Editorial

Muscle Wasting in Kidney Disease: Let's Get Physical

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For maintenance dialysis patients, physical performance matters. The extension of Medicare coverage to ESRD services in 1972 indeed was predicated on the assumption that the dialysis population would be fully rehabilitated and active in the workforce. In addition, considerable data exist that as a group, maintenance dialysis patients have low levels of physical function and that survival and hospitalization rates are directly proportional to physical performance (1). Despite the obvious importance of physical performance capacity, there are disturbing data to suggest that dialysis patients as a group have markedly lower levels of daily physical activity than healthy control subjects, to the extent that a 30-yr-old hemodialysis patient is likely to have less daily physical activity than a 70-yr-old healthy sedentary individual. The majority of maintenance dialysis patients in the United States seem to participate in little or no physical activity beyond basic activities of daily living.

Why is physical performance so markedly altered in dialysis patients? Maintenance dialysis patients encounter multiple catabolic processes and experience a unique form of protein and energy malnutrition, which is characterized by muscle wasting and decreased visceral protein stores. The pathophysiology of muscle wasting in chronic kidney disease clearly is complex, multifactorial, and not fully elucidated (Figure 1). What is clear is that abnormalities in muscle function, exercise performance, and physical activity begin in earlier stages of chronic kidney disease and progressively worsen as ESRD ensues (2).

What can be done to improve physical performance in dialysis patients? Despite the close relationship between anemia and physical performance in many other chronic disease states, exercise performance does not seem to be completely "rescuable" by maintenance of hemoglobin concentration at required levels with erythropoietic agents (2). Accordingly, studies have focused on improved nutritional delivery, sometimes coupled with increased exercise and/or anabolic support to prevent and/or treat muscle wasting in hopes of improving physical performance in maintenance dialysis patients. These studies generally involved small patient numbers and relatively short duration of the intervention. In this issue of *JASN*, Johansen *et al.* (3) report their results regarding the effects of two separate anabolic strategies that aim to improve muscle mass and physical functioning in chronic hemodialysis patients. Specifically, the investigators performed a 2 × 2 factorial-design, randomized, clinical trial to examine individual and combined effects of resistance exercise and nandrolone decanoate (ND), an anabolic steroid, during a period of 3 mo. Their results indicate that ND was effective (and resistance exercise ineffective) in improving lean body mass (LBM), whereas only resistance exercise improved muscle strength. These results are critically important for the nephrology community because they provide clear-cut evidence that muscle wasting and/or weakness related to kidney disease may be a treatable condition.

In healthy individuals, resistance exercise can alter protein and energy homeostasis by enhancing skeletal muscle sensitivity to insulin, stimulating the uptake of amino acids, increasing intramuscular amino acid availability, and promoting rates of muscle protein accretion. The lack of a significant change in LBM in response to resistance exercise in the study by Johansen *et al.* could be related to several factors, including inadequate size, lack of precision in measurement of LBM, and limited effect of the intervention in the involved compartment (the leg area). The last hypothesis is supported by the significant increase in thigh muscle size as measured by magnetic resonance imaging along with significant improvement in the function of muscles that involve that area. An alternative explanation for the lack of systemic effect of resistance exercise is that exercise-driven muscle anabolism requires adequate substrate availability to promote protein synthesis that overcomes protein breakdown (4). When exercise is performed in the fasted state, there is increased skeletal muscle protein turnover, but often the rate of protein breakdown exceeds the rate of protein synthesis, resulting in net muscle protein loss. It has been shown that amino acid availability is significantly decreased during hemodialysis, similar to a fasting state. Therefore, resistance exercise alone without adequate nutritional supplementation would be inadequate to promote any systemic protein anabolic effects, as was observed by Johansen *et al.*

In the same study, ND administration resulted in a significant improvement in LBM, in contrast to the resistance exercise protocol. These results are consistent with earlier reports that were published by the same group which demonstrated that clinically stable dialysis patients respond to anabolic interventions such as anabolic steroids. Other studies have shown that the anabolic response to insulin and growth hormone, two

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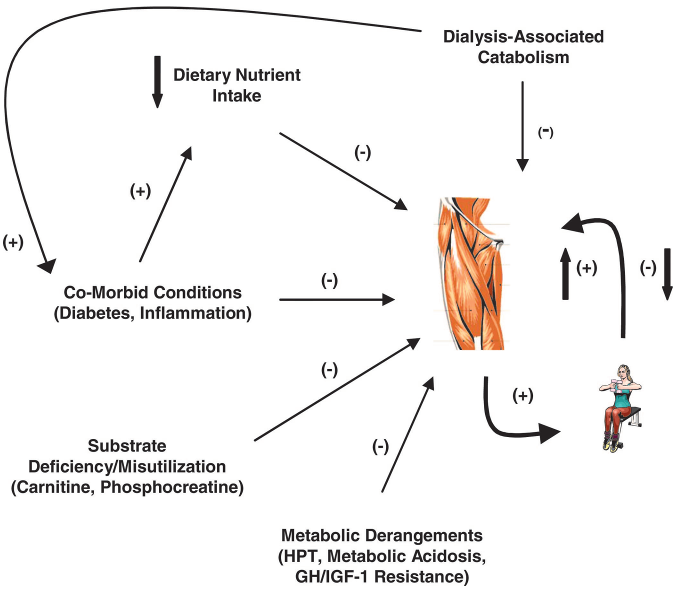

Figure 1. A simplified schematic representation of muscle wasting and weakness leading to decreased physical performance in patients with ESRD. In addition to specific issues noted in the diagram, decreased physical activity and sedentary lifestyle are major contributors to the muscle abnormalities that are observed in these patients. HPT, hyperparathyroidism; GH, growth hormone.

hormones with widely known protein anabolic properties, also is intact in dialysis patients (5). Despite beneficial effects on LBM, the lack of any significant effect of both interventions on physical performance and activity measures is somewhat disappointing. It is possible that the study period of three months might not be long enough to observe any significant effect of these interventions on these measures, as pointed out by the authors. In any case, any outcomes of this study other than LBM should be interpreted with the caveat that they are secondary, and any conclusions related to physical activity, physical functioning, and muscle function should be considered as preliminary because of limited sample size. Additional limitations in interpreting this study are that dietary protein and energy intake was not measured, and changes in eating habits might have influenced the results. In addition, the results that pertain to visceral protein stores were not reported.

The nutritional status of maintenance dialysis patients and their physical performance have always been important components of their clinical management. To date, most efforts have been targeted toward prevention of the problem. Now, there is evidence emerging that active treatment, perhaps by combining nutritional interventions, pharmacologic therapy, and resistance exercise, may be able to reverse at least a component of the ensuing muscle wasting and weakness. The timely study by Johansen *et al.* should be a call to action to answer the many remaining questions: Can less stable, dialysis patients with more inflammation achieve similar benefit? Can these interventions improve overall physical performance if they are administered for longer periods? Will the changes in muscle mass and function result in improved hospitalization and death? Can the original promise of rehabilitation with maintenance dialysis be achieved?

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Please see the related article, "Effects of Resistance Exercise Training and Nandrolone Decanoate on Body Composition and Muscle Function among Patients Who Receive Hemodialysis: A Randomized, Controlled Trial," on pages 2307–2314.