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«Maximal oxygen uptake in Rheumatoid Arthritis»

by

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To my brother Athanassios Kyprianos

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Abstract

Background and objectives:

Low cardiorespiratory fitness (CRF) is a significant predictor of cardiovascular disease (CVD). Exercise interventions increase CRF and reduce CVD risk. A specific exercise prescription coming from the results of CRF tests, aims to optimize the beneficial results of exercising, provided that patients reach their cardiorespiratory limitations during the CRF test. However, this has never been investigated in rheumatoid arthritis (RA). The aim of this study was to investigate if patients with RA can achieve well-established criteria during CRF testing.

Methods:

105 patients with RA were evaluated for age, gender, height, weight, and body mass index (BMI) and CRF. CRF was determined on the basis of maximal oxygen uptake (VO_2max) using a calibrated breath-by-breath system. The criteria used to determine CRF were: a) VO_2 plateau, b) respiratory exchange ratio (RER) > 1.1 and c) achieved maximum predicted heart rate (220-age). Al participants were assessed at baseline the CRF capacity (VO_2MAX), Disease Activity Score 28 (DAS28) and Disease Severity (HAQ).

Results:

Only 26.6% of the patients achieved the VO_2max test criteria. More specifically, 4.7% of patients reached a VO_2 plateau. The RER ratio was reached by 78% of the patients while HRmax was achieved by 27.6% of the studied patients. Between the two groups, i.e. those who met the VO_2max criteria and those who did not, we found that there were no significant differences in DAS 28 ($p>0.05$) and BMI ($p>0.05$). However, HAQ ($p=0.04$) was significantly improved in the patients who achieved VO_2max.

Conclusion:

Approximately 1/4 of the patients with RA completed the CRF testing as they met the VO_2max criteria. It seems that other reasons are responsible for terminating a CRF test in RA patients. Our results suggest that this may be due to the overall physical disability (HAQ) caused by the disease.

Περίληψη

Εισαγωγή και στόχοι:

Τα χαμηλά επίπεδα καρδιοαναπνευστικής ικανότητας αποτελούν ένα σημαντικό προγνωστικό παράγοντα καρδιαγγειακών παθήσεων . Οι ασκησιογενείς παρεμβάσεις αυξάνουν την καρδιοαναπνευστική ικανότητα και μειώνουν τον κίνδυνο καρδιαγγειακής νόσου. Η συνταγογράφηση της άσκησης που προέρχεται από τα αποτελέσματα αξιολόγησης της καρδιοαναπνευστικής ικανότητας , έχει ως στόχο την βελτιστοποίηση των ευεργετικών αξιών της άσκησης, υπό την προϋπόθεση ότι οι ασθενείς πληρούν τα κριτήρια μέγιστης καρδιοαναπνευστικής ικανότητας κατά την διάρκεια αξιολόγησης της μέσω του τεστ κοπώσεως. Ωστόσο, αυτό δεν έχει διερευνηθεί έως τώρα σε ασθενείς με ρευματοειδή αρθρίτιδα (PA). Ο σκοπός της παρούσας μελέτης ήταν να μελετήσει εάν οι ασθενείς με PA επιτυγχάνουν τα καθορισμένα κριτήρια κατά τη διάρκεια του τεστ κοπώσεως.

Μεθοδολογία:

105 ασθενείς με PA αξιολογήθηκαν για την ηλικία, το φύλο, το ύψος, το βάρος, και δείκτη μάζας σώματος σε σχέση με την CRF. Η καρδιοαναπνευστική ικανότητα προσδιορίστηκε βάσει της μέγιστης πρόσληψης οξυγόνου (VO_2max) χρησιμοποιώντας ένα βαθμονομημένο σύστημα ανάλησης των παραγόμενων προϊόντων του κύκλου της αναπνευστικής διαδικασίας. Τα κριτήρια που χρησιμοποιήθηκαν για τον προσδιορισμό της CRF ήταν: α) VO_2 plateau, β) RER (αναπνευστικό πηλίκο) > 1.1 και γ) επίτευξη της μέγιστης προβλεπόμενης καρδιακής συχνότητας (220-ηλικία). Τα αποτελέσματα αφορούν τις αρχικές μετρήσεις όλων των συμμετεχόντων ως προς την αξιολόγηση της καρδιοαναπνευστικής ικανότητας (VO_2max), Δραστηριότητας της Νόσου (DAS28) και Βαρύτητας της Νόσου (HAQ).

Αποτελέσματα:

Μόνο το 26,6% κατάφερε να φθάσει τα όρια που τέθηκαν για μια εκτίμηση VO_2max σε ασθενείς με PA. Συγκεκριμένα, το 4,7% των ασθενών έφτασε σε VO_2 plateau, ο δείκτης RER επιτεύχθηκε από το 78% των ασθενών, ενώ η μέγιστη προβλεπόμενη καρδιακή συχνότητα (HRmax) επιτεύχθηκε κατά 27,6% των ασθενών που μελετήθηκαν. Μεταξύ των δύο ομάδων, δηλαδή εκείνων που πληρούσαν τα κριτήρια της VO_2max και εκείνων που δεν τα πληρούσαν, διαπιστώσαμε ότι δεν υπήρχαν στατιστικά σημαντικές

διαφορές στην DAS 28 (p> 0.05) και BMI (p> 0.05). Αντιθέτως, η ομάδα των ασθενών που εκπλήρωσαν τα κριτήρια της VO_2max, είχαν καλύτερα αποτελέσματα στην αξιολόγηση HAQ (p = 0.04).

Συμπέρασμα:

Το ένα τέταρτο των ασθενών με RA σταμάτησε το τεστ κοπώσεως λόγω των κριτηρίων της VO_2max. Φαίνεται ότι και άλλοι λόγοι είναι υπεύθυνοι για τον τερματισμό του τεστ κοπώσεως στους ασθενείς με RA. Τα αποτελέσματά μας δείχνουν ότι αυτό μπορεί να οφείλεται στην συνολική σωματική ανικανότητα (HAQ) που προκαλείται από την ασθένεια.

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Cardiorespiratory fitness: (CRF)

Cardiovascular disease: (CVD)

Rheumatoid arthritis: (RA)

Maximal oxygen uptake: (VO_2max)

Respiratory exchange ratio: (RER)

Disease Activity Score 28: (DAS28)

Disease Severity: (HAQ)

Body mass index: (BMI)

Anticitrullinated protein antibody: (ACPA)

Leukocyte antigen: (HLA)

Nuclear factor κB: (NF-κB)

Anti–citrullinated protein antibodies: (ACPA)

Type 17 helper T cells: (Th17)

Tumor necrosis factor a: (TNF-a)

Vascular endothelial growth factor: (VEGF)

Interleukin-6: (IL-6)

Interleukin-1: (IL-1)

Interleukin-17: (IL-17)

Membrane-Proximal sub-domain: (SD4)

Matrix metalloproteinases: (MMPs)

Scatter factor: (SF)

Tissue inhibitors of metalloproteinases: (TIMPs)

High-density lipoprotein: (HDL)

Low-density lipoprotein: (LDL)

American College of Rheumatology: (ACR)

European League against Rheumatism: (EULAR)

Health Related Quality Of Life: (HRQOL)

Behavioural Risk Factor Surveillance System: (BRFSS)

American College of Sport Medicine: (ACSM)

Electrocardiogram: (ECG)

Coronary artery bypass surgery: (CABS)

Percutaneous transluminal coronary angioplasty: (PTCA)

McMaster Toronto Arthritis Disability Questionnaire: (MACTAR)

Health Assessment Questionnaire: (HAQ)

1. Introduction

RA is the most common type of chronic Inflammatory Arthritis and an Autoimmune Disease. This results not only in joint destruction and functional disability but also in systemic manifestations such as increased body fatness, loss of muscle mass, hyper metabolism and increased risk for CVD, which is significantly higher in RA patients compared to normal population (1). It is well stated in current literature that physical inactivity (2), vascular dysfunction (3–5) and obesity (6,7) are independent CVD factors. Yet, the factors that lead to this phenomenon are not well defined. It has been shown, that individualised aerobic and resistance exercise in RA patients, significantly improves endothelial function in different vascular beds and reverses the unfavorable cardiovascular risk seen in RA (3)(8). Therefore, exercise may be crucial for the prevention of classical and novel CVD risk factors in RA patients and is associated with significant improvements in cardiorespiratory fitness (CRF), an independent CVD disease risk factor (1–4,8–10).

In order to improve CRF, patients need to increase their level of physical activity. However, due to disease manifestations, patients with RA refrain from exercising as they think by doing so, it may exacerbate the disease's symptoms. This unfounded belief is reinforced by the rheumatology health professionals that advice patients not to exercise. As such, it is not a surprise that the literature consistently shows that RA patients lead a sedentary lifestyle in comparison with age and gender matched controls. In contrast, 2 systematic reviews and metanalyses from the Cochrane Library reveal that exercise is safe for RA patients and may reverse the diseases' symptoms. As such, exercise should be a fundamental part of managing the disease.

In order to set the intensity of exercise to the correct level, patients need to perform a VO_2max test in order to identify their maximum heart rate. This information is then used to develop an effective exercise prescription. However, patients with RA may stop CRF testing due to functional limitations and not volitional exhaustion. Volitional exhaustion is determined by specific criteria that are: plateau, maximum heart rate and respiratory exchange ratio. This is crucial information in order to develop the best possible exercise prescription. Currently, there are no studies that have investigated whether patients with RA stop CRF

testing due to cardiorespiratory limitations using the aforementioned criteria. As such, the aim of the present study was to assess for the first time the established CRF criteria in RA.

2. Aims

The aim of this study is to evaluate the established criteria of a successful maximal CRF test in patients with RA. This can lead to an optimization of the exercise prescription in order to minimize the possibility of CVD.

