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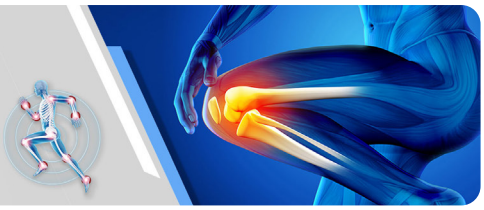

Beneficial Effects of Physical Activity in Rheumatoid Arthritis Patients: Focus on Active Biomolecules

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Abstract

Physical Activity (PA) has a fundamental role in subjects with Rheumatoid Arthritis (RA), in terms of motility, joint function, muscle wasting, BMI (Body Mass Index), Cardiovascular Fitness (CRF), mental health, but also changes in bioactive molecules that might influence the disease activity and patient's wellbeing. Literature was searched for clinical trials, randomized-controlled trials, and pilot studies published in the last 15 years. Studies using as adjunctive therapy aerobic exercise, High-Intensity Interval Training (HIIT), and moderate training were included. The available papers shown that exercise programs improve joint's mobility and flexibility and the overall health status, without differences regarding age, gender or disease activity. All these findings are supported by the modulatory role of exercise-induced cytokines as interleukin-6 (IL-6) and irisin, together with a reduction of inflammatory markers.

Keywords: Rheumatoid arthritis; Physical exercise; Quality of life; IL-6; Myokines; Irisin; Rowing

Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune symmetrical polyarthritis that leads to chronic synovitis, joint destruction, and poor life quality. RA affects nearly 1% of adult population, it increases with age, and is more common with females (the female to male ratio is 2-3:1). It is characterized by symptoms such as fatigue, pain, stiffness, and swelling that may have devastating effects on quality of life and functional abilities [1]. The psychological impact of RA is also of primary importance, because a considerable number of RA patients often show depressive symptoms [2]. In this context sport and Physical Activity (PA) in general may provide a mental and physical benefit to the subjects because increases endorphin release and improves cognitive function, as recently reviewed [3].

The World Health Organization (WHO) defines PA as "any bodily movement produced by the skeletal muscles that requires energy expenditure". The suggestion for the general population is 150 min/week of moderate-intensity aerobic exercise or 75 min/week of vigorous-intensity aerobic activity [4]. Research suggests that RA patients are known to have an augmented risk of CVD (cardiovascular disease), diabetes and bone and muscle loss, pathologies which are known to respond well to physical activity (PA), reducing their incidence. In this context, considering exercise as a therapy [5] may be particularly beneficial for RA patients as PA may bring an improvement of symptoms related to the chronic inflammatory

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status, and therefore, of their quality of life, particularly if the exercise program prescribed to the patient is carefully chosen to maximize benefits. In RA a proper understanding of the biomolecular mechanisms, such as variations in inflammatory cytokines and myokines underlying this disease is important to help patients with the correct prescription of exercise. Moreover, it is important that the disease activity is also evaluated through DAS28 (Disease Activity Score in 28 joints) and the Modified Health Assessment Questionnaire (M-HAQ) to have a comprehensive insight of patient's status.

Considering that many other papers already dealt with the beneficial effects of sport and physical activity in general, this work is meant to specifically evaluate the effects of physical activity on the production of bioactive molecules, as cytokines, in patients with rheumatoid arthritis subjected to a sport therapy protocol.

Methods

A literature research of pilot studies, clinical trials or Randomized Clinical Trials (RCT) written in English and published between 1995 to 2020 using PubMed and Scopus, for the following search terms: "exercise", or "physical activity", or "sports", combined with "rheumatoid arthritis" and "inflammatory cytokines", or "cardiorespiratory fitness" (CRF), or "cachexia", or "IL-6", or "irisin", or "leptin", or "NO" (nitric oxide), or "COMP" (Cartilage Oligomeric Matrix Protein). On the basis of these search criteria we retrieved 848 papers and 30 have been selected to be included in this review. Inclusion criteria were: written in English; clear inclusion/exclusion criteria of patients; enrolling patients aged 18 years or older with a diagnosis of RA and able to perform physical training; clear description of the training protocol; and studies focusing on the possible beneficial effects of PA in terms of improvement of symptoms. Exclusion criteria were: evaluation of the effects of pharmacological therapies; concomitance of other rheumatological diseases or severe disabilities; concomitance of psychotherapeutic sessions; use of dietary supplements; and administration of musculoskeletal rehabilitation therapies rather than training programs.

Results

Physical activity benefits and improvement on body composition

The major role of exercise in RA patients

PA has a fundamental role in RA patients, in terms of motility, joint function, muscle wasting (cachexia), BMI (Body Mass Index) and reducing incidence of CVD.

