Helpful or Harmful? Potential Effects of Exercise on Select Inflammatory Conditions

DOI: 10.3810/psm.2013.11.2040

Jennifer L. Thomas, BS, AFAA[1]

[1]Health Educator, Sandia National Laboratories, Albuquerque, NM; Department of Health, Exercise, and Sports Sciences, University of New Mexico, Albuquerque, NM

Abstract: Inflammation has been characterized as a double-edged sword, requiring a balance between health as maintained by regular exercise and activities that would exacerbate inflammatory diseases. The influence of exercise on inflammation is complex and has been widely studied in both healthy patient populations as well as populations of patients with many inflammatory and/or autoimmune rheumatic diseases. Inflammatory markers can be affected by the type of exercise and muscle contraction, as well as the intensity, duration, and consistency of the exercise sessions. Because of these potentially important effects, many members of the general public, as well as some clinicians, believe that exercise could exacerbate symptoms and accelerate the progression of such conditions. The effects of different types of exercise have been studied among patients with inflammatory conditions such as ankylosing spondylitis, systemic lupus erythematosus, rheumatoid arthritis, osteoarthritis, fibromyalgia, and idiopathic inflammatory myopathies, as well as congestive heart failure, type 2 diabetes mellitus, and metabolic syndrome, which are considered low-grade systemic inflammatory diseases. This review will help exercise professionals and clinicians understand the effects of exercise on inflammatory markers, as well as offer effective treatment options and recommendations for patients exercising with rheumatic or inflammatory conditions.

Keywords: inflammation; exercise; rheumatic diseases; cytokines; physical activity

Introduction

Cytokines are polypeptide inflammatory mediators produced primarily by peripheral blood mononuclear cells, adipocytes, hepatocytes, and skeletal muscle. Cytokine levels, and ultimately inflammation, can be influenced by aging, sex, antioxidant supplements, calcium homeostasis, and anti-inflammatory drugs. Cachexia, sepsis, and exercise-induced muscle damage all activate proinflammatory signaling pathways, such as nuclear factor κB (NF-κB) transcription factor activation and tumor necrosis factor α (TNF-α) activation.[1,2] These and other cytokines are associated with the initiation of protein degradation and suppression of protein synthesis.[3] For this reason, exercise that increases inflammatory markers has earned a bad reputation, and people are misled into thinking exercise is detrimental to inflammatory status. Because many devastating chronic diseases have a significant pathophysiological inflammatory component, many members of the general public, as well as some clinicians, think that exercise should be avoided by patients experiencing these types of conditions. This article discusses the impact that exercise has on inflammation and addresses concerns for patients with select inflammatory diseases.

Correspondence: Jennifer L. Thomas, BS, AFAA,
1221 Parsons St NE,
Albuquerque, NM 87112.
Tel: 505-845-8828
E-mail: jothling@unm.edu

The Role of TNF-α

Increased concentration of TNF-α has been found to increase the activity of ubiquitin-conjugated protein degradation while also inhibiting insulin and insulin-like growth

factor (IGF)–mediated protein synthesis.[4–7] Anabolic processes are also inhibited by TNF-α, which destabilizes myogenic differentiation and alters transcriptional activity.[8,9] Suppression of the insulin/IGF signaling pathway by TNF-α induces insulin resistance[10–12] and blocks protein synthesis through a decrease in IGF-1 and IGF binding protein gene expression.[6,7] Intravenous administration of TNF-α to patients shows a significant increase in free ubiquitin and ubiquitin gene expression, which highlights the role of TNF-α in muscle proteolysis.[5] It has been shown that TNF-α impairs muscle protein synthesis and increases muscle protein degradation in patients.[3] Additionally, elevated TNF-α levels have been observed in patients with ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), osteoarthritis (OA), fibromyalgia (FM), idiopathic inflammatory myopathies (IIM), congestive heart failure (CHF), and type 2 diabetes mellitus (T2DM), as well as metabolic syndrome. For this reason, many treatments for these conditions focus on the neutralization of TNF-α. However, there have been some mixed results because of TNF-α's additional role as an immunoregulatory molecule that can alter the balance of T-regulatory cells.

The Role of NF-κB

Activation of the NF-κB transcription pathway, activated by cachectic factors such as TNF-α, is sufficient to induce skeletal muscle atrophy in patients. This is mediated in part via NF-κB–mediated upregulation of muscle RING-finger protein 1, an E3 ubiquitin ligase that promotes protein degradation during muscle atrophy.[1] The binding of TNF-α to its receptor at the cell membrane initiates a cascade of intracellular events, including the release of NF-κB through the activation of the inhibitor of kinase β (Ikβ).[13] This leads to the expression of genes involved in multiple cell processes, including ubiquitin-mediated protein degradation.[14–18] Because NF-κB is activated by TNF-α, it plays a central role in inflammation through its ability to induce transcription of proinflammatory genes. For this reason, elevated NF-κB levels have also been observed in patients with inflammatory conditions.

