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Exercise as an Anabolic Intervention in ESRD Patients

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Abstract

Muscle wasting and accompanying structural derangements leading to abnormalities in muscle function, exercise performance, and physical activity are common in end-stage renal disease (ESRD) patients. Accordingly a number of studies have been performed examining the effects of exercise in this patient population. Most of the studies have assessed the effects of cardiopulmonary fitness training and a few have examined the role of resistance (i.e. strength) training. Despite the proven efficacy of resistance exercise as an anabolic intervention in otherwise healthy elderly and certain chronic disease states, recent studies in maintenance hemodialysis patients have not been encouraging in terms of long-term improvements in markers of muscle mass. Preliminary studies indicated that a combination of simultaneous exercise and nutritional supplementation could augment the anabolic effects of exercise, at least in the acute setting. However, a recent randomized clinical trial failed to show further benefits of additional resistance exercise on long-term somatic protein accretion above and beyond nutritional supplementation alone. Further research is necessary to both understand the observed lack of obvious benefits and strategies to improve the exercise regimens in ESRD patients.

Maintenance dialysis patients encounter multiple catabolic processes and suffer from a unique form of protein and energy wasting (PEW), which is characterized by increased muscle protein catabolism and decreased visceral protein stores. Muscle function, exercise performance, and physical activity abnormalities begin in earlier stages of chronic kidney disease, and progressively get worse as end-stage renal disease (ESRD) results ¹⁻².

Although the pathophysiology of protein energy wasting and associated derangements in muscle mass and function is clearly complex, multifactorial, and not fully elucidated, much has already been learned. Clearly, the nutritional and metabolic derangements in ESRD patients cannot be attributed to any single factor. Irrespective of the specific etiologic mechanisms, it appears that the common pathway for all the metabolic derangements is related to exaggerated protein degradation relative to protein synthesis. Factors that contribute to net negative protein balance include, but are not limited to, decreased relative nutrient intake, catabolic effects of renal replacement therapies, metabolic derangements such as chronic inflammation and insulin resistance, hormonal abnormalities including resistance to anabolic actions of growth hormone and androgens and concurrent morbid conditions such as frequent hospitalizations, depression and gastroparesis. In addition to these, several factors that are specific to muscle function are also altered such as exaggerated

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phosphocreatinine depletion of muscle during exercise, alterations in muscle capillary density and oxygen transport, alterations in overall muscle blood flow during exercise, and possibly alterations in muscle carnitine content ³. The muscle structure in MHD patients is also altered with a unique pattern of abnormalities ⁴. There is fiber atrophy that predominantly involves type IIx/IIb fibers, which show marked myofilamentous loss. Mitochondria appear swollen and disrupted and degenerative changes are found in fibers adjacent to other fibers showing evidence of regeneration.

Given the significance of the problem, as well as the complexity of the pathophysiological basis of PEW in advanced CKD, it is evident that the prevention and treatment options of condition are both critical and complex. To date, there is not a single treatment approach that will alleviate the multiple adverse consequences of PEW completely. Therefore, management of nutritional aspects of ESRD patients should involve a comprehensive combination of preventive maneuvers to diminish protein and energy depletion, in addition to therapies that will avoid further losses. Unfortunately, for some of the therapies currently in use, there are only empiric data showing clear benefits, if not data showing lack of benefits, although some are derived from secondary outcomes as part of large clinical trials. These include provision of adequate dialysis, treatment of metabolic acidosis, adjustments of dietary requirement and intake, prophylaxis and treatment of infections, and even factors that are not obviously linked to nutrition but affect ESRD patient in a way that may further affect nutrition such as fluid overload.

Exercise as an Anabolic Intervention in ESRD Patients

Based on the evidence that maintenance dialysis patients are commonly physically inactive and show many maladaptive changes in skeletal muscle, a number of studies have been performed examining the effects of exercise in this patient population. Since exercise training can maintain and/or improve exercise capacity and endurance in the general population, most of the studies have assessed the effects of cardiopulmonary fitness training in ESRD patients ⁵. On the other hand, a few have examined the role of resistance (i.e. strength) training. Resistance exercise has been shown to increase muscle mass, strength and appetite as well as lessen muscle weakness and frailty in the elderly population. Resistance exercise also has a profound stimulating effect on muscle growth by increasing oxygen consumption.