Approximately more than half of RA patients suffer musculoskeletal affections, first initially to the small joints, then to the large ones. In these patients, RA causes synovial inflammation with significant loss of joint function. The "RAPIT" (Rheumatoid Arthritis Patients in Training) study [6] correlated exercise program and RA included a total of 146 patients (mean age 54 and mean duration of RA 5 years) who undertook subjected to an intensive exercise program (strength and endurance training for 2 years, twice a week, for 75 min) like running, stair climbing, and/or throwing. The exercise program and was changed periodically every 8 weeks. The study found that after 2 years, over 78% of patients were satisfied and would endorse the program to other patients, as a matter of fact it was also noted found that disease severity did not negatively impact on the compliance in intensive exercise programs [6].

Body composition changes in RA patients

RA patients are often affected by body composition changes, such as obesity and rheumatoid cachexia, the latter is being characterized by increased fat and loss of muscle mass. It is known that the long-term beneficial anti-inflammatory effects of exercise are mainly based on body composition and on the reduction of the size of adipocytes [7,8]. Rheumatoid cachexia and BMI (Body Mass Index) may be considered as biomarkers for severe rheumatoid disease, because cachexia increases inflammation, especially in joints, with a consequent worsening of prognosis for CVD-related morbidity [9].

Several studies have been conducted in patients with RA in which the PRT (progressive resistance training) program has tested for effectiveness. Ten patients (mean age 53 ± 13) with well-controlled RA were trained 2.5 times per week for 12 weeks. Patients with similar disease activity were studied with a control group. In response to PRT a significant increase in lean mass (especially at arm and leg level) and in total body protein was observed without any exacerbation of disease activity. Post-intervention a significant loss of body fat mass, mainly in the trunk, was also achieved, suggesting that intense PRT seems to be effective and safe for stimulating muscle growth in patients with RA [10]. In a similar study, the efficacy of high-intensity PRT twice a week, in restoring muscle mass and function and to investigate the role of Insulin-Like Growth Factor (IGF) following exercise-induced muscle hypertrophy was tested in patients with RA. The study, conducted on enrolled 28 RA patients subdivided in 2 groups (13 PRT and 15 controls) followed for 6 months, demonstrated that PRT increased lean body mass reduced trunk fat mass, improved training-specific strength and knee extensor strength. In addition, following PRT, an increase in IGF-1 and IGF binding protein 3 was observed due to muscle hypertrophy [11].

The studies here reported suggest that despite body composition is being strongly related to inflammatory state in RA patients, fat distribution can be modified with an appropriate training program and physicians should pay close attention to BMI index in particular in subjects with rheumatoid cachexia.

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Physical activity improves cardiorespiratory fitness in RA patients

The maximal oxygen uptake (VO_2max) test is commonly considered as the best method to assess Cardiorespiratory Fitness (CRF), the test evaluating the maximum oxygen intake during an exercise was first described in 1923 [12]. As expected, RA patients have a limited tolerance to physical stress and their CRF should be improved to prolong their life expectancy. High-Intensity Interval Training (HIIT), performed 3 times weekly at 60-85% of maximum heart rate, for duration of 30-60 minutes, is recommended to increase CRF [13].

In a 10 week study walking-based HIIT program was prescribed to 12 previously inactive patients (aged 64 ± 7 years) with bone erosion. Training sessions were set at 30 minutes 3 times/week of HIIT at 80–90% of VO_2 reserve. At the end of the program an improvement in CRF, with a reduction in DAS28, number of swollen joints, plasmatic inflammatory cytokines, and blood pressure. Patients well tolerated the prescribed physical activity and the observed improvement in inflammatory markers might be responsible for the reduced disease activity [14].

Another study recruited 68 RA patients (age = 55 ± 13 years, BMI: 27.8 ± 5.4 kg/m^2, median of disease duration = 5 years) and using the International Physical Activity Questionnaire (IPAQ) and the GT3X (accelerometer) the subjective and the objective PA level was evaluated and correlated with the VO_2max test results obtained during the study. IPAQ-reported moderate and vigorous PA positively correlated with VO_2max, while all PA levels derived from accelerometry positively correlated with VO_2max, and eventually a negative association to Sedentary Time (ST) has emerged. The authors concluded that accelerometry data are of importance when self-reported PA levels are taken into account in RA patients [15]. A study from UK enrolled 36 RA patients (28 female and 8 male, mean age 53.9 ± 9.9 years, BMI 28.8 ± 5.1 kg/m^2) equally distributed in 2 groups to receive 6 months of individualized aerobic and HIIT 3 times/week or control (advised on exercise benefits and lifestyle changes). At the end of the 6 months VO_2max, blood pressure, triglycerides, High Density Lipoprotein (HDL), BMI, body fat, 10-year CVD event probability, C-Reactive Protein (CRP), and DAS28 were significantly reduced in the active group. VO_2max improvement was the major and strongest predictor for all of the assessed CVD risk factors and disease characteristics in RA patients [16].