Exercise and Inflammation

Many exercise protocols have been used to investigate cytokine responses to muscle damage, such as downhill running, eccentric contractions of various muscles, and traditional resistance exercise. Exercise induces systemic and local cytokine responses in patient skeletal muscle. Therefore, studies have investigated the relationship between cytokine responses and markers of muscle damage and report that plasma cytokine concentrations correlate with plasma creatine kinase (CK) activity and myoglobin concentrations after exercise, which are muscle damage markers.[19–21] Other research has investigated the relationship between cytokines and muscle damage more directly by comparing cytokine responses to concentric versus eccentric actions,[19,22–25] submaximal versus maximal eccentric contraction,[26–31] and single versus repeated bouts of eccentric exercise.[23,28,32–35]

Concentric Versus Eccentric Exercise

Several studies have examined cytokine responses to eccentric exercise, which causes greater muscle damage to patients than concentric exercise. Bruunsgaard et al[19] demonstrated that the concentration of serum interleukin (IL) 6, a cytokine produced from muscle, and CK activity are higher after eccentric cycling compared with concentric cycling; increases in IL-6 levels are associated with increased muscle protein degradation[3] and CK is a marker of muscle damage. Other researchers[22,23] also have reported greater strength loss and gene expression of the IL-1 receptor, which is a cytokine receptor that binds IL-1 and monocyte chemotactic protein-1, a chemoattractant cytokine that recruits monocytes, dendritic cells, and memory T cells to sites of injury and/or infection, after eccentric actions compared with concentric actions of patient quadriceps. Conversely, other researchers[24,25] have reported no differences in the plasma cytokine responses to level running versus downhill running, despite higher plasma CK activity and myoglobin concentration in patients after downhill running, which is eccentric exercise. Variation in exercise protocols, training status of study participants, and sampling times may account for the variability in the study data. Based on these mixed results, patients with inflammatory conditions may want to avoid eccentric exercise, at least when starting a fitness program; patient symptoms may be acutely exacerbated due to the greater increases in muscle damage caused by eccentric exercise, such as downhill running or eccentric cycling.

Exercise Intensities

Other studies have compared muscle damage and cytokine responses to submaximal and maximal eccentric exercise, which cause differing degrees of muscle damage.[26,27] Patient loss of strength was found to be greater 1 day after downhill running at a gradient of 8° versus 4°, but no changes in serum of muscle cytokines after either exercise trial were detected in patients.[26] Similarly, patient muscle damage, demonstrated by loss of muscle strength, was greater after

maximal contractions compared with submaximal eccentric actions of patient elbow flexors; however, patient cytokine responses were similar between the 2 trials.[27]

Researchers observed a 40% decrease in TNF-α protein content in patient skeletal muscle after 8 weeks of cycle training. This result suggests that sustained, low-intensity aerobic exercise elicits a positive effect on low-grade inflammation and metabolic status of patients.[28] In response to strenuous exercise such as muscle-damaging eccentric resistance training and marathon running, significant increases were observed in circulating systemic TNF-α[29,30] and TNF-α mRNA levels 3 days after a 45-minute bout of downhill running.[31] These findings are indicative of an acute inflammatory response associated with exercise-induced muscle damage in patients. Therefore, due in part to changes in TNF-α, it seems that exercise is capable of generating proinflammatory and anti-inflammatory effects on patient skeletal muscle, depending on the intensity and perhaps duration and mode of exercise. Patients with inflammatory conditions should avoid strenuous intensities and eccentric exercises due to the pronounced and acute increases in TNF-α levels. Instead, patients should be encouraged to engage in consistent, low-intensity aerobic exercise with a gradual progression of intensity in order to avoid the high spikes in cytokine levels associated with eccentric exercise.

Repeated Bouts

Two studies found that monocyte chemotactic protein-1 gene expression in the vastus lateralis is higher after a repeated bout of eccentric actions,[23] whereas gene expression is lower after electrically stimulated muscle actions[32] are performed 4 weeks after an initial bout of eccentric actions. This discrepancy may reflect differences in muscle fiber recruitment between voluntary and electrically stimulated muscle actions. Inconsistent research findings may also be due to differences in exercise protocols, training status of study participants, and sampling times.

An acute bout of endurance exercise (60 minutes at ~75% peak oxygen consumption [VO_{2max}]) decreases Ikβ content and increases NF-κB phosphorylation in rodent skeletal muscle,[33,34] whereas long-term cycling (8 weeks, 4 times per week for 45 minutes at 70% VO_{2max}) increased Ikβ and reduced TNF-α protein content in patient skeletal muscle.[28] Lambert et al[3] found that mRNAs for proteins involved in inflammation were significantly reduced by 12 weeks of aerobic and resistance-training exercise but not by weight loss in obese elderly individuals with functional impairment.[3] Sousa et al[35] found that prolonged physical exercise reduced mRNA levels of NF-κB1, inhibitor of Nf-κB1, and Ikβ kinase A. Researchers also observed a concomitant reduction in cytokine concentrations. These findings suggest that there is a protective effect of repeated bouts of exercise on the inflammatory response of patients, which may be a very important process in skeletal muscle adaptation. This research points to the importance of a consistent exercise program for patients with inflammatory conditions in order to maintain protection against inflammatory responses.

