Title
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EDITORIAL

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Introduction

CHRONIC KIDNEY DISEASE (CKD) is a major health epidemic in the United States, and the role of nutritional evaluation and intervention has never been more urgent. The articles highlighted in this issue of the *Journal of Renal Nutrition* shine a klieg light on the critical problem of protein-energy wasting (PEW), which is commonly observed in patients with advanced CKD and end-stage kidney disease (ESKD). Skeletal muscle is central to the body's framework and movement, but it also plays an essential metabolic role in health and disease. Sarcopenia, also known as muscle wasting, is a consequence of PEW and refers to decreased skeletal muscle mass and function in older adults (primary sarcopenia) and in patients with chronic illness (secondary sarcopenia). Since sarcopenia is usually associated with muscle weakness (dynapenia), it often affects functionality and health-related quality of life. If sarcopenia is associated with significant (>10%) unintentional weight loss over a relatively short period of time (ie, 6 months or less months), it heralds cachexia and its associated frailty.[1] The negative effect of PEW and its associated sarcopenia results in increased infectious disease complications, dependency, low quality of life, and a sedentary and inactive lifestyle that jeopardizes cardiovascular health.[2-4] From the patient's perspective, PEW adversely affects their perception of health, physical performance, and quality of life.[5] A report by Cheng et al. in this issue of the *Journal of Renal Nutrition* provides some metrics surrounding the impact of sarcopenia on basic and instrumental activities of daily living in patients receiving maintenance hemodialysis.[6] They report that 79.9% of their patient population exhibited sarcopenia and that gait speed is a valuable diagnostic tool for sarcopenia (area under the receiver-operating characteristic curve, >0.8). It is, therefore, critical to understand the mechanisms of PEW better and identify when it is present at all stages of CKD because interventions can be better targeted and more effective.

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Epidemiology and Clinical Impact

PEW is among the most consequential complications of CKD and ESKD. The controversy over the terminology makes it difficult to characterize the prevalence of PEW accurately. Still, clinicians know it when they see it, as Supreme Court Justice Potter memorably invoked about illicit imagery. Muscle wasting often becomes apparent in advanced stages of CKD and is progressive, frequently accelerating after the initiation of dialysis. The prevalence of PEW has been estimated; <2% in CKD stages 1-2 and 11-54% in CKD stages 3-5.[7] The reported prevalence of muscle wasting in the ESKD population is 30-70% depending on what methods are used to determine nutritional status.[3,8] Those with the most advanced PEW marked by frailty die at alarmingly high rates; the lava flow dates back several years, making it difficult to slow. As PEW damages the body's organ systems, patients with CKD and ESKD die primarily from cardiovascular and infectious complications. It is hypothesized that immunity is compromised in patients with severe PEW due to altered myokine's physiology, decreased thermogenesis, and fatigue of muscles of respiration in stressed conditions, such as pneumonia or sepsis.[9] The association of PEW with cardiovascular mortality is in large part mediated by inflammation. Dialysis ameliorates several metabolic complications of ESKD, including metabolic acidosis, excess interleukin-6 (IL-6), and other inflammatory cytokines, but PEW is a constant and prevalent challenge to manage.[10] Remarkably, patients receiving hemodialysis can lose up to 4 kg of lean mass annually, which is devastating.[11] Several factors, including the dialysis procedure, which removes proteins and is inflammatory, have been implicated.

