Exercise as an anti-inflammatory therapy for rheumatic diseases—myokine regulation

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Abstract | Persistent systemic inflammation, a typical feature of inflammatory rheumatic diseases, is associated with a high cardiovascular risk and predisposes to metabolic disorders and muscle wasting. These disorders can lead to disability and decreased physical activity, exacerbating inflammation and the development of a network of chronic diseases, thus establishing a 'vicious cycle' of chronic inflammation. During the past two decades, advances in research have shed light on the role of exercise as a therapy for rheumatic diseases. One of the most important of these advances is the discovery that skeletal muscle communicates with other organs by secreting proteins called myokines. Some myokines are thought to induce anti-inflammatory responses with each bout of exercise and mediate long-term exercise-induced improvements in cardiovascular risk factors, having an indirect anti-inflammatory effect. Therefore, contrary to fears that physical activity might aggravate inflammatory pathways, exercise is now believed to be a potential treatment for patients with rheumatic diseases. In this Review, we discuss how exercise disrupts the vicious cycle of chronic inflammation directly, after each bout of exercise, and indirectly, by improving comorbidities and cardiovascular risk factors. We also discuss the mechanisms by which some myokines have anti-inflammatory functions in inflammatory rheumatic diseases.

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Introduction

Persistent systemic inflammation is a central symptom of most inflammatory rheumatic diseases and is involved in the broad spectrum of clinical features and a poor prognosis;[1] therefore, blocking inflammation is a cornerstone of the major treatment strategies in rheumatology. Epidemiological evidence from patients with rheumatic diseases shows that chronic systemic inflammation might account for the substantially increased cardiovascular risk[2] and associated comorbidities of muscle wasting, anaemia, insulin resistance, dyslipidaemia and accelerated atherosclerosis,[3–8] negatively affecting the ability of patients to engage in physical activity.[9–11] These comorbidities, along with decreased physical activity, might contribute to inflammation, establishing a 'vicious cycle' of chronic inflammation in patients with inflammatory rheumatic diseases.

The prescription of exercise as a potential anti-inflammatory tool is a relatively new concept.[12] Skeletal muscle can communicate with other organs by secreting proteins called myokines; this muscle 'secretome' consists of several hundred peptides that are the conceptual basis for a new paradigm of muscle communication with tissues including adipose tissue, liver, pancreas, bone and brain.[12,13] Myokines include various muscle-secreted cytokines such as IL-6, IL-7 and leukaemia inhibitory factor (LIF), and other peptides such as brain-derived neurotropic factor (BDNF), insulin-like growth factor 1 (IGF-1), fibroblast growth factor 2 (FGF-2), follistatin-related protein 1 (FSTL-1) and irisin.[13,14]

Some myokines can induce an anti-inflammatory response with each bout of exercise. For example, during exercise, IL-6 is the first detectable cytokine released into the blood from the contracting skeletal muscle and it induces a subsequent increase in the production of IL-1 receptor antagonist (IL-1ra) and IL-10 by blood mononuclear cells, thus having an anti-inflammatory effect.[15] Moreover, IL-6 and other myokines, such as IL-15 and FSTL-1, mediate long-term exercise-induced improvements in cardiovascular risk factors (for example, fat distribution and endothelial function), thus potentially having indirect anti-inflammatory effects.[13,14]

Many studies have shown that fewer inflammatory markers are detectable after long-term behavioural changes involving both reduced energy intake and increased physical activity (reviewed elsewhere[12]). In the past, exercise was not recommended to patients with rheumatic diseases for fear of exacerbating inflammation;[16,17] the current general consensus is that exercise might actually be used as an anti-inflammatory tool for the management of patients with these diseases.

In this Review, we appraise clinical exercise training studies of patients with rheumatoid arthritis (RA) and other inflammatory rheumatic diseases, with a focus on the potential anti-inflammatory effect of exercise. We also analyse evidence that exercise has anti-inflammatory effects in RA, systemic sclerosis, idiopathic inflammatory myopathies, systemic lupus erythematosus (SLE) and

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The authors declare no competing interests.

Key points

- Persistent systemic inflammation is a typical feature of inflammatory rheumatic diseases such as rheumatoid arthritis and systemic lupus erythematosus
- Chronic inflammation predisposes to insulin resistance, dyslipidaemia, endothelial dysfunction, accelerated atherosclerosis and neurodegeneration, and thereby to a network of chronic diseases such as type 2 diabetes mellitus, cardiovascular disease and dementia
- Disease-specific symptoms and comorbidities might negatively affect mobility, physical activity and physical capacity of patients with inflammatory rheumatic diseases
- Physical inactivity can cause the accumulation of visceral fat, which, along with comorbidities, might further enhance the development of chronic diseases in a 'vicious cycle' of chronic inflammation
- During exercise, skeletal muscle produces myokines, which might mediate either a direct anti-inflammatory response with each bout of exercise or improvements in comorbidities, thereby indirectly having anti-inflammatory effects
- Exercise is no longer thought to aggravate inflammation; rather, physical activity is now advocated as an anti-inflammatory therapy for patients with rheumatic diseases

