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Skeletal muscle dysfunction in chronic renal failure: effects of exercise

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Adams, Gregory R., and Nosratola D. Vaziri. Skeletal muscle dysfunction in chronic renal failure: effects of exercise. *Am J Physiol Renal Physiol* 290:F753–F761, 2006; doi:10.1152/ajprenal.00296.2005.—A number of chronic illnesses such as renal failure (CRF), obstructive pulmonary disease, and congestive heart failure result in a significant decrease in exercise tolerance. There is an increasing awareness that prescribed exercise, designed to restore some level of physical performance and quality of life, can be beneficial in these conditions. In CRF patients, muscle function can be affected by a number of direct and indirect mechanisms caused by renal disease as well as various treatment modalities. The aims of this review are twofold: first, to briefly discuss the mechanisms by which CRF negatively impacts skeletal muscle and, therefore, exercise capacity, and, second, to discuss the available data on the effects of programmed exercise on muscle function, exercise capacity, and various other parameters in CRF.

atrophy; substrate availability; insulin resistance; inactivity; protein degradation

THE IMPORTANCE OF PHYSICAL activity for the maintenance of health has become increasingly evident (8, 22, 112). For example, recent data indicate that poor diet and physical inactivity account for a substantial portion of death from all causes in the United States (68, 83). In many parts of the world, the occupational pursuits of much of the population have become increasingly sedentary (30). In these settings, the substitution of some level of leisure or programmed exercise is thought to confer benefit for health maintenance (e.g., Refs. 30, 36, 68).

A number of biologically diverse chronic illnesses such as renal failure (CRF), obstructive pulmonary disease (COPD), and congestive heart failure (CHF) result in a significant decrease in exercise tolerance. In each of these disease states, treatments aimed at the primary pathology have provided powerful palliative effects. However, in general, improvements in exercise tolerance following such interventions are delayed and incomplete. This has led to an increasing awareness that secondary treatment strategies, such as prescribed exercise, designed to restore some level of physical performance and quality of life can be beneficial. For example, the American Heart Association has recently taken the position that exercise rehabilitation has an important place in the treatment of heart failure (87).

A number of studies have demonstrated that programmed physical activity can provide supportive and even palliative effects in certain chronic diseases (64). One such example is chronic obstructive pulmonary disease (COPD). Studies have shown that, despite permanent reduction in lung function, exercise training can significantly increase exercise tolerance in COPD patients (94). Similarly, in a review of the literature, Smart and Marwick (103) concluded that exercise training

improves exercise tolerance and may potentially reduce adverse events and mortality in patients with heart failure.

Declines in skeletal muscle function¹ appear to be a stronger predictor of exercise tolerance than measurements directly associated with the primary disease in patients with CHF, COPD, and CRF. For example, Gosker et al. (40) recently reported that fat-free mass (FFM) is a better predictor of exercise capacity than lung function or left ventricular function in patients with COPD and CHF, respectively. Similarly, Harrington et al. (44) found that CHF patients with relatively severe impairment of left ventricular function but preserved muscle mass are capable of near-normal exercise performance. Regarding CRF, it is not clear whether and to what extent the decline in muscle function is a direct result of the disease-related changes in skeletal muscle physiology as opposed to the reduction in physical activity and malnutrition. However, a growing consensus has emerged that decreased muscle function stems from disorders that can be ameliorated independently of strategies that address the primary underlying disease.

CRF AND EXERCISE TOLERANCE

Compared with the healthy individuals, indicators of aerobic capacity such as peak oxygen uptake are impaired in patients with end-stage renal disease (ESRD) (59, 101). The limitations imposed by these impairments are sufficient to negatively impact routine daily activities (13, 101). While ESRD is associated with anemia, a number of studies have shown that the decrements in exercise tolerance seen in ESRD patients are not fully ameliorated by correction of anemia with erythropoietin treatment (61, 75, 80). In addition, a large percentage of patients with ESRD develop hypervolemia and some degree of

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¹ The literature cited throughout this review includes an extremely heterogeneous array of metrics, ranging from isometric strength measurements to sit-and-stand testing, that have been used by the various investigators to evaluate the ability of skeletal muscles to generate force.

heart failure, which can limit physical activity (e.g., Ref. 102). However, correction of hypervolemia with ultrafiltration does not correct the CRF-associated exercise intolerance.

