Molecular effects of exercise in patients with inflammatory rheumatic disease

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SUMMARY

Exercise is now known to be beneficial for patients with inflammatory rheumatic disease. In patients with rheumatoid arthritis, exercise can improve physical performance, cardiorespiratory fitness and muscle strength, and reduce disease activity and systemic inflammation, as evidenced by reductions in erythrocyte sedimentation rate and other systemic markers of inflammation. Similar effects on physical performance and cardiorespiratory fitness have been observed in patients with polymyositis and dermatomyositis. Improved muscle performance in these patients is associated with an increased ratio of type I : type II muscle fibers and increased cross-sectional area of type II muscle fibers, suggesting that myositis-affected muscle retains the ability to respond to exercise. In addition, resistance exercise training can reduce the expression of genes involved in inflammation and fibrosis in patients with myositis, and *in vitro* mechanical loading of chondrocytes can suppress the expression of proinflammatory cytokines, indicating that exercise can also reduce inflammation in the local tissue environment. Further studies of the systemic and local responses underlying exercise-associated improvement in muscle performance, soft tissue integrity and health outcomes are warranted.

KEYWORDS exercise, muscle atrophy, myositis, physical activity, rheumatoid arthritis

REVIEW CRITERIA

PubMed was searched for full papers and abstracts during March–April 2008 using the following keywords, alone or in combination: "CRP", "dermatomyositis", "disease activity", "exercise", "IL-6", "muscle atrophy", "myositis", "NFκB", "polymyositis", "rheumatoid arthritis", "TNF-α", and "training". Papers on the effects of biochemical stress on cartilage were identified based on our own, as well as our colleagues, knowledge of this area.

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INTRODUCTION

Our understanding of the role of exercise in rheumatic diseases has undergone important changes during the past three decades. For many years, patients with chronic inflammatory disease of joints or muscles were advised to rest rather than to stay active. In 1976, however, the beneficial effects of physical exercise in patients with rheumatoid arthritis (RA) were reported for the first time.[1] Exercise was demonstrated to improve physical performance, cardiorespiratory fitness and muscle strength without worsening joint inflammation in patients with RA.[1] Since then, several studies have demonstrated that different types of physical exercise have a clinically meaningful effect on both the muscle and cartilage of patients with rheumatic diseases.[2,3] As a result, physical training is now a standard part of treatment in patients with RA. Several controlled trials that analyzed the effects of exercise in patients with RA were summarized in a comprehensive review in 2003.[2] Exercise was shown not only to improve physical performance and fitness in these patients, but also to reduce disease activity: disease activity, measured as the number of swollen or tender joints or by disease activity indices, was reduced in 6 of 14 randomized, controlled exercise studies, but remained unchanged in the others.

Until the 1990s, exercise was considered to be contraindicated in patients with polymyositis or dermatomyositis (two subgroups of idiopathic inflammatory myopathies that are collectively named myositis) because of the fear of exacerbating muscle inflammation. When the effects of exercise were evaluated systematically, however, it became evident that exercise is not only safe, but can also improve muscle strength and performance in daily activities when used in combination with conventional immunosuppressive treatment.[4–12]

In addition to the improved clinical performance observed in patients with rheumatic disease, the molecular effects of exercise, detected as a local effect in muscle tissue or as a systemic effect, are increasingly being studied. In this Review, we

present available data on the systemic molecular effects of exercise, as well as the molecular effects of exercise on skeletal muscle, in patients with RA or myositis and in healthy individuals. In addition, we discuss the effects of biomechanical strain on cartilage in experimental models and its potential effects *in vivo*.