Despite the proven efficacy of resistance exercise as an anabolic intervention in otherwise healthy elderly and certain chronic disease states⁶⁻⁷, recent studies in CHD patients have not been encouraging in terms of long-term improvements in markers of muscle mass. In follow-up to earlier studies indicating type 1 and type 2 muscle fiber hypertrophy and increased peak torque of the leg extensors of the dominant leg in response to exercise in hemodialysis patients, Johansen *et al.* reported in a randomized clinical trial that 12-week of moderate intensity lower body progressive resistance exercise training (PRT) can improve quadriceps muscle area measured by MRI, although this was not detectable by dual energy X-ray absorptiometry (DEXA) ⁸. Of note, these changes were accompanied by a significant increase in body weight and fat mass. In another randomized controlled study, Cheema *et al.* showed that 12-week high-intensity PRT administered during routine hemodialysis treatment did not improve skeletal muscle quantity measured by computed tomography (CT) scan, although there were statistically significant improvements in muscle attenuation (intramuscular lipid content via attenuation evaluated by CT), muscle strength and other anthropometric data ⁹. A further analysis of 24 weeks of intervention did not result in any additional benefit either. Kopple *et al.* studied the effects of different forms of exercise training (endurance, strength, or a combination in which patients underwent about one-half each of the endurance and strength training of the first two groups) on mRNA levels of

genes in muscle that may contribute to increased exercise capacity¹⁰. Although there were no significant changes in lean body mass (LBM) with any of the individual exercise regimens over 6 months, it was concluded that exercise training in hemodialysis patients induces changes in skeletal muscle mRNA and increases muscle insulin-like growth factor-1 (IGF-I) protein, which may promote protein anabolism.

Combination anabolic interventions

Collectively, the aforementioned studies indicate that the presumed beneficial effects of resistance exercise such as improvements in muscle quality and quantity, strength and physical functioning are not consistently observed in maintenance dialysis patients. While the exact mechanism underlying this limited beneficial response is not clear, an overlapping aspect of these studies is the lack of any attempt to increase nutritional intake in the exercising patients, especially around the time of exercise. While exercise has a direct stimulatory effect on the rate of muscle protein synthesis, the rate of muscle protein breakdown is also increased as a consequence of exercise, thereby blunting the extent to which net balance between synthesis and breakdown is improved¹¹⁻¹². Multiple studies demonstrated that resistance exercise combined with oral nutritional supplementation facilitates muscle uptake of amino acids and muscle protein accretion in healthy subjects, which is believed to be due to increased blood flow to the muscle, increased inward transport of amino acids and enhanced insulin signaling in the cellular level¹³⁻¹⁴. Accordingly, studies suggest that post-exercise muscle protein synthesis is enhanced in fed subjects compared with fasted subjects¹⁵. In accordance with these data, several short-term studies in CHD patients showed that net muscle protein accretion and albumin synthesis are increased with nutritional supplementation combined with exercise when compared to supplementation alone¹⁶⁻¹⁸.

In a series of studies, our laboratory examined the effects of simultaneous exercise and nutritional supplementation in prevalent chronic hemodialysis (CHD) patients. Initially, we studied six CHD patients at two separate hemodialysis sessions: 1) intradialytic parenteral nutrition (IDPN) administration only and 2) IDPN plus exercise¹⁸. Patients were studied 2 h before, during, and 2 h after an hemodialysis session by use of a primed-constant infusion of L- (1-¹³C) leucine and L- (ring-²H₅) phenylalanine. Exercise combined with IDPN promoted additive 2-fold increases in forearm muscle essential amino acid uptake (455 ± 105 mol/100ml/min vs. 229 ± 38 nmol/100ml/min, $P < 0.05$) and net muscle protein accretion (125 ± 37 μ g/100ml/min vs. 56 ± 30 μ g/100ml/min, $P < 0.05$) during HD when compared to IDPN alone. Measurements of whole-body protein homeostasis and energy expenditure were not altered by exercise treatment. In a follow-up study, we showed that combination of exercise during hemodialysis with IDPN significantly improved the fractional synthetic rate of albumin beyond what is observed with IDPN alone ($26.2 \pm 3.1\%$ per day versus $17.7 \pm 1.9\%$ per day, $P < 0.05$)¹⁷. This observation indicated that the beneficial effects of exercise extended beyond skeletal muscle mass alone.