Mode of Exercise

One study observed the effects of different modes of exercise on proteolytic markers.[36] Six experienced resistance training and running patients underwent muscle biopsies before, immediately after, and at 1, 2, 4, 8, 12, and 24 hours postexercise; the resistance training patients underwent biopsies from the vastus lateralis and the running patients underwent biopsies from the gastrocnemius. The resistance training group performed 3 sets of 10 repetitions of bilateral knee extensions at 70% of 1-repetition maximum, whereas the running group performed 30 minutes of treadmill running at 75% patient VO_{2max}. The resistance training group had elevated levels of IL-6, IL-8, and TNF-α mRNA at 2 to 12 hours postexercise; the running group exhibited a biphasic response, with immediate elevation of IL-6, IL-8, and TNF-α levels, followed by a second elevation at 2 to 24 hours postexercise. In general, the timing of the gene induction indicated that patients experienced early elevation of proteolytic genes, followed by prolonged elevation of cytokines and suppression of myostatin. This study suggests that there is a greater observance of proteolytic genes and cytokines in patients after running compared with resistance training.[36] Overall, this study illustrates that any form of exercise may initially increase patient inflammation; however, this is followed by positive adaptations with consistent patient participation as discussed in the previous section.

Another study found that strength training can promote anti-inflammatory effects in patients.[37] Elderly women participating in 12 weeks of strength training displayed decreases in C-reactive protein levels, which is a protein found in the blood that increases in response to inflammation; these women also exhibited an inverse relationship between muscular thickness and TNF-α levels. These results suggest that an increase in muscle mass is related to a reduction in patient inflammation. Resistance training may be a more appropriate form of exercise for patients with inflammatory conditions because it incites a smaller increase in inflammatory markers than running; resistance training is also favorably associated

with increases in muscle mass and decreases in TNF-α levels. However, patients with inflammatory conditions should not avoid aerobic exercise because it still has been effective in reducing inflammatory markers in patients after consistent training.

Is Inflammation Really That Bad?

According to a review by Gillum et al,[38] exercise leads to an increase in the release of proinflammatory cytokines in patients, such as TNF-α and IL-1β. However, cytokine inhibitors, such as IL-1 receptor antagonists as well as TNF receptors, and anti-inflammatory cytokines, such as IL-10, are also released after exercise and are known to limit the inflammatory response of exercise. Gillum et al state that with repeated training, patient cytokine production is reduced during an acute bout of exercise and a high level of training may even contribute to patient immunosuppression. The cytokine profile of any given person is dependent on the intensity and duration of exercise, as well as the person's fitness level.[38] Although acute inflammation is often beneficial to patients, chronic or subclinical inflammation is detrimental and contributes to many disease states. Exercise may contribute to a decrease of chronic inflammation, and therefore should be recommended to patients with inflammatory conditions.

Practical Applications

Because of the observed acute increases in inflammatory markers with exercise, many members of the general public, as well as some clinicians, believe that exercise could flare up disease activity and exacerbate inflammation in patients with inflammatory or autoimmune rheumatic diseases. However, researchers have found that exercise can have substantial benefits for patients with inflammatory conditions, including but not limited to AS,[39–41] SLE,[42,43] RA,[44,45] OA,[46] FM,[47] and IIM,[51–53] as well as CHF,[48] T2DM,[49] and metabolic syndrome,[50] which are considered low-grade systemic inflammatory diseases (Table 1).

AS

Ankylosing spondylitis is a form of arthritis that primarily affects the spine and causes inflammation in the vertebral joints, which leads to chronic patient pain. Severe cases of AS in patients can cause bone growth and fusion in the spine and subsequent spinal immobility. Exercise training has been shown to increase joint mobility and decrease disease severity in patients with AS. Exercise also has been associated with increased serum levels of the anti-inflammatory cytokine tumor growth-factor β 1 in patients with AS.[39] Altan et al[40] demonstrated that 12 weeks of Pilates training (60 minutes 3 times per week) improved clinical parameters such as functional capacity, fatigue, pain, swelling, morning stiffness, spinal mobility, and chest expansion in patients with AS. Similarly, it was determined that patients with AS participating in 12 weeks of a home-based exercise program (≥ 30 minutes 5 times per week) consisting of range-of-motion exercises, stretching, strengthening, posture, and respiratory exercises experienced significant improvements in disease indexes, pain, mobility, and health-related quality of life compared with patients exercising < 5 times per week.[41] Physicians should recommend ≥ 150 minutes per week of consistent physical activity that focuses on range

