Rheumatoid Cachexia: causes, significance and possible interventions

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A B S T R A C T

Rheumatoid arthritis is a chronic autoimmune disease characterised by joint pain and stiffness but also systemic multi-organ involvement. Several features are due to excessive production of inflammatory cytokines, particularly tumour necrosis factor alpha, interleukin-1 and interleukin-6. These are implicated in both local synovial inflammation, which causes joint destruction, but also systemic inflammation, which can cause loss of body cell mass, amongst other phenomena. Body cell mass breakdown in rheumatoid arthritis leads to the classical, but largely ignored, metabolic abnormality known as rheumatoid cachexia. Cachexia is a very strong predictor of adverse functional outcome and death in many disease states. In this review we highlight the mechanisms linked with rheumatoid cachexia and discuss possible interventions that may limit this in patients with rheumatoid arthritis.

I N T R O D U C T I O N

With an estimated prevalence of 0.5–1\% in Europe and North America (currently 0.8\% of the adult population in the UK) \cite{1}, rheumatoid arthritis (RA) is the commonest chronic inflammatory joint disease and affects more women than men. The cause of RA remains unknown, but genetic predisposition, aberrant immune responses, and physical stress have, amongst others, been identified as significant factors in its pathogenesis.

The main site of inflammation in RA is the synovial membrane (synovium). Rheumatoid synovium becomes a hyperplastic, highly vascularised tissue heavily infiltrated by chronic inflammatory cells. RA is genetically linked to certain major histocompatibility complex class II antigens (HLA-DRB1*0404 and 0401). Class II molecules present antigenic peptides to CD4\textsuperscript{+} T cells, and this suggests that RA is caused by a, yet unidentified, antigen. CD4\textsuperscript{+} activated T lymphocytes are central to rheumatoid chronic synovitis. They can stimulate monocytes, macrophages and synovial fibroblasts to produce cytokines such as interleukins (IL) -1 and 6 and tumour necrosis factor alpha (TNF\alpha). Through cell-surface signaling (e.g. CD69 and CD11 or CD40 ligand and CD28) or through the release of specific cytokines (e.g. interferon gamma, IL-17 and others) they also regulate the secretion of matrix metalloproteinases (MMPs) and other effector molecules (e.g. free radicals) from macrophages and the stimulation of B cells to produce antibodies. Activated inflammatory cells and their products may have multiple effects. They can promote further inflammatory cell recruitment by activating...
endothelial cells to express adhesion molecules and by releasing chemokines such as IL-8: this could, in part, explain the flares and overall chronicity of the disease. They can stimulate neo-angiogenesis, which would explain the increased vascularity of the inflamed synovium. They may be involved in cartilage and bone degradation through multiple mechanisms including MMP and free radical release, and direct effects on osteoclasts and chondrocytes, which can explain the erosive damage to the joint [2]. The main inflammatory cytokines, IL-1, IL-6 and TNFα, also have important effects on distant organs, e.g. the liver, muscle, fat and vascular endothelium. These systemic effects explain several other phenomena, including the acute phase response (which is used for monitoring the inflammatory activity of RA in every-day clinical practice), rheumatoid cachexia [3] (the loss of lean body mass), and a constellation of effects, which may collectively promote atherogenesis [4,5] (e.g. dyslipidaemia, insulin resistance, thrombogenesis, and endothelial dysfunction amongst others). It is interesting that the extent of inflammatory activity in RA, assessed by the acute phase response (e.g. erythrocyte sedimentation rate, or C-reactive protein), clinical measures (e.g. joint swelling) or indices combining both, associates not only with the extent of joint damage and disability, but also with cardiovascular events and death [6-10]. Effective control of inflammatory activity using disease-modifying anti-rheumatic drugs, may, in contrast, confer functional and survival benefits [11-15], but there may be significant differences between individual drugs, requiring further investigation.

