

REVIEW ARTICLE

An Inquiry into the Role of Muscle Atrophy in Rheumatoid Arthritis and Current Treatment Scenario

Prasanna Phutane*, Gaurav Mude, Pranali Shastrakar

Datta Meghe College of Pharmacy, Datta Meghe Institute of Higher Education and Research, (Deemed to be University), Wardha, Maharashtra, India.

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ABSTRACT

Around the world, 0.5 to 1% of adults suffer from rheumatoid arthritis. It is a chronic autoimmune inflammatory illness distinguished by inflammation of hands, knees, wrists, and feet, causing bone and cartilage degradation, joint deformity, and muscle atrophy and thus movement limitations. Inflammatory mediators like necrosis factor and interleukins along with other inflammatory cytokines, execute a vital role in the initiation and advancement of rheumatoid arthritis (RA) as well as muscle atrophy. Existing literature discusses extensively the RA condition. However, the muscle atrophy related to this condition has received little attention, despite the substantial role of muscle atrophy in morbidity caused by RA. The review aims to highlight the relationship between muscle atrophy and RA, the mechanisms of muscle atrophy in RA and the association between oxidative stress and muscle atrophy in RA. This review will be useful for getting insights into the etiopathogenesis of muscle atrophy brought on by rheumatoid arthritis and available treatment alternatives for RA and muscle atrophy caused by RA. Discussion on the potential therapeutic targets and agents to treat skeletal muscle atrophy will help advance the knowledge to improve the condition of muscle atrophy associated with RA.

Keywords: Cachexia, Muscle atrophy, Muscle wasting, Oxidative stress, Rheumatoid arthritis.

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INTRODUCTION

A chronic disease called RA is considered by synovitis tissue in joints, which can lead to joint damage.¹ Symmetrical polyarthritis is a typical characteristic of RA, along with some extra-articular manifestations. This autoimmune disease initially impacts small joints, followed by trouble in larger joints. Such damage to the joints results into bone erosion causing deformities.² Apart from the joints, RA impacts numerous other tissues causing significant extra-articular manifestations. Other systems that get affected include the skin, eyes, heart, lungs, gastrointestinal tract, and kidneys. These extra-articular manifestations play a substantial role in shortening the life of RA patients. It also adds to existing morbidity due to RA. One example of such extra-articular manifestation is the heart disease in RA. Heart problems are more common and fatal in the RA population than in the general population.³ This disease generally manifests with morning joint stiffness which lasts for more than half an hour, tender and swollen joints along with rheumatoid nodules near the joints under the skin. A sensitive swelling of the joints, soreness and restricted mobility are some of the symptoms of

this chronic, autoimmune, systemic, inflammatory sickness that affects hands, knees, wrists, and feet. Widespread weakness, weight loss, fatigue, and a low-grade fever are some of its systemic symptoms. The multi-step process involved damages the tissues permanently as the sickness worsens; the breakdown of bone and cartilage produces joint deformation, muscular wasting, and possible progression to other joints in the body.⁴ Progression of RA may lead to many complications including permanent joint damage, vasculitis, and Felty syndrome.

RA is distinguished by the occurrence of autoantibodies against immunoglobulin G (IgG). The well-known autoantibodies related to RA are RF and anti-cyclic citrullinated protein (anti-CCP) antibodies, which exists even before the initiation of the disease.

Although the precise etiopathogenesis of RA is unspecified, it is supposed to be the outcome of a multi-step process in which environmental factors cause specific protein mutagenicity, which in turn prompts pathologic immune system activation in people with genetic susceptibility and eventually results in the clinical onset of the disease.⁵ Predisposing factors involved

*Author for Correspondence: prasannaphutane@gmail.com

in development are not only environmental but also genetic. Age and gender also play a role. Some of the predominant environmental factors include exposure to air pollutants, tobacco smoking and alcohol consumption. Out of these risk factors, most factors are controllable thus reducing the risk of developing and progressing RA.

