Physical Activity in ESRD: Time to Get Moving

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Studies over the last 3 decades among ESRD patients on maintenance dialysis have demonstrated greatly impaired physical performance and cardiorespiratory fitness compared with the general population (1–4). Levels of habitual physical activity are also markedly lower in these patients. For example, Johansen *et al.* reported that among 34 maintenance hemodialysis patients, directly measured physical activity was nearly a third lower compared with healthy "sedentary" controls (5). Using data from the US Renal Data System (USRDS), Stack *et al.* reported that 56% of incident dialysis patients did not engage in any exercise, even once weekly (6). Accurate measurement of physical activity can be challenging in both ESRD patients and the general population. In large samples of participants, the most feasible technique is the use of questionnaires that ask about a range of potential physical activities that individuals may have engaged in within a fixed time period. "Gold-standard" measurement of physical activity relies on the use of a monitoring device worn at the waist or the leg that detects acceleration and records the duration and intensity of movement. The correlation between the self-reported questionnaires and directly measured activity varies widely but is often modest, including in renal disease patients (7).

In this issue of *CJASN*, Mastsuzawa and colleagues performed a single-center prospective observational cohort study among 202 maintenance hemodialysis patients (8). Physical activity on 4 sequential nondialysis days was measured directly using uniaxial accelerometry. The authors defined "habitual physical activity" as the average daily activity consistent with at least "gentle walking," corresponding to at least an intensity of 1 on a 0–9 semi-quantitative scale. On the basis of prior studies in healthy adults cited by the authors, this corresponds to at least approximately 1.9 times the baseline energy expenditure occurring at rest (9). The authors considered a cut-point of at least 50 minutes average daily activity on nondialysis days as indicating a high level of activity, based on prior research suggesting that activity above this threshold is associated with maintenance of physical function in hemodialysis patients. Among the 202 participants, 37% met this threshold of activity. As expected, those hemodialysis patients who were more active were younger and had lower burden of overall comorbidity but surprisingly were not significantly less likely to have diabetes or heart disease. Over 7 years of follow-up, a total of 34 deaths occurred, 19 attributed to cardiovascular disease. The estimated cumulative survival was markedly different between the two groups, at 93.3% in the high-activity group versus 77.2% in the low-activity group. After adjustment for comorbidity, each 10-min/d increment in activity was associated with a 12% lower risk of all-cause mortality, a difference that was highly statistically significant.

It is perhaps not surprising that physical activity should predict longevity and mortality in ESRD. A number of prospective cohort studies have identified physical activity as a strong predictor of mortality after accounting for demographics and comorbid conditions (10). These studies have generally been conducted among the general population, and the few studies conducted among renal disease patients relied on self-reported rather than directly measured activity. Increasing physical activity has a number of well described beneficial physiologic effects on cardiorespiratory fitness, endothelial function (11), BP (12), dyslipidemia (13), muscle strength, and inflammation (14), among others. These effects offer plausible biologic pathways to explain the relationship of greater physical activity with lower risk of mortality. The major contribution of the study by Mastsuzawa *et al.* is to demonstrate that the apparent survival advantage of those with higher levels of physical activity extends to ESRD patients on maintenance dialysis, as determined by objective measures of physical activity.

The results of this study should be placed in appropriate context. At first glance, it might seem surprising to nephrologists caring for maintenance hemodialysis patients in the United States that nearly 40% of such patients engage in high levels of physical activity, as was the case in the Japanese center in this study. Comparison of the overall levels of activity in this study with the results of other ESRD studies is made challenging by the different methods used to quantify activity. A potential frame of reference might be the consensus guidelines from the US Centers for Disease Control and Prevention (CDC), which suggest that adults engage in at least 150 minutes of "moderate to vigorous" physical activity per week (15). With mean daily activity duration of 42 minutes on each of the 5 nondialysis days in this study, one might expect the average weekly activity to well surpass these CDC recommendations. However, it is unclear to what extent the activity performed by the ESRD patients in this study would constitute moderate to vigorous activity.

