Η άσκηση ως θεραπεία στη ρευματοειδή αρθρίτιδα.

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ΠΕΡΙΛΗΨΗ

Αποτελέσματα συλλογικών ερευνών αποκαλύπτουν σημαντικές ευεργετικές επιδράσεις της σωματικής δραστηριότητας σε διαφορετικές παραμέτρους υγείας ασθενών με Ρευματοειδή Αρθρίτιδα (ΡΑ). Ωστόσο, οι ασθενείς με ΡΑ παραμένουν σωματικά αδρανές, το οποίο οφείλεται σε παράγοντες που αφορούν τόσο τον ασθενή όσο και τον επαγγελματία υγείας. Στην παρούσα βιβλιογραφική ανασκόπηση, περιγράφουμε τις ευεργετικές φυσιολογικές επιδράσεις της φυσικής δραστηριότητας στη ΡΑ και διερευνούμε τους πιθανούς λόγους για τους οποίους οι ασθενείς με ρευματοειδή αρθρίτιδα εξακολουθούν να παραμένουν σωματικά αδρανές.
Exercise as medicine in rheumatoid arthritis.

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ABSTRACT

Collective research evidence reveals a beneficial impact of physical activity on a number of different health outcomes in patients with Rheumatoid Arthritis (RA). However, RA patients still remain physically inactive due to factors involving both the patient and the health professional. In this review, we describe the beneficial effects of physical activity in RA and we explore the potential reasons why RA patients still remain physically inactive by a) investigating whether current provision for incorporating physical activity in clinical management is adequate/sufficient and b) discussing evidence from both the patients’ and healthcare providers’ perspectives as to why RA patients still remain physically active.

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INTRODUCTION
Rheumatoid arthritis (RA) is a disabling form of systemic inflammatory arthritis that has a prevalence of ~1% and is characterized by long-term inflammation, pain, and fatigue; therefore, increased functional disability and joint damage. With no known cure, the current treatment strategies for RA focus on reducing pain, minimize symptoms and potentially prevent further disease progression. Rheumatoid arthritis is, however, a debilitating disease not only for its disease-related symptoms but also its accompanying systemic manifestations. The predominant of these manifestations is an increased risk for cardiovascular disease (CVD). Moreover, RA also influences psychological wellbeing, with a recent meta-analysis revealing that ~40% of RA patients suffer from depression. As such, it seems that this disease affects the health of individuals at multiple levels, and thus, relevant interventions that address and improve these health outcomes are warranted.

Physical Activity in Rheumatoid Arthritis
Physical activity is any bodily movement produced by skeletal muscles that result in energy expenditure above resting levels; whereas exercise is a planned, structured and repetitive physical activity. The World Health Organization has identified physical inactivity as the 4th leading cause of overall mortality in adults. However, data reveals that the majority of the adult population still remain physically inactive. At present, the guidelines for physical activity state that adults need to engage in physical activity for at least 150 minutes/week of moderate-intensity, at least 75 minutes/week of vigorous-intensity or some combination of the two intensities. These cut-off points have been shown to result in beneficial physiological and psychological adaptations that may improve health. These levels of physical activity are evidently difficult to achieve for the majority of the adult population due to a range of barriers mainly pertaining to perception of time and/or lack of motivation. Patients with chronic musculoskeletal diseases such as RA may be even more physically inactive compared to the normal population, as disease-related symptoms may further hinder the participation in physical activity. However, increasing physical activity and/or exercise (i.e., structured physical activity aimed at improving a specific characteristic of fitness, such as cardiorespiratory fitness) is indeed an intervention that impacts positively on the most important clinical and systemic manifestations in patients with RA.

