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Review

Exercise as a therapeutic tool to counteract inflammation and clinical symptoms in autoimmune rheumatic diseases

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ABSTRACT

Chronic inflammation is a common feature shared by several autoimmune rheumatic diseases, such as rheumatoid arthritis, systemic lupus erythematosus, idiopathic inflammatory myopathies, systemic sclerosis, and ankylosing spondylitis. Therefore, blocking or reducing inflammation is one of the major treatment strategies in these diseases. In this context, exercise training has emerged as a potential therapeutic tool in counteracting systemic inflammation, thereby leading to better clinical outcomes. The aims of this review are i) to provide a summary of the clinical effects of exercise training in selected autoimmune rheumatic diseases; and ii) to discuss the potential anti-inflammatory role of exercise training in autoimmune rheumatic diseases, stressing the gaps in literature and the clinical and scientific perspectives in the field.

Contents

1. Introduction

Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), idiopathic inflammatory myopathies (IIM), systemic sclerosis (SSc), and ankylosing spondylitis (AS) are autoimmune rheumatic diseases that share common clinical features, including periodic pain, chronic fatigue, depression, reduced physical fitness, and, as a consequence, hypoactivity and poor health-related quality of life [1–5]. Importantly, the main clinical signs and symptoms of these diseases have been strongly related to a sustained inflammatory condition [5–10].

Glucocorticoids and immunosuppressive drugs are the cornerstone of the treatment for autoimmune rheumatic diseases. Yet, these medications may not be fully effective in hampering the progression of disabilities [4]. Moreover, the long-term use of these drugs has been associated with several deleterious effects, including bone and muscle mass wasting and cardiovascular dysfunction [11].

In this context, exercise training has as a non-pharmacological strategy aimed at improving a variety of clinical symptoms in patients with autoimmune rheumatic diseases [1–5,12–14]. This notion is in line with a growing body of literature revealing that regular exercise

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training may lead to anti-inflammatory effects in chronic diseases characterized by a low-grade systemic inflammation, such as type 2 diabetes mellitus and congestive heart failure [15,16].

Given the potential role of inflammation in the etiology as well as in the clinical symptoms of autoimmune rheumatic diseases, one may postulate that exercise training, if able to alleviate the inflammatory process, could also be helpful in treating the symptoms, as well as in modifying the disease's natural course of autoimmune rheumatic diseases, as illustrated in Fig. 1.

The aim of this review is two-fold: first, to provide a summary of the clinical effects of exercise training in selected autoimmune rheumatic diseases; second, to critically discuss the potential anti-inflammatory role of exercise training in autoimmune rheumatic diseases, stressing the gaps in literature as well as the clinical and scientific perspectives in the field.

2. Exercise training as an adjuvant treatment in autoimmune rheumatic diseases

2.1. Idiopathic inflammatory myopathies

Despite the empirical belief that exercise could flare up disease activity and impair inflammation in IIM, recent studies have shown otherwise [1,5,17]. In fact, there is evidence that exercise training can improve aerobic capacity [18,19], muscle strength [17]), fatigue [20], and health-related quality of life [21] in IIM patients.

Spector et al. [22] submitted inclusion body myositis (IBM) patients (n = 5) to a three-times-a-week progressive strength training program for 12 weeks. As a result, both isometric and dynamic strength increased, whereas fatigue symptoms and inflammation markers (i.e., interleukin-2 and natural killer cells) remained unchanged. In contrast, Arnardottir et al. [23] evaluated seven IBM patients who underwent a 12-week home-based exercise training program, which comprised 15 min of body weight exercises and 15 min of self-selected speed walking. Neither muscle damage and inflammation nor isometric peak force was affected. The lack of "positive" outcomes may be a consequence of the low training regimen applied in this study.

Recently, our group introduced a novel exercise prescription to IIM patients [1,17]. We tested the effects of low-intensity strength training [50% of one-repetition maximum (1RM)] associated with vascular occlusion in a patient with IBM who was unresponsive to conventional therapy, including "traditional" physical exercises. Following the intervention, we observed augmented thigh cross-sectional area, increased muscle strength and function, and improved health-related quality of life. Importantly, there was no evidence of disease flare, muscle damage or exacerbated inflammation. This training mode is currently being applied to a larger cohort of IBM patients to confirm our preliminary findings.