Table 1. Effective Exercise Treatments for Inflammatory Conditions

Condition	Type of Training Shown to Improve Inflammatory Markers and Symptoms
Ankylosing spondylitis	• 60 minutes of Pilates 3 times/wk[40] • Range-of-motion, stretching, strengthening, posture, and respiratory exercises 5 times/wk, ≥ 30 m[41]
Systemic lupus erythematosus	• Treadmill walking 3 times/wk, 25–40 m at 70% HR_{max}[42] • Wii Fit 3 times/wk, 20–30 m[43]
Rheumatoid arthritis	• Low-impact aerobics 3 times/wk, 1 h at 60%–80% HR_{max}[44] • Knee and shoulder dynamic and isometric exercises 5 times/wk at 70% of maximal voluntary contraction, combined with aerobic bicycle training 3 times/wk, 15 m at 60% HR_{max}[45]
Osteoarthritis	• One strength training bout consisting of 25 sets of 10 repetitions of leg presses every 1.5 minutes at 60% of 1-repetition maximum[46]
Fibromyalgia	• Aquatic exercise 2 times/wk, 60 m[47]
Congestive heart failure	• Aerobic training (cycling) 5 times/wk, 30 m at 60%–80% HR_{max}[48]
Type 2 diabetes mellitus	• Aerobic training (walking, running, cycling, or calisthenics) 4 times/wk, 45–60 minutes at 50%–75% of $VO_{2\,max}$[49]
Metabolic syndrome	• Aerobic interval training 3 times/wk of 4 intervals of 4 m at 90% HR_{max}, with 3 m active recovery period at approximately 70% HR_{max} between each interval (43 m, including warm-up and cool-down periods)[50]
Idiopathic inflammatory myopathies	• Resistance training 3 times/wk[51,52] • Aerobic training (bicycle and step aerobics) 2–3 times/wk, 1 h at 60% HR_{max}[53]

Abbreviations: HR_{max}, maximum heart rate; $VO_{2\,max}$, maximum oxygen consumption.

© The Physician and Sportsmedicine, Volume 41, Issue 4, November 2013, ISSN – 0091-3847

of motion and strengthening to patients with AS in order to improve patient symptoms and overall wellness.

SLE

Systemic lupus erythematosus, or *lupus*, is an autoimmune disease that leads to systemic inflammation and tissue damage in patients. Multiple studies have indicated that exercise is a safe and effective strategy to improve fatigue, depression, aerobic capacity, pain, autonomic control, and health-related quality of life in patients with SLE.[42–43] Clarke-Jenssen et al[42] determined that treadmill walking for 12 weeks (≥ 25 minutes 3 times per week at 70% of maximum patient heart rate [HR_{max}]) led to improvements in patient VO_{2max} and better patient scores on the physical functioning scales; however, patient pain scores remained unchanged, perhaps due to the short duration of the study. Yuen et al[43] found that using a video-game exercise program involving Wii Fit for 10 weeks (20–30 minutes 3 days per week) led to a significant reduction in patient fatigue; additionally, patient symptoms of anxiety and depression improved, and the overall intensity of total pain experienced by patients decreased. This research suggests that physicians should recommend engaging in physical activity ≥ 3 times per week to patients with SLE. Additionally, it should be noted that these studies observed changes in patients starting with low to moderate disease activity. More research is warranted to observe the effects of activity on patients who experience SLE with a high level of disease activity.

RA

Rheumatoid arthritis is a type of chronic arthritis affecting patient joints; RA is associated with joint pain and swelling, stiffness, and fatigue. Research has provided strong evidence supporting the benefits of moderate exercise training, which improves patient fatigue, muscle strength, aerobic capacity, pain, and disabilities in patients with RA. One study has determined that a moderate-intensity (60%–80% HR_{max}), low-impact aerobic-training class program (1 hour 3 days per week for 12 weeks) for patients with RA leads to reduced patient fatigue, pain, and depression and increases walking time; patients also experienced no significant increases in measures of disease activity, including C-reactive protein or the number of tender and swollen joints.[44] Resistance training for patients with RA has also been investigated. Van den Ende et al[45] showed that knee and shoulder dynamic and isometric exercises (5 times per week at 70% of maximal voluntary contraction) combined with aerobic bicycle training (15 minutes 3 times per week at 60% HR_{max}) during a 24-week period led to a reduction in RA symptoms in patients, such as pain and the number of tender and swollen joints; patients also experienced increased muscle strength, joint mobility, and functional ability. The current clinical practice guidelines for RA do not outline specific physical activity recommendations other than to encourage regular exercise to patients. This research suggests that improvements in muscle function have a positive effect on joint inflammation; physicians should recommend that patients with RA engage in dynamic exercises ≥ 3 times per week to observe these positive effects.

