Review

The effect of exercise on patients with rheumatoid arthritis on the modulation of inflammation

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ABSTRACT

A healthy lifestyle is critical to maintaining safety and preventing rheumatic disease before reaching old age. Rheumatoid arthritis (RA) is a chronic autoimmune and systemic illness involving joint changes, including inflammation, joint pain, tiredness, elevated risk of developing coronary and heart disease, and rapid loss of muscle mass. The role of exercise in improving the inflammatory pattern has tended to focus on the latest research. However, some physical activities represent a non-pharmacological treatment strategy due to their many benefits, such as improved muscle mass, strength, and efficiency, especially in patients with RA. During exercise, skeletal muscle releases myokines, triggering a direct anti-inflammatory effect with each activity or enhancing comorbidity. The level of inflammatory biomarkers, such as tumour necrosis factor, C-reactive protein, and interleukin-6, is significantly lower for athletes and patients with RA who exercise regularly. However, understanding the precise roles of some environmental and genetic factors can help to prevent rheumatic disorders. This review highlights the influence of exercise and training on the inflammatory module in patients with rheumatic disease. More detailed data is needed to clarify the benefits of exercise in the context of RA and inflammation.

Introduction

Exercise is broadly acknowledged to prevent and treat chronic and degenerative diseases (1). The lack of, or insufficient levels of, physical activity promote a sedentary way of life and are one of the major causes of preventable mortalities (2). Physical exercise stimulates various inflammation changes that align with a person's lifetime, health status, and exercise intensity/duration (3). Due to numerous cells, mediators, and mechanisms, inflammation is difficult to determine (4). Moreover, the progression of dementia, depression, and neurodegeneration may be affected by a lack of physical activity (2). Conversely, these physical activities have many mental and physical advantages for personal health. Most are due to the capacity of exercise to encourage changes in some organs (*e.g.* endocrine, nervous system, cardiovascular, and musculoskeletal) (5) and reduce mortality risk, which leads to enhanced longevity (6). Regular exercise enhances energy metabolism throughout the body, maintains muscular robustness, and provides resistance to fatigue (7). Exercise hyperaemia is associated with an increase in skeletal muscle blood flow resulting from muscular activity (8). Hence, a high level of muscular oxygenation leads to successful exercise (9).

Many factors are involved in the difficulties associated with rheumatic disorders, including numerous pathophysiological conditions and infection/autoimmune functions (10). Different forms have been identified for the rheumatoid involvement of the nervous system, such as subclinical electrophysiologic outcomes, peripheral nerve entrapment, autonomic dysfunction, and vasculitis neuropathy (11). Rheumatoid arthritis (RA) is a systemic autoimmune and chronic inflammatory disorder that affects the synovial joints in particular; few treatments are currently available (12, 13). RA treatment plans change marginally each year, particularly given the developing knowledge on treatment methodologies appropriate to clinical practice (14). For example, biological disease-modifying anti-rheumatic drugs permitted for the treatment of RA comprise five different modes of action:

IL-6 receptor inhibition, B-cell depletion, tumour necrosis factor (TNF) inhibition, T-cell co-stimulation blockade, and interleukin-1 inhibition (15). Delays in detecting RA and implementing successful treatments have been associated with poor outcomes (16). However, plain radiographs, negative serology, and ordinary inflammatory markers are not legitimate reasons for delaying referral when RA is recognised as part of the patient's signs and symptoms (17). Bone loss is another disease characteristic of RA and includes localised, periarticular, and chronic bone loss (12). Additionally, the risk of severe infection (SI) for patients with RA is higher than in patients without RA (18). SIs notably include those of the respiratory system, joints, and skin as well as sepsis, bacterial infections of the bloodstream, cardiovascular disease (CVD), osteoporosis, and cancer (16, 19). Even if RA is untreatable, modern therapeutic strategies provide outstanding disease management (20). Often, orthopaedic surgery is necessary due to the involvement of joints for patients with inflammatory rheumatoid diseases (IRDs) (21).

Over the past two decades, scientific findings have revealed the effect of exercise on rheumatic disease care (22). Consequently, exercise is thought to be a potential treatment for patients with a rheumatic disease rather than medication, contradicting fears that physical activity may irritate inflammatory pathways (22). This is why, to relieve pain and provide overall health benefits, physical activity is recommended for its relative ease and availability (3).

Inflammation is an immune system biological response to avoid, restrict, and reverse damage caused by invasive pathogens or endogenous biomolecules (23). However, it is a two-edged sword. The inhibition of an inflammatory response can cause chronic inflammation, although it mainly manifests as a protective reaction to the removal and healing of injured tissues or deteriorated stimuli (24). Conversely, inflammation is necessary to prevent infection (25) and is generally classified as acute or chronic, each marked by different pathways. The regional vasculature, the immune system, and wounded site cells participate in acute inflammation (4). Chronic inflammation increases with age and is related both to visceral fat mass and inverted muscle mass (26). When cells sense pathogens or tissue wounds, inflammation is triggered by the innate immune system (4). The common feature of IRDs, such as RA and systemic lupus erythematosus (SLE), is chronic systemic inflammation (22). However, chronic inflammation and RA autoimmunity occur just before the onset of joint inflammation (27). Increases in oxidative stress with age may also lead to chronic inflammation and disease progression (28).

As a person ages, the rate of inflammation in healthy people increases; even though it may be low, the mortality rate is increased (26). Furthermore, patients who had RA for over 10 years showed higher death rates than the normal population (29), although rheumatic diseases seldom appear on death certificates as the cause of mortality (30). Today, the pharmaceutical care of IRDs ultimately aims to achieve and sustain relief, which includes the complete suppression of inflammation and pain and the avoidance of excess injury and organ damage (30). There is clear evidence that increasing regular exercise may simultaneously improve symptoms and reduce the impact of chronic events in RA (31). Hence, the induction of anti-inflammatory tracts and inflammation resolution is a treatment strategy for long-term disease control in patients with RA (32).

