Improving Muscle Strength and Preventing Sarcopenia and Cachexia in Chronic Kidney Disease and Transplanted Patients by Physical Activity and Exercise

THIS ISSUE OF the *Journal of Renal Nutrition* (JREN) is dedicated to the topic of physical activity and exercise in kidney disease, which is inherently related to several themes and keywords. They include muscle strength, lean body mass, adiposity, muscle wasting, sarcopenia, cachexia, frailty, and other relevant terms. These conditions have an important bearing on clinical outcomes in chronic kidney disease (CKD). The invited commentary by Wilund et al[1] highlights the goals of the "Exercise in CKD Working Group," which is affiliated to the International Society of Renal Nutrition and Metabolism. The Working Group has initiated important efforts to develop exercise programs in dialysis clinics with the goal to engage students and interns from different universities and academic centers in the vicinity of the dialysis clinics. The group faces several important questions related to knowledge gap and controversies such as the following: Does hemodialysis therapy induce a catabolic state for the patient and should these patients avoid resistance exercise during dialysis? Should an intradialytic exercise program be only allowed in the first 1-2 hours of the dialysis treatment but not in the final hour given higher likelihood of hemodynamic instability in the latter part of the treatment? Should patients with higher amounts of fluid retention not be allowed to exercise during dialysis?

In this issue of the *JREN*, there are 2 meta-analyses relevant to physical activity and muscle status in CKD: Hwang et al[2] conducted a meta-analysis to examine the global association of handgrip strength with survival in dialysis patients by including 9 prospective cohort studies and found that a low handgrip strength was associated with increased risk of all-cause mortality in these patients. In another meta-analyses, Silva et al[3] investigated the putative effect of creatine supplements on renal function by including 15 and 6 studies in their qualitative and quantitative analyses, respectively, and found that creatine supplementation did not significantly alter the measured serum concentration of creatinine or urea. Although the investigators concluded that creatine supplementation does not induce renal damage in the studied amounts and durations,[3] caution is prudent when CKD patients consume creatine products given prior reports about side effects.[4]

This issue of *JREN* includes several clinical and observational studies related to physical activity and body composition in CKD: Wickstrom et al[5] studied the association of vitamin D deficiency with gait and balance disorders, including falls, across different stages of CKD using the 1999-2004 data of the *National Health and Nutrition Examination Survey* (NHANES) of 8,554 middle-aged adults older than 40 years. They found an incrementally higher rate of self-reported balance and falling issues and slower gait across worsening CKD severity stages and across lower serum vitamin D levels. These findings call for randomized controlled trials of correcting vitamin D deficiency in an effort to examine the impact on preventing gait imbalance and falls in CKD patients.[5]

In a clinical study by Kittiskulnam et al[6] in 60 Californian dialysis patients, the validity of the "Low Physical Activity Questionnaire" was examined against more objective measures including spontaneous walking activity by wearing a pedometer. The study by Matsuzawa et al[7] in 817 Japanese hemodialysis patients suggested that patients with a declined functional status are at higher death risk. Examining the so-called muscle biomarkers among dialysis patients, Delanaye et al[8] studied the utility of 5 biomarkers, i.e., activin A, procollagen III N-terminal peptide, follistatin, myostatin, and insulin-like growth factor-1 (IGF-1), and found that myostatin and IGF-1 were more strongly associated with handgrip strength, muscular mass, and 1-year mortality in 204 Belgian dialysis patients. Of note, using the receiver operating characteristic curves, the ability of myostatin and IGF-1 to detect a low handgrip strength was not significantly different from serum creatinine,[8] suggesting that the serum creatinine level continues to be a useful marker of outcomes in dialysis patients.[9]

Another interesting study of this *JREN* issue is conducted by Ziolkowski et al,[10] who have revisited the controversial topic of "obesity paradox" in CKD, which is often discussed under the broader concept of 'reverse epidemiology."[11] The authors examined the associations between obesity indices and survival in persons with non-dialysis-dependent CKD using several adiposity metrics in addition to the body mass index, including dual-energy X-ray absorptiometry (DEXA) derived fat mass index and percent body fat, in 2,852 NHANES participants with CKD from 1999 to 2006, whose subsequent death data were ascertained by linking the NHANES to the National Death Index data.[10] The investigators found that higher body fat mass was associated

Financial Disclosure: The authors declare that they have no relevant financial interests.

Address correspondence to Kamyar Kalantar-Zadeh, MD, MPH, PhD, University of California Irvine, Orange, CA. E-mail: kkz@uci.edu

1051-2276/$36.00

https://doi.org/10.1053/j.jrn.2019.09.005

with greater survival especially among persons with lower muscle mass,[10] i.e., the group with the so-called "sarcopenic obesity".[12] Interestingly, a higher weight loss >10% was half as common among obese than non-obese CKD patients,[10] which may suggest that obesity protects against the ravages of weight loss and impending cachexia in CKD.[13]

In a single-center, prospective study by Rymarz et al,[14] 56 male dialysis patients were compared to 15 non-CKD controls and found that free testosterone level was significantly lower in the dialysis patients group. Testosterone level was strongly and positively correlated with lean tissue index and body cell mass ($R > 0.50$ for both) and negatively correlated with fat tissue index.[14] Given the high prevalence of testosterone deficiency and its association with mortality among men undergoing dialysis therapy,[15] low lean tissue mass and body cell mass can be used to screen for low testosterone level in dialysis populations.