Influence of Diabetes and Race

The presence of diabetes mellitus was the strongest predictor of lean body mass loss independently of clinically relevant variables such as age, gender, serum albumin, markers of muscle wasting, inflammation, and dialysis modality.[11] Patients with diabetes lose disproportionately more lean mass than those without diabetes. The developing consensus in studying various models of muscle wasting in dialysis patients indicates a common pathway that is dependent on activation of insulin/IGF-1 signaling. Insulin administration enhances amino acid uptake and stimulates protein synthesis.[12,13] Although protein synthesis has not consistently been demonstrated in human subjects receiving insulin infusion, insulin withdrawal in patients with type 1 diabetes is associated with negative nitrogen balance, suggesting a link between impaired insulin signaling and muscle protein degradation.[14] In the absence of diabetes, insulin resistance develops during kidney disease in many patients, even at early stages.[15] The cause of insulin resistance is not clear. Still, some have argued that the loss of muscle mass, resulting in a decrease in insulin receptor density, is a significant cause of insulin resistance in CKD. The thought is that if there is less muscle mass available for insulin-mediated glucose disposal, then the blood glucose would remain elevated, suggesting that a loss of muscle mass is the principal cause of insulin resistance in CKD.

The impact of race on the survival of patients receiving dialysis has been debated and studied.[16] Racial differences may exist, and for years the paradox among African Americans has been a focus of the investigation.[17] However, the developing consensus is that nutritional status and body composition are significant determinants of survival. Several studies, including a large study from Japan, showed the independent associations between a higher lean mass index and a lower risk of cardiovascular death (hazard ratio, 0.87; 95% confidence interval, 0.81–0.94) in dialysis patients.[18] Higher baseline BMI and serum creatinine levels appear to be more important in predicting survival. Therefore, there appears to be a direct association between increased body mass, particularly muscle mass, and improved survival on dialysis regardless of race.

Detection of Muscle Wasting

Myokines. Myokines are cytokines synthesized and released by myocytes, which have paracrine and endocrine effects on muscle, adipose tissue, liver, and other organs. Myokines are implicated in the regulation of muscle metabolism, growth, and atrophy.[19] The effects of several myokines, including myostatin, IL-6, adiponectin, and others, have been characterized in CKD models.[20] Among the myokines that have been investigated clinically is irisin, which is linked with muscle hypertrophy. The article by Chiang et al. in this issue of the *Journal of Renal Nutrition* highlights the role of irisin in PEW observed in CKD.[21] Irisin concentration typically rises acutely after exercise, and levels correlate with intensity. The findings in healthy individuals suggest that serum irisin is associated with muscle fitness, hypertrophy, metabolic vigor and favorable outcomes in healthy individuals. This supposition is supported by the observation that serum irisin concentration is lower in patients with advanced CKD and ESKD. However, a large cohort of maintenance dialysis patients shows that increased levels, counterintuitively, are associated with increased mortality, similar to several other paradoxical findings in dialysis patients under the reverse epidemiology doctrine such as obesity paradox or lipid paradox. The authors propose that in patients with ESKD that high serum irisin reflects chronic muscle injury and oxidative stress associated with inflammation. Therefore, serum irisin as a trial balloon may potentially have a clinically beneficial role as a marker of muscle maladaptation to chronic inflammation in ESKD patients. Ultimately, serum irisin levels may be a component of a clinical probability assessment tool as part of a diagnostic algorithm to help identify PEW. Still, much more work is needed to characterize the determinants of serum irisin levels and their correlation with specific causes and outcomes.

Creatinine is a Muscle Marker

Creatinine is derived from the Greek kreas, meaning flesh, and constant conversion from creatine in muscle.[22] Serum creatinine levels are a surrogate of muscle mass, and higher levels are associated with *better* survival in dialysis patients, and race does not modify the association.[23] This might be counterintuitive because clinicians might associate a higher serum creatinine with lower residual renal function or underdialysis, and therefore worse outcomes. However, in ESKD, a higher serum creatinine is predominantly influenced by muscle mass. Among the studies examining this phenomenon by Parker et al., who showed that serum creatinine levels below 8.0 mg/dL in hemodialysis patients predicted higher mortality, whereas those above 10 mg/dL were associated with greater survival.[23]