Inflammatory rheumatic diseases

Autoimmune and IRDs are major global health problems (33). The following is a discussion of both. IRDs are a heterogeneous category of chronic autoimmune disorders (34) that work via synovial inflammation, hyperplasia, progressive cartilage, and bone destruction (21, 35). IRDs are diseases that are commonly presented with multiple variables, and thus, multiple results are evaluated in most of these disorders (30). They represent a group of inflammatory conditions, including musculoskeletal findings, inflammation, and multi-system disorders (36) (the group includes over 100 of the latter) (37). Blocking or reducing inflammation is one of the essential treatment methods for these diseases (38). Systemic and local bone loss in IRDs comprises a typical result regarding functionality, representing the strong connection between the immune system and bone (37). Typically, such systemic inflammation contributes to chondrocalcinosis, psoriatic enthesopathy, gout, ankylosing spondylitis (AS), and early-stage RA (39). However, RA, SLE, idiopathic inflammatory myopathies, AS, systemic sclerosis, and Sjögren's syndrome are rheumatic autoimmune diseases with similar clinical properties, including chronic fatigue, depression, reduced physical activity, alternative pain (33, 38), morning stiffness and number of enthesis (30); therefore, these result in a poor quality of life in terms of human health and hypoactivity (38).

Globally, there is a growing number of elderly people with chronic IRDs (40). The proportion of IRDs is comparatively high in older age in patients with inflammatory diseases of the spine and joints, which may cause complicated diagnostic issues (41). Some patients with numerous IRDs have skin symptoms that cause impairment and significantly affect the patient's health (42). Personalised attention must be given to older patients with IRDs (40). Furthermore, there is an increase in mortality and morbidity due to elevated CVD pressures in patients with IRDs (43). However, many recent studies have found an elevated incidence of obesity-related RA, while no longitudinal studies for other inflammatory rheumatic diseases have been conducted (44).

Rheumatoid arthritis

The most common IRD is RA, which tends to impact the joints, triggering tenderness, joint damage, and swelling with bone loss in the joints at the articular and periarticular sites of inflammation (37) and in the connective tissue. It affects a wide range of age groups. RA initially starts when people are in their 40s (34) and is defined by a failure to relieve inflammation spontaneously (32). The disease affects nearly 1% of the population (17, 29, 45) and may

lead to permanent joint damage. Systemic treatment is an essential element of rheumatic disease therapy (46). Severe joint damage in RA, which greatly impairs a patient's quality of life, can be avoided by the use of therapeutics (47). For example, the early detection of RA enables better treatment with anti-rheumatic agents (48), *e.g.* detection using biomarkers and combining neurons into a network to calculate whether these outputs lead to RA based on magnetic resonance imaging (MRI) (47). The systemic autoantibodies characterising RA can be identified and produced from sites far from the synovial joint before the onset of symptoms (49). However, this early diagnosis remains challenging as it focuses primarily on clinical knowledge obtained from a patient's history and physical analysis in conjunction with blood and imaging tests (12). RA involves the wrists, hands, and feet; however, unusual signs may only be observed in joints like the knee (16).

In most cases of RA, symptoms of the hand and its functions begin early along with a loss of muscle strength, functional ability, and bone (50, 51). Attention should be paid to patients with RA in any case involving joint rigidity, discomfort, or swelling that lasts for more than two weeks (16). Usually, joint pain is symmetric and polyarticular, but it can also be monoarticular, asymmetric, or oligoarticular (including 2–4 joints) (16). However, according to a recent analysis by the European Group for Bone Marrow Transplantation, transplant operations for RA have now almost stagnated. Seventy patients with RA showed relatively high tolerance to haematopoietic stem cell transplantation (HSCT) with a 100-day transplant-related mortality of 1% and an overall survival rate of 94% (52). Although the transplant group has successfully adopted the concept of HSCT as a treatment for severe rheumatological conditions, it has slowly been discarded as chronic inflammatory arthritis and biological treatment options are also beneficial and potentially healthier (52).

Many patients with RA experience symptoms in other organs, including interstitial lung disease, bronchiectasis, pleural effusion, and pericarditis (16). RA fatigue is viewed by patients as debilitating, uncontrollable, and sometimes, untreatable because it is differentiated from natural fatigue (53). RA also increases CVD risk by about 2–3 times (54) and is directly correlated with CVD symptoms (55). The level of pentraxin 3 (a potential marker for severity in coronary artery disease [CAD]) in patients with IRD and CAD was found to be higher than in patients without IRD or those in the negative (healthy) control group (56). However, monitoring and preventing disease in these patients is essential since the CVD mortality rate is relatively high (55). As Carbone *et al.* stated, the main issue of mortality in patients with RA was established by CVD (57).

Understanding the major risk factor for RA

The risk of RA development significantly increases with early disease symptoms like palindromic rheumatoid disease (16). A high body mass index can also impact the prevalence of RA due to high alcohol consumption, reduced/skipped meals, poor dental hygiene, low socio-economic conditions, and smoking (16). Several studies have identified a link between smoking and RA estimated at around 20% to 30% of the environmental risk factor for this illness due to exposure (58). Hence, in rheumatological training, counselling against smoking for patients and their families should become a requirement (59). The increased risk of RA was correlated with several environmental and genetic factors. Among these, the highest correlations were family background, female gender, shared epitope (SE) as a heritage factor, obesity, and smoking (45, 60). SE alleles can contribute to more than 40% of the genetic factor of RA; however, other studies identified few correlations (45, 61). Several studies have also identified the link between physical activity levels and inflammation by gender and/or muscle mass (28). The highest risk factor for potential RA was linked with increased body mass and smoking (45). For gendered risk factors in RA, Frisell et al. argued that risk trends indicated that familial factors affect RA equally in both genders, which is less critical in the late stage of RA (61). While the genetic factors of RA are better understood, the role(s) of many of these genetic factors in the overall development of RA remains uncertain (45). Besides genetic factors, other factors are crucial, *e.g.* RA has been correlated with various environmental, nutritional, and lifestyle factors (Fig. 1).