Weisinger et al. [18] evaluated dermatomyositis (DM) and polymyositis (PM) patients (n = 14) before and after six weeks of moderate aerobic training [i.e., 60% of maximal heart rate (HRmax)]. Aerobic

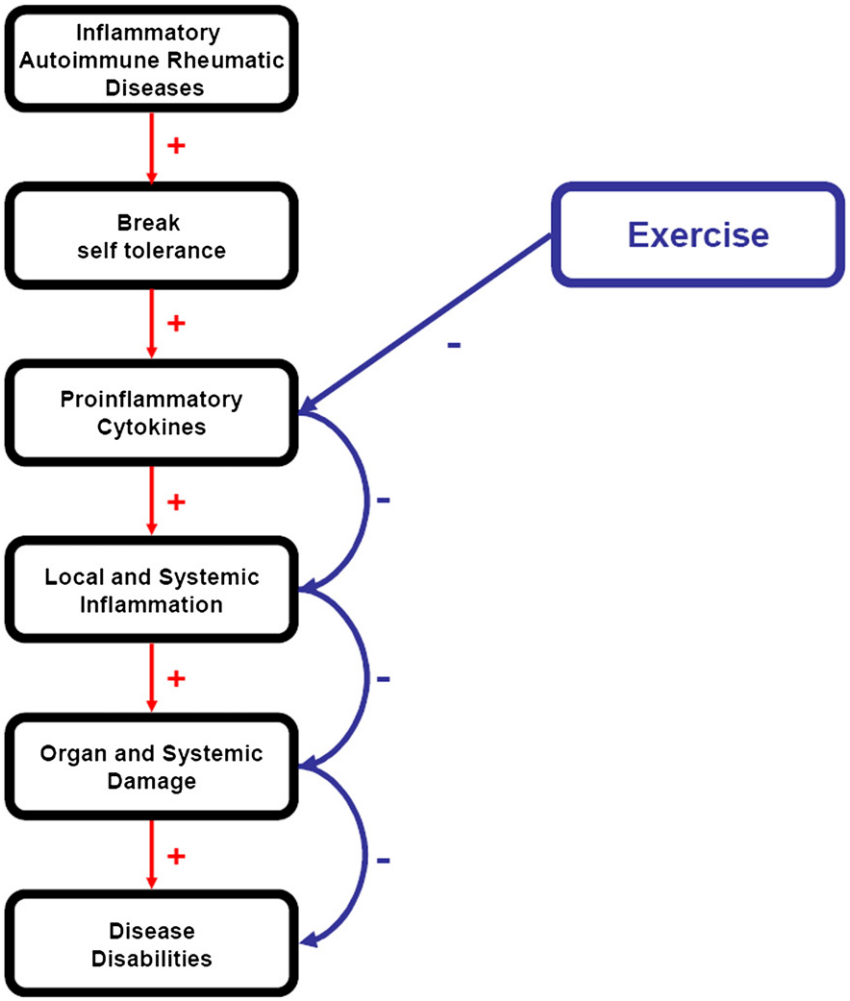

Fig. 1. Physiopathologic cascade leading to poor clinical outcomes triggered by exacerbated inflammation in autoimmune rheumatic diseases (red arrows). The potential role of exercise in "stalling" this cascade by preventing inflammation is illustrated in blue.

exercise improved both maximal oxygen uptake (VO_2max) and isometric peak torque. In a subsequent randomized controlled trial with DM and PM patients (n = 14), Weisinger et al. [19] demonstrated that an exercise program was capable of improving isometric peak force, exercise tolerance, VO_2max, and anaerobic threshold intensity. In the aforementioned studies, aerobic exercise training did not affect muscle enzymes, suggesting that this training mode is safe for IIM patients.

Varjú et al. [20] assessed the efficacy of strength exercises (65–70% of 1RM) combined with stretching and respiratory exercises in DM and PM patients (n = 21). After the training, patients presented increases in their strength and forced vital capacity, and reductions in fatigue. Harris-Love [24] also found increased peak isokinetic and isometric strength without muscle damage or inflammation in a 64-year-old PM patient who underwent 12 weeks of sub-maximal eccentric strength training. Supporting these findings, Alexanderson et al. [25] demonstrated significant improvements in muscle strength and function without adverse events in DM and PM patients (n = 9) following a nine-week intensive strength training program (10–15 RM). Taken together, these studies suggest that even higher-intensity exercise programs can be efficient, tolerable and safe in IIM patients.