SYSTEMIC MOLECULAR EFFECTS OF EXERCISE

In several studies of exercise in patients with RA, signs of reduced clinical disease activity have been associated with systemic effects, such as decreased erythrocyte sedimentation rate.[13,14] Reduced disease activity scores and lower erythrocyte sedimentation rates have been observed following different types of exercise, after short-term and long-term (>2 years) exercise programs, at different phases of the disease course, and even in patients with high disease activity.[15] Detailed information on systemic molecular effects of exercise in RA is scarce. In one study, increased protein catabolism observed in patients with RA, compared with healthy subjects, was no longer evident after a 12-week strength-training program, indicating that this form of training can prevent muscle loss by reducing protein degradation.[16]

At the systemic level, there are several reports indicating a reduction in circulating levels of inflammatory biomarkers following long-term physical exercise in healthy or overweight individuals. These biomarkers include interleukin (IL)-6, C-reactive protein (CRP), and adhesion molecules (e.g. P-selectin and s-ICAM1).[17–19] Reductions in plasma levels of CRP and IL-6 were reported to be dose dependent, according to the level of regular, leisure-time physical activity.[17] In healthy men, there was an inverse relationship between oxidative capacity (VO_2max) and serum levels of IL-6, CRP and fibrinogen, supporting previously reported evidence of the beneficial effect of training on systemic inflammation.[20] An exercise-dependent reduction in plasma levels of IL-6 was also observed in men with type 2 diabetes mellitus.[19] In patients with chronic heart failure, physical training induced decreased serum levels of tumor necrosis factor (TNF). Little information is available on the long-term systemic effects of exercise in patients with polymyositis or dermatomyositis. Available information, however, demonstrates that clinical disease activity, measured by clinical scores and by serum levels of the muscle enzyme creatine kinase, is reduced in response to exercise in these patients.[12]

Overall, the findings show that long-term exercise has beneficial effects on systemic inflammatory biomarkers both in healthy individuals and in patients with chronic inflammatory diseases. This is of particular importance in the context of the increased cardiovascular-disease-associated mortality in patients with chronic inflammatory disorders.[21] In healthy individuals, regular exercise lowers risk factors for cardiovascular disease and reduces cardiovascular-disease-related mortality. Whether this is also the case in patients with RA, myositis or other chronic rheumatic diseases is not known. The increased mortality due to cardiovascular disease in patients with chronic inflammatory diseases is correlated with the inflammatory burden of disease, at least in patients with RA.[22] This correlation raises the possibility that exercise training might reduce systemic inflammation and, therefore, the risk of cardiovascular disease in patients with chronic inflammatory rheumatic diseases.

MOLECULAR EFFECTS OF EXERCISE ON SKELETAL MUSCLE

Impaired muscle performance in patients with inflammatory rheumatic disease

Skeletal muscle involvement is common in patients with chronic inflammatory rheumatic disease, and loss of muscle mass can affect daily activities and decrease quality of life.[23] In patients with RA, a 25–50% reduction of muscle strength and a loss of muscle mass have been reported in up to two-thirds of patients.[2] Myositis may co-occur with RA;[24] however, muscle histopathology is often normal in these patients, with no evidence of infiltrating inflammatory cells (Figure 1). A selective type II (fast twitch) fiber atrophy has been described in patients with RA.[25] Whether this type II fiber atrophy affects all muscles to a similar extent is not known. Furthermore, there is no evidence that these small, scattered type II fibers could explain the low muscle performance and loss of muscle mass in patients with RA. Currently, the mechanisms responsible for muscle impairment in patients with RA are unclear; the functional deficits cannot be explained by histopathological changes alone. Several mechanisms are likely to be involved, and could predominate in different phases of disease. One suggested explanation