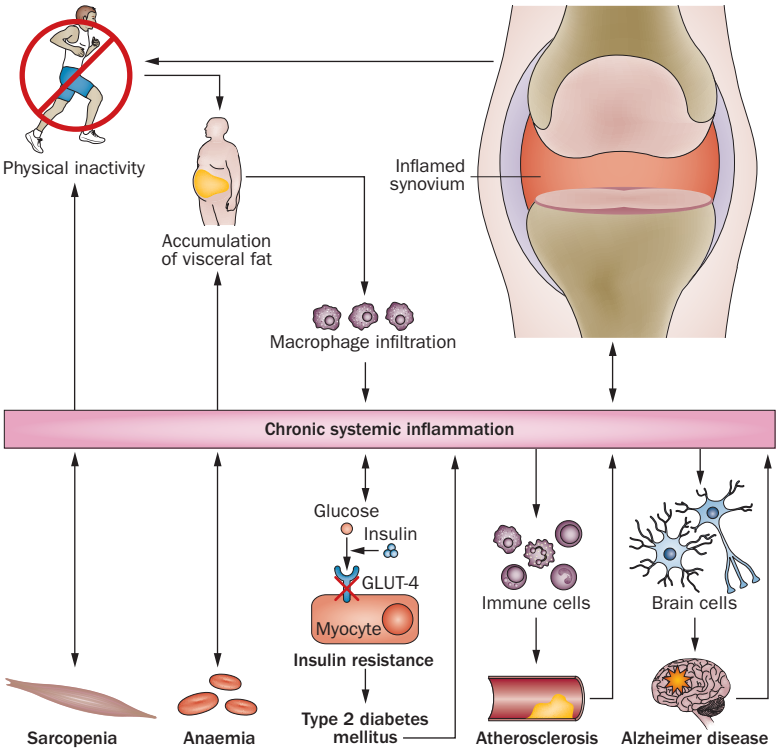

Figure 1 | The vicious cycle of chronic inflammation. In inflammatory rheumatic diseases, the state of chronic inflammation is accompanied by anaemia, fatigue and muscle wasting. Together with other comorbidities and disease-specific symptoms this inflammation will decondition the muscles and exacerbate chronic inflammation. This outcome will negatively affect cardiovascular performance and physical activity in a positive feedback loop. For example, in rheumatoid arthritis, local inflammation of the synovial membranes of the knee joint can lead to chronic systemic inflammation, which can predispose to conditions that contribute to disability or decreased physical function, including insulin resistance, dyslipidaemia, endothelial dysfunction, accelerated atherosclerosis, neurodegeneration, anaemia and muscle wasting. Lack of physical activity, in turn, can cause the accumulation of visceral fat and thereby exacerbate inflammation and promote metabolic disorders, atherosclerosis and the development of a network of chronic diseases. Abbreviation: GLUT-4, glucose transporter type 4, insulin-responsive.

ankylosing spondylitis. Finally, we identify myokines that could be regulated by exercise and that might therefore have an anti-inflammatory function in these diseases.

The 'vicious cycle'

We propose that a 'vicious cycle' of chronic inflammation is established in patients with inflammatory rheumatic diseases (Figure 1). Disease-related excessive production of cytokines might predispose these patients to atherosclerosis, loss of muscle mass and metabolic disorders such as insulin resistance and dyslipidaemia. These comorbidities can be proinflammatory and can lead to disability and decreased physical activity, which are risk factors for the accumulation of visceral fat, thereby further contributing to the network of inflammatory pathways implicated in the onset of metabolic disorders, atherosclerosis and other chronic diseases.

Inflammatory rheumatic diseases have shared pathogenic mechanisms triggered by a systemic loss of immunological tolerance and subsequent dysfunctional immunity. Localized tissue-specific autoimmunity can exacerbate inflammation and affect cytokine release into the circulation, causing persistent systemic inflammation.[2] Such systemic inflammation is causally associated with the development of many chronic diseases, including type 2 diabetes mellitus, atherosclerosis, cardiovascular events, dementia and anaemia.[3,18] Notably, these comorbidities are also common in patients with inflammatory rheumatic diseases (as reviewed elsewhere[3–5,19]).

The proinflammatory cytokines TNF and IL-1β detrimentally affect insulin sensitivity,[20] lipid metabolism[21] and endothelial function, thereby predisposing individuals to the development of atherosclerosis.[22] Moreover, a number of neurodegenerative diseases, such as Alzheimer disease[23] and Parkinson disease,[24] are linked to systemic inflammation. Finally, inflammation-induced alterations in iron homeostasis and erythropoiesis might play a major part in the pathogenesis of iron deficiency anaemia.[3]

TNF

TNF is one of the most important of the many cytokines involved in the immunopathogenesis of inflammatory rheumatic diseases. *In vitro* studies have shown that TNF has direct inhibitory effects on insulin signalling (as reviewed elsewhere[13,14]), and TNF infusion into healthy humans can induce insulin resistance in skeletal muscle.[25] TNF has been proposed to indirectly cause insulin resistance by increasing the release of free fatty acids from adipose tissue,[26] and to increase fatty acid incorporation into diacylglycerol.[27] TNF might also negatively affect the lipid profile by increasing hepatic free fatty acid and triglyceride synthesis, and by decreasing endothelium lipoprotein lipase activity, thus potentially leading to increased triglyceride and reduced HDL levels and increased synthesis of highly atherogenic LDL particles.[21] Finally, TNF induces the expression of endothelial cellular adhesion molecules and suppresses the expression of endothelial nitric oxide synthase and cyclooxygenase 1 (also known as prostaglandin G/H synthase 1), impairing endothelial-dependent dilatation.[28]

Therefore, evidence suggests that high systemic levels of TNF predispose patients to endothelial dysfunction and subsequent atherosclerosis.[22,29,30]

IL-6

IL-6 is also strongly associated with the pathogenesis and comorbidities of inflammatory rheumatic diseases (reviewed elsewhere.[31,32]). However, the metabolic functions of IL-6, particularly with regard to insulin resistance, are controversial.[33–35] During rest, IL-6 has no effect on endogenous glucose production,[36] whereas it mediates endogenous glucose production during exercise.[37] Studies have also shown that IL-6 can activate AMP-activated protein kinase (AMPK) to enhance lipolysis and fat oxidation.[33] Moreover, IL-6 knockout mice develop mature-onset obesity and insulin resistance.[38] Interestingly, ~1% of the population produce anti-IL-6 autoantibodies that impair IL-6 signalling *in vivo*, and these autoantibodies seem to be involved in the pathogenesis of a subset of type 2 diabetes.[39]

The interplay of TNF and IL-6

Individuals with the high-risk promoter polymorphisms *TNF* –308G>A (causing increased TNF transcription) and *IL6* –174C>G (causing decreased IL-6 transcription) have the highest incidence of type 2 diabetes.[40] The generally held view that IL-6 is detrimental to metabolism can now be challenged as these data support the theory that a combination of high TNF and low IL-6 production contributes to metabolic syndrome.

