

ANSWER TO REVIEWERS

August 31, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 10688-Review.docx).

Title: Muscle wasting in Rheumatoid Arthritis: the role of oxidative stress

Authors: Antonios Stavropoulos-Kalinoglou, Charikleia Deli, George D. Kitas, Athanasios Z. Jamurtas

Name of Journal: *World Journal of Rheumatology*

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Firstly please allow me to thank the reviewers for their thorough work and the very encouraging comments. Also, we thank them for indicating several weaknesses in our paper. We feel that our manuscript has been significantly improved due to these suggestions. Please find below a detailed description of all the corrections we have made as a response to their comments.

1. We have updated the format of the manuscript according to journal guidelines
2. We have modified the references in accordance to the journal guidelines and the reviewer's comments. We have now included PMIDs and DOIs wherever available
3. Reviewer 00458932 made the following comments:
 - a. This manuscript is interesting. However, it needs some improvements in English language
 - b. Also, few inaccuracies should be correct, f.e. RA as the commonest inflammatory arthritis

We thank the reviewer for the encouraging comments.

In response to the reviewer's comment, regarding the quality of English language used in our manuscript, we have modified the text in numerous sites to improve its clarity. It is not possible to mention all the changes we have performed in a point-by-point fashion, however we append below the manuscript with all the changes highlighted should the reviewers wish to view them.

In response to the comment about inaccuracies, we have removed our notion that RA is the most common chronic inflammatory arthritis. However, we are not sure which other part of our text the reviewer considers inaccurate. In our work, we try to minimize any inaccuracies by using published and well accepted theories and observations. If the reviewer believes that any of our sayings are not accurate we would like those to be pointed out so we can correct them or argue for them.

4. Reviewer 460875 made the following comments:
 - a. This is an interesting review on role of oxidative stress on muscle involvement in rheumatoid arthritis. The paper is write in a clear manner. References aren't cited as indicated in "Instructions of Authors", and some of those should be corrected (journal title not is always in its abbreviated form as shown in PubMed)

We thank the reviewer for the positive feedback. Indeed our references did not conform to

the journal guidelines. We have now changed that. We also corrected journal titles to appear in their abbreviated form.

We would like once again to thank you for considering our paper for publication in the *World Journal of Rheumatology*.

Sincerely yours,

Antonios Stavropoulos-Kalinoglou, PhD
Post-doctoral research fellow in clinical exercise physiology
School of Physical Education and Sports Science
University of Thessaly
Trikala, 42100
Greece
Email: antonios.stav@gmail.com
Tel: +302431047038

Abstract

Rheumatoid Arthritis (RA) is a debilitating disease leading to functional and social disability. In addition to the joints, RA affects several other tissues of the body including the muscle. RA patients ~~have exhibit~~ significantly ~~lessewer~~ muscle mass compared to the general population. ~~The reason for this remains unknown however s~~Several theories have been proposed ~~to explain this~~. High grade inflammation, a central component in the pathophysiology of the disease, has long been proposed as the key driver of muscle wasting. More recent findings however, indicate that inflammation on its own cannot fully explain the high prevalence of muscle wasting in RA. Thus, the contribution of other potential confounders, such as nutrition and physical activity, has also been studied. Results indicate that they play a significant role in muscle wasting in RA, but again neither of these factors seems to be able to fully explain the condition. Oxidative stress is one of the major mechanisms thought to ~~significantly~~ contribute to the development and progression of RA ~~but. However,~~ its potential contribution to muscle wasting in ~~thesesueh~~ patients has received limited ~~scientific~~ attention. Oxidative stress has been shown to promote muscle wasting in healthy populations and people with several chronic conditions. Moreover, all of the aforementioned potential contributors to muscle wasting in RA (i.e. inflammation, nutrition, and physical activity) may promote pro- or anti-oxidative mechanisms. This review aims to highlight the importance of oxidative stress, as a driving mechanism for muscle wasting in RA ~~and, by underlying or inducing several previously proposed hypotheses. Moreover, it~~ discusses potential interventions that may promote muscle regeneration via reductions in oxidative stress.