3. Literature Review

3.1. Rheumatoid Arthritis (RA)

3.1.1. History and Definition

It is very probable that rheumatoid arthritis appeared thousands of years ago in early Native American populations, but until the 17th century, it had not occurred in Europe (11). RA is a chronic, symmetrical, polyarticular, and systemic inflammatory disease that mainly affects the synovial membrane of the small joints of the hands and feet (11). Even though the aggressive form of tissue called pannus damages local articular structures apart from synovial inflammation and hyperplasia ("swelling"), which is the joint lining, autoantibody production (rheumatoid factor and anticitrullinated protein antibody [ACPA]), cartilage destruction, bone destruction ("deformity") and systemic characteristics, contain cardiovascular, pulmonary, psychological, and skeletal disorders (12,13). It is the most common inflammatory rheumatic disease that can lead to long-term functional inability and disability (11). Long-term prognosis is not considered good for the treatment of disease: 80%of patients suffering from RA are disabled after 20 years (10), and life expectancy has fallen by an average of 3-18 years. (15)

3.2. Pathophysiology of RA

From the explanatory side, it seems that many factors, such as environmental, genetic, hormonal and immunological, are involved in the pathogenesis of the disease, but the exact cause is not known (16) . Questions vary as which genetic-environmental factors cause autoimmunity and why does that spawn articular localization? Furthermore, why is synovial inflammation prolonged, leading to local destruction and joint dysfunction? Additionally, in patients with rheumatoid arthritis what is the cause that leads to systemic disease (13).

3.3. Pathogenesis of RA

3.3.1. Genetic Factors

It is well documented that there is a genetic predisposition regarding the development of rheumatoid arthritis. Genome wide analyses confirm that the immune regulatory factors form the basis of the disease (13). It has been found that the prevalence of the disease is higher in RA patients who are positive for rheumatoid factor or ACPA and leukocyte antigen (HLA)-DRB1 alleles (17). These results show that some predisposing T-cell repertoire selection, antigen presentation, or a change in peptide affinity, play a role in promoting auto reactive adaptive immune responses (13). Moreover, a potential pro-inflammatory signaling function contains molecular mimicry of the shared epitope by microbial proteins. The increased T-cell senescence is induced by a shared epitope containing HLA molecules (18,19). Furthermore, another potential pathway for RA pathogenesis is the nuclear factor κB (NF-κB) that implicates dependent signaling and T-cell stimulation, activation, and functional differentiation. Other identified risk alleles in ACPA- positive rheumatoid arthritis consistently aggregate functionally with immune regulation (20–23). Finally, genetic risk factors for ACPA-positive diseases are considered more significant than ACPA-negative diseases and patients with ACPA-negative disease have a more propitious prognosis than those with ACPA-positive disease (13).

3.3.2. Environmental Factors

Regarding the effects of gene-environment, smoking and other types of bronchial stress (e.g., exposure to silica) increase the risk of RA among individuals delicate to HLA-DR4 alleles (24). Furthermore, the combination of smoking and HLA-DRB1 alleles increase a person's risk to present ACPA (25).

3.3.3. Infectious Related Agents with RA

Viruses such as Epstein–Barr, cytomegalovirus, proteus species, and Escherichia coli and their by-products (e.g., heat-shock proteins) have also been linked in experimental studies with the development of RA (26,27). The immune system triggering may be caused by the induction of a rheumatoid factor and a high-affinity autoantibody against the Fc portion of immunoglobulin, which has been used for a long time as

a diagnostic pointer of RA and it is involved in its pathogenesis. Finally, RA seems to be linked with periodontal disease (28) and gastrointestinal microbiome (29).

3.3.4. RA and the Nervous System

It is accepted that a connection exists between the hypothalamus-pituitary-adrenal axis and cytokine production, which is the starting point of RA (30). The molecular explanations for such phenomena come from animal models of inflammation (30). The central nervous system is usually associated with immune regulation and homeostasis. In addition, neuroimmune logic effects modulate disease growth in rodent models with arthritis. These kind of influences might function locally (some neurotransmitters are called synovitis in RA) or centrally (cytokines are quickly up-regulated in the hypothalamus during peripheral inflammation) (31).

3.3.5. Synovial Immunologic Processes and Inflammation

The micro environmental modifications resulting to Synovitis at RA happens when leukocytes enter the synovial compartment and cause profound synovial architectural reorganization and local fibroblast activation. Leukocyte gathering mainly indicates migration instead of local proliferation as a consequence of neo-angiogenesis, which occurs by local hypoxic conditions and cytokines (32,33).

3.3.5.1. Adaptive Immune Pathways

Humoral adaptive immunity is inseparable to RA (13). Great importance is given to the role of type 17 helper T cells (Th17), that creates interleukin-17A, 17F, 21, and 22 and tumor necrosis factor α (TNF-α) (33,34). RA is traditionally thought to be a disease caused by type 1 helper T cells (34,35). The macrophage-derived and dendritic-cell–derived transforming growth factor β as well as interleukin-1β, -6, -21, and -23 offer an environment that supports Th17 differentiation and efface differentiation of regulatory T cells, shifting T-cell homeostasis toward inflammation (36). Other clinical remarks support the role of B cells and their progeny in the pathogenesis of RA to contain auto antigen and cytokine production (e.g., interleukin-6, TNF-α) (13).

3.3.5.2. Cytokines and Intracellular Signalling Pathways

After the successful therapeutic blockage of the membrane, the soluble and the receptor in patients with RA of the two cytokines, the importance of TNF-α and interleukin-6 was established (13). They play crucial roles in the aggravation of RA, although IL-1, VEGF and probably IL-17 also play a significant influence on the development of the disease (37). These cytokines, through complex mechanisms, activate genes responsible for inflammatory reactions (37). TNF-α is very important for the activation of cytokines, the expression of chemokines, the expression of molecules for attachment to the endothelial cells, the prevention of synovial fibroblasts, the contribution to the production of angiogenesis and the feeling of pain, as well as the suppression of regulatory T-cells (38). Respectively, IL-6 activates the local production of leukocytes and autoantibodies, as well as mediating the body's response during acute systemic reactions of the body in cases such as anaemia, cognitive dysfunction, and lipid-metabolism dysregulation (13). Regarding IL-1, although strongly expressed in RA, when assessing the affect it has on leukocytes, endothelial cells, chondrocytes and osteoclasts, the clinical benefits upon inhibition are moderate. This result, which is a paradox as it is exactly the opposite of what one would expect, is under investigation (39) (40). Other cytokines, such as the IL-17, which is allegedly involved intensely in the pathogenesis of inflammatory and autoimmune diseases, including RA, have the important role of secreting a CD4-cell subset in synovitis (41–43).

3.3.6. Cartilage Damage

Cartilage destruction in RA occurs when the cytokines TNF- a, IL-1 and IL-6 trigger synoviocytes, resulting in the secretion of matrix metalloproteinases (MMPs) in scatter factor (SF). Also, chondrocytes will immediate the release of additional MMPs in the cartilage (16,44). Endogenous enzyme inhibitors, such as tissue inhibitors of TIMPs, fail to reverse these processes; articular cartilage has limited regenerative capacity, while the cartilage is gradually deprived chondrocytes, which undergo apoptosis. All this will eventually lead to the destruction of the cartilage (13).

3.3.7. Bone Erosion

80% of patients newly diagnosed with RA, develop bone erosion associated with chronic and extended inflammation (45,46). The articular cytokines, mainly the macrophage-stimulating factor and receptor activation of NF-kB, promote osteoclast differentiation and invasion of the surface of the periosteal, adjacent to the articular cartilage (47). Osteoclasts are multinucleated cells generated from mononuclear compound ancestors belonging to the family of monocytes or macrophages (48).

RA is caused by mediators such as cytokine Dickkopf-1 and frizzled protein 1 associated with the inhibition of differentiation of the mesenchymal precursors into chondroblasts and osteoblasts (49). Mesenchymal stem cells, which can differentiate into adipocytes, chondrocytes and osteoblasts can be detected in the synovial (50,51). Nonetheless, their biological characteristics and the effect of local inflammation in their properties remains unknown (13). All these provide little evidence of the treatment of RA, in contrast to other chronic inflammatory arthropathies (49).

3.3.8. Systemic Consequences of Rheumatoid Arthritis

The relationship between CVD in patients with RA is well established and demonstrates that it is more than three times possible to occur compared to the general population, but this is not explain the increased prevalence of well-established risk factors (52). Specifically, the CVD related mortality rate is higher and RA patients are more likely to die from myocardial infarction, stroke, and heart failure (53–55). All this happens because of the connection of RA with pro-atherogenic complex changes which results in a systemic inflammation (56), which share the same biological pathways with atherosclerosis. This metabolic pathway leads to the release of cytokines TNF- a, IL-6 and IL-1 from synovial tissue, and causes widespread dysfunction altering the function of adipose tissue, skeletal muscle, liver and vascular endothelium (56), called collectively “inflammatory metabolic syndrome” (57,58). This, in turn, leads to insulin resistance, increased global oxidative activity and the relation of RA with dyslipidaemia which is characterized by low overall and high density lipoprotein (HDL), cholesterol, elevated triglycerides, lipoprotein levels and an increase in small, low-density lipoprotein species (LDL) (56). Although the reduction of inflammation in

patients with severe RA after treatment through the use of a biological agents can result in elevated levels of total HDL and LDL cholesterol (and probably triglyceride), but the reduction of inflammation, nevertheless, reduces the risk of CVD (59) . In addition, studies have shown that elevated levels of interferon concentration of IL - 6 in plasma, typical of patients with RA, cause potentiall detrimental cardiovascular symptoms such as myocardial infarction (60). Furthermore, prolonged inflammation in RA patients also affects the brain, causing fatigue and decreased cognitive function while also affecting the lungs through the induction of inflammatory and fibrotic disease. Moreover, it affects the liver through increased acute phase response and chronic anaemia. Finally, it affects the function of exocrine glands (secondary syndrome Sjögren) and muscles causing sarcopenia, as well as bone osteoporosis(61–63) .

3.3.9. Criteria of RA

As there is no Gold Standard for the diagnosis of RA, the guidelines used over the last three years (2011-2014) as a basis of RA diagnosis are based on research conducted by Aletaha and his research team which is approved by the American College of Rheumatology (ACR), Board of Directors and the European League Against Rheumatism (EULAR) Executive Committee. In the new criteria set, classified as “definite RA” is based on the confirmed presence of synovitis in at least 1 joint, the absence of an alternative diagnosis that better explains the synovitis, and the achievement of a total score of 6 or greater (of a possible 10) from the individual scores in 4 domains: number and site of involved joints (score range 0–5), serologic abnormality (score range 0–3), elevated acute-phase response (score range 0–1), and symptom duration (2 levels; range 0–1) ‘’ (64).