In addition, a European study revealed in a 6-month supervised CT (combined strength and endurance training) program with 40 RA subjects (41-73 years of age, 26 female and 4 male) divided in 2 groups, that PA resulted in considerable improvements in muscle strength, cardio-respiratory endurance, lean/fat mass rate, and functional ability. The results showed that long-term training consisting of sets of weight bearing exercises for all major muscle groups combined with systematic endurance training on a cycle ergometer two times per week is useful to reduce disease activity and pain with no deleterious effects [17]. Similarly, an Irish study included 66 patients (34-74 years of age, 80% female, median duration of disease 10.5 yrs.) with RA, of which only 45 completed the program, and assigned to a personalized exercise program (daily exercises for cardiovascular health and strength training) or standard care for 3 months, evaluated CRP, DAS28, and CVD risk factors. RA subjects in the exercise group showed a significant reduction in BMI, waist circumference, and truncal fat percentage, with an increase in VO_2max of 18.9% [18].

Noreau et al. [19] studied 29 persons (19 cases and 10 controls), with mean age of 49.3 ± 13 years for cases and 49.4 ± 12 years for controls, who participated in a 12-weeks (twice weekly) dance-based exercise program. For the first 3 weeks the target was individually fixed to 50% of the maximal heart rate reserve (determined with Karvonen formula) and for the last 9 weeks to 70% of the maximal heart rate reserve, to demonstrate a significant improvement in aerobic power. Positive changes have been observed in physical and mental wellbeing, less use of pain killers, joint pain and swelling, DAS28 and psychological state after the 12-wk training program and at the 6 months follow-up]. In a shorter study on 12 sedentary subjects (11 female, 1 male; mean age 64 ± 7 years) performing a 10 weeks program of 3 × 30 min sections/week of supervised treadmill workout demonstrated an improvement in CRF, specifically in the VO_2peak ($p<0.001$ vs. basal values) [14].

Indeed, a recent randomized clinical trial, involving 15 RA patients in 8-h experimental conditions showed promising results with a clear distinction according to the intensity of training. While the interruption of sitting, characterized by a 3-min bouts of light-intensity walking every 30 min of sitting, produced an improvement in glycemic and inflammatory markers; 30-min bout of moderate-to-vigorous exercise followed by prolonged sitting improved lipid profile and hypotensive responses [20].

These studies indicate that improved CRF plays a fundamental role in RA patients, leading to a reduction in CVD risk and improving quality of life. However future studies should direct more efforts on PA prescription programs, including larger cohorts and longer follow-up.

Biomolecular aspects of physical activity in RA patients

Skeletal muscle as endocrine organ

Since the skeletal muscle is the largest organ in the body, its production and consumption of energy is critical for regulating the whole systemic metabolic control. Skeletal

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muscle has been recently identified as an endocrine organ that secretes hundreds of the so-called myokines, including IL-6 and irisin [21]. These myokines act both locally in the muscle in an autocrine/paracrine way, and through their release into the bloodstream as endocrine factors to regulate physiological processes in other tissues. It has been shown that the release of myokines, through muscle contraction, is at least partially responsible for the beneficial effects of PA. In fact, PA plays a protective role against the main low-grade chronic inflammatory diseases such as RA, type 2 diabetes, insulin resistance, metabolic syndrome and many others [22].

Biomolecular bases of Immunopathogenesis in RA and the role of physical activity

From a genetic point of view there is a robust association between RA and HLA-DR4, a genetic anomaly, found in 70% of subjects affected by RA, of the human leukocyte antigen. Basically, in RA there is an aberrant inflammatory response to an unknown antigen which eventually leads to joint injury, induced by T-lymphocytes (CD4- CD8) that prime B-lymphocytes. These latter, eventually differentiate into antibody-producing (Rheumatoid Factor, Polyclonal Antibodies) plasma cells, and activated macrophages which further sustain inflammation [23]. Systemic manifestations are due to the release of proinflammatory cytokines into the circulation, mainly represented by TNF-α, IL-6, IL-1 and IFNγ. Physical exercise has a role in an attempt to modulate the inflammatory response through the reduction of these cytokines.

In particular, TNF-α is one of the main inflammatory cytokine involved in the development of joint destruction in RA and as a matter of fact the most relevant innovation in the treatment of moderate-severe RA was the introduction in the therapeutic algorithm of anti-TNF-α antibodies [20]. TNF-α is produced usually by activated macrophages in the synovial membrane tissue in RA patients and is responsible for triggering the expression of other inflammatory molecules, such as IL-1 and IL-6. Moreover, IL-6 was first recognized in 1986 and it is a cytokine that has a function of last effector and rules the activity of IL-1 and TNF-α. It is commonly produced by macrophages and now is identified as a pleiotropic factor that activates B and T cells, macrophages, osteoclasts, chondrocytes, and endothelial cells [24]. Some studies demonstrated no differences in inflammatory cytokines plasma levels, dosed by radioimmunoassay (RIA) post-exercise programs [25,26], however these findings are in contrast with the results obtained in more recent studies, which employed improved detection techniques, such as ELISA test, to quantify plasma variations, even minimal, of cytokines and myokines pre and post exercise sessions [27].

