EDITORIAL

Medical Nutrition Therapy for Diabetic Kidney Disease

DIABETES MELLITUS IS a devastating disease affecting 463 million adults worldwide.[1] In the United States alone, more than 34 million people suffer from diabetes, of whom ~20% are undiagnosed, and among diagnosed cases, the majority (~90-95%) are attributed to type 2 diabetes.[2] Compounding these estimates, an additional 88 million US adults have prediabetes,[2] many of whom are afflicted by associated metabolic complications including insulin resistance, obesity, and dyslipidemia.[3]

As one of the most prevalent complications of this endocrine disorder, chronic kidney disease (CKD) affects 30% and 40% of patients with types 1 and 2 diabetes, respectively.[4] Diabetes has unique health implications and distinct management considerations across the spectrum of kidney disease (Figure 1). In early stages, patients with diabetes experience glomerular hyperfiltration and renal enlargement leading to increased proteinuria, kidney dysfunction, and diabetic kidney disease (DKD) over time.[5,6] Once kidney disease develops, patients with DKD have more rapid CKD progression versus those without diabetes.[7] As such, diabetes is the leading cause of end-stage renal disease (ESRD) in the United States, affecting 47% and 39% of incident and prevalent cases, respectively.[8]

Even after developing terminal kidney failure, patients with ESRD continue to suffer from the sequelae of diabetes,[9] including worse survival compared with their nondiabetic counterparts.[10] Although some patients with non–dialysis-dependent (NDD) CKD transitioning to ESRD experience spontaneous resolution of hyperglycemia, normalization of HbA1c, and cessation of antidiabetes medications in a phenomenon known as "burnt-out diabetes,"[9] they are at heightened risk for hypoglycemia[11-13] as a consequence of decreased renal gluconeogenesis, impaired insulin degradation and clearance by the kidney and liver, coexisting comorbidities (protein-energy wasting [PEW], gastroparesis), uremic toxins, and glucose shifts during hemodialysis.[9] While kidney transplantation as the gold standard treatment for ESRD may ameliorate these metabolic derangements, dysglycemia is frequently observed in the immediate/early post-transplant period owing to surgical stress and hypercortisolemia, infection, and receipt of high-dose glucocorticoids.[14] While glycemic derangements may improve with reduction in immunosuppression over time, patients who manifest persistent hyperglycemia 45-days after transplant are diagnosed with post-transplant diabetes mellitus.[15,16] Although the underpinnings of post-transplant diabetes mellitus have not been fully elucidated, there are shared risk factors with the general population, plus those unique to transplantation (receipt of glucocorticoids, calcineurin inhibitors, and mammalian target of rapamycin inhibitors; hepatitis C and cytomegalovirus; hypomagnesemia).[14] In the same vein, even in the absence of preexisting diabetes, patients with CKD are at risk of hyperglycemia owing to insulin resistance, impaired insulin secretion, and exposure to high glucose peritoneal dialysate loads.[9]

Given the pervasive presence of dysglycemia across the spectrum of kidney disease, medical nutritional therapy (MNT) is a cornerstone in the multidisciplinary management of DKD.[17,18] Because increased dietary protein intake (DPI) exacerbates glomerular hyperfiltration,[19] there is growing recognition of the impact of low-protein diets in attenuating DKD progression.[17,20,21] The 2020 National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Nutrition in CKD recommend that patients with stages 3-5 CKD with diabetes adjust their DPI to 0.6-0.8 g/kg ideal body weight per day.[22] While there are ongoing studies examining the effects of source of DPI on kidney health (i.e., plant-dominant low-protein diet, also known as the PLADO diet[21]), a consensus conference convened by the American Diabetes Association, American Society of Nephrology, and National Kidney Foundation has emphasized DPI from vegan and nonfat/low-fat dairy sources.[23,24] Increasing evidence suggests plant-based diets have benefits[21,25] that are relevant to the DKD population, including better glycemic and blood pressure control, as well as improved acid-base balance as highlighted in an article by Goraya et al.[26] in this issue of the Journal of Renal Nutrition (JREN).

Although a large body of research has focused on the role of DPI, there remain major knowledge gaps regarding other dietary interventions in DKD management.[17] First, while various recommendations for carbohydrate reduction in patients with diabetic non-CKD may also pertain to those with DKD, 1 important distinction is that low carbohydrate diets that are replaced by increased DPI should be avoided in

Financial Disclosure: C.M.R. has received honoraria from AstraZeneca, Fresenius, Otsuka, Reata, and Roche. The remaining authors have no relevant financial disclosures.