Between 0.5 and 1% of adults worldwide are affected by RA, making it the most prevalent systemic autoimmune inflammatory disease. The existing cases of RA differ geographically in the world. The reasons for such variance can be different demographics, diverse genetic factors, lower reporting of cases and higher exposure to risk factors in developed countries. Population analysis indicates the onset in the mid-thirties which progresses with aging, but young children can also develop juvenile RA. RA has been reported to show greater prevalence in females with a prevalence ratio of 3:1 in females/males.⁶ A study investigated the disproportions in the prevalence of RA by gender. Using a paired sample t-test, the authors of this study found that the prevalence of RA differed significantly between the sexes in LMIC. This difference was statistically significant ($p < 0.0001$). The researcher conducted a separate meta-analysis comparing the incidence of RA between sexes in low- and middle-income countries. RA prevalence in males was 0.16% (95% confidence interval: 0.11–0.20%). In contrast, the prevalence among women was five times greater, at 0.75% (95% CI: 0.60–0.90%).⁴ However, sex and gender-based inconsistencies are still under-reported in clinical trials, thus studies with precise reference to gender are required to derive any concrete conclusion. Nonetheless, the prevalence of RA has been increasing. But the modern therapies along with overall better management of symptoms resulted in decreased severity of RA.⁷

With no available medications to cure RA, the therapy aims to lessen the pain and delay further harm. To achieve this aim, pharmacologic as well as non-pharmacologic therapies play an important role. It helps to improve quality of life, manage the symptoms and lessen the joint damage.

Here, we present a review on RA that aims to focus on the muscle atrophy caused by RA. The objective of this review is to highlight relation between muscle atrophy and RA, and the mechanisms of muscle atrophy in RA with an emphasis on the contribution of oxidative stress in muscle wasting. The review also examines the role of inflammatory mediators in RA, the etiopathogenesis of RA-induced muscle atrophy, the molecular pathway in RA-induced muscle atrophy and various interventions including exercise, pharmacotherapy and drugs used in the treatment of RA.

Relation between Rheumatoid Arthritis and Muscle Atrophy/Cachexia

Atrophy is the wasting of the body mass due to several reasons causing loss of functionality of respective tissues. It is also referred to as cachexia. Skeletal muscle atrophy, often known by means of a loss of muscle mass, happens when the ratio of protein synthesis to protein breakdown is deficient. The underlying causes include malnutrition, ageing, and a wide

range of severe and usually chronic illnesses like chronic heart failure, cancer, AIDS, sepsis, renal failure, obstructive lung disease, immunological disorders, and dystrophies.⁸

Rheumatoid cachexia is the medical term for such loss of body cell mass associated with RA with simultaneous loss of muscle strength and mass. It is one of the common symptoms of RA which contributes to considerable health burden. It is also termed as muscle wasting or muscle atrophy. Rheumatoid cachexia involves loss of cell mass not only from skeletal muscles but also from the visceral organs and immune system, thus leading to weakened muscle and loss of functional ability. Despite being controlled, RA manifests with muscle wasting in 10 to 20% while in case of active RA, more than 40% of cases manifest muscle wasting. Thus, *Rheumatoid cachexia* results in muscle weakness, functional impairment, poor quality of life, and fatigue with amplified morbidity and mortality.⁹

Such muscle wasting associated with RA is experienced by approximately 67% of people with RA if their condition is not controlled. Muscle wasting contributes to the tired and achy feeling that people with RA experience. It can also cause serious complications like heart disease. RA with muscle wasting may result into a shorter life expectancy. Muscle wasting in RA causes “elevated resting energy expenditure”, which means the usage of energy by the muscles even when muscles are resting.

Reduced muscular strength is greater compared to what could be expected due to a decrease in muscle size. An altered intramuscular contractile function is attributed to such greater loss of muscle strength. muscular weakness caused by RA results from a combination of intrinsic muscular weakening, altered Ca^{2+} transport, and free radical signaling. Figure 1 illustrates the steps that must be taken in order for skeletal muscle fibers to contract. The dihydropyridine receptor (DHPR) functions as a voltage sensor and controls the release of calcium from the sarcoplasmic reticulum. (1) Surface repolarization triggers a signal from the DHPR to RyR1. (2), RyR1 triggers a transient elevation of intracellular Ca^{2+} by inducing Ca^{2+} release from the sarcoplasmic reticulum (SR). (3) Ca^{2+} binds to the troponin complex, which alters the position of the tropomyosin filaments. (4) This allows actin and myosin to connect and generate force by exposing actin's active regions for myosin binding. (5) The SR Ca^{2+} -ATPase pulls Ca^{2+} back into SR, restoring Ca^{2+} to resting levels, and causing the contraction to cease. The myosin binding sites on actin are hidden by tropomyosin filaments in the resting state, when intracellular Ca^{2+} is low, and force production ceases.¹⁰