	Score
Target population (Who should be tested?): Patients who 1) Have at least 1 joint with definite clinical synovitis (swelling)* 2) With the synovitis not better explained by another disease† Classification criteria for RA (score – based algorithm: add score of categories A – D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
1 large joint¶	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)#	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification)††	
Negative RF and negative ACPA	0
Low – positive RF or low – positive ACPA	2
High – positive RF or high – positive ACPA	3
C. Acute – phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms§§	
<6 weeks	0
≥6 weeks	1

Table 1. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis (64).

3.3.10. Quality of life

While investigating fatigue levels and depression in patients with RA, the results showed that the release of a hormone called corticotrophin schetozotane, increased rates of fatigue, dysthymia, irritability and depression (65,66). Participants in the study reportedly had cytokines and NF -a, IL-1 and IL-6 (66). Furthermore, many researches show that arthritis and specifically RA has a significant impact on multiple dimensions of Health Related Quality Of Life (HRQOL) and Behavioural Risk Factor Surveillance System (BRFSS). Namely, older adults with RA reported a poorer general health, physical health, mental health, and sleep than their healthier counterparts. Additional, activity limitation and pain is a substantial problem among RA individuals compared to a healthy population (67–71).

3.4. Exercise and RA

A large proportion of RA patients are suffering from limited joint mobility and generally reduction of functionality in everyday activities. This happens due to the symptoms of the disease which are: joint structural damage, stiffness, pain, loss of bone density and muscle weakness (72). As a result, there is a significant reduction in levels of physical activity, which is combined with the fear of the patients regarding the aggravation of the disease. To make matters worse, health professionals still insist on limiting exercise for patients (73). Recent research have shown that a properly structured exercise program can achieve a sustained improvement in the health of patients without causing adverse effects on the activation of the disease and further joint damage. The main objective of an exercise program for patients with RA is to maintain functional capacity and improve physical fitness.

3.4.1. Resistance Training

Researches have already implemented resistance training programs with success in patients with RA, either of isometric nature of low intensity or range-of-motion exercises (74). Given the diversity of the disease, patients with extensive structural damage in their joints were excluded (75). However, results from exercise intervention studies showed an increase in function ability (76), without aggravating the feeling of

pain or disease activity (77). Nevertheless, it is known that the types of high intensity resistance exercise brings better results in increasing muscle strength in relation to the most conservative protocols, but there is no evidence so far with respect to deterioration of symptoms (78). In contrast, literature mentions that resistance exercise slows joint destruction in patients with RA (79,80) compared with those who do not exercise. This however, has to be further studied (81,82).

Therefore exercise emerges as an effective and safe intervention when it is well structured and characterized by a progressive increase in the intensity of resistance (83). Besides the beneficial effects on stimulating muscle growth, it may even reverse rheumatoid cachexia (83). This is a metabolic disorder of unknown aetiology, subjectively affecting nearly 75% of all patients with RA and characterized by involuntary loss of muscle mass and progressive increase in fat mass in the presence of stable or even slightly reduced weight (84).

It is a fact that non-randomisation researches, studying the effects of resistance exercise in RA, differ in their methodological implementation. As a result of this, a variety of different effects surface that are difficult to interpret. By referencing the American College of Sport Medicine (ACSM) guidelines (85), a successful exercise program with resistance in patients of advanced age that have a sedentary lifestyle, must include at least two sessions a week and consist of 8 to 10 exercises for the major muscle teams and consist of 10-15 reps for each exercise. Randomized Control Trials that followed these instructions and applied them to RA patients found significant differences in the improvement of functional ability (79,86,87), and muscle strength without affecting the existing types of structural joint damage (86,88).

3.4.2. Aerobic training

Patients with RA are characterized by hypo-motility which result in reduced levels of physical activity and capacity in comparison with corresponding healthy peers (73,89) . The following forms of exercise that are applied in RA studies are:

3.4.3. Cycling

Cycling is an aerobic activity where muscle use is confined to the muscles of the lower extremities. This benefits the patients, as the body weight is not applied to the legs, making it a more accessible option. The opportunity presented in these applications, either in a clinical or outdoor environment, both individually and in groups (90), make it highly effective (91) as an intervention, even under minimum supervision conditions (92). Although protocols that have already been applied so far vary, it is shown that cycling has beneficial effects on aerobic capacity, functional capacity and muscle strength (7).

3.4.4. Aquatic

Due to the benefits of buoyancy, exercise in water is an ideal exercising environment for patients with RA (93). This view is supported by the general opinion of patients that believe that this type of exercise improves functional ability (94). To date, studies show that exercise in water improves aerobic capacity (95–97), muscular strength (81,98)and the psychological status (96).

3.4.5. Dance

The effects of exercise through dance are highly beneficial. More specifically, improvements can be seen in aerobic capacity, walking ability, muscle strength (99,100) and psychological factors such as anxiety and depression (99–101).

3.4.6. Walking and Running

Walking as an intervention has already been used for the improvement of the diseases symptoms (95,102,103), the assessment of functional capacity through gait analysis (104–106) and as a method of predicting VO_2max (107) . Walking and running are included in exercise protocols for RA patients, without though determining the exact intensity, frequency and duration (7).

3.4.7 Combination of Aerobic and Strength Training

The combination of aerobic and resistance exercise is the most widespread and effective kind of therapeutic workout. It produces an effective natural stimulus that helps achieve the desired physiological adaptations (7). Studies have shown that in recent-onset (86), active (108) or inactive RA (108) patients have experienced improvements in cardiorespiratory capacity and muscular strength. This lead the American College of Rheumatology to introduce the treatment guidelines for the management RA patients by implementing dynamic exercises due to their effectiveness (109).

3.5. Maximal Oxygen Uptake (VO_2max)

The term “maximal oxygen uptake” was first used by Hill et al.(110,111) and Herbst (112) in the 1920’s (113). VO_2max (also known as functional aerobic capacity), is defined as the maximum rate of oxygen utilization by the exercising muscle (113,114). It is considered the "gold standard’’ of establishing the functional limitations of the cardiorespiratory system (113,114). The most objective way of measuring the functional aerobic capacity is the stress test. It provides useful information for assessing the physical fitness as well as diagnosing and determining the prognosis of ischemic heart disease (115). The results are also necessary for the prescription of exercise-induced cardiovascular rehabilitation programs (115). The stress test is considered the most accurate method for assessing the aerobic capacity and as a consequence, VO_2max (116,117). The stress test is performed through the use of a treadmill and bicycle ergometer.

The treadmill is a more familiar and functional way of exercise and has been shown to have a greater diagnostic sensitivity than the bicycle ergometer (118) . However, this method has been restricted in elderly people with balance problems as well as in cases such as arthritis that may cause joint pains. VO_2max values during the bicycle ergometer test are on average 11% lower (range, 8% -15%) than those on the treadmill, mainly due to the participation of smaller volume of muscle mass (119–122). The VO_2max value decreases as a person gets older (123–125). Reports show that after the third decade of ones life, the VO_2max ability reduces by approximately 1% per year (126). This is associated with advanced age, gender, heredity and / or the lack of physical activity which can significantly reduce the functional capacity of an individual (exercise

standards), (127–129). Any further reduction of the aforementioned values can dramatically affect the quality of life. For instance, it will negatively affect the performance of activities in everyday life and this may impede the ability of one individual to live independently (128,130,131).

The main criterion for achieving VO_2max varies in the literature provided. Nevertheless, most studies agree on fulfilling 2 of the 3 following criteria: respiratory exchange ratio (RER) must be greater or equal to 1.1 (132–134) , the maximum heart rate rhythm (HRmax) which can be defined by different equations (most known of all is the ''220-age'') (135,136), and a plateau in oxygen consumption (VO_2 plateau), defined variously as an increase in oxygen uptake of 1.5 ml/min per kg (137) to 2.0 ml/min per kg (126,138). Furthermore, measurement of VO_2max depends heavily on subjective factors such as muscle fatigue, perceived exhaustion, and level of motivation. Finally, the clinician's willingness to allow participants to exercise to exhaustion is of crucial importance (139).

However, most studies use young adults as samples but almost all patients are older than 70 years of age (140,141). The very high initial intensity and long duration of the various protocols prevent the successful completion of tests in older adults (142). The heart and lungs are not the only limiting factors, but dyspnoea (143,144), fear of overexertion (145,146), muscle weakness (143,144), lack of motivation (143) and the appearance of electro-cardiographic abnormalities (147) are also deterrents of a successful assessment. For these reasons and for patient safety, measurement of VO_2max is often calculated indirectly by linear regression equations, relating performance to exercise VO_2max (148,149). Due to the large number of clinical situations, many of these asymptomatic results may lead to erroneous predictions (150–152).

3.5.1. Association of VO_2max with CVD

With regard to the cardiovascular response to exercise, Fletcher et.al defined that: '' Exercise, a common physiological stress, can elicit cardiovascular abnormalities not present at rest and can be used to determine the adequacy of cardiac function. Exercise is only one of many stresses to which humans can be exposed; therefore, it is more appropriate to call an "exercise" test exactly that and not a "stress test." (153)

There is relation between VO_2max and CVD risk. The lower the VO_2max value an individual has, the higher CVD risk possibility occurs. The first is to provide authoritative answers about the status of physical capacity for the patients' health. The second is to determine the intervention, when required, as well as for prevention CVD (153).

The main clinical signs of CVD include the risk of arrhythmia, myocardial damage (which is reflected by the left ventricular function) and the degree of myocardium in jeopardy. With regard to the risk of arrhythmia, the stress test is the only diagnostic method, given the close relationship with abnormalities of the left ventricle. Relative to myocardial ischemia, clinical symptoms during the stress test includes angina, ST segment depression and ST segment elevation over ECG areas without Q waves (diagnostic agents of the heart through the use of electrocardiogram). However, it is difficult to predict the amount of ischemia (153).