Exercise and Mortality

In addition to the obvious negative impacts of CRF-related functional impairment on daily life, reduced aerobic capacity may be associated with increased risk of mortality. For example, Seitsemä et al. (100) recently reported that peak oxygen uptake ($\dot{V}O_2$) is a strong predictor of survival in ESRD patients. These authors suggested that, given the predictive value of $\dot{V}O_2$, the ability to improve this parameter via exercise training may potentially increase survival. In addition, Macdonald et al. (76) recently reported that 3 mo of high-intensity interval training conducted during hemodialysis resulted in a reduction in extracellular fluid volume sufficient to allow for a decrease in antihypertensive medication in ESRD patients.

RENAL FAILURE AND SKELETAL MUSCLE

The skeletal muscle system is heavily impacted by CRF. However, the etiology of muscle dysfunction in CKD has not been definitively established. This is primarily due to the inability to differentiate the potential mechanisms that are responsible for the changes in skeletal muscle performance parameters in a chronic disease. The potential mechanisms by which CKD may negatively impact skeletal muscle are multifaceted and complex, resulting from alterations in muscle perfusion, substrate delivery, and catabolic state mediated by various factors such as metabolic acidosis, corticosteroids, proinflammatory cytokines, and decreased physical activity, among others. In the following sections, we will attempt to briefly review the perturbations that appear to be germane to skeletal muscle dysfunction in CRF. The citations provided are intended to be current rather than exhaustive and will preferentially include recent reviews when possible.

Skeletal Muscle Catabolism

ESRD is associated with muscle wasting that manifests as significant myofiber atrophy across all fiber types in both locomotor and nonlocomotor muscles (62, 97, 98). In addition, as shown by Diesel et al. (26), there is evidence of degeneration/regeneration cycles, fiber splitting, fiber-type grouping, myofibril derangement, and the presence of abnormal mitochondria in the muscles of ESRD patients.

Many of the studies designed to address uremic cachexia have been conducted with patients maintained on hemodialysis for extended periods. Hemodialysis itself appears to be associated with processes that may significantly impact muscle. In addition, many CRF patients exhibit the so-called malnutrition syndrome, which is associated with muscle wasting (53). As a result, it is not clear to what extent CRF per se as opposed to secondary factors including dialysis procedures engenders the catabolic state in skeletal muscle (73). An overview of the factors that impact muscle metabolism in CRF is provided below.

Muscle protein balance. With regard to the most proximal mechanisms for the maintenance of muscle mass, atrophy results from a change in the ratio of protein synthesis to degradation. Net loss of muscle protein could be a result of either increased degradation, decreased synthesis, or a combination of the two. As an example of this change in equilibrium, Adey et al. (3) recently reported that the rate of muscle protein synthesis was significantly lower in as-yet dialysis-independent CKD patients compared with the healthy control persons, suggesting that renal failure per se can result in a catabolic state. In addition, hemodialysis has been shown to promote degradation of the muscle as well as whole body proteins (52).

The initial step in degradation of the contractile apparatus in skeletal muscle cells involves dismantling of actomyosin protein structures by caspase-3 (Fig. 1) (28). In this regard, Du et