Mechanisms of Muscle Wasting in RA

Several factors are reported to have subsidized in muscle wasting in RA. Some of the significant ones are inflammation, physical inactivity, nutrition, adiposity, insulin resistance and endothelial dysfunction. Inflammatory cytokines in plasma at high levels are supposed to activate muscle wasting but are not the most significant contributor to muscle loss. Physical inactivity contributes to muscle wasting as there is lack of anabolic stimulus for muscle buildup from regular exercise due

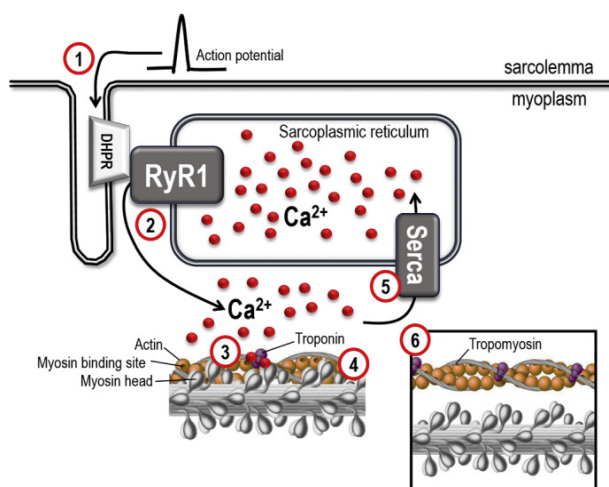


Figure 1: Representation of intracellular sequences causing contraction of skeletal muscle fibers¹⁰

to the adoption of a sedentary lifestyle. An inactive lifestyle is adopted by RA patients due to many reasons including stiffness and pain in joints along with fatigue. Thus, there exists a negative self-accentuating process that activates the muscle loss process.

As per the World Health Organization (WHO), *adiposity* refers to a body mass index exceeding 30 kg/m². Adiposity is a natural outcome of taking on a sedentary lifestyle, in the absence of an adequate reduction in calorie intake that leads to a steady growth in subcutaneous and visceral adipose tissue. The adipose tissue is a recognized contributor to inflammatory mediators. The cells in adipose tissue act as a source of inflammatory cytokines. It is probable that the processes that induce sarcopenia in healthy, sedentary elderly persons and muscle mass loss in RA patients are comparable.¹¹

Insulin resistance causes disproportionality between protein formation and degradation, leading a muscle wasting. Insulin resistance especially in endothelial cells that cover the lumen of arteries, leads to reduced supply of blood and nutrients to muscles. In healthy endothelial cells, in periods after meals, insulin activates the production of nitric oxide that leads to the dilation of arteries and arterioles. Such dilatory effect on arteries and arterioles ensures a maximum supply of glucose and insulin to muscles. This effect is lacking in endothelial cells with insulin resistance.¹² Although above-discussed factors provide considerable elucidation for muscle wasting, they have been reported to be unable to fully explain muscle wasting. Besides these factors, oxidative stress is also considered to be one of the prime processes for the initiation and development of RA. However, research into its putative role in muscle wasting in these patients is scant.¹³

Oxidative stress in RA

Free radicals have been indicated to have a part in the advancement of inflammation. These free radicals might take the form of either reactive oxygen or reactive nitrogen species. These free radicals are generated in the body during normal biological processes. During the utilization of oxygen by the

cells to generate energy, ROS are generated as by-products of cellular redox processes. Other bodily processes that generate free radicals are inflammation, psychological stress, ischemia, infection and aging. They are also produced due to the impact of external sources such as pollutants, tobacco smoke, radiation, chemicals, etc. There are times when the body can't get rid of all the free radicals it produces, so they build up inside it. Oxidative stress is the name for this buildup of free radicals.¹⁴

In a healthy population, free radicals are neutralized by the effective antioxidant defense mechanisms of our body. But inflammation tends to weaken this defense mechanism. Moreover, inflammation itself has a role in the generation of endogenous free radicals. Thus, inflammation results into the accumulation of free radicals.¹³ There are several ways by which free radicals are generated in RA leading to high oxidative stress. The immune system cells at inflamed joints produce free radicals. During exercise which causes joint movements, the synovial cavity pressure increases causing hypoxic reperfusion injury. Such injury is another source of free radicals. RA patients have exhibited a substantial enhancement in ROS formation, lipid peroxidation, oxidation of proteins, damage of DNA and loss in antioxidant defense system activity leading to oxidative stress. Tissue injury and illness persistence are the inevitable results.¹⁵