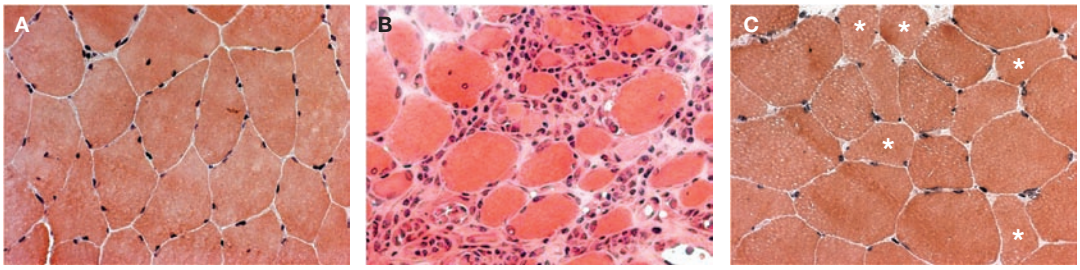

Figure 1 Photomicrographs depicting cellular and pathological changes in skeletal muscle of (**A**) a healthy individual, (**B**) a patient with myositis, showing characteristic immune cell infiltrates, endomysial fibrosis and fiber size variation, and (**C**) a patient with rheumatoid arthritis showing small angled atrophic fibers (asterisks). Cross-sectioned skeletal muscle was stained with hematoxylin and eosin. Images courtesy of Dr I Nennesmo, Karolinska University Hospital at Solna, Karolinska Institutet, Stockholm, Sweden.

is a direct effect of proinflammatory cytokines on muscle fiber contractility, as supported by *in vitro* studies in which TNF induced contractile dysfunction in muscle fibers, resulting in the muscles being more-easily fatigued.[26] Systemic glucocorticoid treatment, which is often used in these disorders, can also have negative effects on muscle strength and volume. The chronic inflammation might also lead to general muscle atrophy, as discussed below.

By contrast, the histopathological features in muscle from patients with myositis can be pronounced, and range from extensive changes, with large infiltrates of inflammatory cells and many degenerating and necrotic fibers as well as regenerating fibers, to mild changes, such as presence of central nuclei, minor fiber size variation and scattered mononuclear inflammatory cells, or no clear pathological changes at all despite clinical muscle weakness. In typical myositis, fiber size can vary, with both hypertrophic and atrophic fibers being present (Figure 1). Type II fiber atrophy has been reported in patients with myositis; however, this could not be confirmed when adequate sex and age-matched controls were used (Loell I *et al.*, unpublished data). More studies into the association of this phenomenon with myositis are warranted. Patients with chronic myositis sometimes develop general muscle atrophy, with loss of muscle fibers and replacement of muscle tissue by fibrosis, which can be marked.

The lack of T-cell infiltration on histopathological analysis correlates to the degree of muscle weakness in some patients with polymyositis or dermatomyositis, indicating that mechanisms other than direct T-cell-mediated cytotoxic effects on muscle fibers could contribute to impaired muscle performance in these patients. A more-general feature in muscle biopsy samples from these patients is upregulation of major histocompatibility complex (MHC) class I antigen on muscle fibers, which is not seen in muscles from healthy individuals or from patients with RA. Studies of MHC class I transgenic mice and patients with dermatomyositis suggest that aberrant MHC class I expression might lead to endoplasmic reticulum stress, which could negatively affect muscle performance.[27] Thus, both systemic and local effects in the muscle are likely to be involved in muscle impairment in patients with RA and myositis.

Muscle atrophy in patients with inflammatory rheumatic disease

Over time, chronic inflammation can result in a pronounced loss in lean body mass (mainly skeletal muscle), and occasionally leads to rheumatoid cachexia. Such loss in muscle mass can be a consequence of increased levels of circulating and local cytokines, but also of physical inactivity.[28] The combined actions of circulating and locally produced cytokines with low physical activity levels can result in a vicious cycle that leads to muscle atrophy and further muscle weakening, culminating in long-term disability and reduced quality of life (Figure 2).