Finally, the VO_2max test also helps in determining prognosis in symptomatic. Namely, post-myocardial infarction patients, patients with stable CAD (including silent ischemia), patients having done a Coronary Artery Bypass Surgery (CABS), and patients who had undergone percutaneous transluminal coronary angioplasty (PTCA) (153).

Similarities Between Atherosclerosis and Rheumatoid Arthritis		
	Atherosclerosis	**Rheumatoid Arthitis**
Macrophage activation		
TNFα	↑	↑
Metalloproteinase expression	↑	↑
Interleukin-6	↑ (UA)	↑
Mast-cell activation	↑	↑
T-cell activation		
Soluble IL2 receptor	↑ (UA)	↑
$CD3^{+}DR^{+}$	↑ (UA)	↑
$CD4^{+}CD28^{-}$	↑ (UA)	↑
$CD4^{+}IFN\gamma^{+}$	↑ (UA)	↑
Th1/Th2 balance	↑ Th1	↑ Th1
B-cell activation		
Autoantibodies (oxLDL, HSP)	0 OR ↑	0 OR ↑
Rheumatoid factor	0	↑
C-reactive protein	↑ (UA)	↑↑
Adhesion molecules (VCAM-1, ICAM-1, E-selectin, P-selectin)	↑	↑
Endothelin	↑	↑
Neoangiogenesis	↑	↑
Possible antigens	HSP, 0x-LDL, Infectious agents	Collagen II, Cartilage antigens, HSP, Infectious agents

Table 2.Pasceri V, Yeh E. A tale of two diseases atherosclerosis and rheumatoid arthritis. Circulation. 1999

3.5.2. VO_2max IN RA

Patients with RA exhibit reduced levels of cardiorespiratory endurance (CRF) (73). High levels of CRF protect against cardiovascular disease mortality, (155,156) the presence of cardiovascular risk factors, (157,158) and CRF levels associated with low levels of inflammation (159).

The CRP gene is associated with factors (160,161) that can be significantly increased with training regardless of age, gender, race, and initial fitness levels. (162,163). Patients with increased fitness levels are hospitalized less often and for less time as opposed to inactive patients (164). Therefore, exercise may help to improve cardiovascular risk and the overall health status of patients with RA (8). However, although relevant research has already proved the importance of exercise in patients with RA, during this literature review, there is no study that examines the stress test results in this population. This is to do with observational restrictions on the realization of a true VO2max test. Given the characteristics of chronic inflammation and joint pains, it is highly possible for these people to stop the test, not because of cardiorespiratory limitation but due to other factors associated with the pathophysiology of the disease. This leads to inaccurate results and incorrect prescription of the exercise program. As a result, patients will not get all the benefits of exercise and thus, the risk of future cardiovascular disease remains high.

3.5.3. Exercise in RA and Physical Function

Exercise improves a wide variety of objective physical function tests, including assessments of balance and co-ordination, grip strength, the jump-high test, various different sub-maximal or maximal aerobic fitness tests, and tests designed to reflect the ability to perform activities of daily living (e.g. 30 sec sit-to-stand; 8’ up & go; 30 sec arm-curl; 50’ walk) (165) . Moreover, these beneficial effects are highlighted in two Cochrane reviews confirming that high-intensity aerobic and/or resistance exercise significantly improves physical function in patients with RA [18, 20]. In fact, a promising find in a study by Lemmey et al.(165) revealed that although baseline patients’ physical function was significantly poorer (≈ 20-30%) than age and sex-matched norms, a 24-week high-intensity exercise intervention was sufficient to restore normal physical function in RA patients with long-standing disease. It is also important to note that these benefits

are recognized by patients. In support of this, studies reveal significant improvements in subjective function, such as self-reported fatigue and the McMaster Toronto Arthritis Disability Questionnaire (MACTAR)(83,166–169).

These are indeed very promising findings and support the use of “exercise as medicine” in RA. Giles and his colleagues have demonstrated that the increased adiposity and reduced muscle mass, both independently, predict a poorer self-assessed physical function (Health Assessment Questionnaire; HAQ) in RA patients (170) . it is believed that the effects of high-intensity exercise on physical function are partly mediated by exercise-induced beneficial alterations in body composition. Studies directly investigating this assumption are currently lacking.

3.5.4. Exercise in RA and Body Composition

In RA patients, resistance training alone has been found to significantly increase muscle mass (83,165) probably due to the increased muscle levels of insulin-like growth factor-I that coincided with the hypertrophic response to resistance training (165). Combining resistance and aerobic training also results in increases in the muscle cross-sectional area of type I and II fibers in RA patients, even within six weeks, (167,171) while significant improvements in electromyographic activity and quadriceps femoris cross-sectional area are evident after 21 weeks (172). These findings are in line with the strengthening and hypertrophic responses seen in healthy individuals following appropriate exercise training (173). In fact, Hakkinen et al. has directly compared women with RA with age-matched healthy women and showed comparable absolute and relative increases in strength as well as similar increases in quadriceps femoris thickness and reductions in quadriceps femoris subcutaneous fat thickness following the completion of the same combined strength and aerobic training programme (172). This similarity in the training response is consistent with reports that muscle quality (i.e. muscle architecture, specific force, and voluntary activation capacity) is maintained in RA despite reductions in muscle quantity (174).

Along with increases in muscle mass, significant exercise-induced reductions in fat mass are evident in RA patients(83,165,172). It is of particular interest that high intensity exercise may decrease trunk fat up

to 2.5kg (83,165) which may improve the arterial stiffening in RA patients (175) and therefore, reduce the risk for CVD (176) . In a recent study, Stavropoulos-Kalinoglou et al.(8) showed that a combined aerobic and strength exercise intervention increased VO_2max, and that this increase was the sole predictor of reduced fat mass.

But how can these significant exercise-induced body composition alterations ameliorate disease activity and severity in RA? The answer to this lies in the acute and chronic effects of exercise on the function and structure of both the musculoskeletal system and adipocytes. The contracting (exercising) muscle stimulates cellular immune changes that have a significant anti-inflammatory effect. More specifically, exercise-induced muscle-derived interleukin 6 (IL-6), which is predominantly described as a pro-inflammatory cytokine in RA, may exert an anti-inflammatory and immunosuppressive effect with a down-regulating impact on the acute phase response (177) as well acting as a signal for replenishing depleted muscle glycogen stores (178). Acute exercise also expresses anti-inflammatory effects with increased levels of anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist (174). These phenomena may have a profound effect on the cytokine profile and, thus, inflammatory response in RA patients in whom the disease-driven overexpression of these cytokines leads to increased disease activity and severity. In addition, amongst the long term effects of exercise are increased muscle mass, balance and co-ordination which have a beneficial impact on physical function and thus, disease severity (179). With regards to the effects of exercise on adipocytes, it is accepted that exercise reduces inflammation via the inhibition of adipocyte-derived pro-inflammatory cytokines and improvement in adipocyte oxidative capacity (180). The latter may also be linked with the significant reduction in the cardiovascular risk of RA patients as a result of exercise (3,181).

3.5.5. Exercise in RA and Cardiovascular Risk

It is well established that RA associates with an increased risk for CVD, with cardiovascular events typically occurring approximately a decade earlier in RA patients compared to the general population (182). This may be partly due to the increased prevalence of hypertension [69, 70], hypercholesterolemia

(183,184), vascular dysfunction (5,185) and insulin resistance (186,187) seen in RA patients. In addition, the significant inflammation-induced alterations in body composition (rheumatoid cachexia) have been implicated in this increased CVD risk (6,9). However, all these factors collectively can only partly explain the increased CVD risk in RA. This suggests that an interplay of these factors with other parameters may exist which contribute to this increased prevalence of CVD in RA.

One such parameter is exercise. Lack of exercise and/or physical activity can result in low CRF a major CVD risk factor (188). Metsios et al., (189) demonstrated that physical inactivity in RA, associated with an inferior cardiovascular profile in RA, characterized by exacerbations of both classical and novel CVD risk factors. It appears, however, that high-intensity aerobic and resistance exercise can reverse this phenomenon. Results from a recent trial revealed that such an intervention significantly ameliorated blood pressure, body fat the lipid profile, vascular function and markers of oxidative stress, and the10-year CVD event probability of RA patients (190–192). Interestingly, the increase in CRF was the strongest predictor for each of these observed improvements. This observation is consistent with effects seen in the general population, with meta-analyses revealing that increased CRF leads to improvements in blood pressure (193), high-density lipoprotein (HDL) levels (194) , insulin resistance and body fat (195).

The reasons why high-intensity exercise has such profound effects on the cardiovascular profile in RA, warrants further investigation in appropriately designed trials. However, in patients with RA, exercise-induced reductions in fat mass were independently associated with the improvements seen in blood pressure as well as in inflammatory biomarkers (181). So again, the significant exercise-induced changes in body composition may account for this. Therefore, it seems that exercise holds a significant promise in improving the cardiovascular profile of RA patients.

4. Methodology

4.1. Participants

RA patients attending routine clinics of the Department of Rheumatology, Russell's Hall Hospital, Dudley Group NHS Foundation Trust, Research and Development (RND), UK, were approached.

4.2. Inclusion Criteria

In this research, *RA* (1987 ACR criteria) patients can participate which have been diagnosed in the past 10 years, without co-morbidities prohibiting.

4.3. Exclusion Criteria

Exclusion factors from the study are cases of patients with extended joint pain who are unable to participate in an increased physical activity test as well as cases suffering from a secondary disease that prevents them from an evaluation of the maximal oxygen uptake.

4.4. Study design

4.4.1. General Procedures

The trial was registered with the ISRCTN register. All assessments were conducted within the clinical research unit of Research and Development of Russell's Hall Hospital, Dudley Group NHS Foundation Trust. During the arranged appointment and after a detailed description of the procedures involved, all patients were asked to sign a consent form.

4.4.2. Assessments

4.4.2.1. Anthropometric Characteristics

Demographic data was collected using a self-administered questionnaire. Weight, body fat and fat-free mass wαs evaluated using a Tanita BC-418. Analyser (Tokyo, Japan) and the height (Leicester height measure).