The use of anti-oxidants is one of the preferred interventions to reduce oxidative stress. Vitamins A, C, and E, as well as omega-3 fatty acids, are examples of anti-oxidants. Antioxidant supplementation may improve the impaired antioxidant status seen in RA patients by decreasing their generation of free radicals. Adoption of a diet with adequate antioxidant micronutrients such as beta-cryptoxanthine, and supplemental zinc, along with ingestion of fruits and cruciferous vegetables have been prescribed to shield against the development of RA.

Association between Oxidative Stress and Muscle Atrophy in RA

Oxidative stress is can be explained as the undesirable consequences of a disproportion between generation and removal of ROS and RNS. Numerous findings have reported that oxidative stress is not only a contributor to the pathology of RA, but also it is linked with the inception of RA-associated muscle wasting. Based on the numerous reports studying several other conditions, the role of oxidative stress can be concluded as an important mechanism involved in muscle loss. Oxidative stress itself or factors contributing to oxidative stress leads to conditions ultimately causing muscle wasting. For example, as seen in the above subsection sedentary lifestyle along with inflammation causes the accumulation of ROS. Increased ROS generation and decreased ant-oxidant capability lead to muscle atrophy.

Oxidative stress has been reported to cause muscle atrophy not only in people suffering from various chronic conditions but also in healthy individuals.¹³

Muscle atrophy due to its minimal use or disuse is primarily ascribed to oxidative stress, i.e. reduced anti-oxidant capacity

and increased ROS production.¹⁶ The mitochondrion is the location where an excess production of ROS takes place and in a study, it has been observed that following 14 days of limb immobilization, the production of ROS increased by up to 100%.¹⁷ In muscle disuse, xanthine oxidase and NADPH oxidase also participate in ROS production but to a lesser degree.

It is a well-known fact that oxidative stress has been linked with processes connected to aging. The elder population shows elevated levels of oxidative by-products in comparison with the younger population. In the aging process, ROS are involved in numerous processes for signal transmission within the muscle and influence the expression of genes. In aging too, the mitochondria are the primary locations for the generation of ROS, similar with the case of disuse atrophy. Aging mitochondria generate greater amounts of ROS, such as H₂O₂ in comparison to young mitochondria. The atrophic result of H₂O₂ appears to be intermediated by superoxide dismutase containing copper and zinc.¹³

Role of Inflammatory Mediators

RA is characterized by an adaptive immune response, which comprises of auto-reactive B-cells and the generation of RF autoantibodies as well as anti-CCP antibodies. Macrophages of our immune system provide the first line of defense and execute an important role in the initiation and development of inflammatory processes. Their protracted induction leads to a dysfunctional inflammatory response by producing pro-inflammatory cytokines and inflammatory mediators ultimately initiating a series of inflammatory responses.¹⁸

During the progression of RA, elevated levels of inflammatory mediators such as Tumor Necrosis Factor (TNF), Interleukin (IL-1, IL-6, IL-9, IL-12, IL-15), granulocyte-macrophage colony-stimulating factors (GM-CSF), Interferon (IFN), and others were observed years prior to the onset of clinical RA. IL-15 was found to be more prevalent at the undifferentiated arthritis stage, in patients who developed RA. IL-15 was predominant compared to RF autoantibodies as well as anti-CCP antibodies.¹⁹ ACPA-positive individuals at risk for RA had a lower frequency of naïve and T-regulatory cells (Treg) and a greater proportion of activated T cells compared to healthy controls. This kind of dysregulated T cells is related with a fast progression to rheumatoid arthritis.²⁰

Inflammation is commonly produced when immunity cells sense tissue injury or infection. Pattern-recognizing receptors over the immunity cells recognize threat out-of protein-associated molecular patterns linked with infections or out-of danger-associated molecular patterns created by a variety of endogenously produced stress signals. Natural and adaptive immunity cells infiltrate synovial joints, producing pain, stiffness, and discomfort. As RA develops, immunity cells along with synovial fibroblasts create an inflammation-friendly milieu in the joint, causing joint destruction. TNF, IL-1, and IL-6 are produced by macrophages, IL-7, and IL-15 by memory T-cells, IL-1 and IL-7 by helper T-cells, and IL-1, IL-18, GM-CSF, and Transforming Growth Factor beta(TGFβ)

by synovial fibroblast. Without systemic effects, IL-6 can directly stimulate skeletal muscle atrophy. As seen in Figure 2, muscle loss is thought to be caused by high blood levels of TNF-, IL-1, and IL-6, which are inflammatory cytokines linked to the Pathophysiology of RA.²¹