OA

Osteoarthritis is a degenerative joint disease characterized by joint pain and stiffness. It has been widely considered a condition driven by wear and tear on patient joints; however, OA has also been linked to low-grade ongoing inflammation and synovitis within patient joints. In patients with knee OA, resistance training showed anti-inflammatory effects within knee joints. Researchers found increased levels of IL-10, an anti-inflammatory cytokine, in patient synovial fluid after a single strength training bout (25 sets of 10 repetitions of leg presses every 1.5 minutes at 60% of 1-repetition maximum).[46] Current clinical practice guidelines for OA recommend patient exercise as a core treatment. This research suggests that resistance training may prove to be an effective treatment method for patients with OA; dynamic exercises should be recommended to patients in order to reduce intra-articular inflammation.

FM

Fibromyalgia is a musculoskeletal condition characterized by widespread muscle and joint pain, in addition to chronic fatigue. Fibromyalgia has been linked with increased inflammatory markers in patients. When women with FM participated in an 8-month aquatic exercise program (60-minutes aquatic exercise 2 times per week), they experienced an increase in IL-6 with a concomitant decrease in TNF-α levels after 4 months.[47] At the end of the program, the women experienced a decreased production of proinflammatory and anti-inflammatory cytokines with a similar spontaneous release of IL-1β and IL-6 compared with healthy women; however, the women with FM experienced lower production of TNF-α and higher production of IL-10 compared with healthy women. Production of IL-1β, TNF-α, IL-6, and IL-10 in women with FM also decreased at the end of the program, but patient IL-10 levels remained higher than in healthy women, which suggests that women with FM

experience a more pronounced anti-inflammatory response. The researchers also found a decrease in circulation C-reactive protein at the end of the study, further supporting the anti-inflammatory effects of the exercise.[47] This study found that aquatic exercise had a significant anti-inflammatory effect upon patients; aquatic exercise should be recommended to patients with FM due to its ability to improve the health-related quality of life in patients with FM.

Low-Grade Inflammatory Diseases

Many chronic diseases are associated with low-grade inflammation, including CHF, T2DM, and metabolic syndrome. Patients with CHF who participated in a 12-week home-based bicycle exercise training program (30 minutes 5 days per week at 60%–80% HR_{max}) showed reduced plasma levels of TNF-α.[48] Additionally, patients with T2DM who engaged in aerobic training, such as treadmill walking or running, cycling, and calisthenics involving the upper and lower limbs, for 6 months (45–60 minutes 4 times per week at 50%–75% of VO_{2max}) experienced a reduction in plasma TNF-α and C-reactive protein levels.[49] These results are clinically significant because TNF-α has been shown to produce insulin resistance in patient skeletal muscle.[10]

In one study, 12 weeks (3 sessions per week) of high-intensity aerobic interval training (AIT) significantly reduced the levels of serum IL-18, a proinflammatory cytokine, in patients with metabolic syndrome.[50] The AIT required patients to complete 4 intervals of 4 minutes each at 90% patient HR_{max}; between each interval was a 3-minute active recovery period at approximately 70% patient HR_{max}. In the same study, resistance training (80% of 1-repetition maximum) did not have the same effect in patients. More research is warranted to observe the effects of resistance training on inflammation in patients with low-grade inflammatory conditions because most past studies have observed effects of endurance exercise.[50]

Research on exercise suggests that aerobic training and AIT may promote anti-inflammatory effects in patients with low-grade inflammatory conditions. However, participants in these studies did not have any inflammatory symptoms, especially in the joints; because they did not experience inflammatory symptoms, patients in these studies were able to tolerate higher-intensity exercise. Based on this research, patients with low-grade inflammatory conditions should be encouraged to regularly participate in high-intensity aerobic training ≥ 3 times per week or moderate-intensity training sessions ≥ 4 times per week in order to decrease systemic inflammation.

IIM

Idiopathic inflammatory myopathies are a group of disorders characterized by patient weakness, joint pain, and fatigue, and inflammation of the skeletal muscles. Research has indicated that strength and aerobic training can improve aerobic capacity, muscle strength, fatigue, and health-related quality of life in patients with IIM.[51–53] Additionally, patients did not experience any flare-ups of IIM, muscle damage, or exacerbated inflammation. Nader et al[51] determined that patients with IIM who participated in a 7-week strength-training program (3 sessions per week) displayed a reduction in the expression of genes related to TNF-α. Because TNF-α also is a target of many drugs taken by people with autoimmune diseases, exercise may prove to be an effective treatment alternative because of its ability to inhibit TNF-α and increase anti-inflammatory cytokines in patients. Spector et al[52] also found strength training to be effective without exacerbating patient symptoms. A 12-week progressive-resistance strength-training program (3 times per week) led to patient gains in dynamic strength; the exercise program did not cause patients to experience muscle fatigue or injury and patients did not experience serological, histological, or immunological abnormalities. Additionally, 6 weeks of aerobic training consisting of step aerobics and stationary cycling (60 minutes 2–3 times per week at 60% HR_{max}) resulted in patient increases of VO_{2max} relative to body weight, muscle strength, and well-being. Importantly, there was no increase in patient inflammatory activity.[53] Strength and aerobic training has been shown to be safe and efficacious and should be a recommended activity for patients with IIM.