Although a chronically high level of IL-6, as detected in patients with RA, has a pathogenic role, and blocking IL-6 has been shown to improve the clinical symptoms of RA,[41–43] anti-IL-6 therapy also increases cholesterol and plasma glucose levels, indicating that a functional lack of IL-6 (and not TNF) might lead to insulin resistance and an atherogenic lipid profile.[41–43] In a study to gain further insight into the metabolic actions of IL-6 and TNF in humans, physiological concentrations of recombinant human IL-6 and TNF were administered to healthy humans; both TNF and IL-6 induced lipolysis, whereas IL-6 alone seemed to induce fat oxidation.[44] Furthermore, whereas TNF inhibits glucose uptake, IL-6 might stimulate peripheral glucose uptake (reviewed elsewhere[13,14]).

Given the different biological profiles of TNF and IL-6, and given that TNF might trigger the release of IL-6, one theory is that TNF derived from adipose tissue and inflamed tissues (such as the joints of patients with RA) is the major cause of inflammation-induced insulin resistance and atherosclerosis in these diseases. Of note, in patients with RA, increased levels of circulating IL-6 reflect ongoing transcription of TNF, as blocking TNF substantially decreases the systemic concentration of IL-6.[45]

Comorbidities

The development of comorbidities in patients with inflammatory rheumatic diseases is likely to contribute to a positive feedback loop that further exacerbates systemic inflammation. Cytokine-producing immune cells in atherosclerotic plaques[46] are a source of systemic inflammation and evidence exists that visceral fat is more inflammatory than subcutaneous fat.[47] Moreover, experimental hyperinsulinaemia[48] and hyperlipidaemia[49] in humans, mimicking the metabolic syndrome, have been shown to stimulate proinflammatory cytokine expression. Finally, the anti-inflammatory actions of insulin seem to be impaired in obese patients with insulin resistance, further contributing to inflammation.[50]

Chronic systemic inflammation has also been recognized as a potential cause of sarcopenia.[51] TNF and other proinflammatory cytokines, such as IL-1β, have been suggested to induce loss of muscle mass directly by shifting protein metabolism towards net catabolism and indirectly by decreasing insulin sensitivity.[52] Although more common in patients with RA (known as rheumatoid cachexia),[51] reduced muscle mass is also associated with SLE,[53] systemic sclerosis,[54] inclusion body myositis[55,56] and ankylosing spondylitis.[57] Moreover, these patients often present with lower muscle strength and aerobic capacity, and higher levels of fatigue, when compared with healthy individuals.[58–62]

Physical inactivity and adiposity

Patients with inflammatory rheumatic diseases can experience muscle wasting, fatigue and anaemia, which together with other comorbidities and disease specific symptoms can negatively affect cardiovascular performance, muscle function and mobility, and thereby also reduce levels of physical activity. Notably, patients with inflammatory rheumatic diseases are less likely to be physically active than healthy individuals.[9–11] One systematic review indicated that patients with RA have decreased energy expenditure and spend less time in vigorous activities, compared with healthy individuals.[63]

We hypothesize that the physically inactive lifestyle of patients with rheumatic diseases leads to an accumulation of visceral and ectopic fat (fat accumulated in non-adipose tissue cells), which might exacerbate systemic inflammation and consequently activate a network of inflammatory pathways that promote the development of insulin resistance, atherosclerosis and neurodegeneration, as well as a network of chronic diseases, including cardiovascular diseases (CVDs), type 2 diabetes, Alzheimer disease and other disorders belonging to the 'diseasome' of physical inactivity.[64] Whereas subcutaneous adipose tissue, particularly in lower-body fat depots, might be protective against chronic diseases, strong evidence exists that the detrimental effects of the accumulation of visceral fat, and fat in the liver and in the skeletal muscle[65] might stimulate an inflammatory response. Indeed, abdominal adiposity is associated with CVDs, type 2 diabetes, dementia, colon cancer and breast cancer,[64] as well as all-cause mortality independent of BMI.[65] Therefore, the consequences of increased abdominal adiposity and physical inactivity are similar. Moreover, both physical inactivity[33] and abdominal adiposity[47] are associated with persistent, systemic low-grade inflammation.

In fact, a direct link between physical inactivity and visceral fat has been established in rodents[66] and humans.[67,68]

Box 1 | Exercise is medicine—rheumatoid arthritis

Improved physical capacity
- Increased muscle strength and functional ability in response to resistance[76,114] and resistance plus aerobic exercise programmes[73–75,115,120–122,126]
- Increased aerobic capacity in response to aerobic[72] and resistance plus aerobic exercise programmes[73–75,115,121]
- Decreased self-reported fatigue and self-reported quality of life in response to aerobic plus resistance exercise programmes,[100] and shown by cross-sectional studies[77,100]

Improved body composition
- Increased muscle mass in response to resistance[76,114,116] and resistance plus aerobic exercise programmes[113,115]
- Decreased total and upper-body fat mass in response to resistance[76,116] and resistance plus aerobic exercise programmes[73–75,115]

Improved cardiovascular function
- Improved endothelial function, blood pressure, lipid profile, and insulin resistance in response to resistance plus aerobic exercise programmes[75,102,105]
- Improved autonomic function in response to resistance plus aerobic exercise programmes[107]

Unchanged or improved inflammatory markers
- Unchanged or improved disease activity scores and markers of systemic inflammation (erythrocyte sedimentation rate and C-reactive protein) in response to aerobic,[72] resistance[76,116] and resistance plus aerobic exercise programmes[72,73,76,100,105,118–121]
- Unchanged or slightly improved levels of selected proinflammatory and anti-inflammatory cytokines (IL-1α, IL-1β, IL-2, IL-6 and TNF) in response to aerobic[72] and resistance exercise programmes[72,122,126]

Box 2 | Exercise is medicine—SLE

Improved physical capacity
- Increased muscle strength and function in response to aerobic[78,81] and resistance exercise programmes[78]
- Increased aerobic capacity in response to aerobic exercise programmes in adult[78–81] and juvenile-onset SLE[82]
- Increased self-reported quality of life in response to aerobic exercise programmes[81]

Improved body composition
- Increased lean body mass as shown by cross-sectional studies[112]

Improved cardiovascular function
- Improved endothelial function and lipid profile in response to aerobic[80] and aerobic plus resistance exercise programmes,[106] and shown by cross-sectional studies[80,103,104,106]
- Improved autonomic function in response to aerobic plus resistance exercise programmes in in adult SLE[108] and in response to aerobic exercise programmes in juvenile-onset SLE[82,108]

Unchanged or decreased levels of inflammatory markers
- No changes in disease activity scores or markers of systemic inflammation (erythrocyte sedimentation rate and C-reactive protein) in response to aerobic plus resistance exercise in adult SLE[106,108] and to aerobic exercise programmes in adult[78–81] and juvenile-onset SLE[81]
- Unchanged or improved levels of selected proinflammatory and anti-inflammatory cytokines and soluble receptors at rest and after exercise (IL-6, IL-10, IFN-γ, TNF, sTNFR1, sTNFR2) in response to aerobic exercise programmes[78]

Abbreviations: SLE, systemic lupus erythematosus; sTNFR, soluble TNF receptor.