During an exercise session, the first cytokine released is IL-6, prior to other cytokines, with a different pattern of expression compared to classic inflammatory pathway where IL-6 is stimulated by TNF-α and causes IL-1β release. As a matter of fact, during physical activity IL-6 triggers the release of cytokines, such as IL-1ra (interleukin-1 receptor antagonist) and IL-10, that exert an anti-inflammatory effect. These effects are mediated by lactate, which binds to a specific subtype of G-protein receptor, namely GPR81, on macrophages that in turn stimulates the activation of the p38-calcineurin-NFAT (a transcription factor specific of T cells) pathway and finally IL-6 mRNA production [1,28,29]. The elevation in IL-6 induces also the release of the soluble TNF-α receptor (sTNF-R) which binds circulating TNF-α, thus producing an additional anti-inflammatory effect on rheumatic joints [30,31]. IL-6 blood concentrations increase over 100 fold depending on duration and intensity of exercise following a non-linear trend, with a peak shortly after a training bout and further increase following long sessions [32].

A previously discussed study conducted by Bartlett and coworkers [33] investigated the levels of IL-6 and other cytokines related to physical activity and did not find any difference after 10 weeks of moderate training. The authors enrolled only 12 subjects which however demonstrated a trend of increase in IL-6 levels, while the prescribed physical activity was only 30 minutes of treadmill activity and the program lasted for 10 weeks, thus a medium-short time and a mild volume of exercise to obtain significant results.

In another study with 12 subjects with RA and 9 with prediabetes were assigned to a HIIT supervised program for 10 weeks doing high intensity intervals of treadmill training. In this study an increase in lean mass and in cardiorespiratory fitness with no changes in myokines was observed in RA subjects. At baseline and after training subjects underwent also a muscle biopsy of the vastus lateralis, and IL-6 and TNF-α have been measured together with galectin-3, but no changes in the inflammatory cytokines were noted, except for galectin-3 [34]. Despite the well-known crucial role of IL-6 in RA as a target for the treatment of moderate-severe forms on one hand and the demonstrated beneficial effect of its increase in the reduction of joint inflammation on the other hand, the published papers did not provide evidence that physical activity is able to modify pro-inflammatory cytokines in RA patients.

Irisin and Leptin

The fibronectin type III domain containing 5 (FNDC5) gene encodes a protein in the skeletal muscle that is proteolytically cleaved to the active form, called irisin [35]. Irisin is secreted primarily in skeletal muscle, specifically in the perimysium, endomysium, and nuclear parts, though adipose tissue, pancreas, sebaceous glands, and cardiac muscle have been recognized as secretory tissues [36]. In the skeletal muscles, PA activates the transcriptional regulator Peroxisome proliferator-activated receptor-γ coactivator 1α

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(PGC-1α), which contributes to the synthesis of FNDC5. PGC-1α mediates the programming of energy metabolism in transcriptional biological systems, controls mitochondrial biogenesis, angiogenesis, fiber kind switching, and oxidative metabolism in many cell types [37]. The skeletal muscle is an important site of insulin resistance due to its specific glucose uptake activity. Several experimental studies propose that irisin influences glucose metabolism in skeletal muscle in an autocrine manner [38,39]. However, the impact of exercise on irisin concentration in the blood is controversial and no relevant studies have been published to date in RA patients. Current evidence showed a significant inverse correlations between serum irisin and DAS28, subclinical atherosclerosis (measured by intima-media thickness), BMI, as well as insulin resistance. The study compared 60 RA patients mean age 47.03 ± 9.5 years (88.3% females) with matched controls [40]. More specifically, significantly lower levels of irisin were found in patients with moderate and severe disease, cardiovascular comorbidities including cardiometabolic risk. The vascular improvements promoted by irisin in patients at risk of cardiovascular events have been explored by numerous interventional studies assigning patients to physical activity programme [41], supporting the idea that irisin might have a beneficial role also in RA.