Similar results were observed when (resistance) exercise was combined with oral intradialytic nutritional supplementation¹⁶. Specifically, we performed stable isotope protein kinetic studies in eight CHD patients during two separate settings: with oral nutritional supplementation alone (PO) and oral nutritional supplementation combined with a single bout of resistance exercise (PO + EX). Metabolic assessment was performed before, during and after haemodialysis. As expected, both interventions resulted in robust protein anabolic response. There were no differences in metabolic hormones, plasma amino acid and whole-body protein balance between the interventions. However, during the post-hemodialysis phase, PO + EX retained a positive total amino acid (TAA) balance (primarily due to essential amino acid) while PO returned to a negative TAA balance although this

difference did not reach statistical significance (78 ± 109 versus -128 ± 72 nmol/100 ml/min, respectively; $P = 0.69$). In the post-HD phase, PO + EX had significantly higher net muscle protein balance when compared to PO (19 ± 16 versus -24 ± 10 microg/100 ml/min, respectively; $P = 0.036$).

While the abovementioned results are encouraging, the next logical step is to examine whether the acute beneficial changes observed using the combination of exercise and nutritional supplementation would translate into long-term benefits in muscle mass and strength in maintenance dialysis patients. In order to test this hypothesis, we performed a randomized clinical trial (RCT) in 32 CHD patients over a 6-month period¹⁹. Subjects were randomly assigned to IDON plus resistance exercise (NS+EX) or IDON (NS) alone for 6 months. IDON consisted of a lactose-free formula consisting of protein, carbohydrate and fat. Three sets of 12 repetitions of leg-press were completed prior to each dialysis session in the NS+EX arm. Twenty-two out of 32 participants completed the 6-month intervention. Body weight (80.3 ± 16.6 kg, 81.1 ± 17.5 kg and 80.9 ± 18.2 kg at baseline, month 3 and month 6, respectively, $P=0.02$) and 1-Repetition Maximum (468 ± 148 lb, 535 ± 144 lb, 552 ± 142 lb, respectively, $P=0.001$) increased statistically significantly during the study for all patients combined. However, there were no statistically significant differences between the study interventions with respect to changes in LBM and body weight when comparing NS+EX to NS (Figure 1). There were also no statistically significant differences in any of the secondary outcomes measured in the study such as albumin and prealbumin. Overall, this study did not show further benefits of additional resistance exercise on long-term somatic protein accretion above and beyond nutritional supplementation alone.

While speculative, there may be several reasons why addition of resistance exercise failed to augment protein mass in this particular study. First, the subjects enrolled in this study were younger than the general dialysis population in the U.S. and in relatively good nutritional status. Therefore, interventions aimed at ameliorating muscle mass loss could not be detected as much as in the elderly or subjects with obvious muscle wasting⁶⁻⁷. A second reason for lack of clear benefits can be attributed to the sensitivity and precision of DEXA to evaluate changes in muscle mass, as suggested by a study in which increases in quadriceps muscle area was observed by MRI despite no changes in DEXA⁸. Further, Castaneda et al showed that resistance exercise significantly increased type I and type II muscle fiber hypertrophy detected via muscle biopsies despite a non-significant change in mid-thigh muscle CSA as evaluated by CT scan²⁰. Finally, it is possible that the intensity and duration of exercise in this particular study was not adequate to induce a significant change in muscle homeostasis despite our best efforts to prescribe a progressive leg-press intervention. The overall improvement in the 1-RM during the study period suggests that the exercise regimen provided in this study either falls short of improving leg strength above and beyond of nutritional supplementation alone or that the effect is too small to be detected by our assessment tools. At this point, the addition of resistance exercise to intradialytic nutrition supplementation, although practical, cannot be recommended until further studies confirm its benefits on muscle mass and muscle strength in CHD patients. Additional benefits of resistance exercise not explored in this study such as physical functioning, long-term protein turnover, and cardiovascular outcomes should also be explored in future studies.

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Figure 1.

Thirty-two subjects were randomized to nutrition supplementation during dialysis alone versus a combination of resistance exercise and nutrition. Box and whisker plot of the total lean body mass are shown as measured by dual-energy x-ray absorptiometry at baseline, 3 month and 6 month of follow up. □, nutrition supplementation group; ■ nutrition supplementation plus resistance exercise group. P value comparing the two treatments over time was obtained from the general linear model with bootstrap covariance accounting for correlated measures within a subject. (adapted from ^{reference 19}).