Rheumatoid cachexia: the (undiagnosed, untreated) key to restoring physical function in rheumatoid arthritis patients

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Rheumatoid arthritis (RA) is characterised by adverse changes in body composition, specifically reduced muscle and increased fat masses (FM) (1). These changes, termed *rheumatoid cachexia* (RC), are rarely obvious as <5% of RA patients unintentionally lose weight, and RA patients typically present with bodyweights and BMI's similar to the general population (1). However, when body composition is assessed in stable RA patients, significant muscle loss is usually observed in about 67% and obesity in approximately 80% (1). Unfortunately, as body composition is rarely assessed in rheumatology clinics, RC remains undiagnosed and, consequently, untreated.

This failure to recognise and treat RC has serious consequences for patients as these body composition perturbations significantly contribute to the disability, increased co-morbidity risk, and exacerbated mortality that, despite advances in pharmaceutical treatment, remain features of RA (1, 2). With regard to physical function, Giles *et al*. (3) has shown that RA disability is strongly associated with body composition, with HAQ scores related inversely to appendicular lean mass (a surrogate measure of muscle mass) and directly to total and appendicular FM's. Such links between body composition and physical function are not surprising as they reflect those observed in the general population. Additionally, as in other catabolic diseases, muscle loss is associated with impaired immune and pulmonary function, glucose intolerance, osteoporosis, low aerobic capacity, loss of independence, depression, compromised quality of life (QoL), and increased mortality, whilst excess adiposity, particularly central obesity, is a well-established risk factor for co-morbidities including cardiovascular disease (CVD) (1,2). Disturbingly, RA preferentially predisposes to

trunk obesity (1, 2), and in RA patients, this central obesity has been linked to hypertension, elevated fasting glucose levels, metabolic syndrome and arterial thickening and stiffening (2). As there is an augmented risk of CVD in RA patients, loss of fat, especially trunk FM, should be highly beneficial for this population's CV health (2).

Since RC is thought to be due to overexpression of pro-inflammatory cytokines (1), particularly tumor necrosis factor-alpha (TNF-α), it would be anticipated that reducing inflammation, and especially blocking TNF-α, would attenuate RC in RA patients. However, anti-TNF-α treatment is not effective in increasing muscle mass and relative to treatment with standard disease modifying anti-rheumatic drugs (DMARDs), rather worryingly, increases FM, particularly trunk FM (4, 5).

Similarly, the substantial benefits of the current Treat-to-Target (T2T) strategy in reducing inflammation (i.e. disease activity) have also failed to improve either body composition or objectively-assessed physical function relative to previous treatments [Note: subjective function measures such as the HAQ are influenced by pain and do not necessarily reflect actual changes in function]. A recent study by our group (6) comparing RA patients (n=82) exclusively treated by T2T, with age- and sex-matched sedentary, healthy controls (n=84) showed that whilst T2T was very successful in lowering disease activity (mean DAS28 = 2.8, with 49% of patients currently in "clinical remission" i.e. DAS28 <2.6), it had no benefit on either body composition (relative muscle mass ≈10% less ($p<0.001$), with relative total FM ≈27% greater ($p<0.001$), and trunk FM ≈32% greater ($p=0.001$) than controls) or objectively-assessed function (knee extensor strength, handgrip strength, 8' get-up-and-go, 30 sec sit-to-stand, and 50' walk tests; all 24-34% poorer (p's<0.001) than controls). These results

are identical to those observed in our laboratories (e.g. 4, 7-9) for stable, pre-T2T (commenced treatment 1992-2004) RA patients.

Given that RC is inflammation-driven, why does tight pharmaceutical control of disease activity not attenuate RC or disability? A likely explanation is that RC occurs very early in the course of RA, probably in the *pre-clinical phase* i.e. before initiation of DMARD treatment; as we found a similar incidence and degree of muscle depletion and obesity amongst very recent (<6 months since symptom-onset) patients (4) as for established RA patients (7-9). Thus, successful DMARD treatment, whilst preventing exacerbation of RC, commences too late to prevent it, and not being anabolic, fails to restore body composition or, as a consequence, normal levels of physical function.

Accordingly, in addition to standard drug treatment, interventions that specifically aim to restore body composition and physical function are required, and, if successful, these would not only reduce disability and prolong independence, but could improve QoL, reduce co-morbidities, and increase life expectancy in RA patients.

The intervention that conveys greatest benefit on body composition and objectively–assessed physical function in RA patients is high-intensity (HI) exercise, especially progressive resistance training (weight training). Research has repeatedly demonstrated that HI exercise training increases muscle mass and reduces adiposity in RA patients (7, 10), and substantially improves strength, aerobic capacity, and objectively-assessed physical function (10). Additionally, HI training significantly reduces CVD risk in this population (10).

Unfortunately, participation in regular exercise training is low amongst RA patients, at least in part due to misconceptions about the benefits and safety of exercise (10). Consequently, more widely acceptable anabolic interventions also need to be evaluated. Dietary supplementation with generic protein or creatine have both been shown to elicit

small, but significant, improvements in muscle mass and some function measures in RA patients (9,11). Thus, for patients not prepared to regularly exercise, these supplements may help.

So how should clinicians respond to the problem of RC? Since none of the current standard treatments for RA are anabolic or able to restore normal function, adjunct treatments that specifically improve body composition and function should be discussed with patients, and as RC and its consequences appear to occur very early, these anabolic treatments should be recommended at diagnosis. Due to its vastly superior efficacy and multiple other benefits, exercise should be the most commended therapy option, with the safety of exercise, including HI, stressed (10).

Physiotherapists should be enlisted to prescribe and, at least initially, supervise this training.

Additionally, to reinforce the need for, and evaluate the efficacy of, these interventions, body composition (bioelectrical impedance is a relatively inexpensive, quick and easy method) and objective physical function (walk and/or chair test) should be assessed at least annually.

However, most fundamental of all is that rheumatologists recognise RC as a key contributor to patient disability and well-being.

(1000 words)

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