Disease-Related Symptoms
Data demonstrate clearly that physical activity is an intervention that should be utilised in the management of RA, and currently in the literature there is no single report demonstrating exacerbation of RA-related symptoms as a result of even high-intensity physical activity. In line with this, two Cochrane systematic reviews and meta-analyses confirm that the combination of aerobic and resistance training in RA improves functional outcomes potentially via blunting the inflammatory response. At present, there are no systematic reviews and meta-analyses examining the effects of physical activity on inflammatory biomarker changes in RA; however, in low-grade inflammatory conditions such as diabetes mellitus, such studies demonstrate an effect of exercise on reducing two biomarkers overexpressed in RA, C-reactive protein (CRP, a biomarker of hepatic origin and the most frequently studied biomarker of inflammatory response) and the pro-inflammatory cytokine interleukin 6 (IL-6). The potential role of physical activity on the inflammatory response is also supported by large population cohorts, such as the British Regional Heart study, the Third National Health and Nutrition Examination Survey (NHANESIII), the Cardiovascular Health study (CHS), as well as the Health ABC study, all of which revealed an inverse and independent dose-response association between CRP concentration and level of physical activity, which may be a physiological mechanism mediated by exercise-induced reductions in adiposity levels. Indeed, in RA, reductions in adiposity have been shown to associate with reductions in CRP after a six-month individualized moderate-intensity combined aerobic and resistance exercise program. Although the exact physiological mechanisms by which physical activity ameliorates inflammation in RA have not been studied per se, in the general population, exercise induces physiological adaptations that result in marked improvements in inflammatory status as well as muscle function via reductions in systemic immune cell production of inflammatory proteins that occur locally in the muscle. In adults at high risk of CVD, similarly to RA, physical activity reduces mononuclear cell production of cytokines related to atherogenesis (specifically, tumor necrosis factor alpha [TNFα] and Interleukin 1 [IL-1]), but increases the expression of atheroprotective cytokines (such as Interleukins 10 and 4 [IL-10 and IL-4] and transforming growth factor beta 1 [TGFβ1]). Moreover, contractile properties of the muscle include production of myokines, specifically IL-6, which increases hundred-fold in response to exercise. However, exercise-induced IL-6 has anti-inflammatory properties rather than inflammatory, via stimulating the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist. Specifically, IL-6 produced in response to skeletal muscle contractions may upregulate free fatty acid metabolism via its lipolytic activities but also may upregulate glucose homeostasis by affecting hepatic glucose production and/or muscle glucose utilization. Although these
adaptations may favourably impact on the overall inflammatory responses, long-term engagement in exercise programmes may also improve modulation of intracellular signalling pathways as well as cellular function that are mediated by nitric oxide and reactive oxygen species eventually alleviating inflammation. Indeed, in RA, two recent studies pertaining to the same trial, revealed that tailored exercise leads to significant improvement in specific oxidative stress mechanisms as well as improving measurements related to nitric oxide production. It is necessary that these mechanisms are better understood in relevant trials, however, the overall evidence suggests an exercise-induced anti-inflammatory effect via the mechanisms highlighted in Figure 1.

Cardiovascular Disease Outcomes
A meta-analysis of observational studies reveals that RA patients suffer from an increased risk of cardiovascular mortality. This may be due to the increased prevalence of individual CVD risk factors; specifically dyslipidemia, insulin resistance, hypertension, obesity, potential vascular dysfunction as well as chronic inflammation, which independently associates with cardiovascular mortality and morbidity. In contrast, higher physical activity in RA associates with a significantly better cardiovascular profile in RA patients, and in specific an improvement in both classical (adiposity, systolic blood pressure, insulin resistance and total cholesterol) and novel (fibrinogen, homocysteine, c-reactive protein, von Willebrand factor) CVD risk factors. Moreover, a recent trial revealed that RA patients that embark on a six month aerobic and resistance exercise programme experience significant improvements in CVD classical risk factors (lipid profiles, systolic blood pressure and adiposity), specific biomarkers of oxidative stress, micro- and macro-vascular function, and overall 10-year CVD risk in exercising RA patients compared to RA controls. The exact physiological mechanisms by which these beneficial adaptations occur remain elusive and thus, more research is required in this field. However, the above results are in line with results from relevant meta-analyses for the general population demonstrating beneficial effects of physical activity on systolic blood pressure, lipid profiles, insulin sensitivity as well as adiposity.

Sedentary Behavior in Rheumatoid Arthritis
Sedentary behavior can be defined as any waking behavior characterized by energy expenditure no greater than 1.5 metabolic equivalents of task (METs) while in a sitting or reclining posture. This definition helps to distinguish individuals who are “physically inactive”;

Figure 1. Suggested effects of exercise on inflammatory responses.
that is, individuals who are performing insufficient amounts of moderate-to-vigorous physical activity to meet recommended physical activity guidelines, from those who are engaged in large amounts of sedentary behavior.\textsuperscript{37} This is useful because it is possible for a person to meet recommended physical activity guidelines (e.g., 30 minutes of moderate physical activity per day), while engaging in sedentary behaviors for long periods of time (e.g., working sitting at a desk for several hours).