Conclusions

All of the studies in this review have solid research designs and come from reputable sources. This research demonstrates that exercise is capable of generating proinflammatory and anti-inflammatory effects on patient skeletal muscle depending on the frequency, intensity, duration, mode of exercise, and the training status of the individual. Inflammation is not necessarily detrimental to patients; in fact, some inflammation may be beneficial in skeletal muscle adaptation and the management of inflammatory symptoms and diseases, which include AS, SLE, RA, OA, FM, IIM, CHF, T2DM, metabolic syndrome, and others. Patients suffering from these and other inflammatory conditions should be encouraged to participate in regular physical activity consisting of aerobic and strength training; both types of exercise have been shown to produce anti-inflammatory effects in patients during the long term. Further research should focus on establishing the

© The Physician and Sportsmedicine, Volume 41, Issue 4, November 2013, ISSN – 0091-3847

specific parameters of exercise that are the most beneficial for each condition, as well as determining the maximum amount of exercise that patients with inflammatory conditions should pursue. Although the current clinical practice guidelines for inflammatory conditions do suggest patients engage in regular physical activity, the research discussed in this review offers insight to help physicians and health care providers offer more specific recommendations to their patients (Table 1) and should be considered a relevant therapy technique to manage patient inflammation.

Acknowledgments

The author thanks Dr Christine Mermier and all of the faculty and graduate students at the Department of Health, Exercise, and Sports Sciences, University of New Mexico, for their continued support and guidance.

Conflict of Interest Statement

Jennifer L. Thomas, BS, AFAA, discloses no conflicts of interest.

