Exercising to offset muscle mass loss in hemodialysis patients

DOI: 10.1111/sdi.12805

EXERCISE AND PHYSICAL ACTIVITY IN DIALYSIS PATIENTS

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WILEY Seminars in Dialysis

Exercising to offset muscle mass loss in hemodialysis patients: The disconnect between intention and intervention

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Abstract

Skeletal muscle loss is the most important hallmark of protein energy wasting syndrome as it contributes to declines in physical independence, poor quality of life, and higher mortality risk in individuals with ESRD on maintenance hemodialysis (HD). As such, exercise and nutritional interventions have been investigated with the goal to preserve skeletal muscle mass and overall quality of life. Unfortunately, current efforts are unable to confirm the capacity of exercise to mitigate ESRD-associated muscle wasting. However, the inconclusive data are often accompanied by suboptimal exercise prescriptions. Exercise sessions are often implemented in-clinic during the catabolic and proinflammatory period of dialysis treatment and without concurrent nutritional support. Additionally, indirect considerations like exercise intolerance and exercise program compliance/adherence also inhibit exercise training potential. These shortcomings all stem from the current lack of understanding in skeletal muscle mass regulation within the context of ESRD and intermittent HD. As such, this review summarizes the current understanding of exercise regulation on skeletal muscle mass and ESRD-related obstacles of anabolism to contextualize the ineffectiveness of current exercise interventions for HD patients.

1 | INTRODUCTION

Skeletal muscle mass loss (~1 kg annually) is evident in end-stage renal disease (ESRD) patients receiving maintenance hemodialysis (HD).[1] This muscle mass loss is clinically relevant as it forms a key factor underpinning the decline in overall quality of life and higher all-cause mortality in this patient population.[2,3] Therefore, treatment strategies that effectively counteract muscle mass loss should be a key component of the care process for patients undergoing HD.

Skeletal muscle mass is regulated by changes in muscle protein synthesis and breakdown rates with turnover rates in healthy adults averaging ~1% to 2% per day,[4] which totals ~300 to 600 g of remodeled protein on a daily basis. This constant protein turnover of muscle tissue allows for aged and damaged proteins to be replaced, contributing to the maintenance and protein composition of "healthy" muscle.[5] Positive lifestyle behaviors, such as a healthy diet and ample physical activity, are the main anabolic stimuli to skeletal muscle tissue in healthy adults, and impairments in the responsiveness to these anabolic stimuli over time lead to muscle protein loss.

Currently, there is a lack of understanding of how skeletal muscle mass is regulated by these anabolic stimuli in patients undergoing hemodialysis. This creates a significant challenge when attempting to design more effective exercise and feeding prescriptions to attenuate muscle mass loss in patients on HD. This dilemma is further complicated by the fact that dialysis treatment represents intermittent periods (~4 to 6 hours each treatment) throughout the week where "normal" protein metabolism is altered.[6-8] This often brings into question which moments would be best to apply certain

anabolic strategies (eg, inter- or intradialytic exercise and/or amino acid/protein supplementation) in HD patients.

The purpose of this brief review is to discuss the role of exercise in the regulation of skeletal muscle mass in patients on maintenance HD. There have been mixed results, albeit mostly negative, regarding the effectiveness of exercise to support muscle mass maintenance, and its efficacy to improve quality of life, in HD patients.[9-12] These uneventful data are likely contributing to the general uncertainty in the Nephrology community for implementing exercise programs in HD clinics. We propose that prior to design and successful implementation of exercise interventions, there needs to first be a better understanding of the mechanisms and interactions of both inter- and intradialytic exercise on muscle mass regulation in HD patients. This will allow for greater progress toward more personalized exercise prescriptions to preserve skeletal muscle mass in HD patients.

Practical tips for nephrologists

- Advocate for reduced sedentary time and increased physical activity in maintenance hemodialysis patients to promote muscle conditioning with the ultimate goal of individualized exercise prescription to support muscle adaptations.
- Provide patients with evidence-based recommendations for exercise that accounts for proper frequency, intensity, timing, type, and nutrient support.
- Facilitate interdisciplinary care with coordinated efforts between nephrologists, exercise physiologists, and registered dietitians to develop and implement effective treatment for end-stage kidney disease-associated protein energy wasting syndrome.

Areas for future research

- Investigations to further define end-stage kidney disease-associated muscle pathophysiology.
- Acute exercise manipulations (ie, exercise mode, intensity, or timing) to understand exercise potential on muscle mass regulation.
- Provision of adjunct interventions (eg, postexercise nutritional intake) to maximize exercise-induced muscle anabolism.