Keywords: rheumatoid arthritis; oxidative stress; muscle wasting; inflammation; cytokines; exercise

Core tip: Muscle wasting is common in RA and associates with significant health burden ~~in these patients~~. To date several theories have been proposed to explain why RA patients loose muscle

mass ~~but~~however, the exact underlying mechanisms are not clear. Oxidative stress is a key driver of muscle wasting in the general population; however, its potential role in muscle wasting in RA has not been studied. AS it arises from this review, oxidative stress seems to contribute to muscle wasting in RA. Further research on the subject is warranted, especially focusing on the underlying mechanisms and potential interventions~~This paper reviews the main knowledge in the field and proposes directions for future research.~~

Introduction

Rheumatoid Arthritis (RA) is a debilitating disease affecting ~1% of the population in Europe and North America ^[1]. It is an autoimmune disease affecting mainly synovial joints ^[2] ~~and associates with, manifesting as a~~ high-grade inflammatory condition characterised by, ~~with~~ high levels of circulating pro-inflammatory cytokines, including tumour necrosis factor alpha (TNF α), and the interleukins (IL) 1 and 6. These cytokines are produced in the inflamed synovium and are implicated in joint swelling, pain, and eventually destruction ^[3]. ~~As the condition progresses~~ ~~parallel with the progression of the condition~~, patients very frequently lose their jobs ^[4], ~~their~~ functional ability (movement) ^[1], and eventually their independence ^[5]. Apart from ~~this~~ physical and psychological ~~personal~~ burden ~~on the patients~~, RA has significant costs for the health ~~and social~~ ~~care~~ system ^[6]. Thus, the efforts of the scientific community have focused on the identification and elimination of the potential causes of RA ~~as well as effective treatments, and despite significant therapeutic progress in recent years a cure remains elusive. However, to date, its aetiology and a definitive treatment remains elusive and the best efforts of the managing physicians focus on pain and damage control~~ ^[1].

Apart from the joints, RA affects several other tissues of the body leading to systemic involvement and significant extra-articular manifestations ^[7]. It is these extra-articular manifestations, and not RA itself, that significantly shorten the life of RA patients and add extra layers of morbidity. Cardiac and vascular conditions are especially common among these patients. Heart disease in RA is both more prevalent and more likely to lead to death than in the general population ^[8]. The exact cause for this remains unknown, however genetic predisposition ^[9-12], classical CVD risk factors ^[13, 14] and the effects of systemic inflammation on the vasculature ^[15, 16] are all thought to contribute. Other ~~extra-articular~~ ~~such~~ manifestations are observed in the skin, eyes, lungs, renal, nervous and gastrointestinal systems ^[17].

The reasons for the development of ~~such~~ ~~these~~ manifestations are not fully understood. It is believed that the endocrine functions of the pro-inflammatory cytokines (mainly TNF α , IL1 and 6)

initiate a cascade of destructive processes in distant tissues, with reactive oxygen species playing a central role in cell membrane destruction and cellular death ^[18].

Oxidative Stress in RA

Free radicals and Inflammation

Free radicals, such as reactive oxygen species (ROS), have been proposed to play a significant role both in the development and progression of inflammation, as well as its deleterious effects on cell structure and function ~~both~~ at the site of the inflammation and in distant tissues ^[19, 20].

Free radicals, formed as by-products of normal biological processes – such as cellular metabolism in the mitochondrial electron transport chain, and reperfusion injury – are highly reactive agents that can cause physiological damage ^[21]. Free radicals ~~can damage all~~ are capable of damaging cellular components such as lipids, proteins and DNA. In the general population, they are counterbalanced by effective antioxidant defence mechanisms. However, in inflammatory conditions these defence mechanisms seem to be weakened ^[22].

It is not clear which is the sequence of events but it seems likely that inflammation reduces the anti-oxidant response, thereby increasing the accumulation of free radicals ^[19]. These, further activate pro-inflammatory nuclear pathways (~~in~~ specifically Activator Protein one - AP-1 and nuclear factor kappa beta – NFkB) that transcribe cytokines and adhesion molecules involved in the modulation of inflammation ^[23] resulting in further production of free radicals. ~~Specifically, n~~ Nitric oxide (NO) has a role in the regulation of vascular tone, ~~contributing to cardinal signs of inflammation,~~ superoxide free radical (O₂^{·-}) in fibroblast proliferation, and hydrogen peroxide (H₂O₂) in the activation of pro-inflammatory transcription factors. Other control mechanisms which may be perturbed in inflammation include: the oxidative modification of low density lipoprotein, the oxidative inactivation of alpha-1-protease inhibitor, DNA damage, lipid peroxidation and heat shock protein formed with the activation of neutrophil, NADPH oxidase and endothelial cell xanthine dehydrogenase, which associate with oxidative stress and contribute

significantly to the inflammatory process ^[19, 22, 23]. ~~All these processes are associated with the induction of oxidative stress.~~