In a study in which 10 healthy men reduced their daily activity levels from >10,000 to <1,500 'steps' for 14 days, intra-abdominal fat mass increased without a change in total fat mass, whereas total fat-free mass and BMI decreased.[67] The accumulation of visceral fat was accompanied by impaired glucose and fat metabolism. Evidence also exists of an association between physical inactivity and low-grade systemic inflammation in healthy young individuals.[12] In this context, a link between physical inactivity, central obesity and inflammation is likely to exist also in patients with inflammatory rheumatic diseases. Indeed, patients with RA and SLE are more likely than healthy individuals with a similar BMI to have central obesity, or visceral adiposity.[53,69,70]

Therefore, we propose that chronic inflammation is accompanied by anaemia, fatigue and muscle wasting, which, together with other comorbidities and disease specific symptoms, deconditions muscles and exacerbates inflammation, thereby negatively effecting cardiovascular performance and physical activity. This is the 'vicious cycle' of chronic inflammation in inflammatory rheumatic diseases (Figure 1).

Exercise is medicine

Physical exercise is a unique physiological stressor that is capable of inducing adaptations in nearly all cells, tissues and organs.[71] Among its effects, improvements in skeletal muscle function, and therefore in cardiovascular, metabolic and immune functions, might be of the utmost importance in the treatment of inflammatory rheumatic diseases, as these functions positively affect the inflammatory milieu as well as associated cardiovascular comorbidities. Thereby, exercise is capable of disrupting the vicious cycle of chronic inflammation by direct (after each bout of exercise) and indirect (by improving physical capacity, body composition, comorbidities and cardiovascular risk factors) anti-inflammatory effects in patients with RA (Box 1), SLE (Box 2), idiopathic inflammatory myopathies (Box 3), ankylosing spondylitis (Box 4), systemic sclerosis (Box 5) or other rheumatic diseases. Most randomized controlled trials to study the effect of exercise training programmes on inflammatory rheumatic diseases are of patients with RA or SLE and have focused on physical capacity as a primary outcome. Therefore, future prospective randomized-controlled studies are needed to confirm and comprehensively investigate the effects of exercise.

Physical capacity and functional improvements

One of the most prominent effects of exercise is the improvement in physical capacity of both healthy individuals and those with a disease.[71] This effect is particularly beneficial for patients with inflammatory rheumatic diseases, as exercise increases the capacity for physical activity, and therefore decreases visceral fat, and has indirect anti-inflammatory effects.

Studies have shown that aerobic and resistance exercise training programmes consistently improve the aerobic capacity, muscle strength and self-reported functional ability of patients with RA,[72–77] adult SLE[78–81] and juvenile-onset SLE,[82] ankylosing spondylitis,[83–86] systemic sclerosis,[87–90] and idiopathic inflammatory myopathies, including polymyositis, dermatomyositis and body inclusion myositis.[91–99] Importantly, a number of studies have found an association of these effects with improvements in self-reported fatigue and health-related quality of life.[77,81,88,90,93,100]

Cardiovascular function improvements

Exercise is an established cornerstone for the prevention and treatment of CVD.[101] Although CVD is a cause of morbidity and mortality in patients with inflammatory rheumatic diseases,[2] little is known about the potential cardiovascular benefits of exercise and about the improvements in the risk factors for these patients. Nevertheless, low levels of physical activity are directly associated with an increased risk of CVDs in patients with RA or SLE.[102–104] Furthermore, aerobic and resistance exercise training programmes can improve endothelial function,[80,105] blood pressure, lipid profile[75,106] and autonomic function[82,107,108] in patients with RA or with adult or juvenile-onset SLE. The data, although sparse, support the notion that exercise reduces CVD risk factors and endothelial function, not only attenuating morbidity and mortality associated with CVD, but also inhibiting the vicious cycle of chronic inflammation.

Body composition optimization

Exercise can increase muscle mass[109] and decrease fat mass, particularly visceral fat.[110] Cross-sectional studies have suggested that higher levels of physical activity are associated with a lower percentage of body fat in patients with SLE[102] and an increase in lean mass of patients with ankylosing spondylitis.[111] Moreover, in a 3-year prospective observational study, physical activity was a strong predictor of positive changes in total lean mass in premenopausal women with SLE.[112]

Resistance exercise training, or resistance plus aerobic exercise, increases muscle mass (increased skeletal muscle fibre size and cross-sectional area, thigh cross-sectional area and leg and arm lean masses),[76,113–116] and decreases body fat percentage[73–75] and trunk fat mass[76] in patients with RA (Box 1). In a study of patients with juvenile dermatomyositis, lean mass and fat mass were unchanged after a 12-week aerobic and resistance exercise programme.[117] By contrast, in 2010 Gualano *et al.*[97] showed that a 12-week resistance exercise training programme with vascular occlusion increased the thigh cross-sectional area of a 65-year-old patient with body inclusion myositis, demonstrating the value of exercise as a tool to counteract muscle atrophy.

Effects on inflammation

Safety

For many years, dynamic weight-bearing exercises were not prescribed to patients with inflammatory rheumatic diseases primarily due to the fear that they might aggravate disease by exacerbating inflammation and thereby damage tissues. However, particularly in the last 15–20 years, studies have provided good evidence that aerobic and resistance exercises are safe for patients with these diseases.