2 | TRAINING SPECIFICITY AND THE ANABOLIC MECHANISMS UNDERPINNING SKELETAL MUSCLE ADAPTATIONS

The application of proper exercise prescription (eg, impact of exercise type, duration, and intensity) is preferred when targeting a specific skeletal muscle adaptation regardless of the population. For example, the performance of an acute bout of resistance vs endurance-type exercise differentially regulates transcription, protein translation and expression, enzyme activities, and/or protein intracellular localization in healthy adults. The "classic" pathways that relate to training specificity and the subsequent endurance vs resistance exercise-induced adaptations in healthy adults are shown in Figure 1.

It is the sum of these successive acute exercise-induced alterations in molecular and cellular events that elicit very distinct, yet variable,[13,14] skeletal muscle adaptations over time. In terms of hypertrophy, the load across the muscle and the increased activation of a protein kinase called the mechanistic/mammalian target of rapamycin (mTOR) within complex 1 is most relevant to enhance resistance exercise-induced adaptations.[15,16] Progressive resistance exercise based on linear periodization normally needs to be administered for at least 6 weeks to allow each acute increase in postexercise muscle protein synthesis (2–3 sessions per week) to cultivate into an increase in muscle fiber size in healthy adults.[17] Muscle strength adaptations can occur much earlier within a resistance exercise training program due to the rapid changes within the nervous system that allows for the better coordination of the activation of muscle and subsequent force development.[18]

In terms of skeletal muscle tissue, endurance training results in other local adaptations, such as increased mitochondrial protein content, mitochondrial function, and capillary supply, to enhance exercise capacity and performance.[19,20] These peripheral adaptations can occur within weeks to months after initiating endurance training[21-23] with the magnitude of the specific mitochondria adaptations thought to be linked to exercise intensity and volume.[24]

Endurance exercise activates several signaling pathways due to exercise-induced increases in cytosolic calcium, ATP turnover, and the production of reactive oxygen species to facilitate mitochondrial adaptations in healthy adults (Figure 1).[25] These signaling pathways interact to increase muscle PGC-1α gene expression,[26] which then transcriptionally coactivates nuclear genes encoding mitochondrial proteins. Lastly, endurance exercise stimulates mitochondrial protein synthesis rates to increase mitochondrial protein content, which facilitates an oxidative phenotype.[27]

Combining resistance and endurance exercise into a single session can induce cellular and molecular signaling responses that are quite similar to the performance of resistance or endurance exercise alone.[28] However, the exercise-induced benefits on skeletal muscle may be limited due to the lower exercise intensities being performed with each respective mode of exercise in combined training protocols in healthy adults.[29]

3 | ESRD-RELATED MUSCLE ANABOLIC RESISTANCE

There is very little information with regard to the molecular signals that may be involved in the regulation of exercise-induced adaptations in HD patients. Given the overstimulated state of HD muscles (ie, excessive muscle proteolysis driving increased protein

