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Time to rehabilitate the idea of exercise for patients with chronic kidney disease?

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In this issue of *Nephrology Dialysis and Transplantation*, Greenwood *et al.* [1] examine the risk of death, cerebrovascular accident, myocardial infarction and hospitalization for heart failure among 757 patients referred to a renal rehabilitation program between 2005 and 2017. The 12-week program was modeled on conventional cardiopulmonary rehabilitation and aimed to deliver an individualized rehabilitation program incorporating combined exercise training and self-management education (Table 1) [2]. This study builds on their prior work, which showed that renal rehabilitation resulted in substantial improvement in exercise capacity and functional ability among adults at various stages of chronic kidney disease (CKD), including Stages 3–4, receiving maintenance hemodialysis and after kidney transplant [2]. The primary outcome of the earlier study was the Duke Activity Status Index (DASI), a questionnaire of functional ability across a spectrum from ability to complete activities of daily living to sporting activities [3]. Patients' DASI scores increased by 35% on average after the program. In addition, improvements in physical performance ranged from 21% for the number of sit-to-stand transfers in 60 s, a proxy for muscle endurance, to 44% for the incremental shuttle walk test, a field walking test of cardiopulmonary endurance.

In the current study, the authors compared survival free from cerebrovascular accident, myocardial infarction or hospitalization for heart failure among patients who completed the rehabilitation program and underwent post-rehabilitation assessment after 12 weeks to event-free survival among those who did not start or did not complete the program [1]. They further divided program 'completers' into those who increased the distance on the shuttle walking test by ≥ 50 m ('improvers') and those who did not ('nonimprovers'). A total of 43% completed the program, and 60% of completers improved by at least 50 m on the shuttle walking test. In multivariable analysis, patients who completed the program had a lower risk of the combined outcome {hazard ratio [HR 0.62 [95% confidence interval (CI) 0.39–1.00]}, and completers who improved had a lower risk than those who did not improve [HR 0.60 (95% CI 0.36–0.98)].

Thus this program was administered by rehabilitation specialists according to traditional rehabilitation principles. The unique aspect was the concept of providing a 'renal rehabilitation program'. Designing and implementing such a program involved recognition that functional limitations are common and severe among patients with CKD and can be addressed through exercise interventions, integration of assessment of functional

status into nephrology practice, development of a referral process and employment of exercise professionals familiar with the particular needs of patients with CKD. The result was a program tailored to meet the needs of patients who are deconditioned at baseline and are at high risk of cardiovascular events, to which >750 patients were referred. Thus this program is a major advance over other exercise interventions in patients with CKD in its size, scope and practical delivery within the context of clinical care.

Researchers first identified 'uremic myopathy' [4], characterized by relatively nonspecific findings of fatigue, limited endurance and exercise limitation [5], more than 50 years ago. Exercise physiologists have noted that peak oxygen consumption is markedly impaired among patients receiving dialysis, to levels that would be expected to limit physical functioning [6]. Muscle strength is also impaired, but to a less dramatic extent [7]. Correction of anemia [8] and kidney transplantation [9] improve exercise capacity but do not normalize it. Myriad exercise intervention studies have been performed to address low exercise capacity and weakness [6]. The interventions have mostly taken the form of traditional aerobic or resistance exercise training or a combination of the two. Many have been performed in the dialysis facility, but others have been performed outside of dialysis [10]. Almost all have shown improvements in outcomes, including increased peak oxygen consumption, strength, physical performance or self-reported physical function [6, 10]. However, there has been limited application of exercise therapies in the dialysis population outside of research. Consideration of the reasons why the renal community has generally not embraced exercise for our patients may help to understand why the Greenwood *et al.* [1] study in this issue adds important information.

First, although there have been many exercise interventions, they have not been standardized in terms of modality, duration, intensity or delivery. In addition, most studies have been small, and many were uncontrolled [6]. These design limitations and variability among the available studies have led to confusion and skepticism among nephrologists about exercise in patients with CKD. For example, a recent technical expert panel evaluating a physical function quality indicator for patients treated with dialysis in the USA concluded [11] that 'evidence that interventions can reduce functional decline or improve functional status is weak, with the literature consisting of either observational studies or very small clinical trials'.

Second, exercise interventions, including the program described in the article by Greenwood *et al.* [1], have been designed to improve patients' functional capacity. However, physical activity and physical function have not been areas of clinical focus for nephrologists, despite the severe functional limitations documented by researchers and despite the importance of these limitations to patients. A survey of nephrologists from the USA and other parts of the world found that <40% routinely assessed physical activity and counseled patients about activity [12]. In addition, approximately one-third of respondents reported concerns about the risks of exercise for patients on dialysis, and a higher percentage did not believe that patients would increase activity even if advised to

do so. A follow-up study showed similarly low rates of counseling [13], even after publication of guidelines recommending this practice [14].

Recent studies have highlighted the association of poor functional status and frailty with poor survival in the dialysis population. Application of frailty constructs originally developed by geriatrics researchers to the end-stage renal disease (ESRD) population has revealed a shockingly high prevalence of frailty even among dialysis patients who are not elderly and a strong association between frailty and mortality and other adverse outcomes [15–17]. Although assessment of frailty is not part of routine clinical care of patients with ESRD, the concept of frailty and its high prevalence may have raised awareness of the functional limitations of patients with CKD.