Address correspondence to Connie M. Rhee, MD, MSc, Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology, Hypertension and Kidney Transplantation, University of California Irvine, 101 The City Drive South, City Tower, Orange, California 92868-3217. E-mail: crhee1@uci.edu

1051-2276/$36.00
https://doi.org/10.1053/j.jrn.2021.03.004

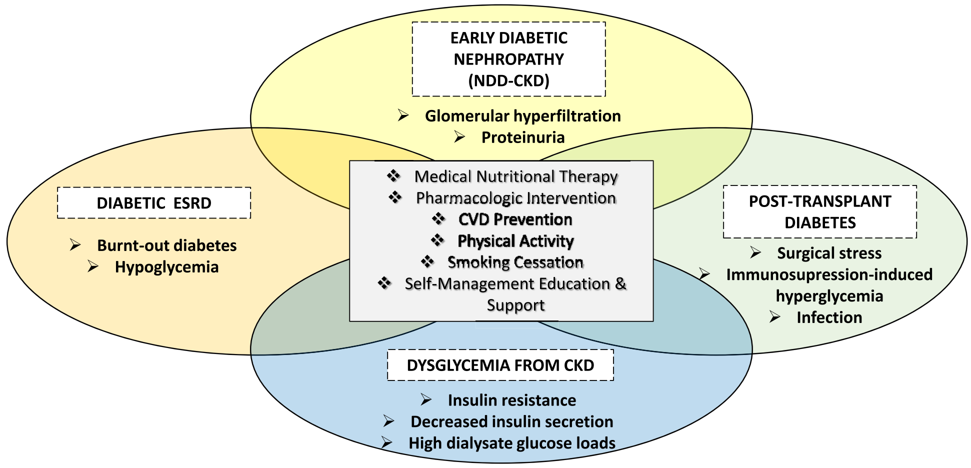

Figure 1. Impact of diabetes across the spectrum of kidney disease. CKD, chronic kidney disease; ESRD, end-stage renal disease; NDD,non–dialysis-dependent.

diabetic patients with NDD CKD. Given the popularity of high-to-moderate protein diets (i.e., ketogenic, Paleo, and so on) as means to reduce weight loss and avoid diabetic complications,[19] rigorous research is needed to determine their safety and efficacy on kidney outcomes. In addition, as data in the broader diabetes population indicate that low-glycemic index diets provide modest improvement in hyperglycemia,[27] further investigation is needed to determine the impact of glycemic index and load on renal end points. Second, while dietary fats such as saturated fat, trans-fat, and cholesterol are avoided in lieu of omega-3 fatty acids and monounsaturated and polyunsaturated fats in patients with diabetic non-CKD, recommendations on dietary fat source and quantity in DKD are mixed across practice guidelines,[28] likely owing to a paucity of research in this area. Third, there are emerging data suggesting that greater adherence to prescribed diets such as the dietary approaches to stop hypertension diet (which is not a low-protein diet) is associated with lower ESRD risk particularly in those with DKD.[29] Given the benefits of the dietary approaches to stop hypertension and Mediterranean diets on CKD risk factors (hyperglycemia, hypertension, obesity),[30] further study is needed to determine their effects on relevant DKD end points. Fourth, although sugar substitutes are used in diabetes to reduce carbohydrate and caloric intake, professional societies have advised there is insufficient evidence of long-term benefits on weight, glycemia, and cardiometabolic risk factors.[27] As recent reports suggest that processed and convenience foods are contributing to the growing coexistence of obesity and malnutrition,[31,32] further research is needed to determine the impact of sugar substitutes on the health of the DKD and broader diabetes populations. Finally, MNT has been shown to be cost-saving in the management of diabetes, whereas there are a lack of studies examining its cost-effectiveness specifically in DKD.[18]

This issue of JREN is comprised cutting-edge articles that highlight the complications of (1) insulin resistance and dysglycemia, (2) obesity, dyslipidemia, and other metabolic derangements, and (3) PEW that are highly prevalent in both diabetic and patients with nondiabetic kidney disease; as well as (4) novel and practical dietary interventions and tools that may improve their nutritional health. Given that higher levels of vitamin K intake and carboxylated osteocalcin (vitamin K–dependent protein used as a biomarker of vitamin K status) have been associated with insulin sensitivity, Kratz et al.[33] examined the relationship between osteocalcin concentrations and carboxylation status with glucose homeostasis in a secondary analysis of 87 patients with moderate-to-severe NDD CKD and 37 healthy controls without diabetes from the study of glucose and insulin in renal disease. As osteocalcin concentrations and carboxylation status were not associated with glucose homeostasis, the investigators concluded that impaired osteocalcin carboxylation did not appear to contribute to impaired insulin sensitivity in CKD.

Several articles in this issue of JREN also underscore various complications ensuing from obesity and metabolic dysregulation in CKD. In a prospective study of 97 patients on hemodialysis who underwent measurement of visceral fat area by bioimpedance analysis and Agatston coronary artery calcification score by cardiac computed tomography by Xiong et al.,[34] greater visceral fat area was associated with heightened risk of cardiovascular events and death, whereas coronary artery calcification score was not associated with these end points. Similarly, in an analysis of 13,223 adults from the National Health and Nutrition Examination Survey, Feng et al.[35] observed a dose-dependent relationship between higher body mass index and risk of self-reported nephrolithiasis. To investigate the interplay between obesity and nutrition on patient-reported outcomes, Yaseri et al.[36] conducted a study of 83 patients on hemodialysis who underwent health-related quality of life Short Form 36, body anthropometry, malnutrition-inflammation score, and Dietary Inflammatory Index (novel tool measuring dietary inflammatory potential) assessments. While patients with obesity reported lower (worse) Short Form 36 physical health, physical functioning, and bodily pain scores versus those of normal weight, patients with higher Dietary Inflammatory Index scores (indicating greater proinflammatory diet potential) had worse health-related quality of life irrespective of obesity status.