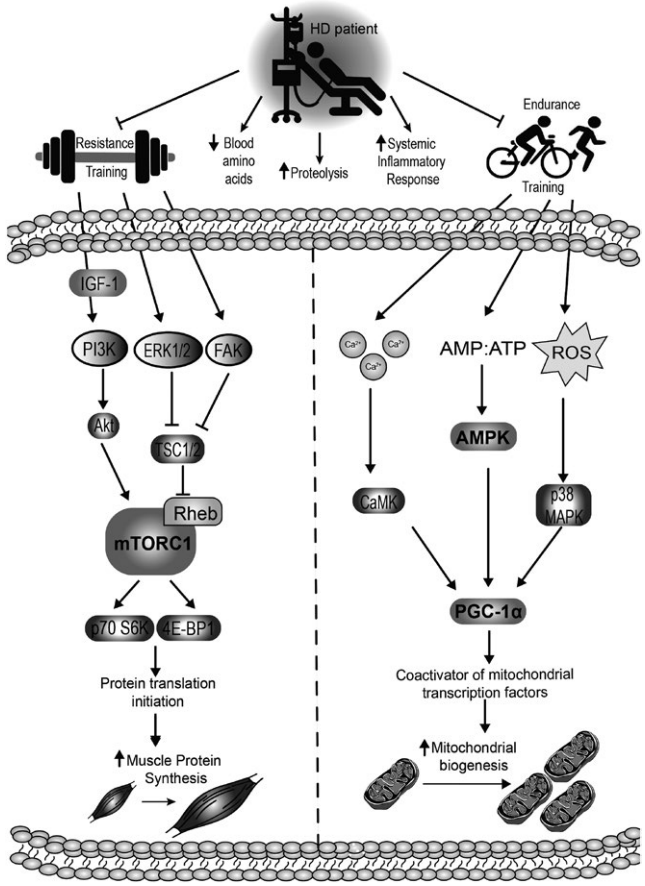

FIGURE 1 Exercise is a subgroup of physical activity that is planned, organized, and repeated on a regular basis with the goal of improving (or maintaining) the various physical fitness components (eg, hypertrophy or endurance). These physical fitness characteristics are targeted with progressive exercise training programs that are either resistance or endurance based. Each single bout of exercise initiates skeletal muscle signaling responses involved in coordinating pre- and posttranscriptional events and protein turnover (ie, synthesis and breakdown) to support hypertrophic or nonhypertrophic protein remodeling. In general, endurance- and resistance-based exercises are on two ends of the spectrum that results in distinct adaptations based on the muscle signaling pathways that are routinely activated. Training-induced adaptations in hypertrophy (ie, resistance exercise) and oxidative capacity (ie, endurance exercise) occur when these exercise activities are performed at the appropriate intensities and for enough time. We speculate that there are several underlying problems with standard exercise prescription in patients on hemodialysis (HD) that are limiting exercise-adaptive muscle protein synthetic responses to support training-induced skeletal muscle adaptations

synthesis rates),[30] it is clear that maladaptive signals are present and may presumably interfere with the stimulation of the exercise-adaptive muscle protein synthetic response in this patient population.

Interestingly, past efforts have shown that muscle mRNA expression of insulin-like growth factor (IGF-1) splice variants is increased to the same extent after ~5 months of endurance, resistance, or combined exercise training programs in HD patients.[12] However, there was no change in lean body mass from pre- to postexercise training with the different exercise regimens.[12] It was speculated that proper exercise prescription was not applied throughout the training program to stimulate a robust skeletal muscle adaptive response due to the degree of deconditioning and comorbidity of the patients on maintenance HD,[12] which is probably true. In healthy aging muscle, however, exaggerated IGF-1 signaling is also apparent after exercise, and this response is believed to be a compensatory mechanism to overcome age-related anabolic resistance of muscle protein synthesis.[31]

Similarly, we have recently established that HD patients also demonstrate muscle anabolic resistance to protein ingestion on a nondialysis day.[30] In particular, we have recently observed that HD muscles are overstimulated for at least 24 hours after HD treatment.[30] This is not a trivial finding as elevated basal muscle protein synthesis would seem to indicate that there is less potential for anabolic stimuli to elicit a robust muscle protein remodeling response. Specifically, basal muscle protein synthesis rates are directly, and inversely, linked to the magnitude of the stimulation of postprandial muscle protein synthesis rates after protein ingestion in older adults.[32] As such, we have put forward the notion that basal-state muscle protein synthesis rates in maintenance HD patients are likely nearing a stimulatory ceiling, or an upper physiological limit, for anabolic stimuli to signal a robust rise in postprandial muscle protein synthesis rates.[30] This hypermuscle protein metabolism in the basal-state will clearly need to be managed for successful implementation of anabolic lifestyle strategies (eg, exercise or feeding interventions) in HD patients.

Overall, the previous observed elevation in IGF-1 signaling in HD patients may not necessarily be indicative of anabolism,[12] but simply an aberrant response in overstimulated and anabolic resistanance muscles of HD patients.[30] Hence, it is important to first define the mechanisms by which different modes and intensities of exercise affect inter- or intradialysis regulation of muscle mass in HD patients. This will provide an evidence-based framework on the effectiveness of a particular exercise paradigm to stimulate muscle adaptive responses prior to the implementation of long-term training studies. This is relevant as prolonged exercise training interventions are often quite costly to pursue when considering the personnel cost and the need to recruit across multiple clinics to gain an adequate sample size to address the research question.