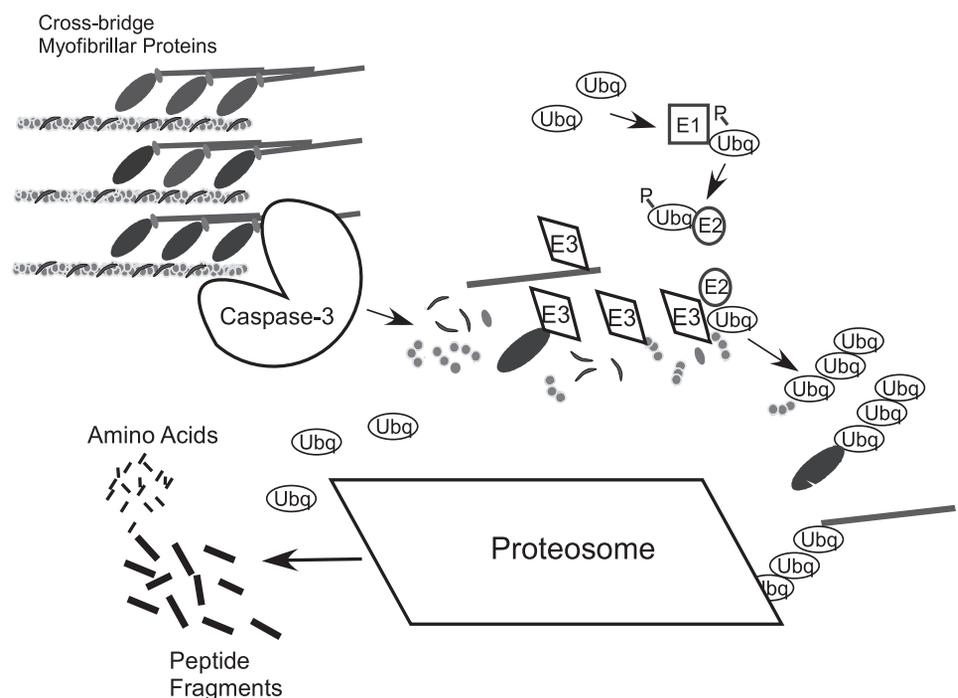


Fig. 1. Mechanisms of muscle protein degradation. Disassembly of the sarcomeric protein complex is thought to be catalyzed by caspase-3. This disassembly is required before further processing and eventual degradation by the ubiquitin (Ubq)-proteasome system. Ubiquitin peptide is activated by E1 proteins (P), and the activated ubiquitin is then transferred to the E3/substrate complex by E2 proteins. Multiple activated ubiquitin peptides are attached to form a chain that is recognized by the 26s proteasome, where degradation proceeds. The E3 ligases provide for specificity by recognizing a limited range of target proteins. In skeletal muscle, the expression of two E3 ligases, atrogin-1 and muscle RING finger 1 (MuRF-1), appears to be important in muscle atrophy such as that seen in renal failure.

al. (28) have reported that caspase-3 activity is increased in the muscles of uremic rats. The dismantling of the contractile apparatus by caspase-3 is followed by further degradation of the given proteins by the ubiquitin-proteasome system (32, 65, 67, 113). Degradation of the target proteins via this system requires their packaging with ubiquitin peptides before entry into the proteasome (66, 113). This process is catalyzed by a series of enzymes termed E1, E2, E3, and E4. On each occasion, a specific E3 ligase binds to the targeted protein. Simultaneously, E1 activates (phosphorylates) ubiquitin peptide and the activated ubiquitin is transferred to the E3-bound target protein by E2 (Fig. 1). The E3 ligase then catalyzes the covalent attachment of the activated ubiquitin to the target protein. Additional ubiquitin peptides are added to the first ubiquitin by either E3 or E4 ligases to form a ubiquitin peptide chain on the target protein. The substrates containing such polyubiquitin tails are then recognized and degraded by 26S proteasome.

The specificity of this degradation system is attained via production of specific E3 ligases that recognize and bind to a limited range of potential substrates. In this regard, Gomes et al. (39) have described a muscle-specific E3 ligase, termed atrogin-1, that appears to be generally upregulated in conditions that induce muscle atrophy. In fact, upregulation of atrogin-1 has been shown to be associated with increased protein degradation in CRF (39, 67). In rat models of CRF, metabolic acidosis has been shown to result in activation of the ubiquitin-proteasome system in skeletal muscles (4, 58).

The expression of muscle E3 ligases atrogin-1 and muscle RING finger 1 is negatively regulated by insulin-like growth

factor-I (IGF-I) and/or insulin signaling via the Akt-mediated phosphorylation of FOXO transcription factors (34, 96, 107) (Fig. 2). It is noteworthy that CRF is associated with impaired insulin and IGF-I signaling, which can potentially contribute to increased expression of these ligases and hence, ubiquitination and degradation of muscle proteins (Fig. 1).

In one of the few human studies exploring this issue, Bossola et al. (11) reported no significant increase in ubiquitin mRNA expression in six ESRD patients maintained on hemodialysis. Based on these findings, they concluded that upregulation of this system may not be involved in the pathogenesis of hemodialysis-associated muscle wasting in patient with mild acidosis (11).

In a more global context, there are a myriad of somatic systems that can regulate the anabolic/catabolic balance in skeletal muscle. As outlined below, renal insufficiency, and in some cases the associated therapeutic interventions, can interact with and alter a number of systems that are critical for the maintenance of muscle mass.

Amino acid homeostasis. In CRF patients, depletion of amino acids can occur as a result of protein malnutrition caused by anorexia, prescription of a low-protein diet (31, 53, 78), and losses during dialysis (72). This potential problem is compounded by a depressed anabolic response to amino acids in CRF patients (18).

