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Chronic inflammation in RA: mediator of skeletal muscle pathology and physical impairment

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Abstract

This review focuses on the effects of chronic systemic inflammation on skeletal muscle and its downstream effect on physical function in individuals with rheumatoid arthritis (RA). The importance of skeletal muscle in the regulation of whole-body glucose and lipid metabolism, and the benefits and barriers to physical activity and exercise training are highlighted. Finally, we identify knowledge gaps that may be important for the development of both pharmacologic and non-pharmacologic interventions (e.g. proper exercise regimens) to protect individuals with RA from physical impairment.

Introduction

The prevalence of physical function impairment and lower levels of physical activity among patients with RA is high compared to matched non-RA controls (1–3), despite tight control of disease activity. More striking is the observation that RA patients in clinical remission lead a more sedentary lifestyle with decreased physical function and worse body composition abnormalities compared to sedentary age- and sex- matched healthy individuals (1, 4). The reason for these differences is not clear, but may be due to inflammation-induced pathology to skeletal muscle and associated impairment of physical function.

It is generally accepted that decreased physical function occurs in early stages of RA and progresses over time in the majority of patients (5). Varying degrees of pain, limited joint mobility, impaired muscle strength, decreased aerobic capacity, fatigue and low levels of physical activity have been identified as contributing factors to lower physical function in patients with RA (6, 7). It is well established that joint inflammation and damage strongly contribute to functional limitations in RA (8), but the deleterious effects of chronic systemic inflammation on skeletal muscle are being increasingly recognized (9).

Physicians and other health care providers recommend exercise for patients with RA, without much evidence-based knowledge on the optimal duration, frequency and intensity of exercise to maximize health benefits in individuals with RA. As the focus on precision medicine grows (<https://allofus.nih.gov/>), and the cellular and molecular mechanisms of physical activity-induced health benefits are elucidated, precision exercise prescription will likely have an increasingly prominent role in the treatment and prevention of chronic conditions like RA and other forms of arthritis (10).

In this review, we focus on the deleterious effects of chronic inflammation on skeletal muscle homeostasis and function. We discuss the importance of skeletal muscle in the regulation of whole-body glucose and lipid metabolism, and the evidence for the beneficial effects of physical activity and exercise training in RA. In the last section, we identify knowledge gaps that may be important for the development of both pharmacologic and non-pharmacologic interventions (e.g. proper exercise regimens) to mitigate progressive physical impairment in individuals with RA.

Effects of chronic inflammation and insulin resistance on skeletal muscle mass and function

Pro-inflammatory cytokines [i.e. tumor necrosis factor(TNF), interleukin-1 β (IL-1 β) and interleukin-6(IL-6)] are thought to be the key mediators of inflammation responsible for stimulating proteasome-dependent proteolysis and inhibiting anabolic and/ or anticatabolic signals, that lead to low skeletal muscle mass in chronic inflammatory conditions, such as RA (11, 12). TNF can also affect skeletal muscle function by depressing muscle fiber contractility through increasing general oxidant activity and nitric oxide activity (13). Interestingly, in a study involving individuals with RA, muscle cytokine levels did not reflect systemic cytokine levels, but were two times higher in RA patients' muscle (14). This finding suggests that muscle cytokines were produced locally, by myofibers, resident inflammatory cells and/ or adipocytes.

Inflammation plays a critical role in ectopic fat accumulation, underscoring the intimate interplay between the immune system and adipose tissue. Proinflammatory cytokines, such as TNF, can decrease the storage capacity of adipocytes in primary fat depots (e.g. gluteofemoral adipose tissue) by inhibiting preadipocyte differentiation and increasing lipolysis (15), which then leads to increased ectopic adipocytes in "nonadipose" tissues, including skeletal muscle. Fat infiltration within the muscle is associated with more disability, lower quadriceps strength and physical activity level, poorer objectively measured physical functional performance, as well as insulin resistance in individuals with RA (16,

17). Adipocytes are metabolically active and are capable of synthesizing a number of biologically active compounds such as pro-inflammatory adipocytokines (18). The stromovascular fraction of adipose tissue includes macrophages (18), which are the primary source of TNF in adipose tissue (19). A recent study suggests a higher abundance of macrophages in adipose tissue of RA versus non-RA controls matched on demographics and BMI is a potent source of inflammatory cytokines in RA (20).