Home-based exercises seem to be another interesting strategy aimed at improving muscle strength and health-related quality of life in IIM [21,26]. In this regard, Alexanderson et al. [26] prescribed a 12-week, five-times-a-week, moderate-intensity strength training program along with 15-min self-selected speed walking to chronic PM and DM patients (n = 10). The exercise training program was able to improve selected subscales of SF-36 (i.e., physical functioning, bodily pain and vitality), without affecting muscle enzymes. Similar results were found by Alexanderson et al. [21] who examined patients with recent onset active DM or PM (n = 11). The exercise training program, which was similar to that described by Alexanderson et al. [26], led to improvements in physical functioning, bodily pain and vitality SF-36 subscales as well as in the functional index.

Recently, our group demonstrated that a 12-week exercise training program comprising aerobic (70% of VO_2max) and strength exercises (8–12 RM) was also able to improve muscle strength and function, aerobic fitness, bone mineral density, and health-related quality of life, without exacerbating disease activity or inflammation in ten children with juvenile dermatomyositis (JDM) [27]. These data extend the applicability of exercise training in IIM to juvenile patients.

Collectively, the literature points out the therapeutic role of exercise training in IIM. It is important to emphasize that none of the existing studies have noticed any sort of adverse events as a consequence of exercise training, irrespective of the training's characteristics (e.g., either low- or high-intensity, strength or aerobic exercise, home-based or supervised exercise) or the patients' characteristics (e.g., child or adult, IBM, DM or PM, chronic or active disease). The number of patients in these studies are however small and long-term follow-up is lacking, reinforcing the need for continuous surveillance.

2.2. Ankylosing spondylitis

Exercise training has been shown to reduce disease severity scores and to increase joint mobility parameters in AS patients [2,28–30]. Although the mechanisms underlying these improvements remain to be elucidated, exercise has been associated with increased serum levels of the anti-inflammatory cytokine tumor growth factor-beta1 (TGF-β1) in AS patients [31], which could be implicated in the beneficial outcomes experienced by AS patients after an exercise training program.

Karapolat et al. [30] performed a randomized controlled trial in which AS patients (n = 45) underwent an exercise program comprised by either: i) stretching exercises plus swimming, ii) stretching exercises plus walking, or iii) stretching exercises alone. The two former groups presented improvements in VO_2max and anaerobic threshold, but only the group which performed stretching exercises along with swimming experienced increased chest expansion circumference.

In a subsequent randomized controlled trial, Altan et al. [29] demonstrated that a 12-week Pilates exercise training (i.e., a modality of training which includes isometric strength exercises along with stretching exercises) performed three times a week, was able to improve clinical parameters in AS patients (n = 55). Specifically, patients presented better scores in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Bath Ankylosing Spondylitis Metrology Index (BASMI) as well as greater chest expansion. However, health related-quality of life remained unchanged.

Following a 12-week home-based exercise program, AS patients (n = 34) had significant improvements in disease indexes (i.e., BASFI and BASDAI), mobility (i.e., chest expansion and morning stiffness) and health-related quality of life [2]. However, when a six-week aerobic supervised program (n = 23) was compared to a home-based exercise program (n = 22), only the supervised training program led to improvements in BASFI, VO_2max, chest expansion, and morning stiffness. Pain was not affected by either intervention [2].

Despite the limited number of trials, one may postulate that exercise training is safe and emerges as a potential therapeutic adjuvant in AS disease.

2.3. Systemic lupus erythematosus

The current literature seems to converge in indicating that exercise training is a safe and effective strategy to improve a number of clinical outcomes in SLE patients, such as fatigue, depression, aerobic capacity, autonomic control, and health-related quality of life [32–38].

Robb-Nicholson et al. [32] conducted, for the first time, an 8-week home-based exercise program in SLE patients (n = 23). Aerobic exercise intensity was aimed to achieve 60 to 80% of HRmax. As a result of the training program, there was no significant increase in VO_2max and depression symptoms, whereas fatigue and exercise tolerance significantly improved. Ramsey-Goldman et al. [33] also submitted SLE patients (n = 10) to an aerobic exercise program composed of two stages. In the first one, the patients who undertook a supervised training at 70 to 80% of HRmax, three times a week experienced improvements in fatigue, aerobic capacity, and health-related quality of life. Following the second stage of the study, which encompassed a home-based exercise program, the patients had similar benefits to those seen as a consequence of the supervised training.