In addition to an obvious impact on substrate availability, amino acid homeostasis can directly regulate the anabolic/catabolic equilibrium in skeletal muscle. A primary mechanism for this effect is thought to reside in the phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) sig-

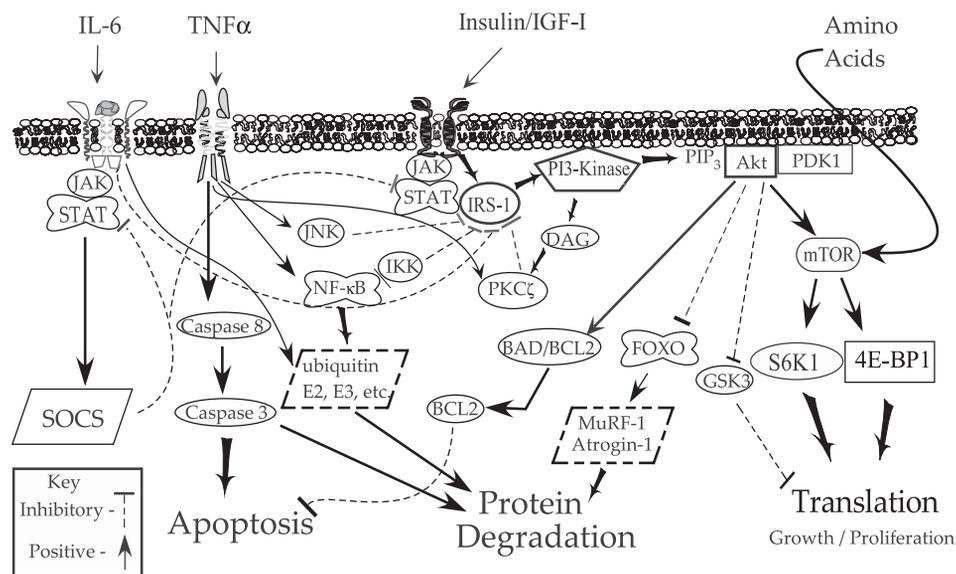


Fig. 2. Potential mechanisms of muscle wasting in renal failure. Insulin and IGF-I receptor-mediated signaling via the insulin receptor substrate (IRS)/phosphoinositide-3 kinase (PI3K)/Akt pathway drives anabolic, anticatabolic, and antiapoptotic processes. A number of responses to renal failure converge on this critical pathway, potentially leading to a catabolic state. The chronic inflammation often associated with renal failure can lead to elevated levels of TNF- α and IL-6. Both of these cytokines are known to induce muscle atrophy. One possible mechanism for this effect is negative modulation of IRS/PI3K/Akt signaling that effectively reduces cellular sensitivity to IGF-I and insulin. In addition, decreased clearance of IGF-I binding proteins results in a reduction in biologically available IGF-I, thereby reducing the probability of receptor ligation. There is evidence that amino acid levels are directly sensed by the mammalian target of rapamycin (mTOR) component of the IRS/PI3K/Akt signaling pathway. A reduction in circulating amino acid levels, as is often seen in renal failure patients, would reduce the anabolic stimulus functioning via this pathway as well. JAK, Janus kinase; STAT, signal transducers and activators of transcription; SOCS, suppressor of cytokine signaling; IKK, I κ B kinase; DAG, diacylglyceride; BAD, regulator of programmed cell death; FOXO, Forkhead transcription factor; GSK3, glycogen synthase kinase-3; S6K1, p70 S6 kinase; PDK1, 3-phosphoinositide-dependent protein kinase; 4E-BP1, eukaryotic initiation factor 4-binding protein-1; Bcl2, regulator of programmed cell death; PIP₃, phosphatidylinositol 3,4,5-trisphosphate.

naling cascade, which is a critical regulator of protein synthesis (Fig. 2). PI3K/mTOR signaling is sensitive to a number of regulatory inputs including muscle loading state, growth factors such as insulin and IGF-I, and amino acid availability (9, 25, 79). There is compelling evidence that hemodialysis and the associated depletion of circulating amino acids contribute to the net skeletal muscle protein loss (e.g., Ref. 52).

Inflammation. CKD, per se, is associated with chronic low-grade inflammation. The circulating levels of interleukin-6 (IL-6) are elevated in nondialyzed CKD patients (e.g., Refs. 10, 47) and may further increase in response to dialysis (54). The latter is due, in part, to the activation of complement, influx of endotoxin fragments, and leukocyte-membrane interactions. Tumor necrosis factor- α (TNF- α) levels are also elevated in ESRD patients both before and after hemodialysis (27). Proinflammatory cytokines such as IL-6 and TNF- α are known to induce muscle wasting (5). In addition, hemodialysis can result in cytokine-induced protein redistribution and net muscle protein loss (27, 93).