Inflammation is also linked with dysregulation of mitochondrial function and biogenesis, and consequently, disruption of muscle oxidative metabolic capacity in the general population (21). Muscle oxidative metabolic capacity is essential for the generation of ATP to fuel skeletal muscle contraction, locomotion, and maintain homeostatic cellular electrolyte balance (i.e. sodium-potassium pumps). In a metabolic profiling study, the concentration of pyruvate in RA muscle was significantly higher than in muscle from controls, and the expression of genes controlling glycolytic metabolism was also significantly upregulated in RA versus controls (14). Pyruvate is the end-product of glycolysis, and normally feeds into the tricarboxylic acid cycle, generating energy intermediates that are critical for mitochondrial ATP synthesis through oxidative phosphorylation. Therefore, pyruvate accumulation in RA muscle could be a sign of poor mitochondrial function. However, further studies are needed to fully elucidate the role of substrate metabolism and mitochondrial function in skeletal muscle of individuals with RA and their effects on disease outcomes.

Insulin resistance in RA

Insulin resistance has been associated with low skeletal muscle mass in RA (22), but the precise mechanism or the extent to which it contributes to the metabolic and physiologic derangements is unknown. Insulin, along with IGF-1, is an important regulator of skeletal muscle mass via stimulation of cell growth and proliferation via AKT signaling (23). Under physiological conditions, insulin also regulates substrate utilization in multiple tissues, including skeletal muscle, liver and adipose tissue (24). Insulin resistance is associated with diminished mitochondrial content and function, resulting in lower skeletal muscle oxidative capacity and higher levels of intramyocellular lipid content (25). In older adults and individuals with type 2 diabetes (T2D), insulin resistance is an independent correlate of poor muscle strength (26–28). Therefore, the high prevalence of insulin resistance among patients with RA may play a very important role in skeletal muscle dysfunction in these patients.

Insulin resistance is much more prevalent in RA patients compared to the general population (51% in recent-onset RA; 58% in long-standing RA; 19% in non-RA controls) (29). Risk factors for insulin resistance in RA include rheumatoid factor seropositivity, prednisone use, higher RA disease activity, and visceral and thigh intermuscular adiposity (2, 30, 31). A recent study concluded that adiposity, but not systemic inflammation, was associated with insulin resistance in patients with RA (17). There is substantial evidence linking both inflammation and excess adiposity with insulin resistance in the general population and in individuals with RA (32–34), and adipose tissue itself can be an important source of inflammatory mediators that can induce insulin resistance. Low muscle mass may be another

important contributing factor of insulin resistance in RA (34), although it has not received much attention. Skeletal muscle plays a critical role not only in movement and locomotion, but also in the regulation of whole-body carbohydrate and lipid metabolism (35). In humans, skeletal muscle is the principal site of glucose uptake in the postprandial state (36); and low appendicular lean mass has been shown to be significantly associated with insulin resistance in early RA (37). This underscores the importance of maintaining lean mass, and the need to better understand the complex interplay among chronic inflammation, ectopic fat accumulation, and skeletal muscle dysfunction. Figure 1 summarizes the potential mechanisms of skeletal muscle dysfunction in RA covered in this review.

Beneficial effects of physical activity and exercise training

Free living physical activity and prescriptive exercise are associated with a myriad of health benefits in individuals with RA, including improvement of disease activity, fatigue, pain, quality of life, physical performance, aerobic capacity, cardiovascular risk, and bone and joint health (38–40). A recent systematic review that guided the 2016 update of the European League Against Rheumatism (EULAR) recommendations for the management of early arthritis supports the beneficial effect of exercise programs on pain and physical function (41). Additionally, a recent Cochrane review found that there was moderate evidence that both short-term (< three months) and long-term (> three months) land-based dynamic exercise programs (endurance training and/ or strength training) have positive effects on aerobic capacity and muscle strength in individuals with RA, with no adverse effects on disease activity (42). Endurance and resistance training improve body composition (i.e. increase lean mass and decrease adiposity) as well as physical function in individuals with RA (43–45). The observed positive effects of endurance training could be due to increased mitochondrial biogenesis and respiratory function, blood flow, and insulin sensitivity (46–48), but published studies on the cellular and molecular effects of resistance training in individuals with RA are almost non-existent. We only identified one case report (44).