Extending the observation that serum creatinine is related to muscle mass and clinical outcomes is a study by Yamamoto et al.[24] Their investigation was premised on supposing that muscle function tests better predict morbidity and mortality in ESKD patients than muscle mass. Canaud et al. developed the creatinine (Cr) index from kinetic modeling of creatinine with hemodialysis, successfully demonstrating that higher creatinine values were associated with more significant skeletal muscle in hemodialysis patients' mass.[25] Refinements were made to the original formula, and 4 components comprise the modified version: age, sex, predialysis serum Cr concentration, and Kt/V for urea.[26] Interestingly, a low modified Cr is associated with falls, bone fracture, cardiovascular events, and mortality in patients undergoing hemodialysis. Yamamoto et al. tested whether the modified creatinine index could predict mortality and cardiovascular hospitalization independently or additively to measures of muscle function.[24] The authors found that the modified creatinine index performed as well as handgrip strength and gait speed predicting mortality in dialysis patients. Furthermore, when the modified creatinine index was added to the regression model with handgrip strength and gait speed, it enhanced the prognostic utility. Dialysis facilities that desire to exceed the quality measures would be wise to implement this practical tool to assess nutritional status.

Imaging

Several imaging modalities are effective for identifying patients at high risk for PEW and sarcopenia. Gold-standard methods for body composition in CKD and ESKD include total body potassium and nitrogen counters, which measures naturally occurring radioactive isotopes present in the body.[27] Whole-body counting is not readily available, and several methods are used clinically, such as bioelectrical impedance, dual-energy x-ray absorptiometry, magnetic resonance imaging, and anthropometric measures. The evaluation of muscle mass is challenging in patients with advanced CKD and ESKD because errors are introduced due to hydration status. For example, dual-energy x-ray absorptiometry assumes a constant 73% water composition, which may not be the case in dialysis patients undergoing evaluation.[28] The study by Bichels et al. utilizes computed tomography (CT), which is not influenced by hydration status.[29] Remarkably, the investigators found that low muscle mass assessed by CT is an independent predictor of mortality in CKD 3-5 patients. The drawback to regular CT evaluations of muscle mass is that it exposes the patients to radiation. Still, it can be opportunistically used when images are available for other diagnostic purposes. Imaging is just one frame in a complicated picture; it is also important to place imaging in the clinical context, including laboratory indices and knowing the patient's level of physical activity.

Modulating and Managing PEW

The International Society of Renal Nutrition and Metabolism and other societies have developed recommendations for preventing and managing PEW, both cause, and consequence of frailty in CKD.[30,31] Correction of macronutrient and micronutrient deficiency and emphasizing protein intake in patients receiving dialysis are mainstays of therapy. It is equally essential to aggressively manage volume status because excess water weight, particularly in dialysis patients, results in fatigue and cardiopulmonary fatigue, resulting in decreased physical activity. Avoiding chronic infections, hospitalizations, ensuring dialysis adequacy, and managing comorbidities, such as diabetes, heart failure, and other sources of inflammation, are also critical. Modifying PEW requires looking upriver at the root causes. The issue includes two articles focused on physical activity and intradialytic exercise, which we will analyze.

Physical Activity

The second article by Yamamoto et al. in this issue investigated the associations between physical activity and cardiovascular and all-cause mortality using an objective measure on both dialysis and nondialysis days.[32] Higher physical activity levels measured by accelerometry on hemodialysis (HD) days and non-HD days were significantly associated with decreased cardiovascular hospitalizations and mortality. Interestingly, patients who had increased physical activity on non-HD days but remained sedentary on HD days did not fare as well. Further, patients on HD days were relatively active but were sedentary on non-HD days and suffered more significant cardiovascular hospitalization and mortality. This important contribution to the literature suggests that evaluating physical activity levels is not straightforward in dialysis patients. Higher resolution is required to assess physical activity on HD days and non-HD days separately. Suppose this is confirmed by other studies or in a prospective fashion. In that case, the categorized physical activity assessment (HD and non-HD days) will be necessary for prognostic stratification and have implications on the management strategies depending on activity patterns.