A number of studies have reported that IL-6 can negatively affect insulin and IGF-I receptor signaling, which may, in turn, promote a catabolic state within the skeletal muscle. This effect appears to be due, in part, to inhibition of insulin receptor substrate-1 (IRS-1) phosphorylation and/or its ability to interact with PI3K (Fig. 2) (58, 114). In support of this supposition, we have recently reported that chronic, low-level IL-6 exposure can decrease phosphorylation of the ribosomal p70 S6 kinase (S6K1) in skeletal muscle, resulting in muscle atrophy (Fig. 2) (42).

Activation of TNF- α receptors can potentially promote muscle protein wasting by a number of intracellular responses (Fig. 2). For instance, TNF- α signaling can activate caspase-3, which has been shown to participate in the breakdown of myofibrillar proteins (28). TNF- α can also stimulate the activation of NF- κ B and, thereby, increase transcription of components of the ubiquitin system (69). In addition, TNF- α -induced activation of c-Jun kinase and I κ B kinase can result in serine phosphorylation of IRS-1 (33, 38). Serine phosphorylation reduces IRS-1 interactions with the insulin or IGF-I receptors and with PI3K as well as potentially increasing IRS-1 degradation. Simultaneously, decreased tyrosine phosphorylation of IRS-1 reduces signaling via the highly anabolic and antiapoptotic PI3K pathway.

Insulin resistance. In addition to its obvious role in glucose metabolism, insulin is a powerful anabolic hormone for skeletal muscle. Several studies have demonstrated that renal failure results in insulin resistance even at relatively early stages of the disease (6, 29, 115). Given the critical role of insulin in both muscle energy metabolism and protein synthesis, CRF-induced insulin resistance may adversely affect skeletal muscle protein balance and energy production. However, a number of studies have suggested that uremia per se does not necessarily interfere with the anabolic actions of insulin (74, 90). One of the possible mechanisms for insulin resistance is inflammation, which is a known consequence of chronic renal disease and dialysis therapies. As noted above, TNF- α signaling can potentially interfere with insulin receptor signaling via the inhibition and degradation of IRS-1 (Fig. 2) (38).

As noted above, CRF is associated with the diminished ability of amino acids to stimulate protein synthesis (18, 19). However, the combination of insulin, glucose, and amino acid

supplementation has been reported to transiently lower protein degradation, increase protein synthesis, and promote net amino acid flux into the protein pool in hemodialysis-treated and untreated CRF patients (19, 74).

Growth hormone resistance. CRF is associated with significant disruption of the growth hormone (GH)/IGF-I axis, which is characterized by marked GH resistance (56). Among the effects of GH resistance is a disruption of IGF binding protein equilibrium, leading to reductions in IGF-I availability (50, 92, 95).

The CRF-induced GH resistance in skeletal muscle appears to be due to increased expression of suppressor of cytokine signaling-2, which attenuates signaling via the Janus kinase/signal transducer and activator of transcription pathway (e.g., Ref. 109). Because the GH-IGF system is instrumental in muscle growth and metabolism, its disruption most likely participates in the pathogenesis of the associated decline in the muscle mass in CRF.

Metabolic acidosis. Metabolic acidosis is an inevitable consequence of renal failure (110). In general, metabolic acidosis is well controlled by peritoneal dialysis. However, hemodialysis patients may experience a less consistent correction of acidosis (55). As noted earlier, the metabolic acidosis associated with CRF contributes to skeletal muscle atrophy via activation of the ubiquitin-proteasome system (4). In fact, even a minimal correction of acidosis can improve whole body protein turnover and the anabolic state of skeletal muscle via downregulation of the ubiquitin-proteasome system (41, 86). In addition to the activation of the ubiquitin-proteasome system, there is evidence that metabolic acidosis and CKD may cause skeletal muscle atrophy by activating oxidation and, thereby, limiting the availability of branched-chain amino acids (77), which play a critical role in the preservation of muscle mass (60, 106).

Using a muscle cell line, Franch et al. (35) demonstrated that the antianabolic action of acidosis may be, in part, due to alteration of the intracellular signaling associated with ligation of the insulin receptor. These authors reported that extended (24 h) exposure of cells to acidic media resulted in decreased insulin-stimulated PI3K activity and diminished phosphorylation of Akt.