Leptin is an adipokine secreted via the white adipose tissue. Crossing the blood-brain barrier, it can elicit satiety via the activation of leptin receptors in the lateral and medial hypothalamic areas for decreasing food consumption [42,43]. There are neuronal pathways that mediate the outcomes of leptin on thermogenesis: leptin activates the hypothalamus to promote strength expenditure in the cardiovascular system [44], and induces thermogenesis through browning adipose tissue activation [45]. Moreover, leptin activity is strictly related to insulin resistance and the development of metabolic syndrome [46]. In a study involving 33 RA patients (9 males, 24 females; mean age 52.5 ± 12.3 years; range 29 to 75 years) and 24 age and sex matched healthy controls (11 males, 13 females, mean age 42.5 ± 14.8; range 18 to 75) leptin was measured to match clinical and laboratory parameters of disease activiy and radiographic progression. RA patients have been divided in low, moderate and high disease activity according to DAS28 score. However, no significant differences have been observed according to disease activity stratification, inflammatory markers, BMI and radiologic progression [47].

Another study compared serum leptin levels in 50 patients with RA and 34 control subjects to investigate the correlation with BMI, DAS28, serum TNF-α levels, and CRP. While the results showed that serum leptin levels were higher in RA patients compared to healthy subjects, no correlation was found with disease duration, DAS28, TNF- α levels. In addition, serum leptin levels positively correlated with BMI in both patient and control groups and was higher in women than men [48]. Conversely, another study involving 41 RA patients and 25 healthy subjects reported that leptin levels, measured in the synovial fluid, correlate with RA duration, CRP, X-ray changes and rheumatoid factor positivity [49]. Given the controversial relations found with leptin and the hallmarks of RA, leptin does not seems an useful biomarker, moreover currently no studies have assigned patients to PA programs to investigate changes in leptin and the clinical features of RA.

COMP

Cartilage Oligomeric Matrix Protein (COMP) is a 435 kDa extracellular, non-collagen protein, also defined as thrombospondin 5, and it is a homopentameric extracellular matrix glycoprotein member of the thrombospondin family of calcium binding proteins, which is primarily located in the cartilage and to a lesser extent in the normal ligaments, menisci and tendons. It binds collagen type I and II molecules and appears to play a role in the homeostasis of fibrils structure and in the renovation of the collagen network [50]. Synovial inflammation in RA triggers a progressive loss of cartilage matrix components due to enzymatic proteolysis which is mediated through a cascade of several cytokines [51].

The results of a randomized clinical trial, the RAPIT study, analyzed serum COMP (sCOMP) levels according to physical activity exposure. The trial enrolled 281 individuals and 145 were assigned to the exercise group, based on intensive weight-bearing exercises, and 136 to the usual care (UC) group, defined as standard physical therapy. While sCOMP levels showed a significant association with large joint damage, no predictive value for future joint damage was identified after three months of PA [52].

In addition, the reduction of COMP levels after PA have been reported in another study involving RA patients and healthy controls. Although limited by the low number of participants, a significant change in COMP, IL-6, IL-1β, L-1ra, IL-10 was observed after resistance exercise session (knee extension, knee flexion, hip abduction and hip adduction), without relevant changes in TNF-α and CRP levels. The authors concluded that inflammation biomarkers have similar changes in response to exercise sessions in women with and without RA and the increase of IL-10 and IL-1rα might indicate that PA may have an immediate anti-inflammatory effect [53].

The importance of a sport therapy in RA patients

Exercise is really useful for people with RA. However, patients and health specialists have expressed concern about the possible harmful consequences of exercise on joint health.

RA patients have difficulties in making simple movements because of the pain in the joints, the goal of physical therapist

is to prescribe exercises to stimulate muscles, bones, and joints. Sport and regular physical activity provide an improved muscle tone, strength, flexibility, and resistance to fatigue. To be supportive the sport therapy has to be prescribed by a specialist that understand the mechanics of bones, joints, and muscles working together, the injuries that can occur, and how to deal with them. Moreover, the type of sport chosen, frequency, intensity, training programme and possibly also the equipment/gear used for sport prescribed may need to be carefully adjusted to maximize benefits over risks. For example, one of the sports that can be of help in keeping the joints as healthy as possible in RA patients is rowing. Rowing can be a recommended sport for patients suffering from rheumatoid arthritis as its technical gesture trains joint mobility (i), the movement involves all muscle groups (ii), the body does not encounter gravity during movement (iii), and furthermore, in the outdoor setting being at close contact with nature provides additional emotional benefits [54]. Irrespective of which sport is chosen, it is essential that clinicians who work with the patient get at least basic knowledge of how the sports is performed, from both biomechanics and physiological perspective. In the case of rowing, it is important to recognize that rowers apply force during the drive phase of the rowing stroke cycle via the hands on the oar(s) and the feet on the foot stretcher, in a cyclic pattern, which has a "drive" or "work" phase and a slightly longer "recovery" phase. The drive phase is initiated when the blade(s) enters the water. The rower's ankles, knees and hips are in a flexed position preparing for the drive phase where the legs extend moving the pelvis towards the bow of the boat, the trunk extends and arms are drawn toward the body. The 'finish' position occurs when the ankles plantar-flex, knees and trunk are extended and the blade(s) are withdrawn from the water. In the above described sequence of movements large joints are involved such as: the scapulohumeral, elbows, knees, ankles, joints of the spine; but even minor joints such as those in the hands and feet have a role in the movement as the rower grips oars with fingers and pushes with feet, thus always keeps all joints active [55]. Rowing has a positive impact on body structures as the subject does not encounter gravity, therefore it has no impact on the joints and while in traction the athlete is in suspension therefore does not oppress large structures.