Inflammation was first recognized as a possible cause of muscle atrophy when muscle loss was reported to occur in conditions associated with elevated circulatory levels of proinflammatory cytokines, such as TNF (formerly known as cachectin), IL-1 and IL-6.[29,30] Although a direct mechanism for the action of cytokines in muscle atrophy remains elusive, it is clear that they can trigger the loss of lean

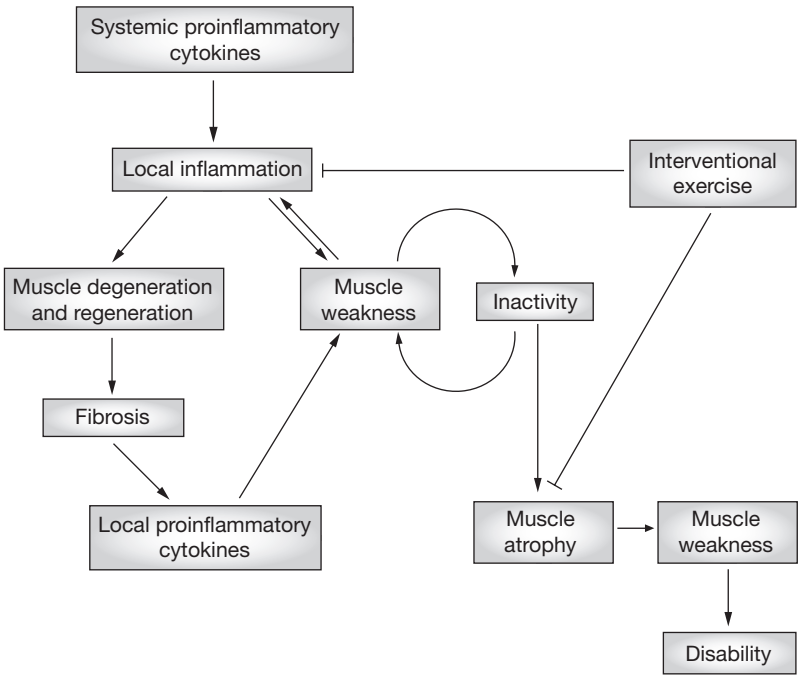

Figure 2 From inflammation to disability: a vicious cycle. Increased systemic circulating levels of proinflammatory cytokines, such as tumor necrosis factor, transforming growth factor β and interleukin-6, can cause local tissue inflammation and promote the activity of immune cells, leading to tissue degeneration/regeneration cycles that can then result in tissue fibrosis and contribute to the increase in local cytokine production. Proinflammatory cytokines can affect muscle function by increasing local tissue inflammation and muscle weakness, leading to a decrease in activity and establishment of a cycle in which increases in inactivity due to pain and weakness will result in further loss in muscle tissue and, therefore, marked muscle atrophy and disability. Exercise has the potential to revert some of the key processes involved in inflammation-induced muscle loss and disability.

body mass by affecting multiple organs. There are four different systems involved in skeletal muscle atrophy:[31] the lysosomal system,[32] the calpain system,[33] the caspase or apoptotic protease system,[34] and the ubiquitin proteasome system.[35] Some of these mechanisms of skeletal muscle atrophy can be triggered by proinflammatory cytokines (Figure 2).[31,36]

TNF is the best characterized proinflammatory cytokine involved in muscle atrophy. A possible mechanism by which TNF might induce atrophy is through TNF-receptor-mediated nuclear factor κB (NFκB) activation and subsequently increased expression of proteolytic genes.[37] This mechanism could prove to be important in the pathogenesis of inflammatory-disease-associated muscle atrophy. In a randomized controlled trial of patients with RA, TNF blockade was shown to normalize the anabolic response to overfeeding; those patients who gained weight and were treated with etanercept increased their fat-free mass to a higher degree than those who were treated with methotrexate.[38] Much remains to be understood about the mode of action of TNF however; its blockade in Freund's adjuvant-induced arthritis did not prevent the induction of atrophy genes,[39] indicating that a more complex mechanism of action might exist in TNF-induced skeletal muscle atrophy. Anti-TNF treatment in patients with polymyositis or dermatomyositis has had varying results. These conflicting effects might depend on the phase of disease when treatment was given and the different types of TNF blockers used.[40,41] Treatment with infliximab had no effect on muscle strength or inflammatory infiltrates in muscle biopsy specimens from patients with severe, treatment-resistant myositis.[41] On the contrary, some patients experienced worsening of muscle inflammation and showed signs of activation of the type I interferon system.[41] These observations argue against a role for TNF as a cause of muscle weakness in longstanding, treatment-refractory myositis.