Taken together, these results suggest that chronic metabolic acidosis contributes to the loss of muscle mass in CRF via decreased inhibition and/or stimulation of the ubiquitin-proteasome system.

ANG II. Activation of the renin-angiotensin system plays a major role in the progression of renal disease (119). In addition, ANG II promotes catabolism and skeletal muscle atrophy (12). Recently, Song et al. (104) demonstrated that the catabolic effect of ANG II is mediated by disruption of intracellular IGF-I signaling in skeletal muscle, leading to activation of caspase-3 and the ubiquitin-proteasome system and apoptosis. This phenomenon may be responsible, in part, for the reduction of muscle mass in such disorders as CHF, malignant hypertension, hepatic cirrhosis, and renal disease in which the renin-angiotensin system is frequently activated.

Inactivity. Decreased muscle loading due to inactivity is known to result in marked skeletal muscle atrophy (1). Therefore, the reduction in physical activity in CRF patients can exacerbate the loss of muscle mass and hence, the decline in exercise capacity in this population.

Malnutrition syndrome. Many ESRD patients exhibit a constellation of abnormalities including weight loss, diminished muscle mass, fatigue, hypoalbuminemia, and hypocholesterolemia, which are commonly referred to as malnutrition. However, the use of this term is frequently misleading because, unlike true malnutrition, the condition is not caused by a primary reduction of food intake or absorption and is not reversed by dietary modifications (82). Instead, the syndrome is primarily due to a hypercatabolic state caused by a combination of inflammation, metabolic acidosis, insulin resistance, uremic toxicity, and dialysis procedures among others as opposed to the mere reduction of food intake. In fact, consumption of a high-protein diet can compound the problem by exacerbating metabolic acidosis, azotemia, and hyperphosphatemia in ESRD patients (43).

SKELETAL MUSCLE FUNCTION

While muscle mass or its cross-sectional area is a primary determinant of the overall ability to generate force, a number of additional factors that can impact muscle function in CRF are briefly addressed in the following section.

Substrate Availability

The availability of metabolic substrate, i.e., fatty acids glucose and oxygen, has a major impact on muscle performance. Substrate delivery to muscles may be altered by a variety of factors in CRF. These include structural abnormalities such as decreased capillarity and increased vascular resistance, reduced oxygen-carrying capacity (anemia) (61, 75, 80, 97, 105), as well as impaired uptake and utilization of fatty acids and glucose (e.g., Ref. 20). There is some evidence that CKD may also affect muscle perfusion characteristics. Recent work indicates that impaired capillary-to-mitochondrial oxygen transfer contributes to decreased exercise tolerance in ESRD patients (99). A number of studies have confirmed that various indicators of oxidative capacity are depressed in the muscles of as yet dialysis-independent CRF patients (3, 21, 85). Decreased physical activity itself may result in an adaptive shift toward lower oxidative metabolism in skeletal muscle. In support of this notion, Sakkas et al. (98) reported that 6 mo of cycle ergometer training increased maximum $\dot{V}O_2$ and the capillarization of the gastrocnemius muscle by ~20% in a group of CRF patients.

In addition, a number of cellular transport systems may be impacted by CRF and/or dialysis. For example, hemodialysis is associated with depletion of carnitine and, thereby, disruption of the carnitine/acylcarnitine balance in skeletal muscle. This, in turn, can reduce the potential for fatty acid oxidation and hence, energy production. (15, 32). Carnitine acts as a carrier molecule for fatty acid transport in the mitochondria, via the carnitine/acylcarnitine translocase system, and as such is a critical factor in lipid metabolism.

It is of note that CRF results in marked downregulations of lipoprotein lipase and the VLDL receptor (70, 71, 116-118) in skeletal muscle, myocardium, and adipose tissue. Lipoprotein lipase is essential for lipolysis of triglyceride-rich lipoproteins (VLDL and chylomicrons), which results in the release and uptake of fatty acids by myocytes. Additionally, the VLDL receptor mediates uptake of VLDL particles by the myocytes. Accordingly, lipoprotein lipase and the VLDL receptor represent the primary pathways of fatty acid delivery for energy

production in skeletal muscles. Downregulation of lipoprotein lipase and the VLDL receptor is largely responsible for hypertriglyceridemia, impaired clearance, and elevated plasma concentrations of VLDL and chylomicrons in CRF humans and animals. Another important but widely ignored consequence of lipoprotein lipase and VLDL receptor deficiencies in CRF is their negative impact on the availability of lipid fuel to the skeletal muscle. This is compounded by insulin resistance, which is both a cause (diabetic nephropathy) and a consequence of CRF and is marked by impaired insulin-mediated glucose uptake in skeletal muscle. Together, the associated defects in availability of glucose and lipid fuel can contribute to the reduction of exercise capacity in CRF patients. Moreover, this phenomenon may promote catabolism and muscle atrophy by necessitating the breakdown of proteins as an alternate source of fuel for energy production. In this context, uremia seems to induce a state of cellular malnutrition independently of the dietary nutrient intake.