Oxidative stress and RA activity

Oxidative stress is frequently reported in patients with RA. Cells present in inflamed joints (e.g., macrophages, neutrophils and lymphocytes), have the ability to produce free radicals ^[24, 25]. These liberate superoxide radical, hydrogen peroxide, elastase, hypochlorous acid and eicosanoids ^[26]. Another source of free radicals in RA is hypoxic reperfusion injury from elevated synovial cavity pressure during joint movement. A fivefold increase in mitochondrial ROS production in whole blood and monocytes of patients with RA compared with healthy subjects suggests that indicates oxidative stress is a significant factor in RA ^[26].

Free radicals, ~~—~~ are implicated in articular damage both indirectly (via increasing inflammation as described above) and directly. They can degrade joint cartilage, by attacking proteoglycans (integral components of structural tissues) and inhibiting proteoglycan synthesis ^[27]. Indeed, in patients with RA, serum and synovial fluid contain end products of lipid peroxidation which correlate with disease severity and activity ^[28]. In parallel ~~On the same line~~, anti-oxidant capacity in ~~of~~ patients with RA seems to be significantly reduced ^[29]. This low antioxidant status has been associated with low levels of tocopherols, beta-carotene and retinols and low activities of glutathione reductase and superoxide dismutase ^[26]. ~~RA~~ heumatoid arthritis has also ~~been also~~ linked to low decreased levels of reduced glutathione- an intracellular antioxidant- in ~~the~~ synovial fluid T cells ~~of patients with RA~~ ^[30]. Reduced glutathione, is among the most prominent defences against reactive oxygen species. It is a substrate for glutathione peroxidases, several transferases and several other enzymes and; it acts as a general radical quencher in cells by removing superoxide anions and hydrogen peroxide ^[26]. ~~Moreover, s~~ Serum concentrations of anti-oxidative vitamins A, C, and E are also significantly reduced in RA ^[19, 23, 31] ~~in RA~~.

Muscle Wasting in RA

A significant but ~~little~~relatively under studied extra-articular manifestation of RA is rheumatoid cachexia (RC). RC is characterised by a high rate of muscle mass and strength loss, typically with preservation, or slight increase, in fat mass ^[32]. RC differs from other forms of cachexia such as those observed in cancer, chronic heart failure, kidney disease or chronic infection as it is rarely accompanied by a net weight loss ^[33]. RC also differs from sarcopenia (the expected age-related muscle wasting in the elderly) as it occurs at a younger age and ~~the~~ muscle mass loss progresses at a substantially higher rate ^[34]. The prevalence of RA in the UK is 0.8% [5]. The exact prevalence of RC is not known today as there is no consensus on its definition and assessment. However, at least 10-20% of patients with controlled RA ^[35, 36] and 40% of patients with active RA ^[37] suffer from muscle wasting. This makes it one of the most common complications of RA.

RC has been shown to associate with poorer disease outcomes including, reduced quality of life, more fatigue, and increased overall morbidity and mortality ^[34, 38, 39], although the independent nature and directionality of many of these associations remain uncertain and require further study. Low muscle mass also associates with dysmetabolic states such as insulin resistance and type II diabetes ^[40, 41] and thus may be partly responsible for the increased cardiovascular risk observed in RA ^[33, 35, 42]. Inflammation associated with the disease is consistently identified as the potential cause of these manifestations. Indeed, inflammatory cytokines produced at the site of the disease (i.e. the joints) have endocrine functions and act on distant tissues such as the muscle ^[43].

