loss especially death with a functioning allograft, intervention on these factors using integrated multimodal approaches that include diet and life style modifications may prolong kidney allograft survival. Similar to nontransplant patients, high dietary protein intake in kidney transplant recipients can cause physiological adaptation in the transplanted kidney initially but pathophysiological changes occur in the long term. These dietary-induced hemodynamic changes are reviewed. Macronutrients and their effect on kidney allograft outcomes are discussed. A plant-based diet including PLADO, Dietary Approaches to Stop Hypertension, Mediterranean diet, and vegetarian diet and their association with kidney allograft function is reviewed.

Several medication-related kidney complications have been discovered particularly current novel pharmacological interventions in other organ systems and conditions. Over the past 3–4 decades when intravitreal vascular endothelial growth factor inhibitors (VEGFi) became utilized for cancer therapy and later on for ophthalmologic lesions such as retinal neovascularization, age-related macular degeneration, and diabetic macular edema, adverse drug events from systemic and intravitreal VEGFi have discovered. The cumulative evidence of intravitreal VEGFi-associated hypertension and kidney diseases including AKI, worsening proteinuria, and glomerulonephritis including the pathological finding of thrombotic microangiopathy were summarized. Moreover, drug history, molecular biology, pharmacokinetics, translational, and epidemiological data related to associated complications of intravitreal VEGFi to other organs were reviewed. Further studies and large scale of the study population as well as pharmacoepidemiology and pharmacovigilance to strengthen the current evidence and identify the population at risk for prevention and therapy were discussed.

Affecting the world over the past 2 years, coronavirus disease 2019 (COVID-19) pandemic has been one of the leading ongoing public health problems. The novel and complexity of pathogenesis of severe acute respiratory syndrome coronavirus 2 involving multiorgan systems especially the kidney which is one of the major organ systems affected in COVID-19-infected patients. Pathogenesis of COVID-19-induced AKI and CKD are comprehensively reviewed. It involves the interplay of severe COVID-19-induced lipid mediator storm, increased thromboinflammation inducing renal ischemic-reperfusion, alteration of immune cell function, renal tubular cell apoptosis, mitochondrial dysfunction, and cytotoxicity. Pharmacologic therapies for COVID-19 are discussed including celecoxib and dexamethasone. Dual prostaglandin D2 receptor/thromboxane prostanoid receptor (DR2/TPr) antagonist Ramatroban, a medication used for allergic rhinitis in Japan over 2 decades, is proposed as promising chemoprophylaxis and therapy in COVID-19 infection to mitigate kidney injury.

Anti-inflammatory and antifibrotic actions of soluble epoxide hydrolase inhibitors as potential kidney protection are discussed. Long-haul COVID is briefly reviewed.

Clinical knowledge in the fields of kidney medicine, hypertension, and transplantation has long been evolved with the further understanding mechanism of kidney disease and its risk factors. Target therapies on specific mechanisms will succeed with implementation science to close the gap between pharamcologic knowledge and nonpharmacologic strategies in practice. We hope that all articles in this 2022 special edition collection *Novel Therapeutic Approaches in Nephrology and Hypertension* provides not only comprehensive content but also motive our clinicians and researchers to initiate future innovative studies. We appreciate all authors who extend their expertise and contribute to this year's article collection. We also encourage our readers to discuss and submit comments or suggestions on the articles in this collection and discussion in future issues of *Current Opinion in Nephrology and Hypertension* to editors or Wolters Kluwer editors.

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Conflicts of interest

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