Clarke-Jenseen et al. [35] evaluated the effects of a moderate-intensity (i.e., 70% of HRmax), 12-week, three-times-a-week, supervised aerobic training in SLE patients (n = 6). The patients presented improvements in VO_2max and better scores in the physical functioning SF-36 subscale, whereas pain scores remained unchanged. Corroborating these findings, Carvalho et al. [36] evaluated 60 SLE patients who undertook a 12-week aerobic exercise training and observed significant improvements in VO_2max, exercise tolerance, and better scores in functional functioning, physical fitness, general health status, vitality, social aspects, and mental health SF-36 subscales. Fatigue and pain, as assessed by the SF-36 questionnaire, remained unchanged. In contrast to the aforementioned studies, Tench et al. [34] failed to find any improvement in aerobic capacity and health-related quality of life after a 12-week aerobic training program at 60% of VO_2max. The relatively low-intensity exercise applied in this study may partially explain the lack of positive outcomes.

Yuen et al. [37] recently proposed the use of a video-game exercise program (Wii Fit®) as an adjuvant therapeutic strategy in SLE. The patients (n = 15) were encouraged to perform the video-game-oriented exercise sessions at home in 20–30 min per day, at a self-perceived exertion ranging between 11 and 13, as assessed by a 6 to 20 Borg

scale. As a result, SLE patients presented significant reduction in fatigue as well as improvement in anxious and depression symptoms.

We performed a randomized controlled trial to examine the effects of a 12-week training program composed of 35–40 min of strength exercises combined with 30 min of aerobic exercises on autonomic function in SLE patients (n = 28) [38]. After the training, important improvements in autonomic control, as assessed by chronotropic reserve and HR recovery, were observed. Notably, a comparison to healthy subjects led to the conclusion that exercise virtually reversed autonomic dysfunction in the SLE patients, with autonomic control parameters being comparable between patients and controls.

Our group also provided the first evidence that a 12-week supervised aerobic training program can be safe and effective in improving aerobic conditioning and physical function in a 15-year-old boy with juvenile SLE and antiphospholipid syndrome [39], reinforcing the possible relevance of exercise training in pediatric population suffering from autoimmune rheumatic diseases. Preliminary data from our laboratory with a larger cohort of juvenile SLE patients have confirmed the efficacy of exercise as an adjuvant treatment in this disease (unpublished data).

Based on the available literature, exercise training has been claimed to have a synergist beneficial effect in the management of SLE. Nonetheless, more controlled clinical trials are necessary to confirm this statement.

2.4. Systemic sclerosis

To our knowledge, only two prospective studies have been conducted to investigate the effects of exercise training on SSc patients [40,41]. In both, there was no evidence of adverse events, as evidenced by the absence of digital ulcers and the Raynaud phenomenon, pointing out the safety of exercise training in SSc [40,41].

In the first trial, we evaluated the efficacy and safety of an eight-week, moderate-intensity (~70% of VO_2max) aerobic training program in SSc patients (n = 7). Data revealed improvements in the VO_2max and the aerobic capacity [40]. No changes in disease activity scores were noticed. Subsequently, we examined the effects of a 12-week exercise training program comprising both aerobic (70% of VO_2max) and resistance exercises (8-12 RM) in SSc patients (n = 11) [41]. After the training program, the patients experienced significant improvement in maximal strength in both the lower and the upper limbs. Sub-maximal parameters of aerobic conditioning were also beneficially modified whereas no changes in muscle enzymes (e.g., CK and aldolase) were verified.

These preliminary studies suggest that exercise training may be a valuable auxiliary strategy in counteracting the poor muscle strength and the aerobic conditioning experienced by SSc patients. The putative role of exercise in the treatment of SSc patients merits further investigations.

2.5. Rheumatoid arthritis

RA is undoubtedly the most studied autoimmune rheumatic disease in the context of exercise training. In this regard, there is strong evidence pointing to the benefits of moderate- and high-intensity exercise training on fatigue, muscle strength, aerobic capacity, pain, and disabilities in RA patients [4,42].