It is well established that exercise training enhances insulin sensitivity in the general population (35). According to a recent review on the effects of physical activity on insulin sensitivity, many studies support a dose-response relationship between physical activity and whole-body insulin sensitivity, whereby higher energy expenditures and higher exercise intensities yield greater benefits (49). Additionally, exercise regimens including both aerobic and resistance training have been shown to be more efficacious in improving insulin sensitivity than either exercise mode alone (49). Although there are no published studies on the effect of exercise training on insulin sensitivity in individuals with RA, we speculate individuals with RA would derive similar benefits.

Physical activity and exercise training barriers and recommendations

In spite of the well-documented evidence that physical activity and exercise are beneficial, most patients with RA are sedentary. A study involving 5,235 individuals with RA across 21 different countries found that the overwhelming majority (71%) did not participate in any regular physical activity; and only 14% exercised 3 or more times weekly (50). Lack of time

and motivation have been the two most frequently reported perceived barriers to physical activity and exercise by patients with RA (51). Conversely, support and encouragement from instructors and healthcare professionals has been identified as the most prominent RA-specific perceived facilitating factor for regular physical activity and exercise (51). A recent study also suggests self-managed physical activity programs using a pedometer may also promote increased physical activity level among individuals with RA (52). In this study, participants were only followed for 21 weeks, but other studies support the long-term effectiveness of pedometer-based interventions (53, 54). Unfortunately, rheumatologists feel they do not have sufficient time to counsel patients on non-pharmacological treatment; and they have low confidence in their competence to prescribe exercise and to motivate patients (51, 55). This underscores the importance of placing greater emphasis on treatment approaches utilizing non-pharmacological and psychosocial strategies to complement the effects of medications in order to address many unmet needs of RA patients across key domains such as physical function, fatigue, pain and mental function (56).

Additionally, more studies are needed to determine the optimal duration, frequency and intensity of exercise required to safely produce substantial health benefits for individuals with RA, and to improve their adherence to exercise. For the time, being general physical activity recommendations for adults can be obtained from the 2018 Physical Activity Guidelines for Americans (57).

There have been studies to assess whether behavioral interventions that foster autonomous motivation and self-efficacy can decrease sitting time, improve physical function and pain, and effectively promote long-term participation in physical activity among RA patients (58, 59). Developing a multi-disciplinary treatment team including physical therapists, occupational therapists, and exercise physiologists with expertise in rehabilitation and exercise prescription may also be critical for promoting increased physical activity and exercise among individuals with RA. Recent pilot research has explored expanding the role of physical therapists in administering a health-enhancing physical activity program in individuals with RA (60).

Conclusion

There is mounting evidence that treatment with disease modifying antirheumatic drugs (DMARDs) and biologic agents is insufficient to restore physical function, body composition and metabolic homeostasis in individuals with RA. To advance our understanding of RA pathophysiology and improve RA patient care, key knowledge gaps ripe for future research include: 1) better understanding the interrelationships of inflammation, ectopic adipose, and muscle dysfunction; and 2) optimizing exercise prescription for RA via dose response trials. Expanding our understanding of the complex etiology of the reduced physical function and identifying therapeutic targets offers a tremendous opportunity to improve morbidity and mortality in RA. Team science, with more collaboration among researchers and clinicians across different fields, may be key to achieving these goals.

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Significance and Innovations

- Systemic inflammation has pervasive effects on skeletal muscle homeostasis and function, which may be pivotal for the pathogenesis of physical impairment in RA.
- It is well established that resistance training has beneficial effects on physical function in individuals with RA, but the underlying mechanisms still need elucidation. More studies are needed to determine the optimal duration, frequency and intensity of exercise required to produce specific health benefits for individuals with RA, and above all, to improve their adherence to exercise.
- Development of a multi-disciplinary treatment team including physical therapists, occupational therapists, and exercise physiologists with expertise in rehabilitation and exercise prescription may be critical for promoting increased physical activity and exercise among individuals with RA.

Conceptual model of biological mechanisms involved in skeletal muscle dysfunction in RA

Figure 1.

Conceptual model of biological mechanisms involved in skeletal muscle dysfunction in RA.