Etiopathogenesis of Rheumatoid Arthritis induced Muscle atrophy/Cachexia

Etiopathogenesis of RA depends on genetic and environmental factors as discussed in previous sections. But there are certain other factors that increase the risk of RA-induced muscle atrophy. Patients with RA lose a significant amount of muscle protein, which weakens their muscles and reduces their functional capacity. Numerous circumstances that result in muscle wasting include distinct intracellular signaling pathways that result in programmed cell death (apoptosis); and diminished activation of satellite cells, which are responsible for muscle regeneration. Enhanced protein degradation by means of autophagy, calcium-dependent proteases (calpains and caspases), and the proteasome system.²²

The pathogenesis of RA includes an intricate interaction among B cells, T cells, and dendritic cells. Multiple factors cause the disappearance of resilience toward the citrulline residue-containing proteins, leading to the generation of autoantibodies such as anti-CCP antibodies and RF antibodies. Such antigenic stimulus may commence the generation of RF-generating B cells which go through isotype switching and are much able to maintain the cascade of inflammation. Participation of RF to develop an immune complex can guide complement fixation and enrollment of macrophages, neutrophils, and lymphocytes, which play a central role in inflammation response. The result is damage to the tissue, which sets off a positive feedback process that makes even more autoantibodies. This could help explain an autoimmune and self-maintaining inflammatory reaction that leads to arthritis.²³

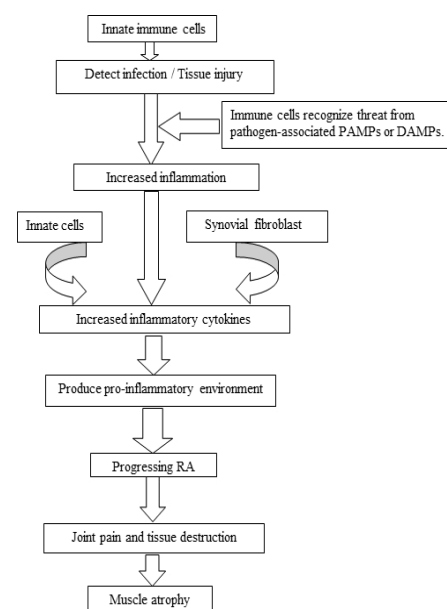


Figure 2: Pathway of progression of RA

Patients with active RA show high concentrations of synovial and serum TNF- α and IL-1. TNF- α and IL-1 cytokines play an essential role in rheumatoid cachexia and muscle wasting. TNF and IL-1 β are hypothesized to destabilize the equilibrium between the breakdown and synthesis of protein in RA, leading to cachexia.²⁴ Protein synthesis may be inhibited and proteolysis accelerated by high quantities of reactive oxygen species.²⁵ The human causes of disuse muscle atrophy are spinal cord injury, mechanical ventilation (diaphragmatic inactivity), space flight, bed rest, and bone fracture (set in a cast or immobilized in traction).¹³ Multiple pathophysiological alterations are responsible for this immobilization-induced atrophy, although the observed reduction in protein turnover likely plays a crucial role.²⁶

Some of the factors that increase risk of RA are discussed in the following section.

Multi-hormonal changes

RA patients exhibit numerous hormonal abnormalities. A common theme in these kinds of problems is that gonadal (estrogens and androgens) hormones aren't being made or working properly. However, adrenal hormones (corticosteroids and DHEA) are suspected of contributing to the development and progression of RA. Intense increases in corticosteroids, estrogen, and progesterone during pregnancy may prevent or slow the progression of RA by modulating cytokine synthesis and activity. On the other hand, during the postpartum period, estrogen and other hormonal changes raise rheumatoid arthritis risk factors.²⁷ In the case of males, lower testosterone levels increase the risk of RA.