Mechanisms of Muscle Wasting in RA

Inflammation

High plasma concentrations of the inflammatory cytokines implicated in RA pathophysiology (TNF α , IL-1 and IL-6) are thought to trigger muscle wasting ^[34, 44]. TNF α -induced activation of the classical NF κ B pathway is now generally accepted to lead to inhibition of skeletal muscle differentiation and regeneration in a variety of muscle diseases, although this has not been

confirmed ~~yet as a mechanism of in~~ muscle wasting in RA patients ~~yet~~. IL-1 among other ~~cytokiness~~ has been shown to prevent the anabolic effect of insulin growth factor 1 (IGF-1) on myoblast differentiation, muscle protein synthesis, and myogenin expression ^[44, 45], while intravenous infusion of IL-6 in healthy volunteers led to net muscle protein degradation in healthy individuals ^[46]. In RA patients, short term (3-6 months) anti-TNF α medication ~~led to elicited great significant reduction of benefits on~~ disease activity, but ~~it~~ did not improve body composition and had no effect of muscle mass ^[47, 48] ~~suggesting~~ indicating that cytokines on their own might not be the most significant contributors s to muscle wasting in RA.

Physical Inactivity

Physical inactivity is the strongest predictor of fat mass in RA ^[49], while resistance exercise interventions ~~may result in are able to~~ increased d muscle mass and strength ~~and partial reversal of muscle wasting~~ in patients with RA ~~and partially reverse muscle wasting among them~~ ^[50, 51]. Therefore muscle wasting in RA seems to be a consequence of a negative spiral between the metabolic and functional consequences of inflammation which enhance muscle catabolism and the premature adoption of an increasingly sedentary lifestyle in which the anabolic stimulus of regular exercise is missing ^[49] ~~with consequent increase in and that will increase~~ fat mass. In line with this hypothesis is the observation that obesity is a common feature of RA and ~~adds to the~~ represents a high risk for the metabolic syndrome and cardiovascular disease ^[34, 52, 53].

Adiposity

It is reasonable to assume that there are parallels between the mechanisms that lead to sarcopenia in healthy sedentary elderly individuals and the mechanisms that lead to muscle mass loss in RA patients. It is also reasonable to assume that there are parallels between the impact of obesity on the rate of sarcopenia and the potential role that obesity ~~in RA~~ plays in the mechanisms that lead to muscle wasting in RA. An inherent consequence of the adoption of a sedentary life-style,

without a reduction in energy intake, is a gradual increase of the subcutaneous and visceral adipose tissue mass ^[54]. Adipose tissue (especially visceral) is a well-known source of inflammation. In addition to adipocytes, pre-adipocytes and fibroblasts, up to 50% of the cell mass in adipose tissue of obese individuals are inflammatory ~~cells~~^{molecules} such as monocytes and macrophages ^[55, 56]. Adipocytes and macrophages both are a source of inflammatory cytokines ^[55, 56]. In addition, the large adipose tissue stores in obese individuals are a constant source of lipolysis and lead to high circulatory concentrations of fatty acids and triglycerides. High plasma concentrations of inflammatory cytokines, FA and triglycerides contribute to the insulin resistance of skeletal muscle and its microvasculature ^[54-56] via mechanisms ~~outlined~~^{explained} below.

Insulin Resistance

The most striking change in skeletal muscle ~~through~~^{to} a sedentary lifestyle is a reduction of the mitochondrial density ^[54] and, therefore, of oxidative capacity of blood-borne fatty acids (NEFA's). Sedentary muscles also have a reduced capacity to oxidize the lipid droplets that are stored in the muscle in the vicinity of the mitochondria ^[54, 57, 58]. This, combined with an increased supply of plasma fatty acids and triglycerides, leads to the accumulation of fatty acid metabolites (long-chain fatty acyl-coenzyme A, diacylglycerols and ceramides). Both these fatty acid metabolites and the exposure of the muscle to inflammatory cytokines activate serine kinases that lead to serine phosphorylation of insulin receptor substrate 1 (IRS-1) and prevent downstream activation of the insulin signalling cascade and, therefore, impair glucose transporter type 4 (GLUT-4) translocation and glucose uptake ^[58]. Insulin resistance (IR) also leads to an imbalance between protein synthesis and degradation ^[59] and is a major cause of the muscle mass loss in sedentary obese elderly individuals.