It seems unlikely that the gentle walking (a score of 1 on the 0–9 semi-quantitative scale) included in the authors' definition of habitual activity would coincide with the intensity recommended by the CDC. In non-ESRD populations, the intensity of physical activity has prognostic significance independent of duration and total energy expenditure (10,16). This study unfortunately does not offer information on the important question of how greater duration and/or greater intensity of physical activity relate to mortality and morbidity risk in ESRD.

The major limitation of this study, however, is the problem of unmeasured confounding, a limitation common to observational studies of physical activity. It is uncertain whether physical activity itself or factors such as comorbidity, which determine both physical activity and mortality risk, are to account for the observed associations in this study. The authors attempt to adjust for comorbidity through the use of a previously devised ESRD-specific comorbidity index, which has been shown to have independent prognostic benefit in predicting all-cause mortality (17). However, this score was derived using administrative USRDS data rather than comorbidity reported by patients or verified through medical records, and has not been validated in non-US ESRD populations. Even if the comorbidity score was accurate in reflecting the presence of chronic medical conditions, it is highly likely that residual confounding would remain, due to differences in the severity and/or chronicity of these conditions (18). For example, although the presence of congestive heart failure may be appropriately captured in this score, differences between patients in systolic function and dyspnea severity would not be measured. Such differences could plausibly affect both physical activity and risk for mortality. Ultimately, it is not possible to know with certainty from these results whether low-activity patients are incapable of being more active—because of comorbidity such as cardiac disease, pulmonary disease, neurologic impairment, orthopedic conditions, or a host of other factors—or whether the level of physical activity is primarily determined by patients' lifestyle and is therefore modifiable.

Even with these limitations, the study raises intriguing questions regarding the potential of increasing physical activity in ESRD patients as an intervention to reduce mortality and morbidity. Over the past 3 decades, a number of interventional studies have examined the clinical and physiologic effects of increased physical activity through structured exercise training interventions in maintenance dialysis patients. As summarized in a recent Cochrane meta-analysis of 32 reported studies (19), exercise interventions resulted in improvements in aerobic capacity, walking capacity, BP, and health-related quality of life. Unfortunately, most of the studies included in the meta-analysis were individually quite small (<30 patients) and suffered from a high risk of bias due to methodologic limitations. Furthermore, the studies varied widely in their approach to exercise training, including aerobic exercise, resistance exercise, yoga, intradialytic exercise, and home-based training. Even if the observed benefits in physiologic measures and quality of life are reliable, it is unclear whether these benefits translate to reduced mortality, which was not examined as an outcome in any of the prior studies. The recent results of the Look AHEAD (Action for Health in Diabetes) lifestyle intervention study in obese patients with type 2 diabetes suggest that these physiologic measures may not be reliable surrogate outcomes; the diet and physical activity intervention in that study resulted in favorable changes in cardiorespiratory fitness, BP, dyslipidemia, and glycemic control (20), but no difference in risk of cardiovascular morbidity and mortality (21).

Undoubtedly, there would be considerable challenges to the design and conduct of a large, adequately powered, interventional study of increasing physical activity in ESRD. As demonstrated by prior smaller single-center studies, there are many different approaches to exercise that could be considered in this population. For example, resistance versus aerobic exercise training, in-center versus at-home exercise, and intradialysis versus nondialysis exercise are among a few of many possible designs of exercise regimens. Difficulties with retention and treatment adherence are common among lifestyle intervention studies, and choice of the control intervention can influence the observed results. On the other hand, one should consider that a variety of pharmacologic interventions to reduce morbidity and mortality in ERSD—including statins (22), noncalcium phosphate binders (23), and anemia correction (24), among others—have already been evaluated in large multicenter trials with largely underwhelming results. These studies were motivated in part based on earlier observational studies suggesting associations of biologic risk factors with morbidity and mortality in ESRD. Perhaps it is time to consider inactivity and impaired physical function as "risk factors" for morbidity and mortality in this population, and to design appropriately powered investigations of increasing physical activity.

Disclosures

None.

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