Rowing can also be practiced indoors using machines called rowing machines, and weak joints can be reinforced as also suggested by the arthritis foundation (https://www.arthritis.org/health-wellness/healthy-living/physical-activity/other-activities/tips-for-using-a-rowing-machine-safely-with-arthri). However, as emphasized above, a proper assessment needs to be made by the clinicians since it also known that rowing is not recommended for in people with severe knee osteoarthritis is not recommended because the cartilage could be damaged [56,57]. Obviously, in addition to rowing, there are some relative not high-impact exercises, including cycling, strength training, water-based aerobic exercise, and others; nonetheless is imperative to remember that any sport therapy has to be carefully tailored on the patient by a specialist to avoid unnecessary injuries and to obtain the maximum results. Moreover, specialists may also be able to provide advice on whether the standard equipment used to practice the sport should be modified in any way to make it safer and more effective.

Conclusions

RA is an autoimmune disease that impacts health in a multifactorial way. Our review aims to highlight supportive therapeutic interventions in RA patients, addressing this aspect to sports medicine, physical education and sports sciences, physiatry, rheumatology and orthopedics specialists. Indeed, through PA we have shown that moderate exercise improves CRF and the quality of life reducing the incidence of CVD and metabolic diseases. Furthermore, the understanding of biomolecular mechanisms can help to stratify RA patients for future clinical trials to identify biomarkers of improved muscle function and mental health function, One of the main clinical unmet need in RA is related to the interplay between limited mobility and disease activity, that in turn affect quality of life, physical and mental health and disease progression.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

None

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Authors' contributions

RR, GF, and GB drafted the paper; FP and CM searched data; JNG, DDM, AB and FT critically revised the paper. All authors have approved the final version.

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References

1. Metsios GS, Kitas GD. Physical activity, exercise and rheumatoid arthritis: Effectiveness, mechanisms and implementation. Best Practice Research in Clinical Rheumatology 32 (2018): 669-682.
2. Chang CL, Chiu CM, Hung SY, et al. The relationship between quality of life and aerobic fitness in patients with rheumatoid arthritis. Clinical Rheumatology 28 (2009):685-691.
3. Akram A, Georgiou P, Shi W, et al. Impact of Change in Lifestyle and Exercise on Cognitive Function in Patients With Rheumatoid Arthritis: A Systematic Review. Cureus 13 (2021): e18268.
4. Verhoeven F, Tordi N, Prati C, et al. Physical activity in patients with rheumatoid arthritis. Joint Bone Spine 83 (2016): 265-270.
5. Puce L, Okwen PM, Yuh MN, et al. Well-being and quality of life in people with disabilities practicing sports, athletes with disabilities, and para-athletes: Insights from a critical review of the literature. Frontiers in Psychology 14 (2023):1071656.
6. Munneke M, De Jong Z, Zwinderman AH, et al: Adherence and Satisfaction of Rheumatoid Arthritis Patients with a Long-Term Intensive Dynamic Exercise Program (RAPIT Program). Arthritis and Rheumatology 49 (2003): 665-672.
7. Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. Journal of Clinical Investigation 127 (2017): 1-4.
8. Summers GD, Metsios GS, Stavropoulos-Kalinoglou A, et al. Rheumatoid cachexia and cardiovascular disease. Nature Review Rheumatology 6 (2010): 445-451.
9. Summers GD, Deighton CM, Rennie MJ, et al. Rheumatoid cachexia a clinical perspective. Rheumatology (Oxford) 47 (2008): 1124-1131.
10. Marcora SM, Lemmey AB, Maddison PJ. Can progressive resistance training reverse cachexia in patients with rheumatoid arthritis? Results of a pilot study. Journal of Rheumatology 32 (2005): 1031-1039.
11. Lemmey AB, Marcora SM, Chester K, et al. Effects of high-intensity resistance training in patients with rheumatoid arthritis: a randomized controlled trial: Arthritis Rheumatology 6 (2009): 1726-1734.
12. Hill AV, Lupton H. Muscular exercise, lactic acid, and the supply and utilization of oxygen. QJ Medicine 16 (1923): 135-171.
13. Stenström CH, Minor MA. Evidence for the Benefits of Aerobic and Strengthening Exercise in Rheumatoid Arthritis. Arthritis Rheumatology 49 (2003): 428-434.
14. Bartlett DB, Willis LH, Slentz CA. Ten weeks of high-intensity interval walk training is associated with reduced disease activity and improved innate immune function in older adults with rheumatoid arthritis a pilot study. Arthritis Research and Therapy 20 (2018): 127.
15. Yu C, Rouse PC, Veldhuijzen Van Zanten JJCS, et al. Subjective and objective levels of physical activity and their association with cardiorespiratory fitness in rheumatoid arthritis patients. Arthritis Research Therapy 17 (2015): 59.
16. Stavropoulos-Kalinoglou A, Metsios GS, Veldhuijzen van Zanten JJ, et al. Individualised aerobic and resistance exercise training improves cardiorespiratory fitness and reduces cardiovascular risk in patients with rheumatoid arthritis. Annals of Rheumatic Diseases 72 (2013): 1819-1825.
17. Strasser B, Leeb G, Strehblow C, et al. The effects of strength and endurance training in patients with rheumatoid arthritis Clinical Rheumatology 30 (2011): 623-632.
18. Azeez M, Clancy C, O'Dwyer T. Benefits of exercise in patients with rheumatoid arthritis: a randomized controlled trial of a patient-specific exercise programme. Clinical Rheumatology 39 (2020): 1783-1792.
19. Noreau L, Martineau H, Roy L, et al. Effects of a modified dance-based exercise on cardiorespiratory fitness, psychological state and health status of persons with rheumatoid arthritis. American Journal Physical Medicine and Rehabilitation 74 (1995): 19-27.
20. Pinto AJ, Meireles K, Peçanha T, et al. Acute cardiometabolic effects of brief active breaks in sitting for patients with rheumatoid arthritis. American Journal of Physiology Endocrinology and Metabolism 321 (2021): E782-E794.
21. Barbalho SM, Prado Neto EV, De Alvares Goulart R, et al. Myokines: a descriptive review. Journal Sports Medicine Physiology Fitness 60 (2020): 1583-1590.
22. Graf C, Ferrari N. Metabolic Health - The Role of Adipo-Myokines. International Journal Molecular Sciences 20 (2019): 6159.
23. Jang S, Kwon EJ, Lee JJ. Rheumatoid Arthritis: Pathogenic Roles of Diverse Immune Cells. International Journal Molecular Sciences 23 (2022): 905.
24. Kishimoto T. Interleukin-6: from basic science to medicine - 40 years in immunology. Annual Review Immunology 23 (2005): 1-21.