Intradialytic Exercise

As we have previously noted, patients with ESKD have reduced physical function due to PEW contributing to progressive muscle wasting. Several studies demonstrate that an intradialytic exercise (IDE) program can improve blood pressure control, physical function, depression, quality of life, and reduction in fatigue.[33-35] The evidentiary standard to prove a survival benefit has not been met, given the many positive benefits in the documentary record and the safety associated with participating in an IDE program; however, it should be a strategic imperative for patients who can participate. IDE programs, because there is no financial supplement outside of the bundled payments, are scarce. Nevertheless, as the emphasis on quality metrics and momentum for value-based reimbursement continues, it is not too early to look at the determinants of compliance with a developed IDE program. When offered, most dialysis patients are enthusiastic about participating in IDE programs; reported attendance rates range from 70 to 90%. Retention rates are similar through the first few months, but after 1 year, it falls to half. The study by Parker et al. explores the factors associated with exercise adherence to a formal IDE program.[36] The investigators found that HD patients who had more than two comorbid conditions, were male, or on dialysis longer were more likely to miss IDE sessions. Admittedly, maintaining a regular exercise regimen is reminiscent of the challenges faced even by healthy individuals, but this study provides remarkable insight into the burden of disease associated with ESKD. Despite the proven benefits, IDE programs, even with a kinesiologist present, will lower the medical and psychological obstacles to participation and develop buy-in from patients.

The Editor's Choice article for this issue of the *Journal of Renal Nutrition* is an article by Narasaki et al.[37] This important paper provides some much-needed data on the association of dietary potassium and mortality in patients receiving chronic hemodialysis. The large cohort study demonstrated an increase in mortality associated with lower dietary potassium. Likely reflective of poor appetite, in general, the study sheds light on the need for improved dietary intake for many dialysis patients.

Other highlights of the Journal include an examination by St-Jules et al. of the interest levels of patients receiving chronic hemodialysis for using mobile applications to help patients monitor their dietary phosphorus.[38] Approximately 13% of their patients signed up and began using the app. After the initial excitement, however, researchers observed that interest waned, and they note that more investigation is needed to further develop and understand the utility of technology in self-monitoring.

Two additional articles cover CKD in this issue. Betz et al. examined whether knowledge of nutrition recommendations correlated with adherence in patients with nondialysis-dependent CKD.[39] They found no association between patient responses on a "CKD Knowledge Questionnaire" and their results from a food frequency questionnaire. Their findings suggest that dietary patterns advice may be more effective than nutrient-based diet information. This is insightful dietary research with practice implications, and a line of investigation that deserves further consideration in future research. Sumida et al. examined a question regarding constipation and laxative use in patients with CKD.[40] Because constipation is common in CKD, can affect appetite, and can be exacerbated by insufficient dietary fiber, this paper is important to renal nutrition. They found that half of the patients in their dataset were prescribed laxatives during the 2 years preceding ESKD, and that there was a slight increase in the slope of eGFR decline associated with laxative use. Given the potential harm associated with laxative use in some patients, could a substantial increase in dietary fiber avoid excessive laxative utilization? Additional research on the impact of laxative use on renal function, and the utility of dietary fiber in CKD is needed.

Conclusion

The articles in this issue highlight the need to identify and risk-stratify patients with PEW and sarcopenia. Identifying patients at risk for poor outcomes early may result in earlier intervention and potentially better outcomes. Nutritional assessment and interventions in patients with CKD should not only be the purview of dieticians; clinicians need to be vigilant and prioritize nutrition as a quality metric beyond mineral bone disease management. The modified creatinine index can certainly complement other assessment tools performed monthly in patients receiving maintenance dialysis. The role of physical activity and IDE as an intervention to modify PEW requires additional prospective analysis. We are moving into an era of individualized therapy, recognizing that a one-size-fits-all approach will not be as effective; much more research in this field is required. Ultimately, everyone needs to pick up an ore; nutritional evaluation needs to be at the forefront of nephrology care, beginning when CKD is first identified and continued through dialysis and transplantation.

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