4 | THE MISAPPLICATION OF EXERCISE INTERVENTIONS

Physical activity and exercise are often viewed as therapies to help manage ESRD.[33-35] Prior to investigating exercise therapy effectiveness, it is important to understand and clearly define the differences between the following behaviors: (a) sedentary behavior, (b) physical activity, and (c) exercise, and how each behavior relates to the holistic care of HD patients. Sedentary behavior is defined by any waking

activity characterized by an energy expenditure of ≤1.5 metabolic equivalents in a sitting or reclining posture.[36] Physical activity has a broader definition and includes all forms of daily movement that result in energy expenditure above resting levels.[37] Specifically, physical activity relates to any movement that results in muscle contraction and increased energy expenditure (eg, grocery shopping, walking a dog, etc). Exercise is defined as planned and structured bodily movements aimed at maintaining or enhancing one or more components of physical fitness (cardiorespiratory, muscular strength/endurance, flexibility, or body composition).[38] These physical fitness characteristics are generally targeted by using exercise strategies prescribed at appropriate frequency, intensity, durations, and time (Figure 1). In addition, it is also important to consider "enjoyment" within the exercise prescription for any target population to achieve proper compliance and adherence.[39]

Various exercise training programs (endurance, resistance, or the two combined) have been applied in an effort to offset the loss of muscle mass and ultimately improve physical function and quality of life in patients on HD. There have been mixed results, albeit mostly negative, regarding the effectiveness of exercise to support muscle mass maintenance, and its efficacy to improve quality of life, in patients on maintenance HD.[9-12,40-43] The positive benefits of exercise have mostly been confined to short-term studies where adherence to the program is more likely to occur in HD patients.[43]

There are also several underlying issues with standard exercise prescription in HD patients that might be responsible for the ineffectiveness of exercise paradigms to support long-term muscle adaptations. For example, exercise is normally prescribed in the absence of nutritional support,[12] which may attenuate its true anabolic potential.[44] In addition, exercise is generally applied during dialysis treatment.[45] The performance of intradialytic exercise not only limits the intensity of the performed exercise but also HD is a particularly inflammatory and catabolic time period that may limit muscles ability to elicit an exercise-adaptive muscle protein synthetic response. For example, ~8 to 15 g of amino acids are lost into the dialysate resulting in patients essentially losing an amount of protein contained in a meal during each treatment,[46] rather than receiving adequate nutritional support.

In terms of exercise prescription, intradialytic endurance exercise training often simply involves sitting a cycle ergometer in front of the treatment chair. Moreover, resistance bands or ankle weights are often used to represent strength training. While application of these exercise strategies during HD are convenient and contribute to exercise adherence, we speculate that the outcomes do not suggest that such strategies are conducive to support exercise-adaptive muscle protein synthetic responses.

In theory, interdialytic exercise represents a better anabolic window to exercise as a more robust exercise prescription can be applied to elicit a more distinct phenotypic response. While interdialytic training programs have been investigated, there was no prior confirmation of the efficacy of this approach to stimulate an exercise-adaptive muscle protein synthetic response in HD patients. Notwithstanding, the deconditioned state and underlying comorbidities in HD patients, which often leave them ill and fatigued, make exercise prescription problematic in terms of exercise progression, compliance, and adherence to a more prolonged training program regardless of the targeted exercise period. This ultimately impacts the effectiveness of an exercise training programs to induce skeletal muscle adaptations.

5 | EXERCISE AND NUTRITION ARE COORDINATED STIMULI

Nutritional support during recovery from exercise is required to compensate for the metabolic demands of exercise and to maximize the postexercise muscle protein synthetic response to shift into a positive net protein balance.[47] However, exercise is commonly prescribed in the absence of nutritional support in HD patients.[11,12,43] This ultimately limits the ability of HD muscle to elicit exercise-adaptive muscle protein synthetic responses to improve muscle-related outcomes.

Indeed, past efforts have used combined resistance exercise and feeding strategies before, during, and immediately after HD to augment postprandial whole body anabolism and forearm net amino acid uptake when compared to nutritional supplementation alone.[48] However, models of forearm and whole body net protein balances under nonsteady conditions do not necessarily reflect the protein metabolism occurring in skeletal muscle tissue[49,50] and certainly do not reflect the synthesis rates occurring in specific protein fractions such as myofibrillar (contractile) or mitochondrial (oxidative) fractions. Hence, it was demonstrated that the translation of these acute benefits of combining resistance exercise and feeding on forearm and whole body protein metabolic responses did not translate into beneficial changes in lean body mass as measured by whole body DEXA during a 6-month training program.[9] Similar to past efforts that showed a lack of effect of resistance exercise training on changes in lean body mass in HD patients,[12] it was speculated that a suboptimal exercise prescription was employed and limited the skeletal muscle adaptive response.[9,51]

It is noteworthy that insight into important factors within the exercise prescription that maximizes muscle anabolic potential to feeding have been developed in healthy models. For example, it is necessary to recruit as many muscle fibers as possible to maximize the anabolic action of resistance exercise to subsequent protein intake.[52,53] In particular, a single bout of resistance exercise performed to elicit maximal muscle fiber activation and, with sufficient volume load (repetitions × load),[54] enhances the dietary amino acid sensitivity of muscle protein synthesis rates to protein intake for at least 1 day in healthy adults.[52]