Mitochondrial Function

The published data regarding muscle mitochondrial function in CRF have been inconclusive. For example, Miro et al. (81) found that skeletal muscle mitochondrial function did not appear to be significantly impaired in six young CRF patients compared with controls. However, there were trends toward decreased citrate synthase (CS) as well as depressed mitochondrial complex III and IV activity, which did not reach statistical significance in that study (81).

Using ^{31}P magnetic resonance spectroscopy, Kemp et al. (57) found a number of apparent abnormalities in energy metabolism in the muscles of CRF patients that included increased dependence on nonoxidative ATP synthesis and decreased mitochondrial capacity during recovery. However, when normalized to muscle mass, both nonoxidative and oxidative costs of work were similar between CRF patients and the control individuals. Therefore, these authors concluded that the primary derangement in CRF patients was a loss of muscle mass rather than a mitochondrial defect (57).

The activity of CS is often used as an index of cellular oxidative capacity (49). We recently reported a fairly dramatic (31%) decrease in CS activity in the skeletal muscles of CRF (5% nephrectomized) rats (2). Davis et al. (23) had previously reported that exercise training (swim training) could prevent decrements in CS activity in $3/4$ nephrectomized rats. Similarly, we found that voluntary wheel-running exercise performed by rats blunted the deconditioning effect of CRF via the maintenance of skeletal muscle oxidative capacity (2). Therefore, although the results of human studies are inconclusive, the results of animal studies indicate that oxidative capacity of the muscle is impaired in CRF animals and can be ameliorated by exercise.

Neuropathy

ESRD is frequently associated with mild to severe peripheral neuropathy. This is compounded by diabetic neuropathy in a large segment of the ESRD population. The associated neuropathy can contribute to muscle weakness and atrophy in CRF patients (14).

Gonadal Dysfunction

The hypothalamic-pituitary-gonadal axis is markedly impaired, and the plasma level of gonadal hormones, particularly testosterone, is reduced in patients and animals with CRF (48, 108). Given the potent anabolic action of testosterone on skeletal muscle, diminished production of this hormone must contribute to the reduction of muscle mass in CRF.

Other Factors

Patients with advanced renal failure frequently exhibit hyperkalemia and hypermagnesemia, which can lead to muscle weakness. The associated muscle weakness is rapidly reversible by correction of the underlying electrolyte disorders.

EXERCISE AS AN INTERVENTION

Given the primary focus of this review on the impaired exercise tolerance in CRF, it may seem paradoxical to advocate imposition of exercise as a treatment option. However, as with other chronic diseases such as COPD and CHF, there is a growing body of evidence to suggest that programmed exercise can provide significant benefits. An overview of the available data on this topic is provided below.

Effect on Exercise Tolerance

A number of studies have found that exercise training can significantly improve several indicators of exercise tolerance as well as other symptoms of uremia in CKD and ESRD patients (e.g., Refs. 59, 61, 63, 98, 76). For instance, patients participating in programmed exercise have been shown to experience as much as a 50–70% increase in peak $\dot{V}O_2$ (63).

Effect on Markers of Inflammation

As noted above, CKD is associated with increased levels of circulating proinflammatory cytokines and other markers of inflammation. Casteneda et al. (16) have reported that patients with CKD had elevated measures of systemic inflammation (e.g., elevated IL-6), which were significantly reduced after 12 wk of resistance exercise training.

Effect on Renal Function

Strenuous exercise can cause acute alterations in the renal hemodynamics (89). For instance, exercise has been reported to result in a transient fall in glomerular filtration rate and fluid retention in humans with CKD (111). However, these exercise-induced alterations do not appear to exacerbate preexisting renal dysfunction. In fact, several authors have indicated that carefully controlled exercise is not contraindicated in CKD patients (e.g., Refs. 88, 89).