The RA risk also varied in terms of foods and other variables, such as drugs and supplements (58). The occurrence of a rheumatoid and/or anti-citrullinated protein antibody (ACPA), high levels of C-reactive protein (CRP), or high incidence of erythrocyte sedimentation in a patient with IRD is aligned with an RA diagnosis (62). Additionally, the erythrocyte sedimentation rate (ESR), CRP, anti-cyclic citrullinated peptide, and rheumatoid factor (RF) should be tested in patients with suspected RA before referral to a rheumatologist (16). Emerging statistics suggest that epigenetic processes (*i.e.* the methylation of DNA), altered histone acetylation, and microRNAs lead to RA pathogenesis, possibly associated with gene expression alternations (63). In the development and progression of any autoimmune disorder, the epigenetic modulation of immune factors is essential (64).

According to the findings of Nielsen *et al.*, people with high RFs in the general population have a 26-fold increased risk of long-term RA and a severe risk of developing RA over 10 years of up to 32% (65). Nevertheless, it is unclear if the subsequent development of RA is related to elevated RF rates in individuals without RA in the typical population (65). Frisell *et al.* found a correlation of ~50% between familial risks and ACPA-positive RA and ~20% for a background history of ACPA-negative RA. However, knowledge of the correct function and timing of action for RA risk factors is essential given the introduction of the RA prevention trial and the possibility of effective preventive measures arising from a thorough understanding of genetic and environmental factors within RA (45).

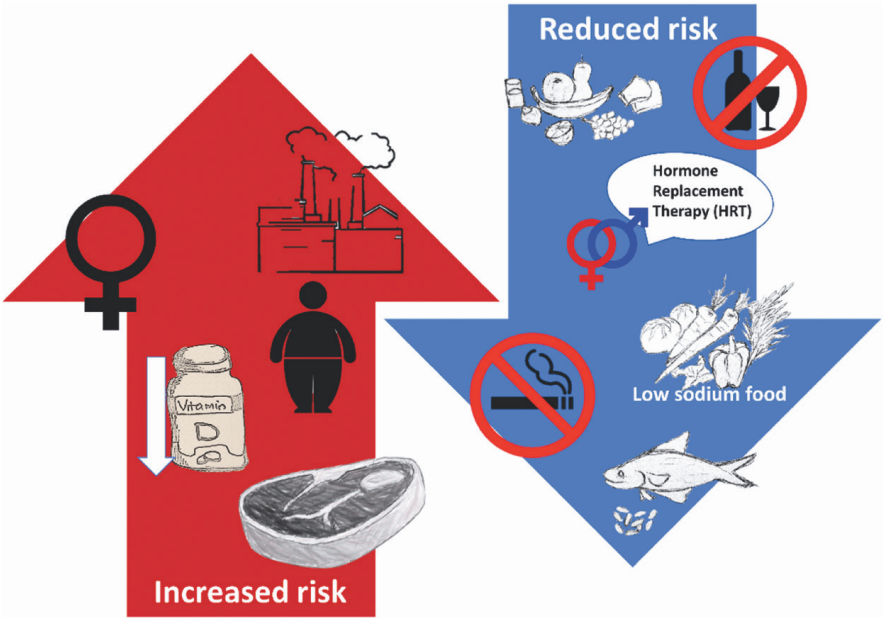

Fig. 1. Factors associated with rheumatoid arthritis risk. These factors that have been related to an increased risk for onset of RA included lower take of vitamin D, gender especially female at high risk, air pollution, obesity and consumption of red meat products; however, some other factors such as high consumption of fish, fruits, low sodium foods like vegetables, avoid consumption of alcohol drinks and smoking.

Synovitis

Rheumatoid synovitis has broad inflammatory characteristics that have been well discussed (66). Synovitis is described as an inflamed joint capsule distinguished by erythema, warmth, palpability, and swelling (16). Tendon symptoms during RA appear as tenosynovitis, with patients suffering from swollen tendons in the legs and hands (46); this can be diagnosed by the physical examination of articular and soft-tissue swellings with sensitivity to palpation due to synovitis (16). It can be described easily via medical evaluation, but advanced imaging may help patients with false symptoms (16).

Synovitis has a pathological characteristic in RA, including the expansion of resident synovial fibroblasts, the formation of new blood vessels, and the use of many different leukocytes (*e.g.* T and B lymphocytes, mast cells, and monocytes/macrophages) (66). Specifically, the structure of synovitis in RA contains various innate immune cells (*e.g.* dendritic cells [DCs], mast cells, monocytes, and innate lymphoid cells) and adaptive immune cells (*e.g.* T-helper 1 and T-helper 17 cells, plasma cells, and plasmablasts) (63). For diagnosing RA and determining appropriate therapeutic responses, synovitis is essential (16). IRDs induce inflammatory responses in different body tissues as a heterogeneous class of frequently chronic immune-mediated disorders (34). A vital concern of the disorder is significant synovial inflammation (synovitis), as pro-inflammatory cytokines, *e.g.* TNF-α, interleukin-1β (IL-1β), IL-6, and CRP, are increased by 3–100 fold (67). It is known that IL-1β plays an essential part in modulating joint inflammation and degradation in RA, and the function of this gene's polymorphisms in promoter region-511C/T has been studied extensively in RA (68). As epigenetics were discussed earlier, epigenetic alterations, especially disease activity, are increasingly understood as being linked to RA (64). In particular, shifts in methylation from RA joints were associated with overly aggressive RA in many parts of the genome of fibroblast-like cells (FLS). Such alterations in methylation are assumed to modify gene expression and stimulate disease development in patients with RA (45).