4.4.2.2. Cardiorespiratory fitness

All participants (105) were subjected to an Exercise Tolerance Test (ETT) on a mechanical treadmill (HP Cosmos Mercury, Nussdorf-Traunstein, Germany). CRF was determined on the basis of maximal oxygen uptake (VO_2max) using a calibrated breath-by-breath system (Metalyzer 3B, CORTEX, Leipzig, Germany). An individualised ramp test protocol, based on the guidelines of the American Heart Association (24) was used. These protocols are more suitable to clinical settings than protocols using large intervals or steps (25). Testing started at a convenient speed for the participants (in most cases 2.0-3.5 mph) and 1% inclination. Speed increased at a perceived brisk walking rhythm by 2.0 mph until 3 min. Thereafter, inclination of the treadmill would increase every 1 min by 1,5 %. Testing was terminated when the participant reached final exhaustion.

4.4.2.3. Disease Activity Score 28

Disease activity was measured with the use of DAS28 (Prevoo et al. 1995). This is a composite assessment consisting of the patient's assessment of overall health during the last week on a visual analogue scale, a 28 joint count and the current ESR. To identify the swollen and tender joints, the nurse had to squeeze the joints of the arms, elbows, hand and knees (Appendix 3) of every participant.

4.4.2.4. Functional Capacity

The anglicised version of the 40-item Stanford Health Assessment Questionnaire (HAQ), (Kirwan and Reeback 1986) was used to measure functional disability. In this assessment, participants rate their ability (over the past week) to carry out 20 activities within eight aspects of daily living (dressing/grooming, rising, eating, walking, hygiene, reach, grip and errands/tasks) on a four-point scale from 'without any difficulty' to 'unable to do' (Appendix 4). For each aspect, patients also responded whether they received assistance from people or used specific devices. The HAQ is internally consistent ($\alpha \geq 0.89$) and has excellent pre to post-physician visit temporal stability ($r = 0.99$).

5. Statistics

We used descriptive statistics to record specific variables such as age, BMI, VO_2max, HAQ and DAS 28.

Independent samples T-test we used to assess the differences between those who achieved the established VO_2max criteria and those who did not in terms of HAQ and DAS 28. All analysis conducted via SPSS and level of significance was $p<0.05$.

Descriptives									
		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
DAS28	Yes	21	4.1781	4.11358	0.89766	2.3056	6.0506	0.64	20.50
	No	62	3.3818	1.59890	0.20306	2.9757	3.7878	0.00	6.28
	Total	83	3.5833	2.47998	0.27221	3.0417	4.1248	0.00	20.50
HAQ_T1_Mean	Yes	27	0.3326	0.42111	0.08104	0.1660	0.4991	0.00	1.56
	No	73	0.5451	0.48946	0.05729	0.4309	0.6593	0.00	1.85
	Total	100	0.4877	.47937	0.04794	0.3926	0.5828	0.00	1.85

Table 3. Statistics of VO_2MAX, Disease Activity Score 28 (DAS28) and Disease Severity (HAQ).

ANOVA						
		Sum of Squares	df	Mean Square	F	Sig.
DAS28	Between Groups	9.947	1	9.947	1.630	0.205
	Within Groups	494.377	81	6.103		
	Total	504.324	82			
HAQ_T1_Mean	Between Groups	0.890	1	0.890	3.991	0.049
	Within Groups	21.860	98	0.223		
	Total	22.750	99			

Table 4. Significance of VO_2MAX, Disease Activity Score 28 (DAS28) and Disease Severity (HAQ).

		Mean	Std. Deviation
Age A	**Male**	59.00	9.959
	Female	52.51	12.816
	Total	54.53	12.328
VO_2max	**Male**	21.8812	5.60930
	Female	19.1603	4.38660
	Total	20.0074	4.93823
Height	**Male**	1.7652	0.08675
	Female	1.6336	0.06423
	Total	1.6745	0.09418
Weight	**Male**	86.030	15.8669
	Female	76.044	18.8324
	Total	79.153	18.4799
BMI_t1	**Male**	27.5881	4.69595
	Female	28.3118	6.18531
	Total	28.0865	5.75049

Table 5: Statistics between groups and anthropometric characteristics.

		Sig.
Age A	**Between Groups**	0.011
	Within Groups	
	Total	
VO_2max	**Between Groups**	0.008
	Within Groups	
	Total	
Height	**Between Groups**	0.000
	Within Groups	
	Total	
Weight	**Between Groups**	0.009
	Within Groups	
	Total	
BMI_t1	**Between Groups**	0.551
	Within Groups	
	Total	

Table 6: Significance between groups and anthropometric characteristics.

6. Results

From the 105 patients who participated in the present study, 73 were women (69.5%) and 32 were men (30.5 %). The average age of the participants was 54.6±12.3 years (52.4±12.8 for women and 59.5±9.9 men). BMI average ratio was 28.2 (women BMI average ratio was 28±6.1 and men 27.5±4.6), which belongs to the overweight category with regard to World Health Organization (WHO) (reference). Of the 105 patients, only 28 out of all (percentage of 26.6 %) managed to meet two of three criteria for a successful CRF test (achieved plateau, RER > 1.1 and HRmax > 220-age). Specifically, 7 were men (success rate 29.1%) and 21 females (28.8% success rate). About VO_2 plateau, only 5 (4 women and 1 man) out of 105 patients reached a plateau, having the very poor percentage of success of 4.7%. With regards to RER, the success ratio was 82 patients (78%), with 59 of them being women (percentage of 80.2%) and 23 were men (percentage of 71.8%). Relatively to HRmax, the total successful number was 29 patients (percentage of 27.6%) with 8 men (percentage of 25%) and 21 women (percentage of 28.7 %).