Endothelial Dysfunction

The overload of the muscle with fatty acids, triglycerides and inflammatory cytokines also leads to major impairments in its associated vasculature. The endothelial cells that cover the luminal wall of feeding arteries, resistance arteries, and terminal arterioles (which control blood supply to the capillaries) normally dilate if they are exposed to meal-induced increases in insulin concentration^[54, 60]. Insulin in endothelial cells activates the enzyme eNOS (endothelial nitric oxide synthase) and the resultant nitric oxide (NO) leads to dilation of the smooth muscle layer in arteries and arterioles. This mechanism ensures that in the period after meal ingestion maximal amounts of glucose, amino acids and insulin are channelled to the muscle to ~~thus~~ maximize glucose uptake, increase protein synthesis and reduce protein degradation^[54, 60]. ~~The~~ Vascular overload with lipids and inflammatory cytokines also leads to endothelial IR and reduces the supply of blood and nutrients to muscles of obese individuals^[54, 60].

Potential Role of Oxidative Stress in Muscle Wasting in RA

To our knowledge, there is no study today investigating the associations of oxidative stress with muscle wasting in RA. However, there are numerous reports in the general population and several other conditions showing that oxidative stress may be a very important underlying mechanisms that drives muscle wasting.

Endothelial Function and Oxidative Stress

Experiments in obese Zucker rats and incubated endothelial cells have shown that high concentrations of long-chain fatty acylCoA and diacylglycerol activate protein kinase C (PKC)- β in ~~aortic~~the endothelium ~~of the aorta of obese Zucker rats~~^[61] and prevent insulin-induced activation of IRS-1, Akt, eNOS phosphorylation and increases in NO production. A high lipid and cytokine load (via PKC-activation) also leads to induction of NADPH oxidase in the vasculature of patients with ~~the~~chronic diseases (metabolic syndrome, hypertension or ~~and~~ cardiovascular disease) ~~and hypertension~~^[54]. ~~A~~ hHigh NADPH oxidase activity will lead to excess production of superoxide

anions (O_2^-) which will scavenge NO thereby reducing basal and insulin-induced NO-production. Superoxide anions react with NO resulting in the formation of peroxynitrite and reducing the amount of NO available for vasodilation ^[62].

Muscle Disuse and Oxidative Stress

Physical inactivity, in a population with constantly high-grade inflammation, such as ~~those~~ ~~with~~ the RA, may lead to significant intramuscular accumulation of ROS, as is the case for muscle disuse (e.g. due to limb immobilization or bed rest) in the general population ^[63]. Muscle atrophy from disuse is mainly attributed to oxidative stress, i.e. reduces anti-oxidant capacity and increased ROS production ^[64, 65]. Mitochondria are the site for excessive ROS production ^[65, 66], and ROS production, such as H_2O_2 , is increased by up to 100% following 14 days of limb immobilization ^[67]. Moreover, xanthine oxidase and NADPH oxidase contribute but to a lesser degree to ROS production in muscle disuse ^[68, 69]. Similarly, lipid peroxidation has been shown to associate with muscle atrophy ^[70].

These affect the balance between protein synthesis and degradation ^[71, 72]. Specifically, disturbed redox balance due to intramuscular ROS accumulation, such as that of H_2O_2 ^[73, 74], may activate transcriptional factors that increase expression of apoptotic pathways, such as the NF- κ B pathway, and Foxo leading to severe protein degradation ^[68, 75]. Moreover, oxidative stress may activate calpain and caspase-3, further increasing proteolytic processes ^[68, 76]. ~~Also, e~~ Oxidation of muscle proteins themselves makes them susceptible to proteolytic damage ^[77].

ROS accumulation may also inhibit signalling pathways controlling protein ~~e~~ synthesis ^[78, 79]. It seems that ROS inhibit mRNA translation at an early stage; ~~this-that~~ reduces the ability of senescent satellite cells to become active and infiltrate the muscle cell ^[79, 80]. However, these studies were performed in cell cultures, and it is not clear if these processes also occur *in vivo*.