References

1. Glass DJ. Skeletal muscle hypertrophy and atrophy signaling pathways. *Int J Biochem Cell Biol*. 2005;37(10):1974–1984.
2. Jackman RW, Kandarian SC. The molecular basis of skeletal muscle atrophy. *Am J Physiol Cell Physiol*. 2004;287(4):C834–C843.
3. Lambert CP, Wright NR, Finck BN, Villareal DT. Exercise but not diet-induced weight loss decreases skeletal muscle inflammatory gene expression in frail obese elderly persons. *J Appl Physiol*. 2008;105(2):473–478.
4. Fernandez-Celemin L, Pasko N, Blomart V, Thissen JP. Inhibition of muscle insulin-like growth factor I expression by tumor necrosis factor-alpha. *Am J Physiol Endocrinol Metab*. 2002;283(6):E1279–E1290.
5. García-Martínez C, Agell N, Llovera M, López-Soriano FJ, Argilés JM. Tumor necrosis factor-alpha increases the ubiquitinization of rat skeletal muscle proteins. *FEBS Lett*. 1993;323(3):211–214.
6. Lang CH, Krawiec BJ, Huber D, McCoy JM, Frost RA. Sepsis and inflammatory insults downregulate IGFBP-5, but not IGFBP-4, in skeletal muscle via a TNF-dependent mechanism. *Am J Physiol Regul Integr Comp Physiol*. 2006;290(4):R963–R972.
7. Williamson DL, Kimball SR, Jefferson LS. Acute treatment with TNF-alpha attenuates insulin-stimulated protein synthesis in cultures of C2C12 myotubes through a MEK1-sensitive mechanism. *Am J Physiol Endocrinol Metab*. 2005;289(1):E95–E104.
8. Langen RC, Van Der Velden JL, Schols AM, Kelders MC, Wouters EF, Janssen-Heininger YM. Tumor necrosis factor-alpha inhibits myogenic differentiation through MyoD protein destabilization. *FASEB J*. 2004;18(2):227–237.
9. Vashisht Gopal YN, Arora TS, Van Dyke MW. Tumor necrosis factor-alpha depletes histone deacetylase 1 protein through IKK2. *EMBO Rep*. 2006;7(3):291–296.
10. de Alvaro C, Teruel T, Hernandez R, Lorenzo M. Tumor necrosis factor alpha produces insulin resistance in skeletal muscle by activation of inhibitor kappaB kinase in a p38 MAPK-dependent manner. *J Biol Chem*. 2004;279(17):17070–17078.
11. del Aguila LF, Claffey KP, Kirwan JP. TNF-alpha impairs insulin signaling and insulin stimulation of glucose uptake in C2C12 muscle cells. *Am J Physiol*. 1999;276(5):E849–E855.
12. Plomgaard P, Bouzakri K, Krogh-Madsen R, Mittendorfer B, Zierath JR, Pedersen BK. Tumor necrosis factor-alpha induces skeletal muscle insulin resistance in healthy human subjects via inhibition of Akt substrate 160 phosphorylation. *Diabetes*. 2005;54(10):2939–2945.
13. Chen ZJ. Ubiquitin signalling in the NF-kappaB pathway. *Nat Cell Biol*. 2005;7(8):758–765.
14. Alkalay I, Yaron A, Hatzubai A, Orian A, Ciechanover A, Ben-Neriah Y. Stimulation-dependent I kappa B alpha phosphorylation marks the NF-kappa B inhibitor for degradation via the ubiquitin-proteasome pathway. *Proc Natl Acad Sci USA*. 1995;92(23):10599–10603.
15. Chen Z, Hagler J, Palombella VJ, et al. Signal-induced site-specific phosphorylation targets I kappa B alpha to the ubiquitin-proteasome pathway. *Gene Dev*. 1995;9(13):1586–1597.
16. Scherer DC, Brockman JA, Chen Z, Maniatis T, Ballard DW. Signal-induced degradation of I kappa B alpha requires site-specific ubiquitination. *Proc Natl Acad Sci USA*. 1995;92(24):11259–11263.
17. Tergaonkar V, Correa RG, Ikawa M, Verma IM. Distinct roles of Ikappa-B proteins in regulating constitutive NF-kappaB activity. *Nat Cell Biol*. 2005;7(9):921–923.
18. Wyke S, Tisdale M. NF-kappaB mediates proteolysis-inducing factor induced protein degradation and expression of the ubiquitin-proteasome system in skeletal muscle. *Br J Cancer*. 2005;92(4):711–721.
19. Bruunsgaard H, Galbo H, Halkjaer-Kristensen J, Johansen TL, MacLean DA, Pedersen BK. Exercise-induced increase in serum interleukin-6 in humans is related to muscle damage. *J Physiol*. 1997;499(3):833–841.
20. Hirose L, Nosaka K, Newton M, et al. Changes in inflammatory mediators following eccentric exercise of the elbow flexors. *Exerc Immunol Rev*. 2004;10:75–90.
21. Nieman DC, Dumke CL, Henson DA, McAnulty SR, Gross SJ, Lind RH. Muscle damage is linked to cytokine changes following a 160-km race. *Brain Behav Immun*. 2005;19:398–403.
22. Chen YW, Hubal MJ, Hoffman EP, Thompson PD, Clarkson PM. Molecular responses of human muscle to eccentric exercise. *J Appl Physiol (1985)*. 2003;95(6):2485–2494.
23. Hubal MJ, Chen TC, Thompson PD, Clarkson PM. Inflammatory gene changes associated with the repeated-bout effect. *Am J Physiol Regul Integr Comp Physiol*. 2008;294(5):R1628–R1637.
24. Peake JM, Suzuki K, Hordern M, Wilson G, Nosaka K, Coombes JS. Plasma cytokine changes in relation to exercise intensity and muscle damage. *Eur J Appl Physiol*. 2005;95(5–6):514–521.
25. Peake JM, Suzuki K, Wilson G, et al. Exercise-induced muscle damage, plasma cytokines, and markers of neutrophil activation. *Med Sci Sports Exerc*. 2005;37(5):737–745.
26. Malm C, Sjodin TL, Sjoberg B, et al. Leukocytes, cytokines, growth factors and hormones in human skeletal muscle and blood after uphill or downhill running. *J Physiol*. 2004;556:983–1000.
27. Peake JM, Nosaka K, Muthalib M, Suzuki K. Systemic inflammatory responses to maximal versus submaximal lengthening contractions of the elbow flexors. *Exerc Immunol Rev*. 2006;12:72–85.
28. Sriwijitkamol A, Christ-Roberts C, Berria R, et al. Reduced skeletal muscle inhibitor of kB beta content is associated with insulin resistance in subjects with type 2 diabetes: reversal by exercise training. *Diabetes*. 2006;55(3):760–767.
29. Del Aguila LF, Krishnan RK, Ulbrecht JS, et al. Muscle damage impairs insulin stimulation of IRS-1, PI 3-kinase, and Akt- kinase in human skeletal muscle. *Am J Physiol Endocrinol Metab*. 2000;279(1):E206–E212.
30. Ostrowski K, Rohde T, Asp S, Schjerling P, Pedersen BK. Pro- and anti-inflammatory cytokine balance in strenuous exercise in humans. *J Physiol*. 1999;515(Pt 1):287–291.
31. Hamada K, Vannier E, Sacheck JM, Witsell AL, Roubenoff R. Senescence of human skeletal muscle impairs the local inflammatory cytokine response to acute eccentric exercise. *FASEB J*. 2005;19(2):264–266.
32. Mackey AL, Brandstetter S, Schjerling P, et al. Sequenced response of extracellular matrix deadhesion and fibrotic regulators after muscle damage is involved in protection against future injury in human skeletal muscle. *FASEB J*. 2011;25(6):1943–1959.