Chronic infections

Chronic hepatitis C was related with an improved risk of RA and Lyme disease caused by *Borrelia burgdorferi*, the symptoms of which include Rheumatoid Arthritis Symptoms.⁹ Clinical and pre-clinical trials have demonstrated the risk associated with infections caused by viruses (Epstein–Barr virus) and bacteria (*Proteus mirabilis*, *Mycoplasma*, *Porphyromonas gingivalis*) in RA etiopathogenesis. The probable mechanisms by which infections induce the development of RA are a production of neo-autoantigens, triggering of loss of tolerance by molecular mimicry, and bystander activation of the immune system.²⁸

Current Treatment Scenario

The treatment for RA generally aims at decreasing joint inflammation, reducing pain and stiffness, optimizing joint functionality to enhance quality of life and countering joint destruction and deformity. A combination of different interventions such as pharmacotherapy, weight-bearing exercises along with adequate rest, proves to be the optimum approach. Some of the interventions are discussed in the following paragraphs.

RA Pharmacotherapy

The first-line treatment aims at reducing inflammation and relieving pain. Drugs used in first-line management of RA include NSAIDs and corticosteroids.

NSAIDs

Inhibitory action of NSAIDs on cyclo-oxygenase blocks the production of prostaglandins, prostacyclin, and thromboxanes which are well recognized for their role in the mediation of inflammation. But common side effects of NSAIDs include nausea, ulcers, bleeding in the gastrointestinal tract and abdominal pain. To mitigate such side effects, the drug needs to be administered with food, proton pump inhibitors and/or antacids. Some of examples of NSAIDs are acetylsalicylate, acetic acid derivatives (diclofenac, ketorolac, etodolac), propionic acid derivatives (Ketoprofen, naproxen) and anthranilic acid derivatives (mefenamic acid). A new class of NSAID called COX-2 inhibitors shows reduced incidences of side effects in the gastrointestinal tract. Examples of COX-2 inhibitors are celecoxib, rofecoxib and valdecoxib.²

Corticosteroid

Corticosteroids are prescribed during acute severity of the disease, as they are anti-inflammatory agents with high potency. However, these are associated with increased side effects leading to its use for a shorter period of time. Examples of corticosteroids are glucocorticoids, methylprednisolone, prednisolone, triamcinolone acetonide.²⁹

Disease-modifying Antirheumatic Drugs (DMARDs)

The DMARDs are employed to treat of RA as second-line drugs. These are defined as drugs capable of blocking or slowing the degenerative changes happening in RA sufferers' joints. The drugs belonging to this category are said to be slow-acting as their therapeutic effect is manifested after weeks or months and are not intended to cater to immediate relief of symptoms. DMARDs can also diminish the risk of getting lymphoma which is associated with RA.³⁰ DMARDs act by immunosuppression and/or immunomodulation. They are categorized as either conventional or biologic DMARDs. Examples of frequently employed conventional DMARDs are sulfasalazine, leflunomide, hydroxychloroquine, and methotrexate whereas examples of biological DMARDs are etanercept, rituximab, infliximab, rituximab, tofacitinib, adalimumab, tocilizumab, abatacept, among others. Biologic DMARDs are usually advised if conventional DMARD therapy fails to treat.³¹

A single drug or combination of drugs can be utilized for the treatment of RA, however many randomized controlled trials have demonstrated the advantages of therapy with a combination of drugs having both biologic and conventional DMARD over single-drug therapy involving solo use of drugs of each category. Some of the combination therapies are given below;

- Tumor necrosis factors inhibitors: Methotrexate in combination with +Adalimumab, golimumab, infliximab, etanercept
- T-cell costimulation blockade: Leflunomide + Abatacept
- Anti-interleukin-6 receptor antibody: Sulfasalazine + Tocilizumab
- B-cell depleting antibody: Hydroxychloroquine + Rituximab

Some of the less frequently utilized DMARDs are Azathioprine, Cyclosporine and Gold.

Treatment in Ayurveda for Rheumatoid Arthritis

Treatment includes Shunthi Kwatha (20 mL) with Eranda Taila (5 mL) on an empty stomach in the morning and Simhana Guggulu two tablets (500 mg) twice a day. Following the complete course of 2 months of above therapy Ashwagandha churna 2 g and Bala churna 2 g BD for 1-month can be given. Once 15 days of treatment were complete, symptoms such as nausea, anorexia were alleviated entirely.³²

Rheumatoid Arthritis Therapeutic Targets

The requirement in the treatment of RA is not fulfilled because certain patients do not respond sufficiently to existing therapies. Relief from symptoms can not be achieved always as the disease conditions do not respond to those treatments. This scenario suggests endeavoring for the discovery of new therapeutic approaches. Some of these approaches are discussed below.