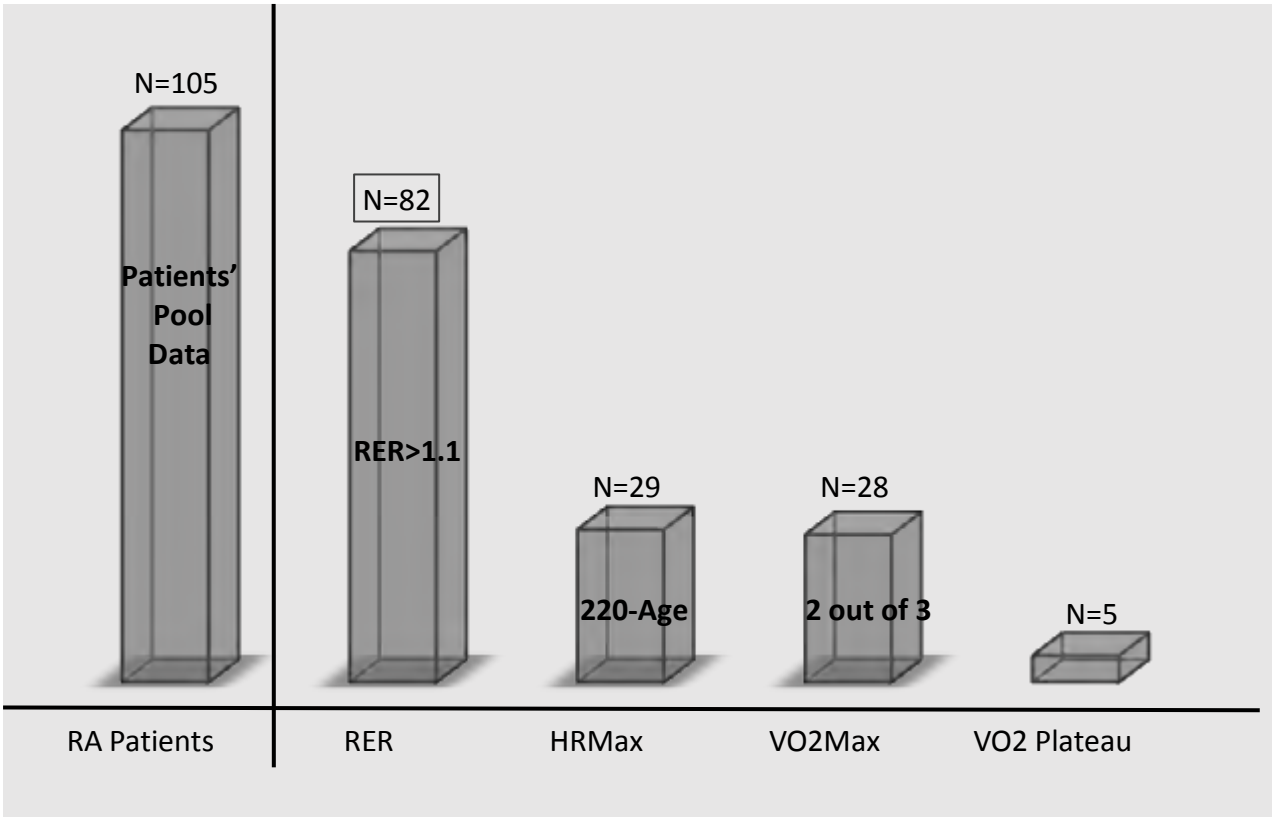

Figure 1: Study characteristics-VO2 Max criteria

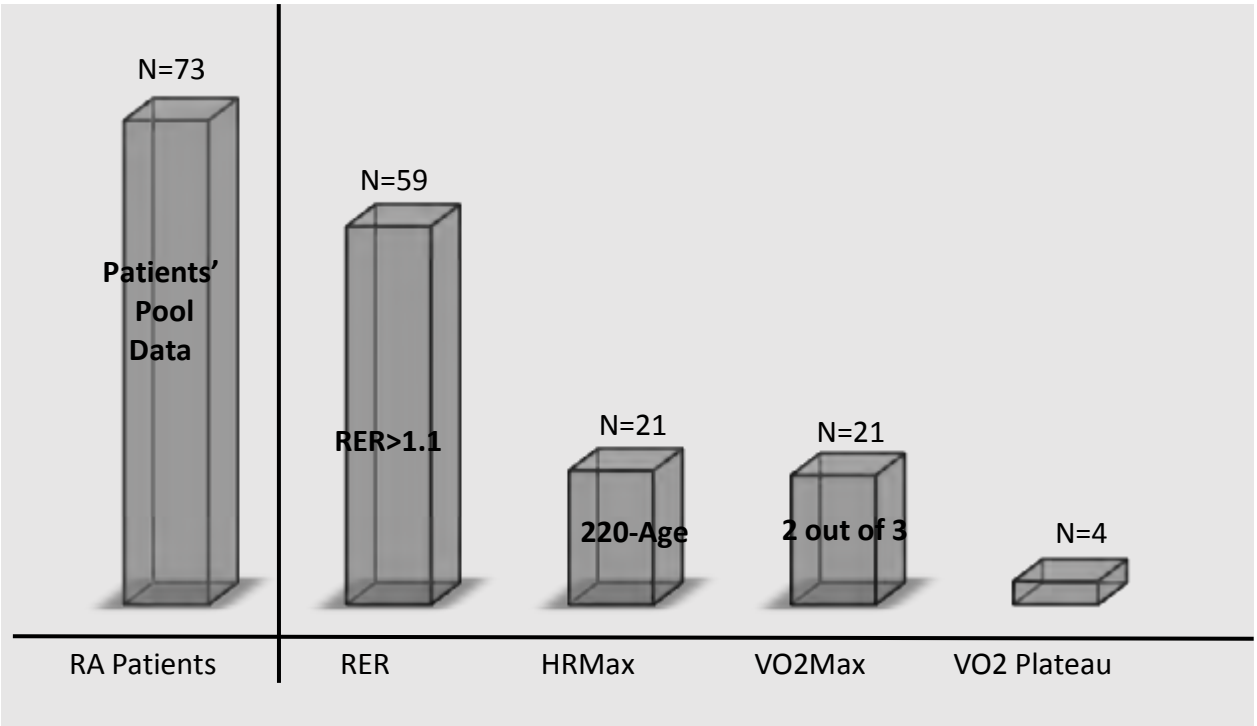

Figure 2: VO2 Max criteria by female

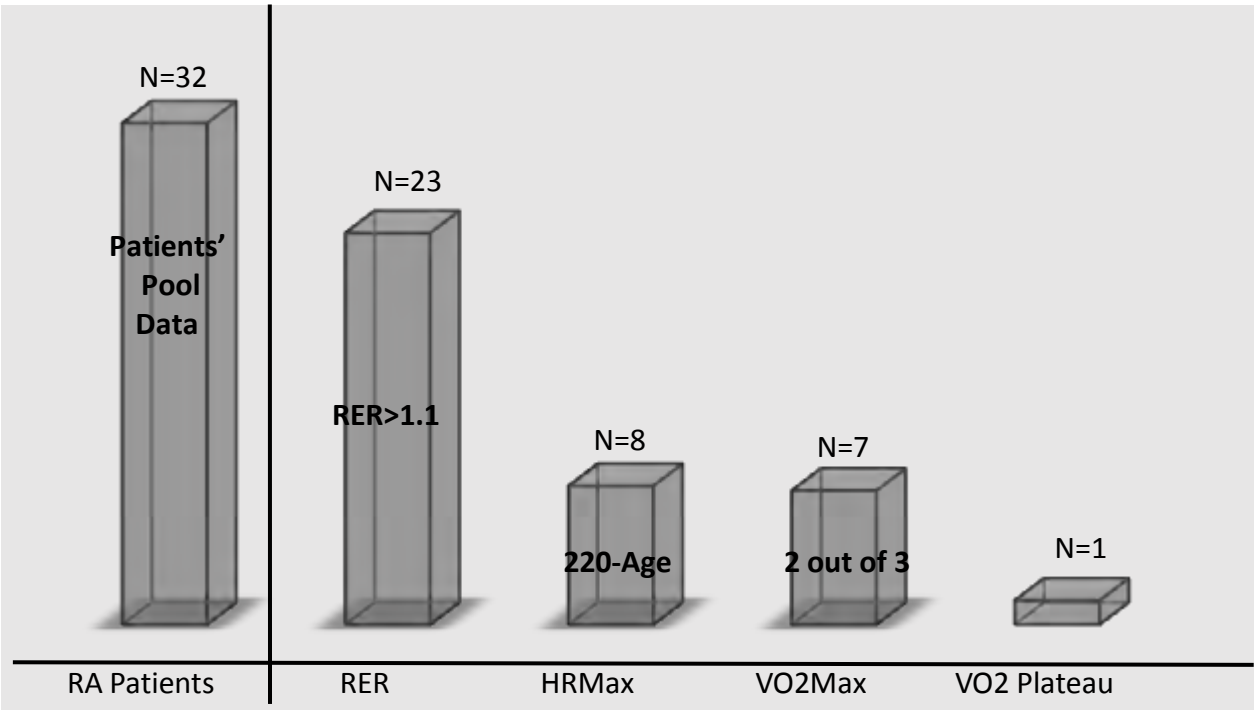

Figure 3: VO2 Max criteria by male

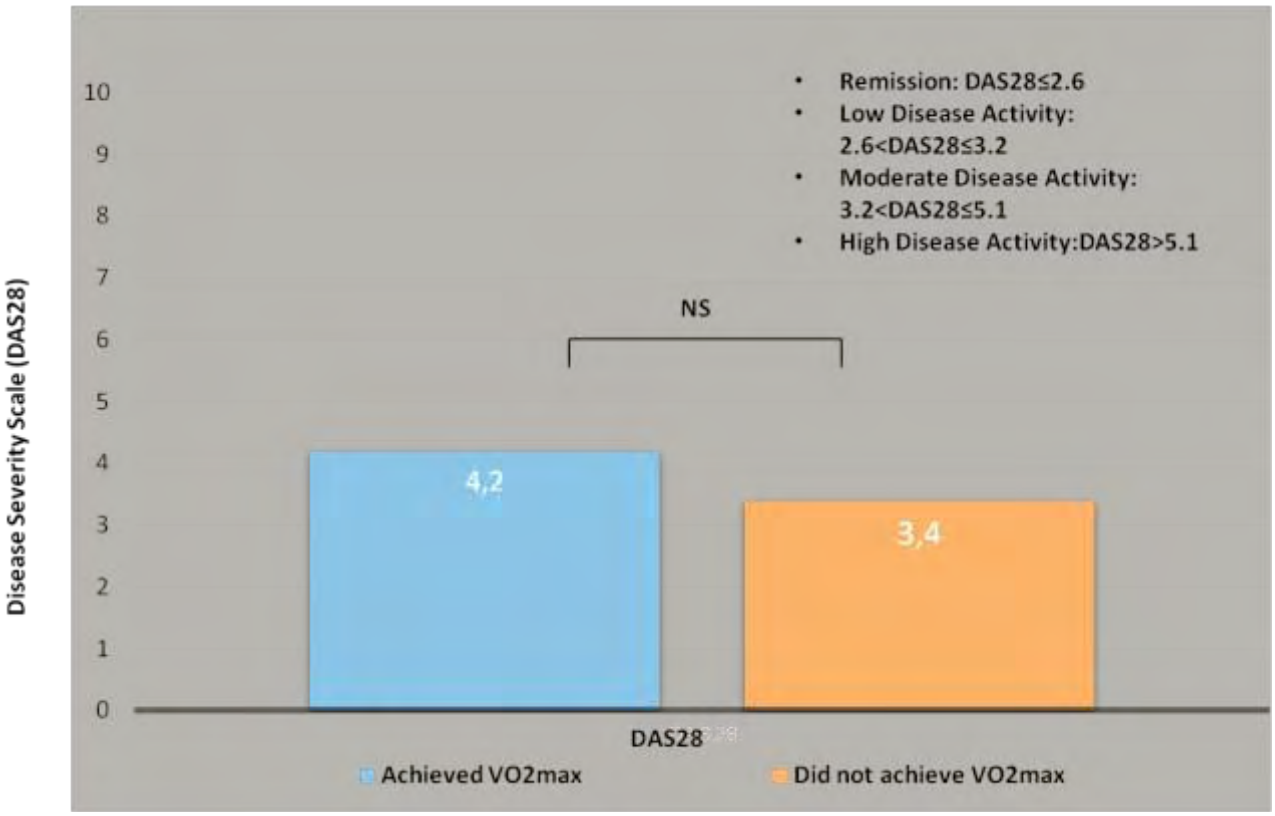

Figure 4: Differences in Disease Activity between groups

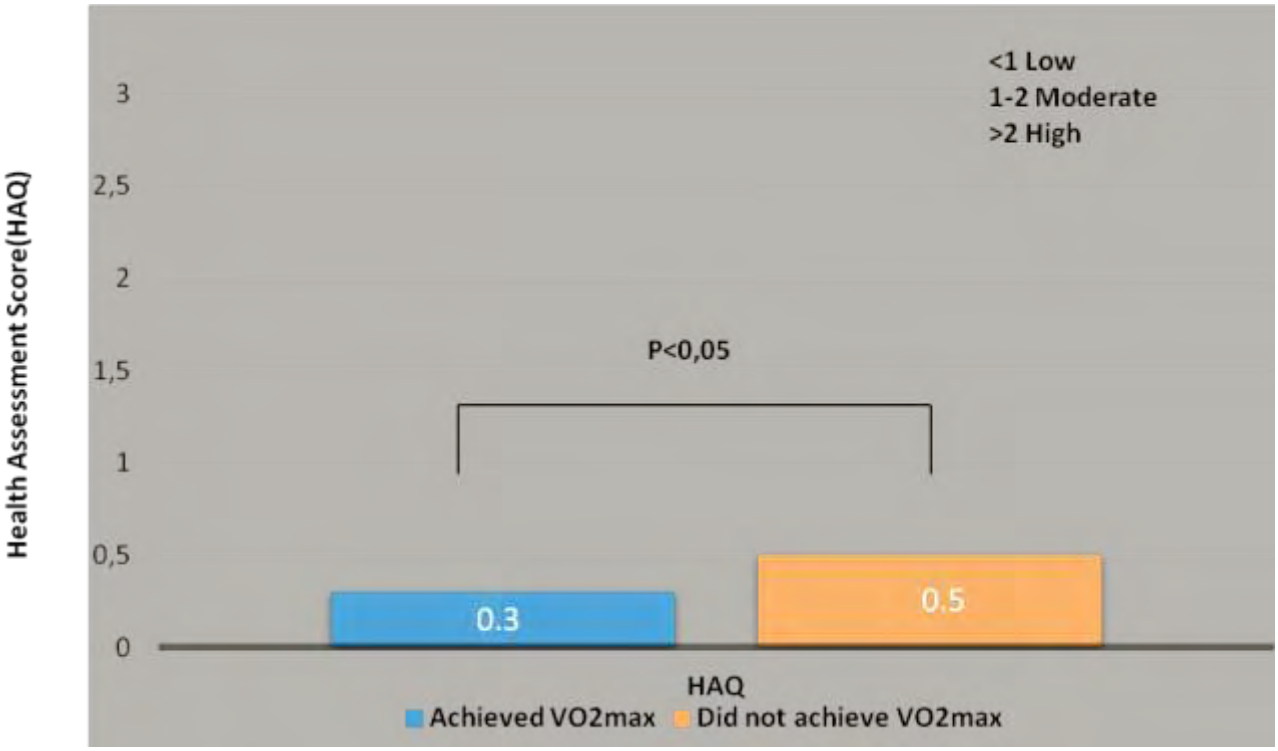

Figure 5: Differences in Disease Severity between groups

7. Discussion

To our knowledge, this is the first study that investigates the criteria for a true maximal CRF test in RA. We found that only 26.6 % of the patients managed to perform a successful VO_2max assessment. Therefore, this is a very small percentage of patients that achieved the criteria of VO_2max testing, indicating that 74.4% of RA patients did not achieve cardiorespiratory exhaustion. Moreover, with regard to the statistical analysis, patients that achieved VO_2max had better results in HAQ. Additionally, since there was no significant difference in DAS 28 evaluation, the outcome indicates the importance of functional ability on performing such types of testing, but not inflammation, given the lack of significant differences between VO_2max and DAS28. This is something that is proved for the first time in contradiction to what was believed until today. Having the above results, it is indicated that further research should be focused so as to improve the patient's functional ability. During the research of the current literature, there are no published studies targeting to increase the functional ability in RA patients before the initial CRF assessment. Although, Lemmey et al revealed, that although baseline patients' physical function was significantly poorer (≈ 20-30%) than age- and sex-matched norms, a 24-week high-intensity exercise intervention was sufficient to restore normal physical function in RA patients with long-standing disease. Thus, we suggest that exercise prescription development should include an individualised aerobic programme during the first 4 weeks before the initial VO_2max testing. Given the beneficial results of exercise in RA and of other chronic diseases, it seems reasonable to suggest that ''exercise can be used as medicine ''. As such, it is very important to prescribe the specific exercise level, just like it is done with prescription medication. Consequently, optimization of exercise prescription is going to gain the biggest benefits, while significantly reducing the high risk of CVD.

The limitations that occurred in our study were two. There were patients without any previous experience in exercise and more specifically, walking on a treadmill. Although we did an induction session on the treadmill for 5 minutes for our patients to become familiar with the process before the test. Additionally, recruited patients with better functional ability and positive bias did not participate in this study.

8. Conclusion

This study demonstrates that the results of RA patient's during the initial CRF assessment, driven to VO_2peak and not VO_2max (26.6 % success rate). Even more, this is not due to the disease activity of RA causing the extended joint inflammation, but because of the disease severity. Further research is required to determine the exact mechanisms behind these phenomena, particularly if the improvement of functional ability before the initial assessment, which can lead to a true VO_2max test. As a result, exercise prescription is going to be optimised and unlike the CVD risk in RA patients, is going to be minimised.

9. Recommendations

Exercise has multiple health benefits for RA patients, supporting the use of “exercise as medicine” in RA. The different training programmes and modes utilised in the literature along with the reported attendance rates indicate that patients with RA can safely perform different types of high intensity exercise programmes, and enjoy the same range and magnitude of benefits as age and sex-matched healthy individuals.

To achieve and maintain the significant benefits of exercise, apart from following established training progression principles (196), specific attention needs to be given to devising tailored programmes for these patients because RA can differently affect each patient. Along with this, it is also important to understand the patients’ preferences in order to devise an effective exercise programme. This will very likely increase adherence to regular structured physical activity and reduce the sedentary behaviours seen in RA (197). We suggest the following specific principles for exercising in RA:

1. Using existing infrastructure and/or a home-based approach (where possible), exercise should be part of the overall management of RA in combination with pharmacological and behavioural interventions.
2. The main targets of exercise in RA should be initially to restore functional ability with the intention to initiate exercise programmes that aim the improvement of CVD risk as well as disease activity/severity which seem to depend on exercise-induced changes in body composition.
3. The development of exercise programmes for RA patients will need to take into account: a) the ACSM relative and absolute contra-indications for exercise testing as well as the risk stratification algorithms for increasing the safety of exercise participation (198) and b) baseline fitness levels, functional ability and personal preferences.
4. Exercise prescription development should include an aerobic mainly programme during the first 4 weeks, followed by a combined high-intensity aerobic and resistance training intervention, as the later seems to improve more both function and cardiovascular profile in RA.

For these suggestions to take effect, it seems peremptory that the rheumatology specialists need to enhance their knowledge on exercise in RA and rectify their opinions about the benefits of exercise. Interventions that target these factors need to be the focus of future research. Importantly, new courses that educate and provide the practical skills for the development of exercise programmes for exercise professionals are also needed.