25. Bearne LM, Scott DL, Hurley MV. Exercise can reverse quadriceps sensorimotor dysfunction that is associated with rheumatoid arthritis without exacerbating disease activity. Rheumatology (Oxford) 41 (2002): 157-166.

26. Rall LC, Meydani SN, Kehayias JJ, et al. The effect of progressive resistance training in rheumatoid arthritis. Increased strength without changes in energy balance or body composition. Arthritis Rheumatology 39 (1996): 415-426.

27. Huffman KM, Jessee R, Andonian B, et al. Molecular alterations in skeletal muscle in rheumatoid arthritis are related to disease activity, physical inactivity, and disability. Arthritis Research and Therapy 19 (2017): 12.

28. Fenton SAM, Veldhuijzen van Zanten JJCS, Duda JL, et al. Sedentary behaviour in rheumatoid arthritis: definition, measurement and implications for health. Rheumatology (Oxford) 57 (2018): 213-226.

29. Ratter JM, Rooijackers HMM, Hooiveld GJ, et al. In vitro and in vivo Effects of Lactate on Metabolism and Cytokine Production of Human Primary PBMCs and Monocytes. Frontiers Immunology 9 (2018): 2564.

30. Pedersen BK, Febbraio, MA. Muscle as an Endocrine Organ: Focus on Muscle-Derived Interleukin-6. Physiology Review 88 (2008): 1379-1406.

31. Muñoz-Canovés P, Scheele C, Pedersen BK, Serrano AL. Interleukin-6 myokine signaling in skeletal muscle: a double-edged sword? FEBS J 280 (2013): 4131-4148.

32. Fischer CP. Interleukin-6 in acute exercise and training: what is the biological relevance? Exercise Immunology Review 12 (2006): 6-33.

33. Bartlett DB, Willis LH, Slentz CA, et al. Ten weeks of high-intensity interval walk training is associated with reduced disease activity and improved innate immune function in older adults with rheumatoid arthritis: a pilot study. Arthritis Research Therapy 20 (2018): 127.

34. Andonian BJ, Bartlett DB, Huebner JL, et al. Effect of high-intensity interval training on muscle remodeling in rheumatoid arthritis compared to prediabetes. Arthritis Research Therapy 20 (2018): 283.