Granulocyte Macrophage-colony Stimulating Factor

The GM-CSF has a role in the maturation, presentation, and growth of antigens by dendritic cells as well as the manufacture of cytokines that promote inflammation. It has been shown in numerous in vitro experiments that GM-CSF promotes the growth of inflammatory dendritic cells. TNF, IL-12, and IL-23 are among the pro-inflammatory cytokines carried by these dendritic inflammatory cells. For RA clinical trials, inhibiting GM-CSF is a desirable therapeutic target. A monoclonal antibody called mavrilimumab targets the GM-CSF receptor's alpha chain.³³

Janus Kinase-signal Transducer and Activator of Transcription Pathway

Four different types of Janus kinase (JAK) are known: JAK1, JAK2, JAK3, and Tyk2. Tyk2, JAK1 and JAK2 are all widely expressed, while JAK3 expression is only seen in certain types of hematopoietic cells. You can connect JAK1 to many different types of cytokines through the normal γ chain receptor subunit (IL-2 and IL-4 receptor families) and glycoprotein 130 subunit. Signal transduction involving interferon type 1 JAK1 plays a part as well.

It has been shown that inactivating mutations in JAK3 and the common chain together cause X-linked, severe combined immunodeficiency. Through the common chain receptor subunit, JAK3 communicates with a wide variety of inflammatory cytokines. Adaptive immunity is severely compromised in x-linked patients with severe combination immunodeficiency due to a paucity of T cells and aberrant B cells. To treat RA, several JAK inhibitors have been evaluated. Tofacitinib selectively blocks JAK1 and JAK3 and has been demonstrated to be effective in several clinical trials.³³

Pharmacotherapy of Arthritis-induced Muscle Atrophy

Nutritional Support for Muscle Atrophy

Diet has the predominant influence on the initiation as well as progression of RA. Figure 3 summarizes the effects of different

kinds of factors on the RA. The diets along with other factors that influence the symptoms of RA are listed on the left side of the image, whereas the effects of various factors on the state of disease are given on the right side of the image. The upper half of the figure illustrates the progression of RA due to specific factors enlisted on the left side, whereas the lower half of the image reveals the positive effects of various diets in slowing down the progression of RA.

n-3PUFA

Omega-3 polyunsaturated fatty acids (n3 PUFA) are a dietary component that reduces inflammation. An analysis with n-3 PUFA showed that for the muscle composition to change noticeably, supplementation with 5 g/day capsules of fish oil containing 3,500 mg Eicosapentaenoic acid (EPA) and 900 mg Docosahexaenoic acid (DHA) is required for at least two weeks. Together, these studies point to the viability of n-3 PUFA as a supplement for maintaining muscle mass in cases of muscle wasting.

Vitamin D

People with muscle wasting illnesses must be checked for their 25(OH)D status, which may be easily treated with low daily doses of vitamin D3 (2000 IU/day). Moreover, vitamin D has a variety of activities in tissues other than muscle.

Dietary Antioxidants

Numerous studies have shown that a number of naturally occurring antioxidants and their equivalents can lessen the atrophy of muscles brought on by inactivity. The majority of the research showing that vitamin E can lessen the degree of atrophy brought on by inactivity has been conducted on animals. Studies have shown that vitamin E prevents rats' hind leg muscles from becoming completely or partially immobile.²⁵

Potential Therapeutic Agents to Treat Skeletal Muscle Atrophy

Treatment of skeletal muscle atrophy could make a significant part of the overall therapy for RA. This section discusses various therapeutic agents that are either already in use or in the stage of preclinical studies for treating muscle atrophy.

- Natural compounds: Hydroxy-methyl butyrate (HMB), Eicosapentaenoic acid, Resveratrol, Ghrelin and its receptor agonist.