The synovium is the primary source of the inflammatory cycle; if left untreated, it can result in permanent damage to cartilage and bones (69). Synovial fluid does not tend to require the diagnosis of RA, especially in patients with polyarthritis (16). The synovial membrane (synovium) is essential for synovial joints and attaches the underlying tissue to the synovial fluid. This membrane contains four or five cell layers and has no membrane basement and no cell epithelium (70). The synovium's structure is very different; it has two main layers comprising the intimal (upper) layer and the subintimal (lower) layer (70). Healthy humans possess a layer of one to three cells, mostly consisting of macrophages and RA synovial fibroblasts (RASFs), in the intimal synovium on the edge of the joint cavity. However, in RA, the depth of this layer increases to 10–15 cells (71). The intimal layer is surrounded mainly by macrophage-like cells (namely, type-A synoviocytes), whereas the subintimal layer includes FLS (namely, type-B synoviocytes) (72). It is a critical feature of invasive synovium in FLS and plays a crucial part in activating and preparing damaging joint inflammation. In RA, FLS may be pathogenic because of their capacity to release immunomodulating cytokines and mediators and a wide variety of adhesive and matrix-modelling enzymes (73). Type A and B are identical in size; however, type A has a thin layer of sinuous attachments, while type B has long branches (72). Unlike type-A cells, type-B synoviocytes are in higher density (72) (Fig. 2).

The interaction between RASFs and some inflammatory cells enhances matrix degradation and the release of pro-inflammatory cytokines. In turn, these factors employ, maintain, trigger, and motivate the distinguishing features of various cell types that relate to the inflammatory cycle in RA (71). Leukocytes permeate the healthy synovial section, while synovial fluid is flooded by pro-inflammatory mediators; these interact to create an inflammatory cascade described by FLS interactions with innate immune system cells, macrophages, monocytes, DCs, etc. The adaptive immune system cells, including T lymphocytes and B cells, cell-mediated immunity, and humoral immunity (12). Based on a study by Filer *et al.*, an immunologic-protective effect

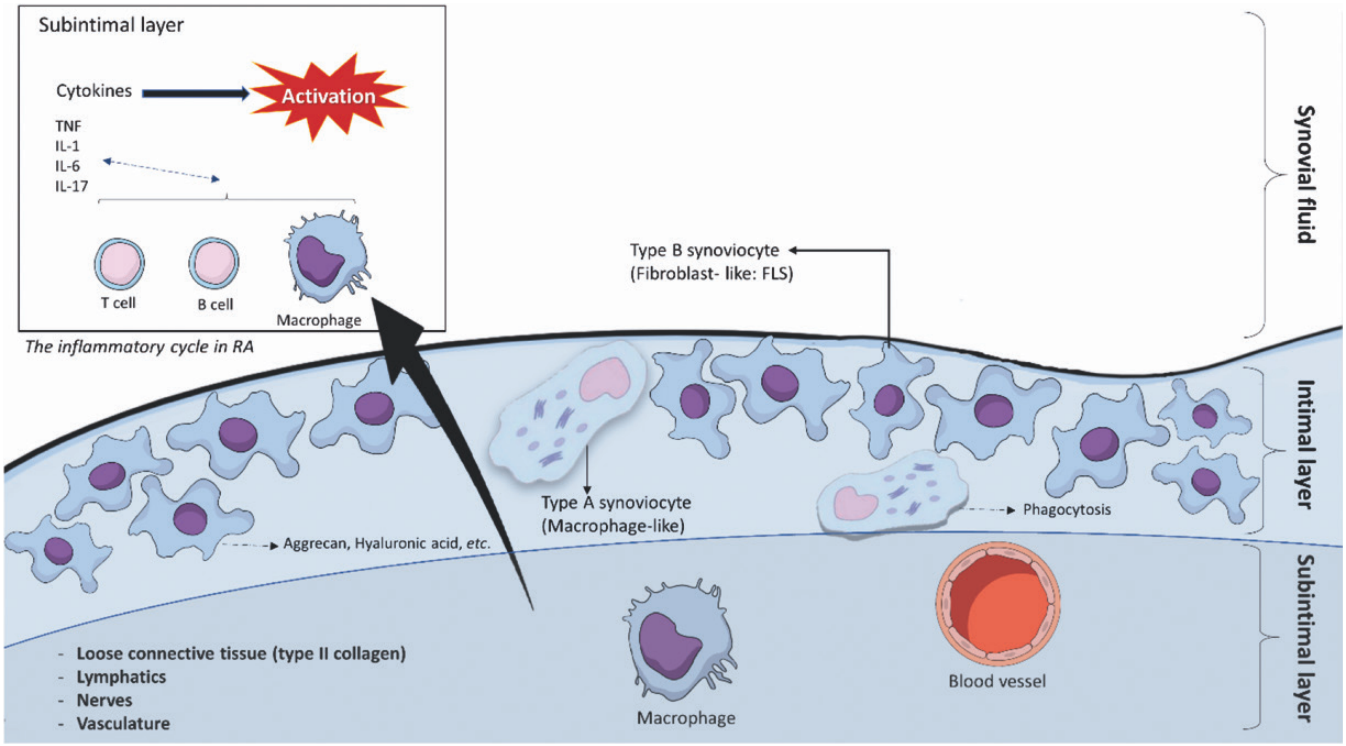

Fig. 2. Rheumatoid arthritis synovitis; The typical intima possesses single to three cells in depth and is comprised of bone-marrow-derived macrophages known like Type A synoviocytes and fibroblast-like Type B synoviocytes. The cells inside the intima generate extracellular matrix molecules and mediate the construction and clearance of synovial fluid. In subinitimal layer some cells offer to maintain and promote joint inflammation by producing collection of cytokines like IL-6.

in the latest patients with RA induced by TNF-exposed synovial fibroblasts prevents the adhesion of lymphocytic endothelial cells in a co-culture. The synovial fibroblast was found to be missing from recent-onset patients with RA who were still suffering from synovitis (66). Van den Ende *et al*. found that performing intense isometric and isokinetic exercises at 70% maximum voluntary contraction along with aerobic training at 60% maximum heart rate for a 24-week period may lower systemic inflammation and disease severity while enhancing muscle strength in patients with RA (74).