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11. Appendix

11.1. Bioethics Approval

University of Thessaly
Department of Physical Education and Sport Science
Internal Ethics Committee

Trikala: 23/04/2014
Protocol Number.: 866

Approval of research entitled:

Examination of the Exercise Tolerance Test results for the maximal oxygen uptake established criteria of patients with Rheumatoid Arthritis.

Scientist responsible – supervisor: Dr. Giorgos Sakkas PhD School of Physical Education and Sport Science, University of Thessaly.

Main researcher – student: Postgraduate Thesis of the student Vitalis Panagiotis, BSc, within the PGC "Exercise and Health"

Institution & Department:
School of Physical Education and Sport Science in collaboration with the School of Sport, Performing Arts and Leisure at the University of Wolverhampton in UK.

The proposed research relates to a:

Research grant ☐ **Postgraduate thesis X** Undergraduate thesis ☐ Independent research ☐

Contact phone: 2431-500-911
Contact email: gksakkas@med.uth.gr

The Internal Ethics Committee (IEC) of the Department of PE and Sport Science (DPESS), University of Thessaly, examined the proposal in its 2-5/23-4-2014 meeting and approves the implementation of the proposed research.

The Chair of the IEC – DPESS

Athanasios Tsiokanos, PhD

11.2. Consent Form

Informed consent form for participation in a research study.

11.2.1. Title of the Study

Examination of the Exercise Tolerance Test results for the VO_2max established criteria of patients with RA.

11.2.2. Aim of the Study

The major purpose of this study is to evaluate the criteria for successful VO_2max in patients with RA. This will lead us to an optimization of the exercise prescription in order to minimize the possibility of cardiovascular disease in the future.

11.2.3. Description of Research Activities

This research consists of a VO_2max test. It is carried out in Russell's Hall Hospital, West Midlands, Dudley Group of Hospitals NHS Trust at the Research and Development (RND) center. In charge of the test will be an exercise physiologist leading the procedure and a cardiac physiologist responsible for the Electrocardiogram. At the beginning, the blood pressure, height, weight, body fat and fat-free mass will be evaluated. Afterwards, in order for the Electrocardiogram procedure to take place, the cardiac physiologist will place patches on your breast (in front of your heart) and the exercise physiologist will place a gas analyzer mask on your face. Initially, you will sit for two minutes on a chair with the mask on your face in order to get used to it. Next, you will step on the treadmill to begin with the test by doing a warm up for two minutes at 1% gradient at approximately your normal walking speed. Then, for the following two minutes we will increase the gradient of the treadmill at 3.0% and the walking rhythm from a comfortable to a brisk walking level for you. Keeping this rhythm, we will only change the gradient by 1.5% for every minute until your request to end and supposed that you have achieved your maximal capacity. In any case, if you experience any symptoms, discomfort or for any reason you want to stop the test, we shall do so immediately. At the end of the assessment, you will have a sit again on the chair for two minutes in order to recover with the mask on your face and repeated blood pressure measurements will be done in order to ensure that you have been

calmed down. When your blood pressure is the same as that of when you arrived, you will be able to leave the hospital.

11.3 Risks/ Discomfort Involved

The VO_2max test stresses the body and as a result, some side effects may occur such as leg and general fatigue, dizziness, shortness of breath and exercise induced hypotension. Moreover, before and after the test you need to get some rest. Finally, the researchers and the hospital staff are there to guarantee your safety, as that is our prime priority.

11.3.1. Expected Impact

Because of the extended joint inflammation, a side effect of RA is inactivity, the most predominant risk factor for CVD. The latest research reports the strong relation of CVD and RA and the benefits of exercise. Nonetheless, there is no research that investigates weather cardiorespiratory limitations are responsible for the discontinuation of the test, or if other factors are responsible. The aim of this study is to investigate the above in order to achieve an optimized exercise prescription program and minimise the possibility of CVD in the future for RA patients.

11.3.2. Dissemination of Results

All research projects belong to the Group of Hospitals, NHS Trust, and all participating patients are subject to ethical review through the NHS National Research Ethics System. The research team has extensive experience in these processes for projects of varying nature and complexity in clinical populations. This includes ethical approval for clinical and basic science data storage and analysis, obtaining biomaterials, long-term storage, and medical publication, collaborations with industry and inclusion or exclusion of future commercial use. The project will be conducted in accordance with the Research Governance Framework for Health and Social Care. All participants will provide their informed, written consent and be aware that their details will be stored in a coded fashion on a secured database with restricted and governed access. In particular, patients will be informed and consented that their data might be used in academic collaborations.

In addition, they will be made aware that they are under no obligation to participate and can withdraw at any point without providing a reason.

11.4. Further Information

Do not hesitate to make questions regarding the aim of this study or the implementation of study design. If you have any doubts or questions, do ask us for clarifications.