Indeed, many studies have shown that aerobic and resistance exercise programmes do not change the number of inflamed joints, radiological joint damage, disease activity or systemic inflammatory markers (C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR]) in patients with low to moderate RA disease activity,[72,73,76,118,119] whereas other studies have detected improvements in these parameters.[73,100,105,118,120] However, caution should be taken with patients who have extensive baseline damage (that is, at the beginning of exercise therapy), as a high-intensity resistance exercise programme can lead to increased joint damage in these patients.[121]

The high degree of safety (that is, no evidence of disease flares or changes in ESR or CRP levels) of exercise training programmes, encompassing aerobic exercises with or without strength training, has also been shown in patients with SLE,[78–82] ankylosing spondylitis[83–85] and systemic sclerosis.[87–90] Moreover, studies have reported no increases in muscle inflammation or damage after resistance exercise training programmes by patients with idiopathic inflammatory myopathy.[93,94,98]

Although preliminary, evidence exists that exercise does not exacerbate systemic inflammation, particularly in patients with RA, SLE or idiopathic inflammatory myopathy. Baslund *et al.*[72] found, in patients with RA, that 8 weeks of moderate intensity aerobic training did not affect a number of resting immune parameters, including circulating concentrations of IL-1α, IL-1β and

Box 3 | Exercise is medicine—inflammatory myopathies

Improved physical capacity

- Increased muscle strength and function in response to aerobic[96] and resistance exercise programmes[93–95,97,98,151]
- Increased aerobic capacity in response to aerobic[96] and resistance exercise programmes[94,99]
- Increased self-reported quality of life in response to resistance exercise programmes[93]

Unchanged or decreased levels of inflammatory markers

- No changes in muscle markers of inflammation and damage (creatinine phosphokinase) in response to resistance exercise programmes[93,94,98,151,152]
- Decreased skeletal muscle fibrosis and profibrotic gene expression in response to resistance exercise programmes[94]
- Decreased skeletal muscle proinflammatory gene expression in response to resistance exercise programmes[94]

Box 4 | Exercise is medicine—ankylosing spondylitis

Improved physical capacity

- Increased mobility in response to aerobic[83] and aerobic plus resistance exercise programmes[84,86]
- Increased aerobic capacity in response to aerobic[83] and aerobic plus resistance exercise programmes[84,85]
- Decreased self-reported pain in response to aerobic[83] and aerobic plus resistance exercise programmes[86]

Improved body composition

- Increased lean body mass as shown by cross-sectional studies[111]

Unchanged level of inflammatory markers

- No changes in disease activity scores or markers of systemic inflammation (C-reactive protein) in response to aerobic[83] and aerobic plus resistance exercise programmes[84,85]

Box 5 | Exercise is medicine—systemic sclerosis

Improved physical capacity

- Increased muscle strength, function and mobility in response to aerobic plus resistance exercise programmes[89,90]
- Increased aerobic capacity in response to aerobic[87] and aerobic plus resistance exercise programmes[88]
- Improved self-reported quality of life and fatigue in response to aerobic plus resistance exercise programmes[88,90]

Unchanged level of inflammatory markers

- Unchanged disease activity scores or markers of systemic inflammation and muscle damage (creatine kinase and aldolase) in response to aerobic[87] and aerobic plus resistance exercise programmes[88–90]

IL-6. Likewise, 12 weeks after progressive resistance exercise, Rall *et al.*[122] found no changes in peripheral blood mononuclear cell production of IL-1β, IL-2, IL-6 or TNF, also in patients with RA.

Reduction in systemic inflammation

Exercise is not only a safe therapy for patients with rheumatic diseases, it is also effective in reducing systemic inflammation. Perandini *et al.*[123] investigated the effects of 30 min acute sessions of moderate and intense aerobic exercise (50% and 70% of peak VO_2, respectively) on the 24 h response of inflammatory cytokines (IL-6, IL-10, IFN-γ and TNF) and soluble TNF receptors (sTNFR1 and sTNFR2) in patients with active and inactive SLE. In inactive disease, changes were not observed in response to moderate-intensity exercise, whereas a slight decrease was noted in sTNFR1 levels, which followed a small decrease in TNF levels 3 h after the intense exercise, when compared with baseline.[124] These results are consistent with the unchanged levels of IL-6, IL-10 and TNF reported immediately after a graded exercise session in patients with SLE.[125] Moreover, despite a slight decrease in IL-6 levels, no other changes were observed 3 h after moderate-intensity exercise in patients with active disease in comparison with resting baseline values. Furthermore, the intense exercise session induced an immediate increase, which was followed, in comparison with pre-exercise levels, by a substantial decrease in IL-6 concentrations 1, 2 and 3 h after the exercise; an increase in IL-10 levels immediately and 30 min after the exercise; a slight increase at 30 min followed by a decrease in TNF levels 2 h after the exercise; and a decrease in sTNFR1 levels 3 h after the exercise. These results suggest that intense exercise by patients with SLE can induce an acute anti-inflammatory effect up to 3 h later. Notably, all reported changes were transient, as the differences were no longer detectable 24 h after exercise.

Evidence from a longitudinal study of patients with inactive disease from the Perandini *et al.*[123] study indicates that a 12-week, moderate-intensity, aerobic exercise programme for patients with SLE in remission is anti-inflammatory.[81] After 3 months of training, sTNFR2 levels and IL-10 resting levels were decreased; in addition, statistically insignificant decreases in resting levels of IL-6 and TNF were detected. Moreover, the 24 h response of IL-10 to an acute session of exercise after the intervention was substantially reduced when compared with the response before the intervention; the responses of IL-6, TNF and sTNFR1 were also decreased, although these data were also not statistically significant. In support of these results, a cross-sectional study showed that physically inactive patients, but not physically active patients with SLE have higher circulating levels of TNF and IL-12 than healthy individuals.[103]

Bearne *et al.*[126] examined the acute and chronic effects of resistance exercise training on the cytokine response in patients with RA. Before the exercise intervention, one resistance exercise session did not significantly change the IL-1, IL-6 or TNF levels when compared with baseline, and after the training programme, the resting levels of these cytokines were not significantly different. However, after the exercise training programme, an acute bout of exercise induced a decrease in the serum concentrations of IL-6 ($P<0.05$) and TNF, although the latter did not reach statistical significance. Considering that patients with RA commonly have 5–15-fold increased baseline resting levels of cytokines, when compared with healthy individuals,[127] these data seem to show that exercise programmes have a modestly positive, but significant, effect on the inflammatory response of these patients.