While the relative contribution of the different mechanisms to the process of muscle atrophy in various diseases is currently being investigated, the involvement of these mechanisms in autoimmune-disease-related atrophy is unknown; therefore, little is known regarding the prevention or treatment of muscle atrophy in patients with these conditions. In healthy individuals, exercise can lead to muscle hypertrophy,[42] which raises the possibility that exercise could be used as a treatment for patients with chronic inflammation.

Effects of exercise on skeletal muscle in patients with inflammatory rheumatic disease

Muscle biopsy for evaluation of molecular mechanisms of disease and interventions

Muscle biopsy is an essential diagnostic procedure in patients with suspected polymyositis and dermatomyositis to confirm inflammation and to exclude other myopathies. Muscle biopsy has also been fundamental to our understanding of the mechanisms of muscle adaptation to training in healthy individuals. A prerequisite for this scientific achievement was the development of the relatively atraumatic, semi-open conchotome and needle biopsy techniques. Both procedures permit clinicians to take repeated muscle biopsy

samples to evaluate the effects of interventions (e.g. exercise) on molecular and physiological variables *in vivo*.[25,43–45]

Histological and molecular changes in response to exercise

Studies on the effects of exercise on histological and molecular changes in muscle tissue from patients with rheumatic disease have mainly focused on patients with myositis and RA. Muscle tissue from patients with polymyositis or dermatomyositis, who are in late, chronic phases of disease and have persisting muscle weakness, can show no evidence of inflammatory infiltrates, indicating that factors other than inflammatory-cell-mediated muscle damage contribute to muscle impairment in patients with myositis.[46] One possible mechanism is the aforementioned endoplasmic reticulum stress, but it is not clear how this could mediate muscle impairment in patients with myositis. Another possibility is that the low frequency of type I (oxidative, slow twitch) muscle fibers in these patients, compared with healthy, age-matched and sex-matched individuals, could account for the previously observed metabolic impairment.[47,48] Interestingly, after a 12-week, moderate-intensity home-exercise program, an increased frequency of type I fibers was recorded, and this correlated with clinically improved muscle performance.[47] The low frequency of type I fibers could, therefore, contribute to the low muscle endurance experienced by the patients. Moreover, the cross-sectional area of type II muscle fibers also increased, suggesting that myositis-affected muscle retains the ability to undergo hypertrophy in response to exercise.[47]

The immunological signaling proteins involved in polymyositis and dermatomyositis are predominantly proinflammatory cytokines, such as TNF and IL-1, chemokines, and, to some extent, anti-inflammatory cytokines, such as transforming growth factor β.[49,50] As discussed above, TNF and other proinflammatory cytokines might exert a direct, negative effect on muscle fiber contractility, but the role of these cytokines in the molecular pathways and as a cause of muscle weakness in different phases of the myositis disease process still needs to be clarified.

Resistance exercise in patients with chronic polymyositis or dermatomyositis with low disease activity leads to improved muscle strength that is associated with changes in expression of genes favoring oxidative metabolism (as seen in the muscle tissue of healthy men following exercise[51]), as well as downregulation of genes encoding proteins involved in inflammation, such as chemokine receptors and adhesion molecules (Nader GA *et al.*, unpublished data). These findings seem to support the observations of a local anti-inflammatory response to training in patients with chronic heart failure, who often develop a myopathy with low muscle endurance and muscle atrophy similar to patients with myositis. In patients with chronic heart failure, training is associated with a significant reduction in the expression of TNF, IL-6, IL-1β and inducible nitric oxide synthase in skeletal muscle.[52]