The metabolic alterations associated to prolonged overproduction of cytokines in RA are significant. Nearly 2/3 of all individuals with RA experience a metabolic abnormality accompanied by wasting of muscle mass, with the presence of stable or even increased fat mass, and no weight loss [16]. This is referred to as rheumatoid cachexia (RC). This condition is developed in RA with no clinical evidence of malabsorption or impaired liver or renal function [17], and the exact underlying mechanisms are not yet entirely clear. Nevertheless, possible contributing factors may be the overproduction of TNFα [16], the synergy of TNFα with IL-1β, other cytokines, hormones and transcription factors active on muscle [18], reduced peripheral insulin action [19,20], and physical inactivity [3] (Fig. 1). In this review, we concentrate on the definition of RC and the most important mechanisms involved in its pathogenesis, i.e. cytokine overdrive and physical inactivity, both of which may be subject to successful therapeutic intervention.

**RHEUMATOID CACHEXIA: DEFINITION AND CONSEQUENCES**

Skeletal muscle mass along with visceral and immune system mass constitute the body cell mass (BCM). This accounts for about 95% of the total metabolic activity of the human body [21]. Loss of BCM leads to reduced energy expenditure, compromised muscular strength, balance and movement ability, and impaired immune function [22]. BCM losses greater than 40% of baseline values associate with almost certain death [23,24].

In general, BCM losses are associated with qualitative and quantitative declines in skeletal muscle mass, termed sarcopenia, and occur with normal aging. Indeed, significant differences have been reported when BCM of normal older adults was compared to that of younger individuals [25]. Although sarcopenia does not require the presence of a disease, this age-related loss of BCM and skeletal muscle mass can be significantly enhanced by the presence of chronic diseases [26].

RA can occur at any age, but the overwhelming majority of prevalent RA cases are predominantly middle-aged and elderly individuals, so some age-related sarcopenia would be expected. However, RA patients experience an accelerated involuntary BCM loss, predominantly in the skeletal muscle [16], over and above that normally expected. This condition, which is clearly different from sarcopenia, is termed cachexia and connotes the loss of BCM occurring due to the illness rather than normal aging [27]. The term RC is used specifically for patients with RA and dates back to the original description of the disease [28]. In RA, BCM loss has been associated with muscle weakness and limited mobility, thus reduced functional ability and quality of life [29,30]. However, RC in RA is also accompanied by little or no weight loss in the presence of stable or increased fat mass: this has led to the introduction of the term “rheumatoid cachectic obesity” [3] and may be of
great importance. It essentially suggests that RA patients with normal or near normal body mass index (BMI) may have a significantly higher fat component in their body composition than age, sex and BMI-matched controls. This increased fat mass may be responsible for intensification and perpetuation of the inflammatory response, as adipose tissue represents one of the predominant sources of IL-6 in the body [31,32]. It may also relate to the well-described association of RA with increased overall and cardiovascular mortality [4].

**Rheumatoid Cachexia and Energy Expenditure**

Daily energy expenditure (DEE) consists of resting energy expenditure (REE) (i.e. the amount of energy required for the body to sustain physiological processes at rest), energy expended for physical activity and bodily movement in general, and the thermic effect of feeding. REE accounts for ~70% of DEE [33] and in normal individuals is highly dependent on BCM [34]. In RA patients, however, the relation between BCM and REE seems to be altered. Such individuals, exhibit significantly decreased BCM with increased REE, accompanied by increased whole-body protein catabolism. These are both driven by pro-inflammatory cytokines and their co-existence leads to RC [3].

**Specific Mechanisms**

The exact pathophysiological mechanisms underlying the development of RC are not yet fully understood. They include: a) excessive cytokine production, b) reduced peripheral insulin action, and c) physical inactivity.

**Cytokines**

Cytokines are extracellular peptides influencing cell proliferation, migration and behaviour by acting upon them through specific receptor interactions. They are produced mainly from cells of the immune system such as monocytes/macrophages and T-cells, but also skeletal muscle, fat and other tissues [35,2]. Although their key physiological role is homeostasis, activation of inflammatory mechanisms, repair and remodelling of damaged tissue, they are also the main orchestrators of the dysregulated responses seen in chronic inflammatory autoimmune diseases. The pro-inflammatory cytokines TNFα, IL-1β, and IL-6 are key to the development and perpetuation of the local and systemic inflammatory response observed in RA. The predominant stimuli, sources and functional effects of IL-1 and TNFα are shown in Figure 2.