Nader *et al.*[94] reported decreased expression of pro-inflammatory and profibrotic gene networks (by microarray) in skeletal muscle after patients with dermatomyositis or polymyositis underwent 7 weeks of resistance training, indicating an important local anti-inflammatory effect of exercise that could be associated with improvements in clinical symptoms. Altogether, these findings support the hypothesis that aerobic and resistance exercises are not only safe, but that they might attenuate systemic inflammation in patients with RA or SLE, and skeletal muscle inflammation in idiopathic inflammatory myopathies.

Myokines—the ultimate link?

When skeletal muscle contracts it produces, expresses and releases cytokines and other proteins, some of which have autocrine, paracrine or endocrine effects; therefore, these mediators should be classified as myokines.[128] Hundreds of secreted peptides have been identified as part of this muscle 'secretome',[129–131] providing a conceptual basis of a paradigm shift in understanding how muscles communicate with other organs, such as adipose tissue, liver, pancreas, bone and brain (Figure 2).[13]

IL-6

IL-6 is the prototype myokine and, although most rheumatologists probably view IL-6 as a proinflammatory cytokine, evidence exists that muscle-derived IL-6 has anti-inflammatory functions.[34,35,132] Both the upstream and downstream signalling pathways for IL-6 differ markedly between myocytes and macrophages (Figure 3).[33] Unlike IL-6 signalling in macrophages, which is dependent upon activation of the nuclear factor-κB (NF-κB)

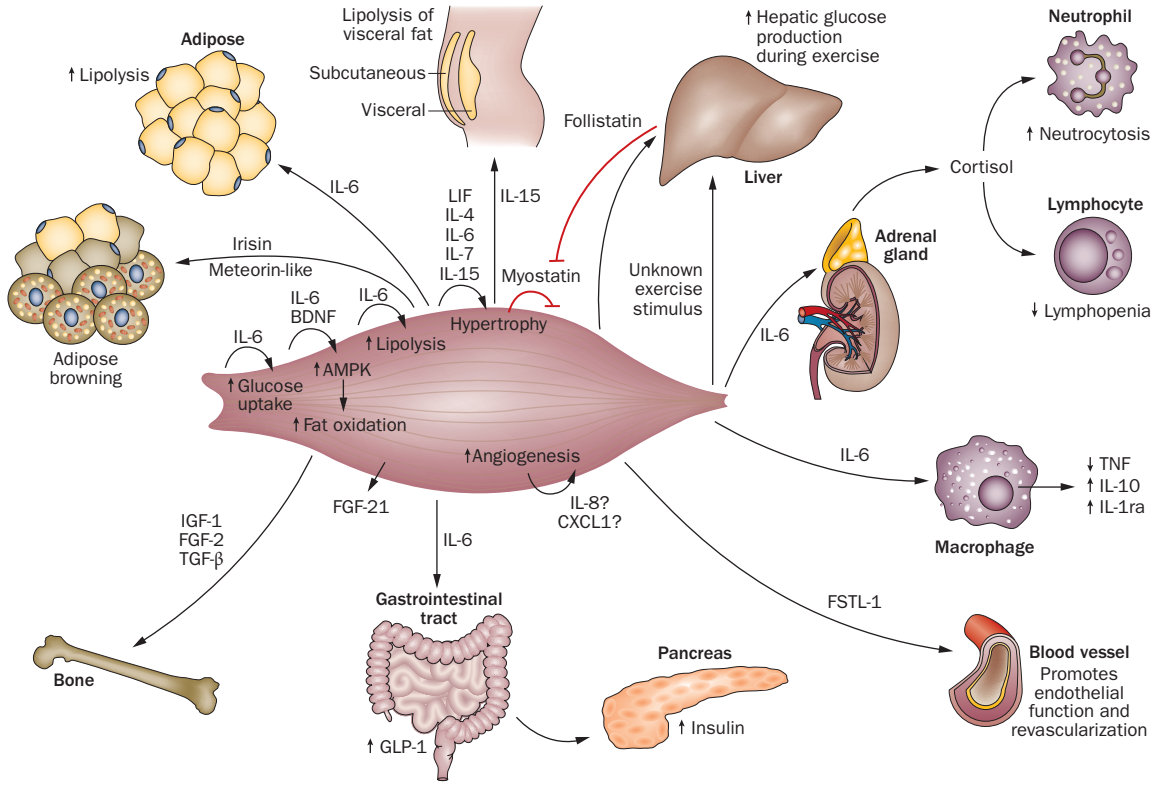

Figure 2 | Skeletal muscle is a secretory organ. IL-4, IL-6, IL-7, IL-15 and LIF promote muscle hypertrophy. Myostatin inhibits muscle hypertrophy and exercise leads to liver secretion of the myostatin inhibitor follistatin. BDNF and IL-6 are involved in AMPK-mediated fat oxidation, IL-6 stimulates lipolysis and IL-15 stimulates lipolysis of visceral fat. IL-6 also enhances insulin-stimulated glucose uptake and stimulates glucose output from the liver, but only during exercise. IL-6 also increases insulin secretion by inducing the expression of GLP-1 by the L cells of the intestine. IL-6 has anti-inflammatory effects as it inhibits TNF production and stimulates the production of IL-1ra and IL-10. Furthermore, IL-6 stimulates cortisol production and thereby neutrocytosis and lymphopenia. IL-8 and CXCL1 might be angiogenic. IGF-1, FGF-2 and TGF-β are involved in bone formation, and follistatin-related protein 1 improves endothelial function and revascularization of ischaemic blood vessels. Irisin and meteorin-like have a role in 'browning' of white adipose tissue. Abbreviations: AMPK, 5'-AMP-activated protein kinase; BDNF, brain-derived neurotrophic factor; FGF-2, fibroblast growth factor 2; FGF-21, fibroblast growth factor 21; FSTL-1, follistatin-related protein 1;GLP-1, glucagon-like peptide 1; IGF-1, insulin-like growth factor I; IL-1ra, IL-1 receptor antagonist; LIF, leukemia inhibitory factor; TGF-β, transforming growth factor β. Adapted with permission obtained from Macmillan Publishers Ltd, *Nat. Rev. Endocrinol.* **8**, 457–465 (2012).[14]

signalling pathway, expression of intramuscular IL-6 is regulated by a network of signalling cascades that probably involves cross-talk between the Ca^{2+}–NFAT (nuclear factor of activated T-cells) and glycogen–p38 MAPK (mitogen-activated protein kinase) pathways.[34] Therefore, when IL-6 activates monocytes or macrophages, it creates a proinflammatory response, whereas contraction-induced activation of IL-6 and its signalling in muscle cells is independent of a preceding TNF response or of NF-κB activation.[34]