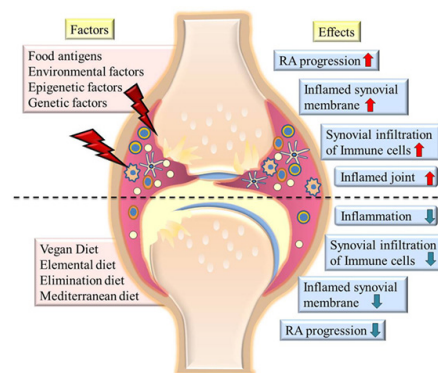


Figure 3: Dietary effects on severity of RA³⁴

- Enzyme inhibitors: Histone deacetylase inhibitors, Phosphodiesterase inhibitors, COX-2 inhibitors
- β -Adrenoceptor agonists: Formoterol, clenbuterol
- Anti-cytokines agents: Anti-TNF α , thalidomide
- Other investigational drugs: Enobosarm, anti-myostatin/activin.
- β -Hydroxy- β -methylbutyrate (HMB): HMB is a metabolic product of leucine. Numerous muscle issues are treated with HMB as a dietary supplement. HMB treatment stops the loss of skeletal muscle by boosting anabolic protein pathways and obstructing catabolic protein pathways.
- COX-2 inhibitors: COX-2 is a cyclooxygenase isoform that has pro-inflammatory activity induced via cytokines as well as mitogens. COX-2 inhibitors have demonstrated inhibitory effects on cachexia. Out of many COX-2 inhibitors, meloxicam and celecoxib are widely used in COX-2-mediated muscle atrophy.
- Formoterol: Formoterol has proved its therapeutic potential by increasing body weight. It acts by stimulating the development of skeletal muscles by suppressing proteolytic systems acting on muscles as well as activating protein anabolic activity.
- Thalidomide: This drug is newly regaining popularity because to a variety of positive benefits, including anti-inflammatory, immune-modulator, anti-emetic, and sedative properties. Moreover, by suppressing TNF α mRNA expression, this medication has demonstrated activity against cachexia in cancer patients. Thalidomide also lowers the blood levels of IL-6 and CRP in cancer patients suffering from cachexia.
- Enobosarm: This drug has already demonstrated its potential to reduce muscular atrophy brought on by cancer. Additionally, it demonstrates enhancements in body composition and performance in adult males and women past menopause.
- Megestrol acetate: It shows suppression of inflammation-inducing cytokines along with IL-1, IL-6, and TNF α which results in increased body mass and reduction in degradation of muscle protein. This drug has already received approval for the treatment of cachexia in case of cancer and AIDS.³⁵

Prevention of Muscle Atrophy by Exercise

The specific alteration that takes place in the structure of the muscle is muscle atrophy when muscles stay in a disuse state for a prolonged duration. Changes that took place in muscles included a reduction of muscle volume and muscle fiber diameter which led to a decrease in muscle mass. Additionally, there are changes in types of muscle fibers which include an increase in the amount of fast muscle fibers and mixed muscle fibers, whereas the number of slow muscle fibers decreases. Appropriate exercise promotes the creation of compensatory muscles, increases muscular strength and flexibility, and boosts muscle control, all of which are helpful for the recovery of skeletal muscle function and regeneration of new muscle cells. It would greatly lessen limb dystonia brought on by muscle atrophy.³⁶

CONCLUSION

Muscle atrophy is a substantial contributor to the morbidity caused in RA as it leads to muscle weakness, loss of functionality and thus dependence to carry out routine activities. Multiple factors are involved in the etiology of muscle atrophy which forms the self-perpetuating cycle. Such muscle wasting associated with RA is experienced by approximately 67% of people with RA if their condition is not controlled. It can also cause serious complications like heart disease. RA with muscle wasting may result into a shorter life expectancy. Thus interventions aiming to abate muscle atrophy can have a larger contribution to overall improvement in the condition of RA. Existing interventions although significant contributors to reducing the sufferings of RA patients, but are not sufficient. More non-pharmacological approaches along with pharmacologic interventions focused on treating muscle atrophy are required to work on and establish as therapies to treat muscle atrophy to reduce the morbidity caused by RA. Physical exercise is one of the most effective therapies, and combination therapies with physical exercise as a significant part of the entire treatment regime needs to develop. Improvement in cachectic conditions will help to improve the quality of life of the large adult population, reducing morbidity and mortality caused by RA. Thus, a novel strategy for treating skeletal muscle wasting must be developed, along with combinational treatment.

AUTHORS' CONTRIBUTIONS STATEMENT

Prasanna Phutane conceptualized the contents of the review. Gaurav Mude gathered the data regarding this work. Pranali Shastrakar did the data analysis and provided helpful suggestions for the layout of the publication. The manuscript is a collaborative effort amongst all contributors.

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