In this issue of *JREN* there are interesting original research data related to body composition in kidney transplantation. Chan et al[16] examined the associations of sarcopenia and adiposity surrogates with clinical outcomes and health-related quality of life in 128 British kidney transplant recipients and found that a low muscle strength was associated with the composite endpoint of mortality and hospitalization, and a low muscle mass and sarcopenia were associated with physical component of the quality of life, whereas muscle mass, sarcopenia, and sarcopenic obesity did not predict outcomes. Workeneh et al[17] employed laborious body composition measures and other novel techniques in a single-center prospective study of 31 living donor kidney transplant recipients in Texas and found that successful kidney transplantation is associated with weight gain from truncal obesity and insulin resistance. Finally, Kemmerich et al[18] compared skinfold thickness measures to DEXA data to estimate body fat in Brazilian kidney transplant recipients and found that, notwithstanding modest correlation and agreement, skinfold thickness underestimated body fat when compared with DEXA at 3 and 12 months after kidney transplantation. Given these interesting studies, we expect that a heightened interest in body composition and the potential impact of physical activity on clinical outcomes among CKD and transplanted patients be engendered and hope that *JREN* can continue to contribute as an effective platform to that end.[19]

Kamyar Kalantar-Zadeh, MD, MPH, PhD
University of California Irvine
Orange, California

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

References

1. Wilund K, Thompson S, Bennett PN. A global approach to increasing physical activity and exercise in kidney care: the International Society of Renal Nutrition and Metabolism Global Renal Exercise Group. *J Ren Nutr.* 2019;29:467-470.
2. Hwang SH, Lee DH, Min J, Jeon JY. Handgrip strength as a predictor of all-cause mortality in patients with chronic kidney disease undergoing dialysis: a meta-analysis of prospective cohort studies. *J Ren Nutr.* 2019;29:471-479.
3. de Souza ESA, Pertille A, Reis Barbosa CG, et al. Effects of creatine supplementation on renal function: a systematic review and meta-analysis. *J Ren Nutr.* 2019;29:480-489.
4. Thorsteinsdottir B, Grande JP, Garovic VD. Acute renal failure in a young weight lifter taking multiple food supplements, including creatine monohydrate. *J Ren Nutr.* 2006;16:341-345.
5. Wickstrom JF, Sayles HR, Graeff-Armas LA, Yentes JM. The likelihood of self-reporting balance problems in those with advanced chronic kidney disease, slow gait speed, or low vitamin D. *J Ren Nutr.* 2019;29:490-497.
6. Kittiskulnam P, Sheshadri A, Johansen KL. Validation of a new physical activity instrument against pedometers among dialysis patients. *J Ren Nutr.* 2019;29:498-503.
7. Matsuzawa R, Kamitani T, Roshanravan B, Fukuma S, Joki N, Fukagawa M. Decline in the functional status and mortality in patients on hemodialysis: results from the Japan Dialysis Outcome and Practice Patterns Study. *J Ren Nutr.* 2019;29:504-510.
8. Delanaye P, Bataille S, Quinonez K, et al. Myostatin and insulin-like growth factor 1 are biomarkers of muscle strength, muscle mass, and mortality in patients on hemodialysis. *J Ren Nutr.* 2019;29:511-520.
9. Wang J, Streja E, Soohoo M, et al. Concurrence of serum creatinine and albumin with lower risk for death in twice-weekly hemodialysis patients. *J Ren Nutr.* 2017;27:26-36.
10. Ziolkowski SL, Long J, Baker JF, Chertow GM, Leonard MB. Chronic kidney disease and the adiposity paradox: valid or confounded? *J Ren Nutr.* 2019;29:521-528.
11. Imam TH, Coleman KJ. Obesity and mortality in end-stage renal disease. Is it time to reverse the "reverse epidemiology"—at least in peritoneal dialysis? *J Ren Nutr.* 2019;29:269-275.
12. Malhotra R, Deger SM, Salat H, et al. Sarcopenic obesity definitions by body composition and mortality in the hemodialysis patients. *J Ren Nutr.* 2017;27:84-90.
13. Zilles M, Betz C, Jung O, et al. How to prevent renal cachexia? A clinical randomized pilot study testing oral supplemental nutrition in hemodialysis patients with and without human immunodeficiency virus infection. *J Ren Nutr.* 2018;28:37-44.
14. Rymarz A, Matyjek A, Gomolka M, Niemczyk S. Lean tissue index and body cell mass can be predictors of low free testosterone levels in men on hemodialysis. *J Ren Nutr.* 2019;29:529-535.
15. Yu J, Ravel VA, You AS, et al. Association between testosterone and mortality risk among U.S. males receiving dialysis. *Am J Nephrol.* 2017;46:195-203.
16. Chan W, Chin SH, Whittaker AC, et al. The associations of muscle strength, muscle mass, and adiposity with clinical outcomes and quality of life in prevalent kidney transplant recipients. *J Ren Nutr.* 2019;29:536-547.
17. Workeneh B, Moore LW, Nolte Fong JV, Shypailo R, Gaber AO, Mitch WE. Successful kidney transplantation is associated with weight gain from truncal obesity and insulin resistance. *J Ren Nutr.* 2019;29:548-555.
18. Kemmerich ADS, Pedrollo EF, Souza GC, Manfro RC, Canani LH, Nicoletto BB. Body fat estimation in kidney transplant recipients: skinfolds thickness compared with dual-energy X-ray absorptiometry. *J Ren Nutr.* 2019;29:556-562.
19. Moore LW, Kalantar-Zadeh K. Opportunities for renal nutrition and metabolism at the dawn of 2020s: an inauguration message from the New JREN Editors-in-Chief. *J Ren Nutr.* 2019;29:1.