Exercise and inflammation

As the treatment for several diseases, exercise has therapeutic potential (6). The anti-inflammatory properties of daily exercise could help to enhance the medical benefits of working out (6). Therefore, one relatively new idea is the use of exercise as a possible anti-inflammatory treatment (22). Since the benefits of exercise are not typically immediate, several approaches can be used to improve them (75). Inactivity and muscle loss are two key contributors to the morbidity and mortality of RA (1). Regular exercise is vital for treating most childhood cases of IRD (75, 76) and for people with RA (77). Therefore, it is not only a safe treatment for rheumatic conditions but also an effective method of reducing systemic inflammation (22). Multiple pathways tend to regulate the anti-inflammatory effects of physical activity (23).

Conversely, as a non-medication approach, training exercises aim to improve a range of clinical symptoms in patients with autoimmune rheumatic diseases (38). For example, Pereira *et al*. reported that resistance training (RT) provides many benefits for patients with RA features. Additionally, RT does not intensify the development of illnesses or any articular diseases that lead to the modulation of inflammation (13). Hence, much evidence suggests that formal aerobic and neuromuscular training in patients with rheumatic diseases can enhance their performance, productivity, and quality of life (75). Van der Ende *et al*. showed that a short-term intense workout programme during active RA is more successful than a cautious one for improving muscular strength (74). Moreover, the health benefits of Tai Chi and yoga are proven to help minimise pain and improve physical function and quality of life in patients with RA (78). Therefore, aerobic and resistance exercises (REs) should be encouraged as part of the regular treatment for all patients with RA (67).

However, there has been no evidence of exercise alleviating systemic inflammation, especially in patients with RA, idiopathic inflammatory myopathy, or SLE (22). Exercise affects many parts of the body, including the central nervous system (79). Similar assessments have been conducted for several specific neurological and psychiatric disorders in relation to exercise. This is caused partly by changes in neurotrophic factors, such as neurotrophic brain-derived factors, decreases in oxidative stress, and neuroinflammation limitations (80). Although a particular exercise programme can cause a transient homeostatic cell imbalance, regular exercise will enhance both immunosurveillance and immunocompe-

tence (23). Therefore, it has been well established that although severe and intensive exercise can result in muscle injury and trigger inflammation, long-term exercise from low to high intensity has been modified negatively to promote an inflammatory reaction (79). However, physical inactivity leads to the decreased synthesis of myocyte proteins and enhanced protein degradation (1).

Several possible pathways combine oxidative stress with inflammation; however, the reactive oxygen species' (ROS) induction of the toll-like receptor on several immune cells plays a crucial role in initiating the inflammatory cascade (23). In reaction to exercise-related stress, including hypoxia, free radical release, overheating, and injury, the body initiates several endogenous defence and recovery systems to modify gene expression and release certain factors that protect the body against other threats (79). In particular, chronic physical activity can affect the immune system's response by supporting a non-inflammatory condition, which seems to be the main factor in improving health in chronic diseases (23). In some cases, inflammatory cytokines have been identified in people's peripheral blood following high-intensity, infrequent exercise, especially after performing extended contractions (28).

Advantages of exercise for patients with rheumatoid disease

Physical exercise can affect various disease-related symptoms and systemic expressions of RA, both beneficially and simultaneously (31). According to a study by Cooney *et al*., exercise is known to be generally beneficial to patients with RA (67). Physical exercise is also linked to improvements in muscle strength in patients with RA (81) and to cardiovascular health (82), and it may be essential for reducing the risk of CVD (31). Routine physical activity decreases the incidence of coronary heart disease, but intensive exercise can also increase the risk of cardiovascular mortality and acute myocardial infarction in vulnerable individuals (83). However, strength and cardiorespiratory training in patients with RA have been demonstrated as a treatment approach (84). The exercise technique has been developed to alleviate pain, reduce the inflammatory cycle, and restore joint mobility and muscle function in these patients (84). Hence, the positive effects of exercise include the improved functioning of skeletal muscle (2). This skeletal muscle energy intake plays a vital role in controlling whole-body energy homeostasis and functions as a thermal engine (7). Increased exercise and training is an approach that can improve both symptoms of RA and other related diseases while simultaneously reducing the overall cost of the illness (31). Additionally, exercise therapy in systemic diseases followed by inflammation has revealed a decrease in chronic inflammation markers, such as IL-6, IL-8, MCP-1, TNF-α, and IL-1β (35).

Conversely, exercise acts as an antioxidant: the ROS produced during hydrotherapy stimulate signalling mechanisms, such as mitogen-activated protein kinases and the nuclear factor (NF), which facilitate the up-regulation of antioxidant enzymes. Oxidative stress is minimised by neutralising ROS while reducing tissue damage and RA (85). Different methods of practice have positive effects on the characteristics of lipoprotein (31). Lecithin cholesterol acyltransferase results in exercise-induced improvements in lipid profiles (31). Acar *et al*. found that, concerning exercise therapy, calprotectin (a zinc-binding bioindicator) can be employed as a useful marker for the significant prediction of local inflammation (35).