The cytokine response to exercise is different to the response to severe infection. Highly strenuous prolonged exercise, such as marathon running, can result in a small increase in the plasma concentration of TNF (reviewed elsewhere[33]). However, in general, the cytokine response to dynamic concentric exercise is not preceded by an increase in TNF or IL-1β; the cytokine response to exercise and sepsis differs with regard to these cytokines (Figure 3). Therefore, human skeletal muscle is unique in that during contraction it can produce strictly TNF-independent IL-6, suggesting that muscular IL-6 has a role in metabolism rather than in inflammation. In support of this hypothesis, both intramuscular IL-6 mRNA expression and protein release are markedly enhanced when intramuscular glycogen levels are low, suggesting that IL-6 might be an energy sensor during exercise.[13,14]

During exercise, IL-6 is the first cytokine released into the blood (Figure 3).[33] The concentration of circulating IL-6 increases in an exponential fashion (up to 100-fold) during acute exercise and consistently declines in the recovery period.[33] Importantly, the circulating levels of the anti-inflammatory cytokines IL-1ra and IL-10 also increase, after the increase in IL-6, thereby having an anti-inflammatory effect (Figure 3).[64] Overall, the combination of mode, intensity and duration of exercise determines the magnitude of the induced increase in IL-6 concentration in the blood. As IL-6 is considered a classical proinflammatory cytokine, the IL-6 response was first thought to involve muscle damage.[133] However, eccentric exercise (when force is generated during muscle lengthening), usually associated with a higher degree of muscle

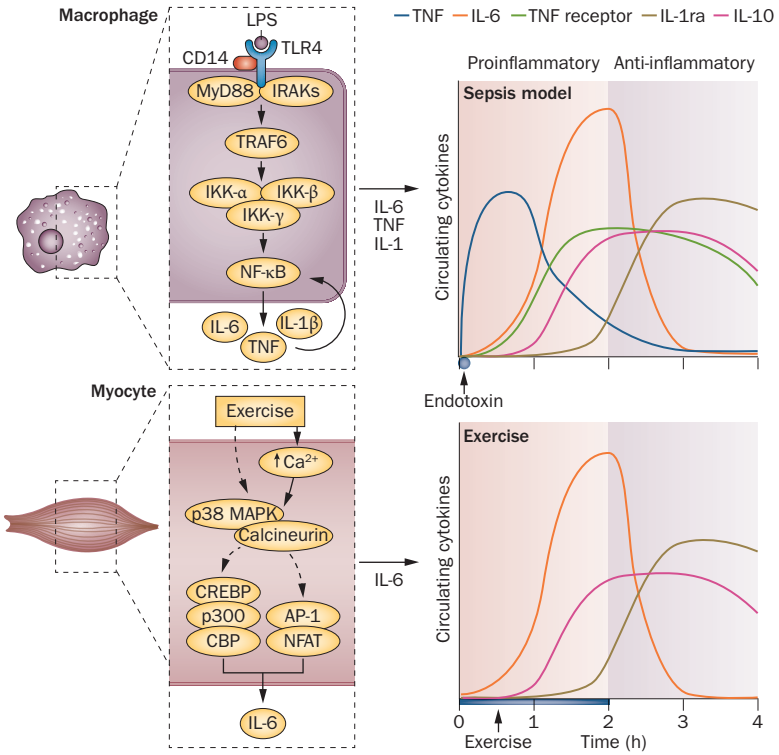

Figure 3 | Sepsis and macrophages versus exercise and muscle. During sepsis, a substantial, rapid increase in circulating TNF occurs immediately after exposure to endotoxin. The increase in TNF is followed by an increase in IL-6. By contrast, the increase in IL-6 during exercise is not preceded by increased TNF production. IL-6 peaks by the end of exercise and stimulates the production of anti-inflammatory cytokines (IL-1ra and IL-10). In macrophages, the transcription of IL-6 and other proinflammatory cytokines, such as TNF and IL-1β, is principally regulated by the TLR signalling cascade that results in nuclear translocation and activation of NF-κB. On the other hand, evidence indicates that contraction of skeletal muscle leads to increased cytosolic Ca^{2+} and activation of p38 MAPK or calcineurin, which activates production of IL-6 and not TNF. Abbreviations: CREBP; cyclic AMP-responsive element-binding protein; IKK, inhibitor of nuclear factor κB kinase; IL-1ra, IL-1 receptor antagonist; LPS, lipopolysachharide; MAPK, mitogen-activated protein kinase; MyD88, myeloid differentiation primary response protein MyD88; NFAT, nuclear factor of activated T-cells; NF-κB, nuclear factor κB; TLR, Toll-like receptor; TNFR, TNF receptor; TRAF6, TNF receptor-associated factor 6.

damage,[134] is not associated with a greater increase in plasma IL-6 compared with exercise involving concentric 'non-damaging' muscle contractions (when force is generated with muscle contraction),[135] and clear evidence exists that muscle damage is not required to increase the concentration of plasma IL-6 during exercise. Rather, eccentric exercise might result in a delayed peak and a slower decrease in the concentration of circulating IL-6 during recovery from exercise.[33]