TNFα was first identified as ‘cachectin’ after its catabolic function. TNFα is involved in biological processes which go well beyond its pro-inflammatory functions [36], possibly due to the differential bioactivities of its soluble and trans-membrane form [37]. TNFα is intimately involved in the metabolic abnormalities observed in RA, leading to significant skeletal muscle wasting and augmentation in energy expenditure and, thus, the occurrence of RC. Concurrent overproduction of TNFα and IL-1β during the acute-phase response in RA causes several systemic changes which, in turn, contribute to metabolic alterations [38]. They significantly affect muscle metabolism by enhancing protein catabolic processes [18]. Since within the muscle balance of protein degradation and re-synthesis is not maintained, continuing cytokine overdrive will tip the balance towards protein breakdown [3]. This is in line with more recent data which revealed that TNFα and IL-1 contribute to central nervous system side affects, increase muscle metabolism and bone marrow suppression, all of which are present in chronic inflammatory diseases [39].

The exact biochemical mechanisms by which skeletal muscles undergo rapid protein loss in response to cytokines, have been frequently studied in vivo and in vitro given that muscle wasting is present in many serious diseases, such as cancer, renal failure, HIV and RA. Enhanced muscle proteinolysis seems to occur through the ubiquitin-proteasome pathway [40], as protein catabolism is targeted by conjugation to ubiquitin [41]. In some inflammatory diseases, TNFα is thought to stimulate muscle catabolism via an NF-kappaB-dependent process that increases ubiquitin conjugation to muscle proteins [42]. Through a cascade of processes, TNFα bound to surface receptors activates the transcriptional NF-κB pathway leading to the degradation of a protein IκBα that inhibits NF-κB [43,44]. NF-κB is one of the most important signal transduction pathways in RA as it is engaged in mediating the production of IL-1 and TNFα and their effects on target cells after they have bound to cell surface receptors [39].

TNFα may also cause reduced protein synthesis through reduced insulin action, as it interferes with the insulin receptor signalling pathway [45]. Several studies suggest that RA associates with reduced peripheral insulin action [19,20]. Insulin triggers intracellular enzyme activity that facilitates protein synthesis by increased amino acid transport through the plasma membrane, RNA cellular levels, and protein formation by ribosomes [46].
IL-1 and IL-6 have also been proposed as mediators of muscle protein degradation in different catabolic conditions. However, the proteinolytic mechanisms involved are not yet fully understood [47, 48].

Human studies demonstrate the association between excess TNFα and IL-1β with RC, but have failed to directly link these pro-inflammatory cytokines with the exact mechanism of muscle wasting. By blocking either TNFα with a recombinant soluble TNFα receptor or IL-1β with a recombinant IL-1 receptor antagonist, it was found that blocking TNFα alone only moderately reduced the loss of skeletal muscle weight. Blocking both TNFα and IL-1β was more effective in preventing undue muscle wasting, indicating that TNFα is an important element in this process, but possibly not on its own [49]. It remains unclear whether these cytokines promote protein degradation or restrain protein synthesis, and whether their effects are direct or through a network of many other hormones and cytokines.

**REDUCED PHYSICAL ACTIVITY**

RA is a chronic progressive disease of the joints associated with systemic involvement, significant morbidity, deformity, and diminished quality of life. Structural damage in the musculoskeletal system can be developed within the first two years of the disease [50]. Pain, joint stiffness and inflammation, fatigue and reduced muscle strength are all elements of RA symptomatology [51]. Physical activity can therefore be significantly compromised in RA patients.

In general, reduced physical activity is associated with an alteration in normal physiological processes leading to muscle atrophy, loss of ability for exercise, insulin resistance, and energy balance variations. Bed-rest studies reveal that lack of effective muscle stimuli decreases the turnover rates of muscle and whole-body proteins, with a prevailing inhibition of protein synthesis [52]. These factors might also be contributing to the initiation and/or progression of RC.

**POSSIBLE INTERVENTIONS**

Since the exact causes of RC are not fully delineated, no definite preventive or therapeutic strategies have been tested to-date. The introduction of anti-TNFα therapy may provide an opportunity to address this problem, but this requires prospective assessment. It is a common clinical observation that RA patients receiving anti-TNFα therapy commonly and rapidly put on weight. It remains unclear whether this is due to a significant change to their body composition and reversal of RC, i.e. whether it is predominantly due to muscle gain or fat gain. Ongoing research in our laboratory investigates the effects of anti-TNFα administration on body composition (body fat and muscle mass) and REE and we will hopefully be able to clarify this. Future directions may involve the co-administration of TNFα and IL-1 blocking agents, whereas anti-IL-6 therapy will soon also become available. In the meantime, enhanced physical activity and lifestyle changes may be a reasonable route to take in RA patients, as it is safe, associates with several other health benefits, and with concerted effort can be provided by health care systems and achieved by RA patients.