The anti-inflammatory impacts of exercises are based on their positive long-term effect on the body's structure. However, it has been noted that early adiposity proliferation and the development of inflammatory processes are triggered in people who are overweight or obese, who show more inflammatory stress than healthy people (31). It also suggested that the regular treatment of middle-aged patients with RA should include physical exercise (84). Therefore, it is not uncommon that, due to their disease, nearly a third of patients with RA have an unemployment rate tenfold higher than the general population (31). Despite the importance of exercise, the age and gender of patients with RA make it difficult to exercise regularly (81); consequently, these patients are less likely to participate in such training programmes (82). While the literature remains uncertain regarding the impact of physical exercise on inflammation based on the duration of exercise and its intensity, form, and repetition, patients with RA are likely to avoid exercising due to their worries regarding worsening their symptoms.

Biomarkers in rheumatoid arthritis

Studies on rheumatological biomarkers have been focused intensively on the need to understand the concepts underlying rheumatic diseases (86). Several biomarkers, such as ESR and CRP levels, can be used before the onset of symptoms to identify people vulnerable to RA (87). The next task is to check whether the clinical responses to treatment biomarkers are reliable for a particular condition or are unique to a specific disease (88), such as RA. Biomarkers can be screened for patients at risk of RA to identify the initial stage of the disease and facilitate therapy to prevent its progression (86, 87). It may be convenient to validate the functional variety of cytokines in the circulation of those at risk of the disease by examining their serum (66). However, a biomarker that can trace the pre-treatment of patients with RA who respond to treatment has not yet been identified (86). There are several scenarios in RA that will benefit from the identification of biomarkers; these can be categorised generally as diagnostic (identified since the onset of the disorder), prognostic (related to the outcomes of an illness), and predictive (connected to treatment responses) (89). To better understand the mechanisms underlying treatment responses in RA, the biomarkers of various data types are likely to have to be assessed in the same people, which allows for a more systematic research approach (88). Also, those biomarkers that identify only tissues are less useful. A single mutated gene does not induce RA or other rheumatic diseases, and there is no reliable use of single or

multiple gene biomarkers (87). While mixed markers prove beneficial for indicating the disease activity and potential progression of joint destruction, several limitations still exist, including differences in data based on drug types, phase of the disease, and cost (90).

Generally, RA is separated into two groups of disorders, namely, seronegative and seropositive. Seropositive disorders include the existence of high levels of two autoantibodies in a patient's serum (45). Diagnostic criteria used by the European League Against Rheumatology/American College of Rheumatology track autoantibodies, such as RF and ACPAs (87). The existence of RF and elevated titres were associated with an increased risk of RA progression (86). ACPAs or RFs are widely used as biomarkers to classify patients with RA into two groups (seropositive and seronegative subsets and ACPA and/or RF negative groups) for medical results and clinical status (91). Cartilage oligomeric matrix protein (COMP) is a biological marker that is used to track joint damage and muscle atrophy in patients with rheumatoid disease or articular illness (13). One of the roles of COMP is to maintain the articular cartilage collagen fibre system, and the reality is that serum levels reflect its discharge from the cartilage. This adversely affects the inside of the joints of patients with RA, who are associated with higher COMP serum levels (77). Serum CRP (sCRP) is another indicator of systemic inflammation in RA; a range above 40 mg/L indicates moderate RA, while above level 100 mg/L in severe mode of this disease (77). A rise in systemic inflammation in RA has been commonly reported, as demonstrated by increased CRP levels (60). However, CRP has been tested in patients with RA under continued exercise without any significant baseline changes (92).

Nonetheless, biomarkers used for the diagnosis of RA, including CRP, ESR, ACPA, and RF, are not always used solely for this disease, and scientists have been attempting to establish new ones, such as disruptive enzymes and inflammatory cytokines (64). Cytokines are essential facilitators of a lesion's production and survival (66). For those who study obesity, diabetes, atherosclerosis, and metabolic syndrome, adiponectin is an adipose-tissue-derived hormone of concern (93). Giles *et al*. demonstrated that patients with RA exhibited elevated levels of radiographic serum adiponectin. The highest adiponectin levels were observed in patients with RA with low rates of visceral fat (94). CRP, leptin, and adiponectin were analysed by enzyme-linked immunosorbent assay (ELISA) (26). For a long time, ELISA was regarded as one of the best standard methods to detect cytokines in IRDs/RA, but today, multiple technological advancements have enabled biomarker programmes to identify entire cytokine systems (89). The following discusses cytokines and their effects on detecting RA.

Cytokines; modulators of preclinical rheumatoid arthritis

At some point in the natural history of RA, cytokines drop their trace (66). Cytokines are inflammatory polypeptides, small proteins, and mediators predominantly generated by hepatocytes, adipocytes, peripheral blood mononuclear cells, and muscles (89, 95). Several cell sources function on the cell on which they are produced (autocrine) or on neighbouring cells (paracrine) (89). Cytokines have pathways for paracrine or autocrine signalling and facilitate the reproduction, discrimination, and control of haematopoietic cells as well as other types of cells for protection (96). They are produced from peripheral afferents, including the peripheral termini of sensory fibres and Schwann cells, and also from some cells in the dorsal root ganglia and spinal cord (97). Leukocytes secrete cytokines for paracrine or autocrine effects, thereby controlling various cellular specialisation, initiation, migration, and protection functions (66). Rheumatic autoimmune disorders are considered to cause either systemic or local inflammation, as demonstrated by elevated cytokine inflammatory rates (38). The notion that pro-inflammatory cytokines can be used pharmacologically to eradicate illness has not yet become an effective treatment for patients with RA (66).