Both supervised and home-based programs have been investigated in RA [43–46]. Following a 12-week supervised moderate-intensity aerobic exercise program (performed in a temperate pool), Bilberg et al. [43] observed that RA patients (n = 43) had improvements in muscle endurance, isometric shoulder endurance, several domains of the SF-36 (i.e., bodily pain, vitality, and physical functioning), Health Assessment Questionnaire (HAQ) scores, and disease activity. In contrast, no changes in the aerobic capacity and the physical subscale of the SF-36 were noticed. Neuberger et al. [44] demonstrated reduced fatigue, pain and depression, and increased walking time in RA patients (n = 220) who underwent a 12-week, three-times-a-week, moderate-intensity aerobic training program (60–80% of HRmax). Baillet et al. [45] also presented improvements in aerobic conditioning and HAQ scores after a short-term (i.e., four weeks), six-times-a-week, exercise training program (60–80% of HRmax). Disease Activity Score 28 (DAS28) and Arthritis Impact Measurement Scale (AIMS2) scores remained unchanged.

The efficacy of exercise training in RA holds true in non-supervised programs. Van den Berg et al. [46] examined the effects of a training program prescribed via the Internet. The training was composed of strength (10 repetitions per exercise), aerobic (60–80% of HRmax), and range-of-motion (ROM) exercises. Patients who performed the internet-based training program had increased moderate- and vigorous-activity levels, but the functional ability and the health-related quality of life remained unaffected.

It was empirically believed that high-intensity exercise could exacerbate the joint disease in RA patients. Nevertheless, a large body of knowledge has indicated otherwise [47–50]. Van den Ende et al. [48] showed that 24 weeks of intensive isometric exercises (at 70% of maximal voluntary contraction), isokinetic exercises (at 70% of maximal voluntary contraction) and aerobic exercises (at 60% of HRmax) was capable of reducing systemic inflammation and disease activity, and increasing muscle strength in RA patients (n = 62). Similar results were found by Hakkinen et al. [49], who investigated the effects of two years of strength exercises (at 50–70% of 1RM) in 70 RA patients. As a consequence of the exercise program, there was a significant improvement in disease activity, as assessed by DAS28, as well as in muscle strength. Importantly, no signs of joint damage aggravation were noticed. de Jong et al. [50] tested a vigorous 24-week exercise training program composed of sports modalities and aerobic exercise (at 70–90% of HRmax) in RA patients. The authors found that the training protocol affected neither disease activity nor muscle inflammation. Furthermore, aerobic capacity, muscle strength and disabilities significantly improved after training. However, the authors pointed out that those patients with more severe joint damage at baseline tended to present greater damage progression following the high-intensity training.

van den Ende et al. [47] compared low-intensity versus high-intensity exercise training in RA patients (n = 100) for 12 weeks. The low-intensity exercise training did not impair disease activity (as assessed by a visual analogue scale), and systemic inflammation (as assessed by an erythrocyte sedimentation rate), but failed to yield gains in physical function and functional capacities. Also, the high-intensity exercise training did not affect disease activity and systemic inflammation, while improvements in VO_2max (+17%), muscle strength (+16.8%), and ROM were observed.

Collectively, the vast literature relative to the role of exercise in RA supports the contention that exercise training, along with drug therapy, constitutes the major cornerstone for RA management. Importantly, studies have also suggested that high-intensity dynamic training may not only be tolerable, but may also be the most effective training mode in improving physical function and quality of life in RA patients.

3. The role of anti-inflammatory effects of exercise in rheumatic autoimmune diseases

Skeletal muscle has been recently recognized as an “endocrine organ” able to express and secrete a number of cytokines (also called “myokines”), which may act in a hormone-like fashion, exerting endocrine and/or paracrine effects [15,51,52]. In response to muscle contraction, the first cytokine secreted is interleukin-6 (IL-6), which is subsequently followed by anti-inflammatory cytokines, such as interleukin 1 receptor antagonist (IL-1ra), interleukin-10 (IL-10) and tumor necrosis factor receptor (TNF-R) [15,51,52]. It is interesting to note that intramuscular cytokine expression differs from that in

macrophages, where IL-6 signaling is dependent upon the activation of the NFκB signaling pathway, thus provoking a proinflammatory response. Conversely, intramuscular IL-6 expression is thought to be activated by a network of signaling cascades involving the Ca^{2+} nuclear factor of activated T cells (NFAT) and glycogen/p38 MAPK pathways regulated independent of a preceding TNF response or NFκB activation. Therefore, IL-6 produced during physical exercise has been considered an anti-inflammatory rather than a pro-inflammatory cytokine [51,52].