Several recent reports have highlighted the importance of functional status to patients with CKD. Ramer *et al.* [18] asked patients with CKD and their nephrology providers about health outcome priorities. Patients' top priority was maintaining independence, but providers were more likely to choose staying alive when asked about the same patients' priorities. The standard outcomes in a nephrology initiative set out to develop a core set of outcomes important to patients, their caregivers and providers [19]. Again, patients prioritized lifestyle outcomes (e.g. ability to travel) and well-being (e.g. lack of fatigue) over survival or biochemical outcomes, and the group put forth a formal recommendation that these outcomes be routinely assessed in clinical trials [20]. Thus the nephrology literature is beginning to focus on issues related to functional status in the CKD population and to recognize the importance of functional status to patients, which may serve to increase interest in interventions to improve functioning. The study by Greenwood *et al.* [1], which reports on one of the largest cohorts to undergo an exercise intervention, is coming at a time when the focus is shifting toward patient-centered outcomes and patients are consistently prioritizing functional status.

Third, given that nephrologists are concerned about outcomes related to mortality and adverse cardiovascular events [20], lack of exercise studies addressing these outcomes, along with fears about risks of exercise in this high-risk population, may have contributed to the reluctance to adopt and apply exercise interventions in the ESRD population. The study by Greenwood *et al.* [1] addresses this key deficit by offering some of the first evidence that referral to a renal rehabilitation program could improve survival and reduce cardiovascular events among patients receiving maintenance dialysis. In light of prior criticisms of the exercise literature in CKD, it is important to recognize that although addressing these 'hard' outcomes is a major strength of the Greenwood *et al.* study, it is nevertheless an observational study whose design introduces a risk of bias. Specifically, the comparison of those who completed and did not complete the rehabilitation program to which they were referred represents a per-protocol analysis. The concern with this approach (and why intention-to-treat analysis has become the gold standard in clinical trials) is that the reasons for nonadherence to the program may be related to prognosis [21]. This is true in general, as participants who adhere tend to do better than those who do not, even after adjustment for other

Table 1. Outline of the renal rehabilitation program

Time spent in activity	Activity	Exercise intensity
Three times per week, 2× supervised, 1× home-based		
10 min	Warm-up progressing from isolated mobilizing exercises to gross mobilizing exercises	RPE ^a 11 (light)
10 min	Aerobic exercise, including treadmill and stationary cycling	RPE 13–15 (somewhat hard to hard)
10 min	Strength conditioning, including closed and open-chain body weight resistance and free weights	Based on 10-repetition maximum score
10 min	Muscular endurance	
10 min	Balance training	
10 min	Cool-down consisting of stretching and balancing exercises	RPE 11 (light)
Once per week, in person		
30 min	Education about the role of exercise; personalizing exercise plans; goal setting; long-term exercise planning; overcoming barriers and relapse prevention	

^aRPE, rating of perceived exertion [22].

prognostic factors. However, adherence is particularly likely to be related to prognosis in a study of an exercise intervention. Patients with worse functional status or higher comorbidity burden may have been less likely to follow through with initiating or completing the rehabilitation program. Indeed, Table 1 provides some evidence to support this possibility, as patients who did not complete the program had a higher prevalence of diabetes and worse performance on the baseline shuttle walk test [1]. The study also appears to have been susceptible to reverse causation, as follow-up began at the time of initial evaluation. Thus events occurring within the first 12 weeks after referral to or initiation of renal rehabilitation could be the cause of noncompletion. However, examination of the Kaplan–Meier curve reveals that most events occurred later in follow-up and suggests that early events were not a major source of bias. A third potential source of bias is unblinded ascertainment of study outcomes. It is not clear from the report how events were adjudicated and whether those who ascertained event status were blinded to whether participants had completed the rehabilitation program or had improved. This could be particularly important for heart failure events, as it can be difficult to differentiate CKD-related volume overload from heart failure.

Nevertheless, it would be unwise to discount this study entirely because it is not a randomized controlled trial with an intention-to-treat analysis. Use of real-world data is playing an increasing role in medical decisions [23], as the resulting real-world evidence can provide important information to bridge the gap between clinical trials and actual clinical practice. The study by Greenwood *et al.* [1] is an important example of this, providing real-world evidence that assessment of functional status can be incorporated into clinical care of patients with CKD, that a substantial proportion of patients referred to a disease-specific rehabilitation program will participate and that such a program is safe and likely beneficial.

The program developed by Greenwood *et al.* [1] is a major advance over other exercise interventions in patients with CKD in its size, scope and practical delivery within the context of clinical care. Results of this study and an earlier report on this program demonstrate conclusively that nephrology practice, or perhaps even culture, can be changed to include a focus on patients' functional status and that patients can safely complete a tailored

exercise-based rehabilitation program. The improved functional status and lower cardiovascular and mortality event rates among patients who completed the program also provide encouraging evidence to suggest that rehabilitation is beneficial to patients with CKD, potentially addressing their number one outcome priority of maintaining independence, as well as a key concern of nephrologists, preventing cardiovascular events and death.

The value patients place on optimizing functional status and the data presented by Greenwood *et al.* [1] provide strong support for assessing functional status as part of the clinical care of patients with CKD and referring patients with poor functional status for rehabilitation. Even in areas where a disease-specific program is not available, providers can refer patients to cardiac rehabilitation programs (upon which the renal program was based) or to physical therapy providers for assessment and treatment. This study should also serve as a springboard for additional clinical trials to solidify the degree of benefit offered by rehabilitation and to identify the best rehabilitation strategies for diverse patient populations defined on the basis of age, functional status and stage of CKD or modality of renal replacement therapy.

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CONFLICT OF INTEREST STATEMENT

Dr Johansen declares no conflicts of interest with the material presented in this article. This article has not been published elsewhere in whole or in part.

(See related article by Greenwood *et al.* Mortality and morbidity following exercise-based renal rehabilitation in patients with chronic kidney disease: the effect of programme completion and change in exercise capacity. *Nephrol Dial Transplant* 2019; 34: 618–625)

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