Aging and Oxidative Stress

Muscle wasting is commonly observed in the elderly, affecting their quality of life and independence ^[81]. Oxidative stress has long been associated with aging related processes ^[82]. The elderly exhibit increased concentrations of oxidative by-products compared to younger individuals ^[83, 84]. In normal aging, ROS participate in a number of processes aiding the transmission of signals within the muscle, and affect gene expression ^[85, 86]. As is the case with disuse atrophy, in aging mitochondria are also the main site for ROS production. Aging mitochondria seem to produce larger amounts of ROS, and especially H₂O₂, compared to younger ones ^[87]. The wasting effect of H₂O₂ seems to be mediated by the presence of the Copper and Zinc containing superoxide dismutase (Cu,ZnSOD) ^[88, 89]. Cu,ZnSOD has been shown to decrease with aging ^[90]. In animal studies, SOD1 (gene encoding Cu,ZnSOD) knockout mice exhibited a form of rapid muscle wasting with similar characteristics to that of aging, including oxidative stress and weakness ^[91].

Prevention of oxidative stress in RA

Nutritional Interventions

The vast majority of ~~the~~ studies in this field have focused on the use of exogenous anti-oxidative agents, such as the administration of vitamins (A, C, E) and omega-3 fatty acids. Vitamin E seems to uncouple joint inflammation and joint destruction in the transgenic KRN/NOD mouse model of RA, with a beneficial effect on joint destruction ^[92]. Some studies have even attributed therapeutic value to antioxidant supplementation as they reported better control ^[93] and improvement of RA-related symptoms ^[94]. Dietary interventions have been suggested to improve plasma levels of vitamin C, retinol and uric acid, which inversely correlate with variables related to disease activity ^[95]. Moreover, proper dietary antioxidant nutrient intake may reduce generation of free radicals and improve antioxidant status in RA patients ^[96]. Finally, intake of certain antioxidant micronutrients particularly beta-cryptoxanthine, supplemental zinc, and possibly diet in fruits and cruciferous vegetables have been suggested to protect against the development of RA ^[97].

Increasing anti-oxidant capacity in RA is a very attractive and potentially effective intervention. In current clinical practice, vitamin and micronutrient supplementation is frequently prescribed. However, we now know, that polypharmacy (prescription of a large number of medications) is one of the most significant reasons why patients forget to take their pills ^[98].

~~However, The most important question~~~~biggest doubt though,~~ concerning use of antioxidants, is that of suicidal oxidative stress ^[19]. In certain conditions, such as presence of transition metals, antioxidants can act as pro-oxidants ^[99]. Similarly, high concentrations of anti-oxidants can cause the cell to undergo severe oxidative stress ultimately resulting in suicidal cell death ^[100].

Medication

In very recent years, the anti-oxidant potential of antiTNF therapy has also been investigated. Infliximab plays an essential role as an anti-oxidative agent against AGE formation, oxidative DNA damage and lipid peroxidation ^[101], whereas etanercept acts as a regulator against pentosidine formation, oxidative DNA damage, and lipid peroxidation in RA patients ^[102].

Exercise and oxidative stress

In the general population, exercise has been shown to increase anti-oxidant capacity. Working via the physiological concept of *hormesis* (an ancient practice where the induction of a sub-lethal dose of toxin was used to increase tolerance of the organism to withstand higher doses of toxins) acute exercise increases free radical production ^[103], in a dose-response fashion (i.e. increasing intensity, increases free radical production). This exercised-induced increase in free radicals is due to the increased electron leak from the mitochondria as well as the alterations in blood flow and oxygen supply that occur in response to exercise ^[104, 105].

However, it has been consistently observed that trained individuals have high levels of antioxidant enzymes (~~Kostaropoulos et al., 2006~~) and certain nonenzymatic antioxidants in muscle ^[106] and demonstrate greater resistance to exercise-induced or -imposed oxidative stress ^[107, 108].

Most likely, these adaptations result from cumulative effects of repeated exercise bouts on the gene expression of antioxidant enzymes. However, the attenuation of oxidative stress by exercise is reduced in the aging muscle, warranting concomitant nutritional supplementation with anti-oxidants to elicit the greatest potential benefits ^[109].