In order to explore the anti-inflammatory role of exercise, Starkie et al. [53] experimentally infused *Escherichia coli* endotoxin to mimic a low-grade systemic inflammation condition in eight healthy individuals who were assessed either when resting or after performing an acute session of cycling exercise at 70% of VO_2max. The resting individuals showed a two- to three-fold increase in the TNF-α plasma concentration 1.5 hour after the infusion. In contrast, when subjects exercised, the TNF-α increase was fully blunted. These findings are of great relevance considering the suggestion that anti-inflammatory effects of regular exercise training may be a summation of stimuli produced after each exercise bout [16]. Corroborating this notion, it was observed that a 12-week aerobic training program at 70–80% of HRmax attenuated TNF-α production in healthy individuals infused with lipopolysaccharide, which triggers TNF-α-mediated inflammation [54].

In fact, a growing body of literature points out to the anti-inflammatory effects of exercise in a variety of low-grade systemic inflammatory diseases, such as congestive heart failure and type 2 diabetes mellitus [15,16,51,52,54–59]. For instance, congestive heart failure patients who performed aerobic training at 80% of HRmax for 12 weeks had reduced levels of TNF-α [55]. Moreover, type 2 diabetes patients who underwent a 6-month aerobic training at 50–70% of VO_2max experienced a reduction in TNF-α and C-reactive protein levels [56]. Interestingly, strength training can also promote anti-inflammatory effects [60]. For example, elderly women who participated in a 12-week strength-training program presented reduced C-reactive protein levels [61]. Additionally, an inverse association between muscular thickness and TNF-α level was observed, suggesting that muscle mass gain was related to a reduction in inflammation. Interestingly, strength training appears to present an intra-articular anti-inflammatory effect in knee osteoarthritis patients [62]. In this study, the authors verified an increase in anti-inflammatory cytokine IL-10 in synovial fluid sampled after a strength training session performed at 60% of 1 RM. In light of these findings, one can postulate that both regular aerobic and strength training may promote anti-inflammatory effects in individuals with or without previous inflammation, and that attenuation in inflammation may precede positive functional and morphological adaptations.

It is well known that rheumatic autoimmune diseases feature either systemic or local inflammation, which is evidenced by abnormal concentrations of inflammatory cytokines [63–66]. Moreover, the levels of the inflammatory cytokines have been associated with disease activity [67–70], suggesting the clinical relevance of treating the exacerbated inflammation in autoimmune rheumatic diseases. However, despite the large body of literature highlighting the role of exercise on inflammation in healthy subjects and patients, there is limited evidence regarding the anti-inflammatory effects of exercise on autoimmune rheumatic diseases. In this respect, an interesting study by Nader et al. [13] showed that DM and PM patients who performed a 7-week strength-training program experienced inhibition in inflammation signaling pathways (i.e., a reduction in PTGS1 and SMAD7 and an increase in FOXP3 mRNA). Moreover, the researchers observed a reduction in the expression of genes related to the pro-inflammatory network (i.e., TNF-α gene network), suggesting that exercise may benefit IIM partially by attenuating inflammation. It is worthy to note that TNF-α has been considered a main therapeutic target in numerous autoimmune diseases, where the use of drugs capable of reducing TNF-α production has been shown to be effective in treating high-grade inflammation and, hence, clinical symptoms