33. Ho RC, Hirshman MF, Li Y, et al. Regulation of IkappaB kinase and NF-kappaB in contracting adult rat skeletal muscle. *Am J Physiol Cell Physiol*. 2005;289(4):C794–C801.
34. Ji LL, Gomez-Cabrera MC, Steinhafel N, Vina J. Acute exercise activates nuclear factor (NF)-kappaB signaling pathway in rat skeletal muscle. *FASEB J*. 2004;18(13):1499–1506.
35. Sousa e Silva T, Longui CA, Rocha MN, et al. Prolonged physical training decreases mRNA levels of glucocorticoid receptor and inflammatory genes. *Horm Res Paediatr*. 2010;74(1):6–14.
36. Louis E, Raue U, Yang Y, Jemiolo B, Trappe S. Time course of proteolytic, cytokine, and myostatin gene expression after acute exercise in human skeletal muscle. *J Appl Physiol (1985)*. 2007;103(5):1744–1751.
37. Ogawa K, Sanada K, Machida S, Okutsu M, Suzuki K. Resistance exercise training-induced muscle hypertrophy was associated with reduction of inflammatory markers in elderly women. *Mediators Inflamm*. 2010;2010:171023.
38. Gillum TL, Kuennen, MR, Schneider S, Moseley P. A review of sex differences in immune function after aerobic exercise. *Exerc Immunol Rev*. 2011;17:104–121.
39. Shehata M, Schwarzmeier JD, Hilgarth M, et al. Effect of combined spa-exercise therapy on circulating TGF-beta1 levels in patients with ankylosing spondylitis. *Wien Klin Wochenschr*. 2006;118(9–10):266–272.
40. Altan L, Korkmaz N, Dizdar M, Yurtkuran M. Effect of Pilates training on people with ankylosing spondylitis. *Rheumatol Int*. 2012;32(7):2093–2099.
41. Aytekin E, Caglar NS, Ozgonenel L, Tutun S, Demiryontar DY, Demir SE. Home-based exercise therapy in patients with ankylosing spondylitis: effects on pain, mobility, disease activity, quality of life, and respiratory functions. *Clin Rheumatol*. 2012;31(1):91–97.
42. Clarke-Jenssen AC, Fredriksen PM, Lilleby V, Mengshoel AM. Effects of supervised aerobic exercise in patients with systemic lupus erythematosus: a pilot study. *Arthritis Rheum*. 2005;53(2):308–312.
43. Yuen HK, Holthaus K, Kamen DL, Sword DO, Breland HL. Using Wii Fit to reduce fatigue among African American women with systemic lupus erythematosus: a pilot study. *Lupus*. 2011;20(12):1293–1299.
44. Neuberger GB, Aaronson LS, Gajewski B, et al. Predictors of exercise and effects of exercise on symptoms, function, aerobic fitness, and disease outcomes of rheumatoid arthritis. *Arthritis Rheum*. 2007;57(6):943–952.
45. van den Ende CH, Breedveld FC, le Cessie S, Dijkmans BA, de Mug AW, Hazes JM. Effect of intensive exercise on patients with active rheumatoid arthritis: a randomised clinical trial. *Ann Rheum Dis*. 2000;59(8):615–621.
46. Helmark IC, Mikkelsen UR, Børglum J, et al. Exercise increases interleukin-10 levels both intraarticularly and peri-synovially in patients with knee osteoarthritis: a randomized controlled trial. *Arthritis Res Ther*. 2010;12(4):R126.
47. Ortega E, Bote ME, Giraldo E, García JJ. Aquatic exercise improves the monocyte pro- and anti-inflammatory cytokine production balance in fibromyalgia patients. *Scand J Med Sci Sports*. 2012;22(1):104–112.
48. Adamopoulos S, Parissis J, Karatzas D, et al. Physical training modulates proinflammatory cytokines and the soluble Fas/soluble Fas ligand system in patients with chronic heart failure. *J Am Coll Cardiol*. 2002;39(4):653–663.
49. Kadoglou NP, Iliadis F, Angelopoulou N, et al. The anti-inflammatory effects of exercise training in patients with type 2 diabetes mellitus. *Eur J Cardiovasc Prev Rehabil*. 2007;14(6):837–843.
50. Stensvold D, Slørdahl SA, Wisløff U. Effect of exercise training on inflammation status among people with metabolic syndrome. *Metab Syndr Relat Disord*. 2012;10(4):267–272.
51. Nader GA, Dastmalchi M, Alexanderson H, et al. A longitudinal, integrated, clinical, histological and mRNA profiling study of resistance exercise in myositis. *Mol Med*. 2010;16(11–12):455–464.
52. Spector SA, Lemmer JT, Koffman BM, et al. Safety and efficacy of strength training in patients with sporadic inclusion body myositis. *Muscle Nerve*. 1997;20(10):1242–1248.
53. Wiesinger GF, Quittan M, Aringer M, et al. Improvement of physical fitness and muscle strength in polymyositis/dermatomyositis patients by a training programme. *Br J Rheumatol*. 1998;37(2):196–200.