Osato et al. (84) reported that swimming exercise in conjunction with mild restriction of food intake attenuated hypertension and hyperlipidemia and improved the glomerulosclerosis index and glomerular filtration rate in rats with adriamycin-induced glomerulosclerosis. Similarly, Heifest et al. (46) showed that chronic exercise training (swimming) for 2 mo slowed the decline in glomerular filtration rate and improved proteinuria, hyperlipidemia, and glomerulosclerosis without changing renal blood flow or arterial pressure in rats with CRF induced by subtotal (70%) nephrectomy. In contrast, using the 5% nephrectomy model, Bergamaschi et al. (7) found that a

relatively strenuous endurance exercise program for 60 days improved renal hemodynamics but did not improve renal function.

Few studies focused on exercise training in renal failure patients have reported changes in renal function. In one study of a small group of patients with moderate to advanced chronic renal failure (average glomerular filtration rate of 25 ml/min), an exercise program consisting of 30 min of bicycling/day for 20 mo significantly increased exercise capacity but did not significantly affect measures of renal function (31).

Effect on Anemia

Studies performed before the advent of recombinant erythropoietin have shown significant amelioration of anemia with regular exercise in ESRD patients. Similar results were found with voluntary exercise in CRF rats (2).

Effect on Muscle Protein Balance

As noted earlier, CRF results in increased degradation of muscle proteins. Davis et al. (24) found that regular exercise (swimming) could attenuate muscle protein degradation in animals with chronic renal insufficiency. In studies designed to assess the catabolic effects of hemodialysis on skeletal muscle, Ikizler et al. (51, 52) and Pupim et al. (90) found that parenteral nutrition (PN) and, in particular, PN coupled with exercise during hemodialysis can transiently increase muscle essential amino acid uptake and muscle protein accretion. In addition, they found that the combination of exercise and PN during hemodialysis resulted in a significant increase in plasma GH level and stability of plasma glucose during the postdialysis period (90). Although the short-term effect of these interventions have been promising, their long-term effect on the course of CRF-induced muscle catabolism has not been demonstrated.

Effect on Muscle Atrophy

A number of studies have reported that resistance training can significantly increase muscle strength and myofiber size in patients with CKD (17, 45). For example, Casteneda et al. (17) have reported that resistance training significantly increased muscle strength and myofiber size in patients with CKD who were on a low-protein diet. Interestingly, extended endurance-mode exercise training has also been reported to result in dramatic increases in myofiber size and muscle strength in CKD and ESRD patients (62). Sakkas et al. (98) reported that 6 mo of cycle ergometer training increased the cross-sectional area of all gastrocnemius muscle fiber types by 32–54%. This finding contrasts markedly with the majority of reports in healthy individuals in whom endurance-mode exercise does not generally lead to large increases in muscle size (e.g., Ref. 91).

Exercise Prescription in CRF Patients

Different exercise training programs have been successfully employed in ESRD populations. For instance, two studies have found that a supervised out-patient program with a relatively high volume of exercise, including sports, results in the greatest increase in the measures of exercise tolerance (59, 63). However, it was noted that scheduling exercise training during hemodialysis procedure might be desirable (despite the obvi-

ous limitations in the exercise modes) due to greater patient participation and program compliance (59, 63). In a study of 48 ESRD patients, followed over a 4-yr period, Kouidi et al. (63) reported that 70% of the patients were still regularly participating in the exercise programs at the end of the study period. These patients exhibited steady and substantial increases in indicators of aerobic capacity (e.g., 50–70% increase in peak $\dot{V}O_2$) during the 4-yr study period (63).

To date, there have been no large studies to compare and contrast various exercise training programs to formulate optimal exercise prescriptions for the CKD patients. Similarly, research on the basic mechanisms by which exercise may interact with, and modulate, muscle function in the presence of CKD has been relatively scarce. However, the existing literature includes a number of exercise programs that appear to be safe and effective in providing positive impacts on muscle function and, by extension, improvements in the quality of life for this population. Along these lines, Fuhrmann and Krause (37) have recently provided detailed suggestions for parameters that can be used in implementing an exercise training program in ESRD patients.

In summary, numerous circulatory and biochemical disorders work in concert to promote skeletal muscle dysfunction, impaired exercise tolerance, and hence a sedentary lifestyle in CRF patients. The reduction in physical activity, in turn, leads to a further decline in muscle mass, progressive disability, and various other untoward consequences. Regular exercise regimens can interrupt this vicious cycle and improve physical condition, biochemical profile, and perhaps, mental performance in ESRD patients. Thus the inclusion of exercise as a standard component of care appears to be warranted in the overall management of these patients.

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