Magnetic resonance spectroscopy has been used to demonstrate that ATP and phosphocreatine levels are reduced in patients with myositis.[48] These metabolic changes were initially observed at rest, and were found to be further accentuated by exercise.[48] Muscle bioenergetic defects even persist after the resolution of inflammation. These observations formed the basis for a randomized, placebo-controlled trial of exercise with or without creatine supplementation. The creatine supplement in combination with an exercise regimen resulted in significantly improved strength and endurance performance compared with exercise alone in patients with polymyositis and dermatomyositis.[53] The clinical improvement was associated with increased ATP and phosphocreatine levels in muscle tissue, supporting a role for these metabolic molecules in this combined exercise and creatine supplementation regimen.

MOLECULAR EFFECTS OF EXERCISE ON CARTILAGE

In addition to the systemic anti-inflammatory effects of exercise, as well as those on skeletal muscle, *in vitro* studies have provided evidence for a direct mechanosensitive, anti-inflammatory effect on joint tissues. Exposure of meniscal or articular chondrocytes to proinflammatory cytokines (e.g. IL-1β and TNF) is reported to result in the expression of cyclo-oxygenase 2, inducible nitric oxide synthase, and genes involved in cartilage catabolism, such as matrix metalloproteinases 9 and 13. By contrast, when cells are subjected to mechanical stimuli in the form of cyclic tensile strain, they display a blunted response to cytokine exposure, thereby antagonizing the proinflammatory and catabolic effects of these cytokines.[54–57] Interestingly, this anti-inflammatory response seems to be mediated by inhibition of nuclear translocation of NFκB and modulation of upstream signaling events associated with

NFκB, suggesting that mechanical activity can act at multiple points within the proinflammatory signaling network to counteract cytokine-induced proinflammatory gene expression.[58]

The importance of these studies is highlighted by the fact that a single component of the exercise stimulus (i.e. the mechanical component) could be isolated and defined in a specific cell type without the confounding variables intrinsic to *in vivo* systems. Although limited, these are promising data regarding the potential beneficial effects of exercise on the degenerative consequences of inflammation in joint tissues. Clearly, the mechanical loading component of the exercise stimulus might be one of the mechanisms by which exercise exerts a protective anti-inflammatory effect at the local tissue level by preventing the expression of proinflammatory molecules. These exciting findings provide a clear and important hypothetical framework for future studies, in intact animals and humans, aimed at determining the safety and efficacy of exercise as a therapeutic tool in inflammatory rheumatic disorders.

CONCLUSIONS

Impaired muscle function and muscle atrophy are commonly observed in patients with rheumatic diseases, but the underlying mechanisms are not fully understood. From a functional perspective, the loss of muscle function in autoimmune disorders can have long-term consequences; the decrease in functional performance and in quality of life can culminate in disability and increase the need for care. Accumulating evidence suggests that physical training can improve performance without exacerbating disease progression, and that training might have beneficial effects on certain molecular processes in skeletal muscle as well as in cartilage. Importantly, exercise training can reduce both local muscle and systemic inflammation, highlighting the role of exercise as an anti-inflammatory intervention. What are the causes of muscle impairment and atrophy in autoimmune disorders? How could physical exercise and physical activity (in combination with pharmacological therapies) help the clinician to prevent disability and comorbidities in patients with these conditions? The answers to these key questions will provide valuable information on how exercise can lead to improvements in muscle function and quality of life, and decrease typical features (e.g. tissue inflammation and disability) of the disease.

KEY POINTS

- Impaired muscle performance and muscle atrophy are common features in patients with chronic rheumatic disorders
- Exercise training can improve performance without exacerbation of disease progress
- Exercise training can reduce systemic inflammation
- Exercise training might have beneficial effects on certain molecular processes in muscle tissue and cartilage that reduce inflammation and fibrosis and promote tissue repair

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