Additionally, cytokines (soluble factors and proteins) play a critical role in regulating all aspects of the immune response (98) and articular damage in the joints of patients with RA (99). The blocking of pro-inflammatory cytokines (*e.g*. TNF and IL-6) by monoclonal antibodies changes the effect on patients with severe RA (66). The function of cytokines is the maturation and triggering of osteoclasts. The receptor activator for the NF-κB ligand (RANKL), along with TNF, IL-1, and IL-7, tends to adopt a hierarchical role in this cycle (99). Inflammation, lymphoid development, homeostasis, differentiation, tolerance, and memory are all regulated by cytokines, which exert their activity by binding to specific receptors on the surface of target cells and inducing a signalling cascade, ultimately resulting in the aforementioned biological effects (98). Therefore, cytokines are a complicated cascading network system that is expected to guide the development and variance of the other cytokines in the patient's blood sample (96). This immune system activation leads to cytokines being characterised as anti-inflammatories (*e.g*. IL-2, IL-4, IL-10, and IL-13) or pro-inflammatories (*e.g*. IL-1, IL-8, TNF-α, IFN-T, vascular endothelial growth factor [VEGF], etc.) (23). It is well known that rheumatic joints promote autoimmunity (85), chronic inflammation, and further joint damage by the differences between pro- and anti-inflammatory cytokines (99). Therefore, IL-6, IL-10, and IL-1β are the clearest examples of the impact of exercise on cytokines (100).

Cytokines released from working muscle have traditionally been studied in terms of endurance exercise, but some data suggests that hormone replacement therapy also causes their release (*e.g*. IL-6 and IL-10) from muscle (26). By secreting exercise-induced proteins called myokines, skeletal muscle may interact with other organs (1). Myokines are proteins with autocrine, paracrine, or endocrine properties (1). IL-6 is a well-known myokine and is an excellent example of the possibility of well-established exercise/physical activity regulation in auto-paracrine and endocrine impacts

- Tumour necrosis factor (TNF)

TNF is a crucial factor in controlling the innate immune response (to prevent infection or trauma) and aseptic inflammatory diseases, including RA (25). It has been over 30 years since this cytokine was identified as a mediator of cachexia and fever and about 20 years since TNF inhibitors were first used for the treatment of RA (101). This cytokine refers to a superfamily of 19 related pro- and anti-inflammatory proteins (101). TNF is a pleiotropic cytokine and is one of the most important of the many cytokines involved in the immunopathogenesis of IRDs, infections, and neurodegenerative disorders (22, 102, 103). TNF stimulates the formation of endothelial cell adhesion molecules, inhibits endothelial-dependent dilatation, and restricts endothelial nitric oxide synthase and cyclooxygenase (22). TNF-α, which is developed mainly in macrophages (104), activates inflammatory responses and is released by activated monocytes, macrophages, and T lymphocytes (12). Many cells are sensitive to TNF (102). Although anti-TNF-α has been a clinical success, treatments for avoiding extensive losses of cartilage and bone are still needed (64). However, anti-TNF-α agents are costly and may cause adverse effects. Therefore, predictors of an effective response to therapy with these medications must be established (105).

- Interleukin-6 (IL-6)

In general, IL-6 is a pro-inflammatory cytokine with a pleiotropic function. Because it is metabolised by both T cells and macrophages, it has significant effects on non-immunological tissues (29). IL-6 facilitates the activation of the immune system, leading to inflammation (23, 106), tissue regeneration (91), induction of fever, differentiation of B and T cells, metabolism of iron and lipids, regulation of normal sleep (29), and maintenance of homeostasis (107). This cytokine includes 184 amino acids and contains a four-helix protein (29). Additionally, IL-6 signalling is a primary target for inflammatory tracts (108); it is found mainly in myofibres and is present in satellite cells and fibroblasts. IL-6 is developed and activated instantly and improves host defence against rising stress by triggering acute-phase reaction (APR) immune responses since homeostasis is distributed by pathogens or tissue injuries (107), including symptoms of APR, anaemia, and fatigue (106). APR is a systemic host defence system against pathogens and a wide range of harmful threats to the body (109). IL-6 also causes immune activation and initiates the destructive process of increasing RA disease activity (106). However, IL-6 inhibition has shown beneficial impacts on the fatigue, pain, and emotions of patients with RA (29). For example, tocilizumab (TCZ) and sarilumab are inhibitors of IL-6 (IL-6 receptor-inhibiting monoclonal antibodies) and are often used for the treatment of RA (106, 108), Castleman's disorder, and juvenile idiopathic arthritis (107). As a monotherapy, the most significant benefit of TCZ is its effectiveness (106).

Many cells generate IL-6, especially at inflammatory sites, including monocytes, T cells, fibroblasts, and endothelial cells (108). Virtually every stromal and immune cell produces IL-6 (29). When IL-6 is made in the stromal cells of bone marrow, the recipient activator κB (NF-κB) ligand (RANKL) is crucial to the distinction and initiation of osteoclasts and promotes FLS (107). VEGF may also contribute to the excess development of IL-6, which contributes to higher vascular permeability and improved angiogenesis (107).

Inflammatory biomarkers and their effect on exercise

Compared with healthy people, in patients with RA with impaired activity of the hypothalamic-pituitary-adrenal (HPA) axis, their levels of IL-6 increased, while their cortisol levels decreased significantly. This could be attributed to changes in the adrenal activity in RA, which plays a significant role in decreasing cortisol levels (110). There is much evidence of the HPA axis and IL-6 being related to RA-associated fatigue, including pain, inflammation, anaemia, poor sleep, and behavioural factors (29). Bernecker *et al*. discovered that in muscle tissue, the mRNA level of TNF-α and IL-6 was increased 2 hours after cycling (104). Thus, during chronic inflammatory stress (as in RA), IL-6 acts as one of the more powerful immune regulatory functions of the HPA axis. The dysfunction of this axis plays an essential role in the aetiology of RA disorders, particularly in association with the immune system (111). The secretion of IL-6 and stimulation of the HPA axis lead to fatigue and sleep problems (29). For instance, in patients with RA, IL-6 induces the HPA axis, which leads to transient hypercortisolaemia during the early hours, which may explain the poor quality of sleep during this time. Also, IL-6 may worsen RA-associated fatigue during its involvement in anaemia in addition to its impact on the HPA axis because IL-6 blocks the ferroportin-mediated transfer of cellular iron and drives hepcidin (29).