Cumulative research suggests a negative dose-dependent relationship of sedentary behavior with mortality from all causes, cardiovascular disease and cancer, while better cardiorespiratory fitness shows the exact opposite trends.\textsuperscript{38,39} Specifically for RA, cardiorespiratory fitness has been found to strongly and inversely associate with CVD risk factors and markers of inflammation;\textsuperscript{40} however, currently there is a dearth of data with regards to sedentary behaviors and their associations with CVD risk factors as well as disease-related manifestations. Relevant research is required in this field to investigate how sedentary behaviors impact on RA disease and systemic manifestations.

**Is exercise incorporated in the clinical management of Rheumatoid Arthritis?**

Given the strong evidence, at least for disease-related symptoms, that is available for RA, it would be reasonable to suggest that physical activity would be actively incorporated in the clinical management of RA patients. As such, as part of this paper, we have gathered the most important official guidelines for patients with RA, in order to investigate the information provided for the utilization of physical activity and/or exercise in the clinical management of RA. The following resources for the management of RA were investigated and the information provided appears below.

**European League Against Rheumatism recommendations**

The European League Against Rheumatism (EULAR) recommendations for patient education for people with inflammatory arthritis suggests that patient education in combination with physical therapy/joint protection exercises or physical activity has positive influences on physical function and activity, reduces pain and improves health status. However, no specific recommendations were discussed or specific mention was brought forward for physical activity and/or exercise. In the same manuscript, it is acknowledged that patients’ needs and expectations are wide about physical exercises without further supporting evidence on this matter. Finally, it is recommended that physical exercise programs could be possible and could be provided with the addition of educational group sessions to be more effective. However, a study in RA has shown that although RA patients’ education/awareness about healthy lifestyles can improve as a result of an educational intervention program, the actual behavior does not improve (i.e. patients are more aware but this does not make them eat healthier or exercise more).\textsuperscript{41}

Moreover, the EULAR recommendations for the role of the nurse in the management of chronic inflammatory arthritis reported nothing about physical activity and/or exercise. Finally, in the EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis, it is mentioned that exercise, as a lifestyle modification, should be provided to all patients with chronic inflammatory arthritis since it may improve CVD risk, however, no specific suggestions were explored.

**British National Institute for Health and Care Excellence guidance**

In the British National Institute for Health and Care Excellence (NICE) guidance for RA, in the subsection for the multidisciplinary team in section 1.1 (Referral, diagnosis and investigations), it is mentioned that patients with RA should have access to specialist physiotherapy to improve general fitness and be encouraged to do regular exercise, as well as doing exercise to enhance joint flexibility, muscle strength and for managing other functional impairments. There is no mention of exercise and/or physical activity in section 4 (Implementation) or any other section.

**Arthritis Research United Kingdom**

The official website of Arthritis Research United Kingdom has a dedicated webpage for all Arthritis diseases combined, but not RA specifically; although the information provided refers – in places – to exercise instructions specifically for patients with “hot” or “swollen” joints. This manuscript in general, describes stretching, strength and fitness exercises. Five to ten sets of stretching exercises are recommended (although no specific information is provided for muscle groups) up to the range of motion that does not exacerbate pain, while holding the stretch for 5-10sec; for patients with “hot” or “swollen” joints, gentle stretching is also recommended one a day of a few repetitions. For strength, general advice is offered on performing these exercises slowly and with to start with a low number of repetition but progress gradually (no specific information is given on muscle groups/repetitions). Specific mention to Pilates training is provided, whereas for patients with “hot” or “swollen” joints, is it recommended to avoid strength training until the joint is back to normal: when this is the case, the exercises should be performed.
gently and with a low number of repetitions. Finally, for fitness exercises, general information is provided for swimming, walking, fitness classes, cycling and joining a gym, whereas there is no information for patients with “hot” or “swollen” joints. The information provided by the Arthritis Research United Kingdom, refers patients very often to seek advice from a physiotherapist about all the above exercises.

**American College of Rheumatology guidelines**
The American College of Rheumatology guidelines documents are only specific to drug updates and recommendations.