Further manipulation of exercise prescription is required to potentiate the postexercise muscle protein synthetic response in older adults vs their younger counterparts.[55] For example, Kumar et al[55] demonstrated that older adults required double the amount of volume to potentiate the postexercise muscle protein synthetic

response when compared to young adults. Hence, the anabolic resistance of aging muscles can be eliminated with appropriate exercise prescription[55] combined with appropriate nutritional support.[47] It is clear, however, that HD muscle demonstrates a unique muscle environment when compared to other compromised patient conditions,[30,56] and this will make it difficult to draw conclusions based on nutrition and exercise response of muscle protein synthesis in healthy populations. Therefore, future studies are required to determine the nutritional and exercise regulation of muscle mass and the ability of different exercise modes to elicit distinct skeletal muscle adaptations in patients on HD.

6 | ADVANTAGES OF IN-CLINIC INTERVENTIONS

A maintenance HD patient is typically presented with multiple comorbidities characterized by a sedentary lifestyle that is associated with reduced exercise capacity and muscle function.[57] These factors are obvious issues when attempting to recommend vigorous exercise programs at appropriate intensities and durations to promote the skeletal muscle adaptive response in HD patients. Painter et al[58] have shown that regular participation in an exercise program resulted in improved exercise capacity in HD patients. As such, a key aspect of the effectiveness of exercise to support adaptations is compliance and adherence to the training program; this underpins the popularity of prescribing intradialytic exercise.

Even though intradialytic exercise is not the most effective time period to support the muscle adaptive response, in-clinic treatment is presumably an advantageous time period for health promotion programs as it would be logistically easier to provide patient education and motivation than coordinating outpatient services. In particular, health promotion programs within the dialysis clinic advocating for increased participation in regular physical activity and minimizing sedentary time represents a good starting point to develop positive lifestyle behaviors in HD patients.

Individualized exercise prescription is also an option based on the HD patient's ability and willingness to participate in an exercise training program. In particular, the routine dialysis session represents a time where patients on HD can practice and be coached on proper exercise prescription to be conducted during interdialytic period. However, the impact of different modes of exercise on HD-related muscle mass regulation is currently unknown and, as such, precludes the ability to design evidence-based exercise prescription and standardized guidelines. Overall, it is clear that a change in the culture of holistic care of HD patients is necessary to counteract ESRD-related muscle mass loss.

7 | CONCLUSIONS

The concept that "exercise is medicine" is true in healthy adults and many clinical populations with anabolic resistance (eg, aging).[59] However, there is a lack of evidence to clearly demonstrate the efficacy of exercise as a treatment strategy to offset skeletal muscle mass loss in HD patients.[12,41] The short-term nature of some of the exercise studies may account for the modest, but inconsistent, improvements in physical function.[11,40,42] However, the poor exercise compliance and adherence to more prolonged exercise training programs is a universal problem in this patient population. The application of intradialytic exercise programs may help with exercise compliance and adherence, but is likely not a conducive period to support exercise-adaptive muscle protein synthetic responses.

In addition, the hyper-protein metabolism occurring in HD muscle, whether related to the dialysis procedure itself or other comorbidities, may limit the effectiveness of exercise to stimulate a skeletal muscle adaptive response.[30] It is clear that HD muscle needs to be preconditioned to allow itself to be in a "healthier" state, or dampen the inflammatory and oxidative stress signals, to be able to adapt to exercise and nutritional interventions. Progress toward this goal can only be achieved by first exposing the mechanisms by which different exercise prescriptions affect the regulation of muscle protein synthetic responses, and determine if nutrition can be used as an adjunct strategy to maximize the skeletal muscle adaptive response. This information will allow for a better understanding of appropriate and standard exercise guidelines to attenuate muscle mass loss in HD patients. It would also provide a rationale to provide nutritional support within the exercise prescription for HD patients. It is evident that most HD patients will benefit from incorporating physical activity and healthy eating behaviors into their daily lives. As it stands, however, the effectiveness of using targeted exercise prescription to promote the components of physical fitness (eg, body composition, strength, or endurance) is generally lacking in HD patients.

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How to cite this article: McKenna CF, Salvador AF, Hendriks FK, Harris APY, van Loon LJC, Burd NA. Exercising to offset muscle mass loss in hemodialysis patients: The disconnect between intention and intervention. *Semin Dial*. 2019;00:1–7. https://doi.org/10.1111/sdi.12805