11.4.1. Freedom of Consent

You are a volunteer participant. You are free to withdraw your consent now or later.

11.4.2. Participant's declaration

I read this form and I understand the procedures involved. I agree to participate in this study.

Date: __/__/__

[Name and signature of participant]

[Name and signature of researcher]

[Name and signature of witness]

11.5. Disease Activity Score 28 (DAS28)

Disease Activity Score in 28 Joints (DAS28)

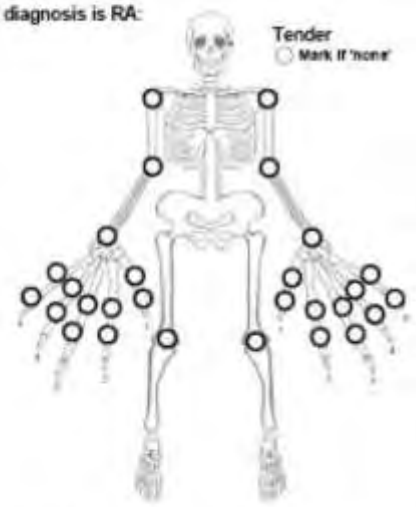
Patient global assessment
Considering all the ways in which illness and health may affect you at this time, please indicate below how you are doing:

VERY WELL ├──┤ **VERY POORLY**

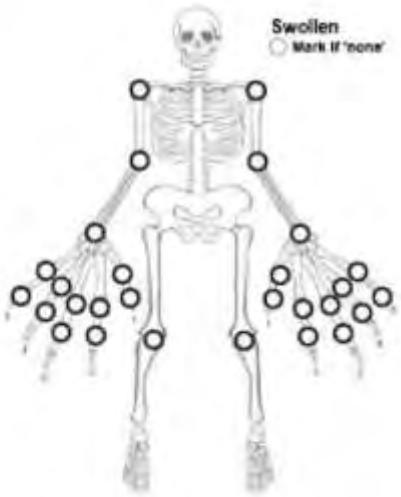
FOR PROVIDER USE ONLY

If diagnosis is RA:

Tender
Mark if 'none'



Swollen
Mark if 'none'



VAS (0-100)

28TJC

28SJC

ESR

DAS28

DAS28=0.56*√(28TJC) + 0.28 * √(28SJC) + 0.70*Ln(ESR/CRP) + 0.014*VAS

How to calculate a DAS28 score:

1. Ask the patient to make a vertical mark on a 100 mm Visual Analog Scale (VAS) corresponding to their general health or global disease activity. Using a ruler, measure from the left-hand side in mm. Note: DAS28 calculations may be performed without a VAS measurement.
2. Perform a swollen and tender joint examination on your patient. Add all of the swollen and tender joints and record the totals in the appropriate boxes.
3. Erythrocyte Sedimentation Rate (ESR) should be measured (in mm/hour). Note: C-reactive protein (CRP) levels may be used as a substitute for an ESR.
4. Plug the appropriate values into the formula (many online calculators are available including http://www.das-score.nl/www.das-score.nl/dasculators.html).
5. If using CRP instead of ESR or calculating a score from only 3 variables please see http://www.reuma-nijmegen.nl/www.das-score.nl/ for the appropriate formula.

Interpretation:

- The DAS28 provides you with a number on a scale from 0 to 10 indicating current RA disease activity.
- Remission: DAS28 ≤ 2.6
- Low Disease activity: 2.6 < DAS28 ≤ 3.2
- Moderate Disease Activity: 3.2 < DAS28 ≤ 5.1
- High Disease Activity: DAS28 >5.1

Adapted from: DAS-Score.nl. Available at http://www.das-score.nl/www.das-score.nl/index.html. Accessed April 15, 2010.

11.6. Disease Severity (HAQ)

HEALTH ASSESSMENT QUESTIONNAIRE (HAQ)

Date: ☐☐☐☐☐☐☐☐ **Patient Name:** ☐

Please tick the one response which best describes your usual abilities over the past week

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do	
1. DRESSING and GROOMING					
Are you able to:					
a. Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐	--------
b. Shampoo your hair?	☐	☐	☐	☐	
2. RISING					
Are you able to:					
a. Stand up from an armless straight chair?	☐	☐	☐	☐	--------
b. Get in and out of bed?	☐	☐	☐	☐	
3. EATING					
Are you able to:					
a. Cut your meat?	☐	☐	☐	☐	--------
b. Lift a full cup or glass to your mouth?	☐	☐	☐	☐	
c. Open a new carton of milk (or soap powder)?	☐	☐	☐	☐	
4. WALKING					
Are you able to:					
a. Walk outdoors on flat ground?	☐	☐	☐	☐	--------
b. Climb up five steps?	☐	☐	☐	☐	

PLEASE TICK ANY AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITIES:

Cane (W) ☐	Walking frame(W) ☐	Built-up or special utensils (E) ☐
Crutches (W) ☐	Wheelchair (W) ☐	Special or built-up chair (A) ☐

Devices used for dressing (button hooks, zipper pull, shoe horn) ☐

Other (specify).....

PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON:

Dressing and Grooming ☐	Eating ☐
Rising ☐	Walking ☐

ID ☐☐☐☐☐☐☐☐

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Please tick the one response which best describes your usual abilities over the past week

	Without ANY difficulty	With SOME difficulty	With MUCH difficulty	UNABLE to do	
5. HYGIENE					
Are you able to:					
a. Wash and dry your entire body?	☐	☐	☐	☐	
b. Take a bath?	☐	☐	☐	☐	--------
c. Get on and off the toilet?	☐	☐	☐	☐	
6. REACH					
Are you able to:					
a. Reach and get down a 5 lb object (e.g. a bag of potatoes) from just above your head?	☐	☐	☐	☐	--------
b. Bend down to pick up clothing off the floor?	☐	☐	☐	☐	
7. GRIP					
Are you able to:					
a. Open car doors?	☐	☐	☐	☐	
b. Open jars which have been previously opened?	☐	☐	☐	☐	--------
c. Turn taps on and off?	☐	☐	☐	☐	
8. ACTIVITIES					
Are you able to:					
a. Run errands and shop?	☐	☐	☐	☐	
b. Get in and out of a car?	☐	☐	☐	☐	--------
c. Do chores such as vacuuming, housework or light gardening?	☐	☐	☐	☐	

PLEASE TICK ANY AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITIES:

Raised toilet seat (H) ☐ Bath seat (H) ☐ Bath rail (H) ☐

Long handled appliances for reach (R) ☐

Jar opener (for jars previously opened) (G) ☐

Other (specify) _____

PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON:

Hygiene ☐ Gripping and opening things ☐

Reach ☐ Errands and housework ☐

HAQ	
0	0.0
1	0.125
2	0.250
3	0.375
4	0.500
5	0.625
6	0.750
7	0.875
8	1.00
9	1.125
10	1.250
11	1.375
12	1.500
13	1.625
14	1.750
15	1.875
16	2.000
17	2.125
18	2.250
19	2.375
20	2.500
21	2.625
22	2.750
23	2.875
24	3.000

ID ☐☐☐☐☐☐☐☐

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11.6. Copyright Statement

Υπεύθυνη Δήλωση

Η κάτωθι υπογεγραμμένη ΝΑΜΕ μεταπτυχιακή/ος φοιτήτρια/ης του Προγράμματος Μεταπτυχιακών Σπουδών «ΑΣΚΗΣΗ ΚΑΙ ΥΓΕΙΑ» του Τμήματος Επιστήμης Φυσικής Αγωγής και Αθλητισμού του Πανεπιστημίου Θεσσαλίας

δηλώνω υπεύθυνα ότι αποδέχομαι τους παρακάτω όρους που αφορούν

(α) στα πνευματικά δικαιώματα της Μεταπτυχιακής Διπλωματικής Εργασίας (ΜΔΕ) μου με τίτλο
«Maximal oxygen uptake in Rheumatoid Arthritis»

(β) στη διαχείριση των ερευνητικών δεδομένων που θα συλλέξω στην πορεία εκπόνησής της:

1. Τα πνευματικά δικαιώματα του τόμου της μεταπτυχιακής διατριβής που θα προκύψει θα ανήκουν σε μένα. Θα ακολουθήσω τις οδηγίες συγγραφής, εκτύπωσης και κατάθεσης αντιτύπων της διατριβής στα ανάλογα αποθετήρια (σε έντυπη ή/και σε ηλεκτρονική μορφή).

2. Η διαχείριση των δεδομένων της διατριβής ανήκει από κοινού σε εμένα και στον/στην πρώτο επιβλέποντα -ουσα καθηγητή -τριας.

3. Οποιαδήποτε επιστημονική δημοσίευση ή ανακοίνωση (αναρτημένη ή προφορική), ή αναφορά που προέρχεται από το υλικό/δεδομένα της εργασίας αυτής θα γίνεται με συγγραφείς εμένα τον ίδιο, τον/την κύριο-α επιβλέποντα -ουσα ή και άλλους ερευνητές (όπως πχ μέλους –ών της τριμελούς συμβουλευτικής επιτροπής), ανάλογα με τη συμβολή τους στην έρευνα ή στη συγγραφή των ερευνητικών εργασιών.

4. Η σειρά των ονομάτων στις επιστημονικές δημοσιεύσεις ή επιστημονικές ανακοινώσεις θα αποφασίζεται από κοινού από εμένα και τον/την κύριο -α επιβλέποντα -ουσα της εργασίας, πριν αρχίσει η εκπόνησή της. Η απόφαση αυτή θα πιστοποιηθεί εγγράφως μεταξύ εμού και του/της κ. επιβλέποντα -ουσας.

Τέλος, δηλώνω ότι γνωρίζω τους κανόνες περί λογοκλοπής και πνευματικής ιδιοκτησίας και ότι θα τους τηρώ απαρέγκλιτα καθ' όλη τη διάρκεια της φοίτησης και κάλυψης των εκπαιδευτικών υποχρεώσεων που προκύπτουν από το ΠΜΣ/τμήμα, αλλά και των διαδικασιών δημοσίευσης που θα προκύψουν μετά την ολοκλήρωση των σπουδών μου.

Ημερομηνία

Η δηλούσα/ων

ονομα