**The European Musculoskeletal Conditions Surveillance and Information Network**
The European Musculoskeletal Conditions Surveillance and Information Network (EUMUSC.net) is a project aiming to raise and harmonize quality of care for rheumatic diseases and musculoskeletal health in specific European countries, and provides an official document for Standards of Care in RA. This document indeed recommends physical activity and/or exercise as part of lifestyle advice, as well as for rehabilitative purposes for this population. In specific, it suggests that RA patients should be educated (on the positive effects) and receive professional advice for exercise in order to improve cardiovascular health and prevent muscle wasting, a common characteristic in RA. In addition, it has a comprehensive analysis of the exercises that can be utilized in the management of RA, however, it suggests that the exercise programmes should be prescribed and supervised by qualified practitioners whereas, it also suggests that the exercise regime should commence with low-intensity exercise. Furthermore, it recommends a breakdown of the program in aerobic (1-3 times per week) and resistance components, however, the recommendations of the latter do not seem to be in line with the available literature. In specific, the suggestions pertain to a once-a-week resistance program consisting of exercises for all major muscle groups, with exercises that last for 30 seconds of contracting a muscle group following 30 seconds of relaxation. In contrast, different comprehensive reviews and meta-analyses in this field, suggest that moderate intensity resistance exercise using standard equipment is safe and significantly improves RA-related manifestations without exacerbating disease symptoms. It appears that there is no consistent provision from the most important European and American resources for incorporating physical activity in managing RA. The EUMUSC.net provided the most detailed guidance, with sufficient information for incorporating physical activity in the management of RA, although more conservative advice was given for resistance exercise. The Arthritis Research United Kingdom also provided very general information which is mainly relevant to arthritis patients, rather than RA.

At present, there is no recent data revealing whether physical activity is indeed utilized or recommended by clinicians in the clinical management of RA. From the available data, however, it seems that patients with RA have still worrying low levels of both cardiorespiratory fitness and physical activity, with the latter remaining unchanged in the last two decades. The potential reasons for these low levels of fitness and activity can be explored by presenting data from the perspective of the patient and the health practitioner separately.

**Patient perspective**
The most recent systematic review in this field concluded again that physical activity levels are still low in RA and has highlighted that disease-related characteristics such as pain and fatigue are commonly reported barriers by RA patients for not engaging in physical activity; interestingly RA patients who are sufficiently physically active report the same barriers as those who are not active but appear to be more capable of overcoming them. Even in countries with excellent educational programmes, RA patients remain physically inactive despite knowing the beneficial effects of exercise, which confirms earlier findings that improving knowledge/awareness may not be sufficient alone to change behavior towards being more active. Importantly, lack of trust in exercise professionals may also be an important factor promoting inactive behaviors, since the approach to exercise prescription for RA patients should not be universal and should be based on the patient’s functional abilities and preferences.

**Health Professionals perspective**
For a long time health professionals have been advising rest rather than exercise for managing RA, due to the fear that exercise may exacerbate disease symptoms. In addition, there is no current provision to train exercise health professionals in order to have specific knowledge to develop tailored exercise prescriptions for RA patients, which has to be developed based on the individual’s functional abilities. These two factors may further contribute to physical inactivity and increased sedentary behavior observed in RA studies. We have previously and recently proposed a pragmatic approach in developing tailored exercise programmes in RA patients, using an adopted model of cardiac rehabilitation. In brief, based on a) baseline assessments that are used to determine the intensity of the programme, b) patient’s history and functional limitations, c) patients exercise preferences and d) RA-
specific trained exercise personnel (when the exercise programme is conducted in a supervised environment), the development of an exercise programme can have significant different effects on multiple different health factors, including improved disease symptoms and cardiovascular profile. Similar approaches have been utilised with similar results by other researchers. Facilitating long-term adherence to physical activity may also be challenging for RA patients, but developing self-autonomous exercising patients and monitoring improvements using specific patient selected outcomes (e.g., weight, fitness) – as per the UK National Institute for Health and Care Excellence (NICE) guidelines – may help achieve this.

CONCLUSION
For more than two decades, patients with RA have reported low levels of physical activity, despite the convincing evidence that physical activity has important benefits in terms of both disease-related and systemic manifestations of the disease. Lack of a universal approach and relevant provision from official guidelines, patient specific barriers as well as lack of knowledge from health professionals may contribute to the low levels of physical activity and subsequent low cardiorespiratory fitness observed. Relevant studies are necessary in this field to identify ways of supporting an increase in physical activity levels in RA patients using behavioral change theoretical models.

References