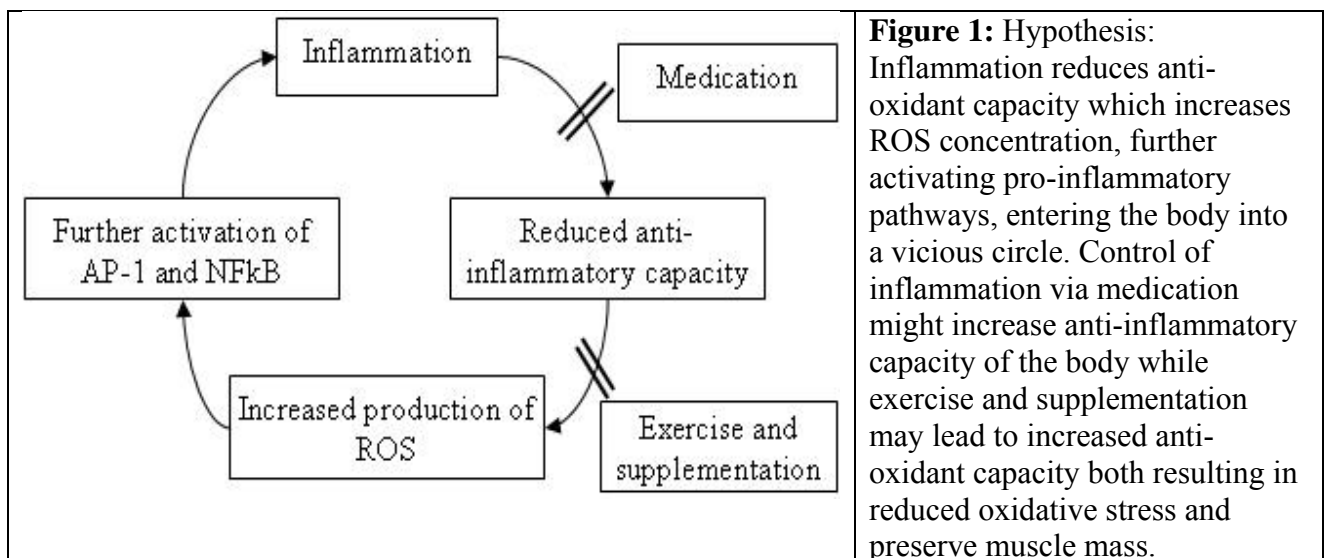
Exercise in Rheumatoid Arthritis

Exercise is a useful tool, with constantly increasing clinical relevance to several conditions.

In ~~the~~ recent years, a large number of studies have investigated the safety of different exercise modalities in RA. Despite the common misconception that it may increase joint pain and damage, all of the studies indicate that properly designed exercise interventions are safe and beneficial for RA patients ^[reviewed in ¹¹⁰]. De Jong *et al.* ^[111-113] have investigated the safety of intensive aerobic exercise (in the form of cycling) in >200 RA patients; they concluded that all patients were able to achieve the pre-determined intensity targets. However, they pointed out that patients with severe joint damage may need attention ^[114]. Along similar lines~~On the same line~~, resistance training improved ~~s~~ body composition and muscle mass without any adverse effects on disease activity ^[115]. Finally, we have recently completed a randomised trial looking at the effects of intensive aerobic exercise on cardiovascular risk factors in RA patients ^[116]. From these and other studies ^[117-121], it is clear that exercise is a safe intervention for RA patients and its use in the clinical setting is gaining significant support. Moreover, it is evident that exercise is able to reverse muscle wasting and increase muscle mass in RA patients. Indeed, the regenerative capacity of the RA muscle seems to be unaffected as the number of satellite cells (muscular stem cells that are utilised for muscular regeneration) present in it are preserved ^[122] but the stimulus for their activation (i.e. exercise) is absent.

Conclusions

The role of oxidative stress in muscle wasting has been clearly demonstrated in several studies. However, to date there is no study looking at this in RA patients. ~~We suggest~~~~This review proves~~ that there is significant scope for such research in RA as the potential mechanisms by which oxidative stress drives muscle wasting have been already described in other populations. Identification of specific mechanisms induced by ~~the~~ RA-associated inflammation could significantly aid towards improvement of ~~pharmacological clinical~~ and non-~~pharmacological clinical~~ interventions aiming to counteract oxidative stress in RA. In addition to effective control of inflammation via medication, exercise and nutrition may prove significant aids towards the reduction of oxidative stress (Figure 1).



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