In normal individuals, health status is highly influenced by lifestyle and physical activity. Active lifestyle and increased levels of physical activity have been associated with decreased body fat, increased aerobic capacity, muscular strength and overall health [53]; even with increased life expectancy [54] while sedentary lifestyle and physical inactivity have the opposite results [55].

Patients with RA tend to lead a sedentary lifestyle and refrain from physical activity, mainly due to joint pain and inflammation, and for fear of aggravating their disease [16]. Consequently, they experience many, if not all of the health problems related to sedentariness. The presence of chronic inflammation further worsens this. Indeed, in patients with RA, deficits of up to 40% in aerobic capacity have been reported; muscle strength in isometric knee extension is 18–60 % lower and flexibility in joints suffering from RA is 20–60 % lower. In functional tasks, such as walking a certain distance or climbing stairs, studies have reported deficits of up to 60% in RA patients. Also increased energy expenditure (30-50 % more than healthy peers) ventilation (up to 27%) and heart rate (19%) at sub-maximal workloads, often result in earlier onset of fatigue, limited endurance and poor neuromuscular control. Thus most of the patients stop exercise due to factors related to exercise intolerance and not pain or other factors related to the disease [56].

Most researchers who studied the effects of exercise on RA patients, used intensities of 60-80 % and duration of 15-60 min, 3-4 times a week. Results demonstrate 12-21 % improvements in cardiovascular performance and 0-55 % increase in strength depending on the type of exercise, as well as significant increases in flexibility [57]. Even though many participants in these studies were de-conditioned at the beginning of the experiments, they were able to exercise at levels necessary to produce a training effect. An unexpected effect of exercise is the reduced joint swelling experienced by some persons after aerobic exercise. Moreover, individuals who exercised more than five hours per week experienced less progression of joint damage, less hospitalization, less work disability and no difference in clinically active joints than those who did not exercise [58].

Specifically for the prevention of RC, strength training is the most important non-pharmacological treatment. Muscle growth and/or maintenance require sufficient physiological stimuli. The beneficial effects of strength exercise in the maintenance of adequate age-related strength levels have been well-established. Strength training programs elic...
significant improvements in muscle strength levels in healthy adults [59] even in healthy elderly adults [60]. In RA, long-term high-intensity exercise programs are more effective than physiotherapy care in improving functional ability of RA patients [61]. Also, significant improvements in muscular strength may be attained with either a low-volume or a high-volume program [62]. Along with effectiveness, these programs are safe since, in well-controlled and recent-onset individuals with RA, application of high-intensity exercise regimes has been found to elicit significant improvements in neuromuscular performance, without aggravating joint pain or damage [63,64].

Apart from strength training, adopting a more active lifestyle can result in health benefits in conditions such as diabetes [65] and metabolic syndrome [66], and probably in RA. Most importantly, physically active individuals can maintain a higher level of physical functioning, reduce the rate of age-related muscle wasting [67], and improve life-satisfaction and well-being [68]. The effects of lifestyle changes in RA have not been investigated.

CONCLUSIONS

The exact mechanisms involved in the pathogenesis of RC remain unclear. In a synergistic manner TNFα and IL-1 significantly enhance muscle catabolic processes but it remains unknown whether this is due to enhanced protein degradation or reduced protein re-synthesis. Reduced peripheral insulin activity and physical inactivity may also play a significant role in the maintenance and/or progression of this condition. Due to the fact that RC increases comorbidity and may be contributing to mortality, future research must focus on the understanding and prevention of this complication. Current preventive methods could include exercise programs and physically active lifestyles. The potentially beneficial effects of biological therapies need to be fully evaluated.

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REFERENCES

18. Lecker SH, Solomon V, Mitch WE, Goldberg AL. Muscle
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55. Ramadan J, Barac-Nieto M. Low-frequency physical activity insufficient for aerobic conditioning is associated with lower