Indeed, IL-6 seems to be central to mediating the acute anti-inflammatory effects of exercise. In one model of 'low-grade' inflammation, a low dose (0.06 ng/kg) of *Escherichia coli* endotoxin was administered to healthy volunteers, who were randomized to either rest or exercise prior to the infusion.[136] In resting individuals, endotoxin induced a 2–3-fold-increase in the circulating concentration of TNF. By contrast, when the participants performed 3 h of ergometer cycling and received the endotoxin bolus at 2.5 h, the TNF response was prevented, suggesting that acute exercise inhibits TNF production. In addition, infusion of recombinant human IL-6 to mimic the exercise-induced IL-6 response inhibited the endotoxin-induced increase in circulating levels of TNF.[136] Therefore, although TNF stimulates the production of IL-6, IL-6 induces a negative feedback to inhibit TNF production. Furthermore, IL-6 induces an increase in cortisol and thereby in neutrocytosis and late lymphopenia, to the same magnitude and with the same kinetics as during exercise, suggesting that muscle-derived IL-6 is involved in exercise-effects on leukocyte homeostasis and trafficking.[15] During inflammatory conditions, IL-6 has also been shown to limit the expression of genes encoding inflammatory cytokines (for example *TNF*, *IL1B*, *NOS2*) and the activation of c-Jun N-terminal kinase (JNK),[137] and it augments the responsiveness of macrophages to IL-4, thereby strongly supporting the idea that IL-6 can diminish inflammation and associated resistance to insulin.[137]

IL-15

IL-15, which can also be considered a myokine, seems to be involved in the regulation of obesity, as overexpression of IL-15 protects mice from the accumulation of visceral fat. Moreover, muscle IL-15 was increased in mice after an 8-week training session of treadmill running (26 m/min for 60 min, 5 days per week),[138] and in human muscle as a result of 12 weeks of endurance training (ergometer cycling five times per week, including interval training twice a week).[139] IL-15 is an anabolic factor, highly expressed by skeletal muscle cells,[140] which induces an increase in the accumulation of the protein myosin heavy chain in differentiated muscle cells[141] and stimulates myogenic differentiation independent of IGFs.[142]

Despite anabolic effects on skeletal muscle *in vitro* and *in vivo*,[143] IL-15 is involved in reducing adipose tissue mass; IL-15 decreases lipid deposition in preadipocytes and decreases the mass of white adipose tissue.[144,145] In humans, a negative association between plasma IL-15 concentration and trunk fat mass exists, and when IL-15 was overexpressed in the muscles of mice, visceral fat mass decreased in volume but subcutaneous fat mass did not.[146] Despite these data, and that IL-15 seems to have a role in muscle–fat cross-talk, IL-15 release from skeletal muscle is yet to be shown in an *in vivo* model.[147]

Other myokines

We suggest that both IL-15 and IL-6 have important roles in lipid metabolism; however, other myokines are likely to be involved in the regulation of adipose tissue mass (Figure 2). BDNF is hypothesized to be a myokine with an autocrine or paracrine mechanism of action with strong effects on peripheral metabolism, including fat oxidation and a subsequent effect on the volume of adipose tissue.[148] Furthermore, erythropoietin might also have a role in muscle–fat cross talk and contribute to minimizing abdominal adiposity.[149] Finally, patients with rheumatic diseases often suffer from muscle wasting due to decreased physical activity or local and systemic inflammation.[51] Large muscle mass probably

protects against the accumulation of visceral fat, and several myokines, including IL-4, IL-6, IL-7, IL-15, LIF and myostatin, might regulate skeletal muscle growth and maintenance.[13]

Other myokines include IGF-1, FGF-2 and transforming growth factor β, which have been identified as osteogenic factors,[13] FSTL-1, which might improve the endothelial function of the vascular system, and the proliferator-activated receptor-γ (PPARγ) coactivator 1α-dependent myokine irisin have been shown to drive the development of a brown-fat-like adipose tissue.[13] Also, meteorin-like has been identified as a myokine that regulates immune–adipose interactions to increase beige fat thermogenesis.[150]

Conclusion

The benefits of physical activity, in lowering the risk of all-cause mortality and improving longevity, have been extensively documented.[151] The state of chronic inflammation in patients with inflammatory rheumatic diseases is maintained by decreased physical capacity, muscle wasting and probably by decreased physical activity along with a higher prevalence of atherosclerosis and associated comorbidities.

During the past two decades, research has contributed tremendously to our understanding of the benefits of exercise at the molecular level and, more recently, to the concept that skeletal muscle is a secretory organ. The identification of the muscle secretome presents a new paradigm, a platform for understanding how muscles communicate with other organs, and explains how healthy muscle tissue is developed and maintained.

Of particular interest for patients with chronic inflammation, each bout of exercise might provoke an anti-inflammatory environment, as muscle-derived IL-6 inhibits TNF production and stimulates the production of the anti-inflammatory cytokines IL-1ra and IL-10. Furthermore, a variety of other myokines might mediate indirect anti-inflammatory effects of exercise. Some of these myokines have been shown to be anabolic. Myokines are also directly involved in prevention of abdominal adiposity and thereby might have a fundamental effect on inflammation. Furthermore, some myokines have been shown to have systemic effects on the liver and to mediate cross-talk between the intestine and pancreatic islets, thereby furthering many of the metabolic effects of exercise. Finally, other myokines are of importance for bone health and the endothelial function of the vascular system.

Exercise probably has pleiotropic positive effects in almost every organ system, potentially having myokine-mediated direct and indirect anti-inflammatory effects in inflammatory rheumatic diseases. Nonetheless, future prospective studies that focus on the specific effects of exercise on systemic and local inflammation (for example, in the joints of patients with RA) in each disease are necessary in order to confirm the still preliminary but optimistic data from currently available studies.[81,103,123,125]

Review criteria

A search for original articles published between 1970 and June 2014 and focusing on physical activity and inflammatory rheumatic diseases and the role of myokines was performed in MEDLINE and PubMed. The search terms used were "muscle", "exercise", "physical activity", "endocrine", "cytokine", "myokine", "inflammation", "insulin resistance", "cardiovascular risk", "lipid profile", "endothelial function", "atherosclerosis", "rheumatoid arthritis", "systemic lupus erythematous (SLE)", "systemic sclerosis", "idiopathic inflammatory myopathies", "dermatomyositis", "polymyositis", "body inclusion myositis" and "ankylosing spondylitis". All articles identified were English-language, full-text papers. Reference lists of identified articles were also searched for further papers.

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Both authors contributed equally to researching data for the article, providing a substantial contribution to discussions of the content, writing the article, and to review and/or editing of the manuscript before submission.