Exercise is a potent physiological improvement to the HPA axis. Intensity and duration are two critical factors that modulate the HPA axis reaction (112). During and after physical exercise, the exercise-induced level of circulating IL-6 increases, while the levels in the brain grow dramatically slower (23). Additionally, IL-6 is associated with liver regeneration and hepatic adaptive immunity for the stimulation of APR (113). The liver has already been recognised as the primary target organ of IL-6 under its previous name, hepatocyte stimulatory factor (113). However, in RA, chemotherapeutic drugs targeting the IL-6 axis become efficient, and other acute and chronic inflammation conditions are broadened (91). Several biological properties are initiated via IL-6. According to Acar *et al*., nitric oxide was also observed to induce joint damage in RA and stimulate the production of pro-inflammatory cytokines, including IL-6, TNF-α, IL-8, IL-18, and IL-1β (35). Table I identifies research that demonstrates the association between elevated activity in patients with RA and inflammatory biomarkers.

Multiple inflammatory parameters have been discovered to be influenced by RE (26). The study by Pereira *et al*. re-

Table I. Selected studies indicating the linked between increase exercise activity and inflammatory biomarkers in RA patients.

N	Age	Physical activity	Inflammatory biomarkers	Reference
34	45-65	Resistance exercise in a 25 min, with one total of 12 repeats at 50 per cent of a maximum repeat (1RM) and one set of eight repeats at 75 per cent of 1RM.	TNF-α ↕, IL-1β ↓, IL-10 ↑, IL-1ra ↑, IL-6 ↑, CRP ↕, COMP ↕	(13)
28	55.1±11.8	Low-density exercise therapy for 8 weeks	CRP ↑, RF ↑	(35)
96	54.4±12.6	A treadmill exercise test monitoring heart rate (HR) at two sessions, 1 min post HR peak and 2 min post HR peak along with CVD risk	HsCRP ↑, WBC ↓, Fibrinogen ↓, ESR ↓	(114)
66	18-75	3-month assessments followed by observation personalised physical activity schedule on disease activity, quality of life, body mass, CVD risk and cognitive.	CRP ↓	(82)
62	49±10	Strength training regulation averaged 1.4–1.5 per week: recreational exercise like walking, cycling, skiing and swimming for 2 or 3 times per week for 30–45 min period of time.	ESR ↓	(51)
64	60	RA patients who have been allocated in the hospital randomly for 14 to 30 days for an intensive exercise program or to a conservative exercise program.	ESR ↓	(74)
24	60±12, 57±14	Intensive exercise training; 2 sessions during and after eight-week combined aerobic and resistance exercise include progressive resistance and walking exercise program.	COMP ↑	(77)

ESR: erythrocyte sedimentation rate; COMP: cartilage oligomeric matrix protein; CVD: cardiorespiratory fitness, HsCRP: high sensitivity C-reactive protein; RF: rheumatoid factor; ↕: fluctuation observed.

vealed that IL-10 and IL-1ra increased after RE in patients with RA and suggests that RE produces an acute and immediate anti-inflammatory effect (13). For some patients with RA, their CRP levels can remain normal, regardless of their operation (115). A study by Azeez *et al*. revealed that the CRP level in the study's exercise group was substantially reduced (82). This reduction level was consistent with earlier exercise activity results, which reduced systemic inflammation markers in the RA group (51). Some studies have shown no link between inflammation or disease activity and autonomic function in RA, while CRP and leukocytes, for instance, have been thought to be associated with autonomic dysfunction, although no such correlation has been identified in the available research (114).

However, the increased risks for CVD in healthy people were related to higher CRP levels. In patients with RA with a prior CVD risk, this could be more significant (82). A recent systematic review has shown that routine exercise activity reduced IL-6 and CRP in elderly people, although there was no significant change in TNF-α (116). Based on the work by Lahaye *et al*., without any activity, older patients with late-onset RA demonstrated higher IL-6 and lower TNF-α levels than younger patients with early-onset RA (40). Santos-Moreno *et al*. (105) indicated that relapses in RF-positive patients treated with anti-TNF-α agents were less prevalent and more serious than in RF-negative patients. Hence, a recommended approach to reducing cardiovascular risk is regular physical exercise (117). However, based on work by Thompson *et al*., the exact rate of sudden heart death associated with exercise differs from the disease's incidence in the sample population. No procedures to assess the potential to reduce exercise-associated CVD have been studied sufficiently (83). In their case study, Sharif *et al*. recommended that RT can be an excellent tool to increase the number of nuclei per fibre field, decrease apoptotic nuclei, and cause fibre hypertrophy in people with RA, and it is expected to improve isokinetic strength and muscle hypertrophy in RA cases (60). Based on the findings of Law *et al*., COMP markers were higher in patients with RA compared with control subjects (77). Wang *et al*. showed that leptin in patients with RA enhanced follicular T-helper cells and IL-6, IL21, and IL12 rates primarily via the stimulation of STAT1 and STAT3 mechanisms (118). However, once training stopped, the positive benefits of exercise were lost.

Conclusion

In conclusion, the evidence supports the use of exercise for patients with RA in terms of its effects on inflammation biomarkers. Now, research is needed to properly understand the implementation of physical exercise in medical care, given the beneficial impacts on clinical RA and the patient results of physical activity. Both aerobics and strength exercise training should be recommended for all patients with RA as part of their routine treatment. This therapy can be recommended by rheumatology healthcare professionals and include social innovation in its application. Based on the nature of RA and the frequency, intensity, and duration of the exercise, specific activities that are most beneficial for treating individual patients can contribute to their successful treatment. Current studies are investigating the role of artificial intelligence (AI) in the onset of RA. The application of AI methods to measure early RA from MRI data has been initiated in the research. According to the ongoing research, it could be practical

to use smartphones or biomedical devices to deliver exercises and physical activities and encourage more patients to take up routine exercise.

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