35. Rodríguez A, Becerril S, Ezquerro S, et al. Crosstalk between adipokines and myokines in fat browning. Acta Physiologica 219 (2017): 362-381.

36. Martinez Munoz IY, Camarillo Romero EDS, Garduno Garcia JJ. Irisin a Novel Metabolic Biomarker: Present Knowledge and Future Directions. International Journal of Endocrinology (2018): 7816806.

37. Boström P, Wu J, Jędrychowski MP, et al. A PGC1-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 481 (2012): 463-468.

38. Kurdiova T, Balaz M, Mayer A, et al. Exercise-mimicking treatment fails to increase Fndc5 mRNA and irisin secretion in primary human myotubes. Peptides 56 (2014): 1-7.

39. Qiu S, Cai X, Sun Z, Schumann U, Zügel M, Steinacker Jet al. Chronic Exercise Training and Circulating Irisin in Adults: A Meta-Analysis. Sports Medicine 45 (2015) 1577-1588.

40. Soliman SA, Gad R, Senosy T, et al. Serum irisin level in rheumatoid arthritis patients: Relationship to disease activity, subclinical atherosclerosis, and cardiovascular risk factors. The Egyptian Rheumatologist 44 (2022) 109-114.

41. Restuccia R, Perani F, Ficarra G, et al. Irisin and Vascular Inflammation: Beneficial Effects of a Healthy Lifestyle Beyond Physical Activity. Current Pharmaceutical Design 27 (2021) 2151-2155.

42. Friedman JM. Leptin and the regulation of body weight. Keio Journal of Medicine 60 (2011): 1-9.

43. Hussain Z, Khan JA. Food intake regulation by leptin: Mechanisms mediating gluconeogenesis and energy expenditure. Asian Pacific Journal of Tropical Medicine 10 (2017) 940-944.

44. Pandit R, Beerens S, Adan RAH. Role of leptin in energy expenditure: the hypothalamic perspective. American Journal Physiology Regulatory Integrative Complementary Physiology 312 (2017): 938-947.

45. Tam CS, Lecoultre V, Ravussin E. Brown adipose tissue: Mechanisms and potential therapeutic targets. Circulation 125 (2012): 2782-2791.

46. Do Carmo Martins M, Faleiro LL, Fonseca A. Relationship between leptin and body mass and metabolic syndrome in an adult population. Review Portuguese Cardiology 31 (2012): 711-719.

47. Gülkesen A, Akgöl G, Tuncer T, et al. Relationship Between Leptin and Neopterin Levels and Disease Activation Parameters in Patients With Rheumatoid Arthritis. Archives Rheumatology 3 (2016): 333-339.

48. Gunaydin R, Kaya T, Atay A, Olmez N, Hur A, Koseoglu M. Serum Leptin Levels in Rheumatoid Arthritis and Relationship With Disease Activity. South Medicine Journal 99 (2006) 1078-83.

49. Hizmetli S, Kisa M, Gokalp N, et al. Are plasma and synovial fluid leptin levels correlated with disease activity in rheumatoid arthritis? Rheumatology International 27 (2007): 335-338.

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DOI:10.26502/josm.511500096

50. Posey KL, Coustry F, Hecht JT. Cartilage oligomeric matrix protein: COMPopathies and beyond. Matrix Biology 71-72 (2018): 161-173.

51. Troeberg L, Nagase H. Proteases involved in cartilage matrix degradation in osteoarthritis. Biochimica Biophysica Acta 1824 (2012): 133-145.

52. Attur M, Krasnokutsky-Samuels S, Samuels J, et al. Prognostic biomarkers in osteoarthritis. Current Opinion Rheumatology 25 (2013): 136-144.

53. Pereira Nunes Pinto AC, Natour J, de Moura Castro CH, et al. Acute effect of a resistance exercise session on markers of cartilage breakdown and inflammation in women with rheumatoid arthritis. International Journal of Rheumatology 20 (2017): 1704-1713.

54. Berretta M, Facchini BA, Garozzo D, et al. Adapted physical activity for breast cancer patients: shared considerations with two Olympic and world Italian sports champions. European Review Medicine Pharmacological Sciences 15 (2022): 5393-5398.

55. Zatsiorsky VM, Yakunin N. Mechanics and Biomechanics of Rowing: A Review. International Journal of Sport Biomechanics 7 (1991): 229-281.

56. Brosseau L, Taki J, Desjardins B, et al. The Ottawa panel clinical practice guidelines for the management of knee osteoarthritis. Part three: aerobic exercise programs Clinical Rehabilitation 31 (2017): 612-24.

57. Multanen J, Rantalainen T, Kautiainen H, et al. Effect of progressive high-impact exercise on femoral neck structural strength in postmenopausal women with mild knee osteoarthritis: a 12-month RCT. Osteoporosis International 28 (2017) 1323-1333.

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