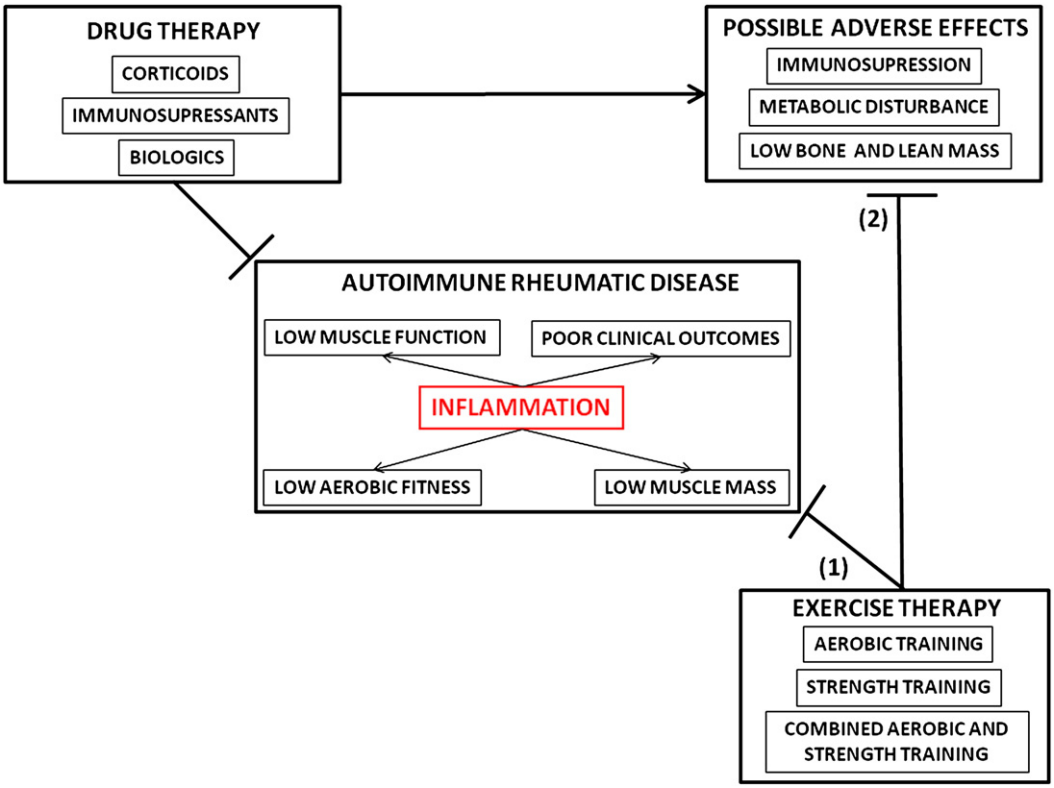

Fig. 2. Theoretical model where exercise could (1) reduce inflammation and, hence, physical disabilities and poor clinical outcomes in autoimmune rheumatic diseases. Additionally, exercise could (2) attenuate adverse effects provoked by the pharmacological treatment in the long-term.

[71,72]. Theoretically, exercise could act similar to such drugs by inhibiting TNF-α production and increasing anti-inflammatory cytokines, ultimately resulting in a reduced inflammatory profile. If this hypothesis is confirmed, one may argue that regular exercise could act as an important adjuvant tool in improving not only overall symptoms but also the disease course in autoimmune rheumatic diseases.

Notably, further work must be done to support this assumption. First, the role of acute exercise on the pattern of cytokine production must be addressed in autoimmune rheumatic diseases, comparing the response to that seen in healthy subjects who benefit from anti-inflammatory effects of exercise. Second, the chronic effects of exercise on inflammatory markers must be examined in large and diversified cohorts of patients with autoimmune rheumatic diseases. Third, the potential synergic effect of exercise along with the current pharmacological therapies (including biologic agents) on inflammation and, consequently, on clinical outcomes is another topic to be explored. In this respect, one may assume that exercise could benefit patients with an autoimmune rheumatic disease by: i) producing anti-inflammatory effects, thereby leading to improvements in physical capacity, disabilities and clinical symptoms (e.g., pain, muscle dysfunction, weakness, fatigue, atrophy, etc.); and ii) attenuating potential adverse effects provoked by the drug treatment (e.g., low bone mass, low muscle mass, metabolic disorders, immunosuppression, etc.). The latter assumption is based on the well-known systemic effects of exercise, which have been comprehensively reviewed elsewhere [73,74]. Fig. 2 illustrates this novel paradigm where exercise emerges as a potential adjuvant treatment in autoimmune rheumatic diseases.

Take-home messages

- Exercise training can counteract exacerbated inflammation in several experimental and clinical conditions.
- Both aerobic and resistance training can improve physical capacity, muscle function and several clinical symptoms in patients with autoimmune rheumatic diseases.
- We postulate that exercise can be of therapeutic relevance in the management of autoimmune rheumatic disease partially by reducing the inflammation.

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