As this issue of JREN coincides with the American Transplant Congress, we are also excited to present topics highlighting tools and interventions for obesity and PEW in kidney transplant recipients. Given the high prevalence of weight gain in transplant recipients, convenient yet accurate tools for determining energy requirements are needed for dietary planning to avoid post-transplant obesity. In a study of 51 kidney transplant recipients, Tek et al.[37] evaluated the agreement between resting energy expenditure (REE) measured by indirect calorimetry versus eight REE predictive equations commonly used in CKD. All predictive equations underestimated REE versus indirect calorimetry as the gold standard, with underprediction values ranging from ~28 to 98%, leading the investigators to develop two novel REE formulas for use in kidney transplant recipients. As high omega-3 fatty acid levels reduce hypertriglyceridemia and cardiovascular risk, Thorsteindottir et al.[38] examined associations of plasma omega-3 polyunsaturated fats (eicosapentaenoic acid, docosahexaenoic acid, docosapentaenoic acid), with cardiovascular risk factors in 53 pediatric kidney transplant recipients. Each of these polyunsaturated fats was inversely associated with triglyceride levels, and higher concentrations of eicosapentaenoic acid were associated with lower blood pressure. Improved methods for risk stratification of elderly patients being evaluated for transplant are also needed. Deliege et al.[39] examined presarcopenia, ascertained by computed tomography–defined skeletal mass index, as a risk factor for adverse post-transplant outcomes among 122 kidney transplant recipients ≥60 years of age, and found that skeletal mass index was associated with longer post-transplant hospitalization and higher risk of wound complications and the composite of death and 1-year graft loss in men.

Several studies in this issue expand on the themes of PEW, nutritional deficiencies, and dietary interventions circumventing nutritional complications in CKD. In contrast to the elder population, PEW is an underrecognized complication in children with CKD. While growing research has focused on patients with pediatric CKD from developed nations, there remains a scarcity of literature characterizing the burden of PEW in children with CKD from low-to middle-income countries. Iygengar et al.[40] examined 123 children with stages 2-5 CKD from India and found that more than half (58%) of patients suffered from PEW. In patients on dialysis who are prone to hypercatabolism and dialytic protein and amino acid losses, high-protein diets and accurate assessment of DPI are needed to mitigate risk of PEW. Zilli Canedo Silva et al.[41] conducted a study of 51 adult patients on peritoneal dialysis who underwent 24-hour dietary recall and protein nitrogen appearance assessments to evaluate their agreement in estimating DPI and across various DPI definitions, and they observed weak correlations (ranging from 0.19 to 0.38) between the two methods, as well as significant proportionality bias indicating that values were influenced by the magnitude of the measures. As metabolic acidosis is a risk factor for PEW and CKD progression, there is growing interest in "prescribing" base–producing fruits/vegetables in place of sodium-based alkaline supplements given the former's salutary benefits. In a post hoc analysis of a trial of 108 patients with nondiabetic stage 3 CKD randomized to fruits + vegetables and oral sodium bicarbonate versus usual care by Goraya et al.,[26] those in the fruits + vegetables and sodium bicarbonate arms had comparable improvement in metabolic acidosis and per household costs. Zinc deficiency is commonly observed in CKD as a consequence of inadequate intake, malabsorption, and dialysate mineral losses and may lead to loss of taste which is a risk factor for decreased appetite. dos Santos Rocha Tavares et al.[42] conducted a study of 21 patients with NDD CKD and 22 healthy volunteers examining the association between plasma zinc and taste sensory perceptions and found that lower zinc concentrations were associated with impaired sensitivity to sour, salty, and bitter flavors.

Given that metabolic complications ensuing from overnutrition and undernutrition abound in patients with CKD, MNT is critical to their health and survival. As telemedicine, online resources, and social media have emerged as powerful tools for education and behavioral interventions, the final study in this issue's JREN collection examining patient-centered digital dietary support by Mejia et al.[43] is timely and relevant. In a study of 100 adult patients on hemodialysis surveyed about interest in participating in an online patient community with dietitian access, 46% were very/extremely interested in this form of MNT and 83% indicated they owned a tablet/smartphone. Given the critical importance of having access to evidence-based information and tailored MNT under the expertise of a kidney dietitian, further research is needed to identify innovative ways of leveraging the broad reach and accessibility of digital tools as we combat the dual public health crises of diabetes and CKD among our patients.

Connie M. Rhee, MD, MSc
Kamyar Kalantar-Zadeh, MD, MPH, PhD
University of California Irvine, Orange, California

Linda W. Moore, PhD, RDN, CCRP
Houston Methodist Hospital, Houston, Texas

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