RHEUMATOID ARTHRITIS

Could IL-6 inhibition prevent exercise-induced fat loss in RA?

Antonios Stavropoulos-Kalinoglou and George D. Kitas

New research indicates that tocilizumab limits the beneficial effects of exercise on abdominal fat loss. What does this mean for patients with chronic disease who are being treated with tocilizumab or other inhibitors of IL-6 signalling?

Refers to Wedell-Neergaard A. S. et al. Exercise-induced changes in visceral adipose tissue mass are regulated by IL-6 signalling: a randomized controlled trial. *Cell Metabolism* https://doi.org/10.1016/j.cmet.2018.12.007 (2018)

Main text

In a new randomized controlled trial, Wedell-Neergaard and colleagues [1] investigated the effects of IL-6 inhibition on exercise-induced changes in visceral adipose tissue mass. They treated abdominally obese adults with either tocilizumab (an anti-IL-6 receptor monoclonal antibody) or placebo as well as either a 12-week aerobic (bicycle) exercise regimen or no exercise. Visceral adiposity was reduced only in the placebo group who were performing the exercise regimen, suggesting that IL-6 signalling is necessary for exercise-mediated reduction of visceral fat. This interesting finding is potentially important for the management of patients with rheumatoid arthritis (RA).

The important role of IL-6 in the pathophysiology of RA is well-established[2]. This pleiotropic cytokine is produced by many cell types, including monocytes, T cells, B cells, fibroblasts, osteoblasts and endothelial cells. Serum and synovial fluid concentrations of IL-6 in patients with RA are high and correlate with disease activity and joint destruction. IL-6 is

involved in a number of pathways that can contribute to pathogenesis of RA, including: T cell differentiation, proliferation and apoptosis; B cell maturation and autoantibody production; neutrophil migration; osteoclast maturation and pannus proliferation. IL-6 is also the primary driver of systemic manifestations of RA, such as the acute phase response, anaemia, fatigue, fever and muscle weakness. This pivotal function of IL-6 has been confirmed in the 'clinical arena', as multiple controlled clinical trials and long-term observational studies have shown that inhibition of IL-6 reduces inflammatory disease activity, improves physical function and decelerates the progression of radiological joint damage.

IL-6 is also involved in energy metabolism and is produced by skeletal muscle, especially in response to repetitive muscle contraction. Initially thought to be secreted as a result of muscle damage, IL-6 is now known to be released as a response to muscle glycogen depletion and seems to participate in glucose homeostasis and lipolysis[3]. In particular, IL-6 seems to enhance visceral adipose tissue lipolysis, as indicated by the new study from Wedell-Neergaard et al. [1]. Notably, these positive effects of IL-6 and other myokines are usually associated with their transient production and short-term action [4]. The effects of chronically elevated IL-6, as in the case of patients with RA, on metabolism have not yet been investigated.

Control of body weight and improvement of body composition are particularly important targets in the overall management of RA because such abnormalities are common in RA patients and associate with disease outcomes, including the well-established increase in their cardiometabolic risk[5]. The role of exercise in achieving these targets in the RA population is increasingly being recognised[6]. Many patients with RA present with altered body composition, often with reduced lean body mass in the presence of unaltered or slightly

elevated weight, a condition termed rheumatoid cachexia. Rheumatoid cachexia is associated with worse RA disease outcomes, increased disability and reduced quality of life[7]. Counterintuitively, being overweight or obese is also very common in RA populations today. Obesity is not only a risk factor for the development of RA, but is also associated with worse disease outcomes and poor response to DMARDs, including some biologic agents [8] but not tocilizumab; this made some authors suggest that it may be a good choice for obese RA patients[9]. In this respect, the findings of Wedell-Neergaard et al., that IL-6 inhibition may attenuate the beneficial effects of exercise on visceral adiposity, are important, as they argue against IL-6 inhibition being a good therapeutic choice in overweight RA patients.

To date, only one study has investigated IL-6 inhibition in relation to body composition in RA [10]. Tournadre et al. [10] showed that after 12 months of treatment with tocilizumab, patient weight and lean body mass were slightly increased. Interestingly, although total fat mass was unchanged in these patients, a change in fat distribution was reported, with truncal to peripheral fat ratio decreasing substantially (that is, relatively more fat was stored in the periphery). These results seem to indicate a beneficial effect of inhibiting IL-6 signalling. However, the lack of an alternative treatment control group and absence of an exercise intervention in this study limits our ability to compare and interpret these findings relative to the findings of Wedell-Neergaard et al. [1]. Nevertheless, some potentially 'telling' differences between these studies might enlighten us.

Wedell-Neergaard et al. [1] investigated people with obesity in a low-grade inflammatory state, whereas Tournadre et al. [10] investigated patients with RA exhibiting chronic high-grade inflammation with elevated levels of IL-6 and IL-6 receptor (IL-6R) expression. Even during targeted inhibition, IL-6 and IL-6R expression can remain high in patients with RA compared with healthy individuals, and this high expression might enable

some IL-6-mediated effects to still occur in certain tissues. The slightly increased lean body mass after IL-6 inhibition in patients with RA reported by Wedell-Neergaard et al. [1] is also an interesting finding that might indicate that adequate levels of IL-6 for muscle regeneration may still be available even after inhibition in RA. IL-6 has a positive effect on the proliferative capacity of muscle stem cells, inducing muscle adaptation and regeneration [4]. Unfortunately neither study reported the level of IL-6 or IL-6R expression post-treatment in blood or relevant tissues, e.g. muscle or fat.

Both studies included mainly female participants, but the patients studied in Tournadre et al.[10] were mostly of normal weight, whereas obese individuals were the focus of Wedell-Neergaard et al.[1]. This difference might indicate that further mechanisms might exist that involve total body adiposity adipocyte size or other factors. Moreover, the duration of the two studies was different, with the Tournadre et al. (9) study lasting 12 months and Wedell-Neergaard et al. (1) only 12 weeks. Perhaps short versus long-term IL-6 inhibition differentially affects mechanisms of lipolysis and energy metabolism, something that has not been assessed in any population.

In conclusion, the paper by Wedell-Neergaard et al.[1] contributes to our understanding of the mechanisms by which exercise can mediate abdominal fat loss in otherwise healthy but obese people. However, limited information exists regarding such mechanisms in the context of chronic inflammatory conditions such as RA, in which IL-6 is a major therapeutic target. Given the importance of adiposity and body composition in RA disease progression and outcome, more research is needed to understand the interaction between pharmacological and lifestyle interventions in this population.

Antonios Stavropoulos-Kalinoglou[1] and George D Kitas[2,3,*]

[1]Carnegie School of Sports, Leeds Beckett University, Headingley Campus, LS63NL, Leeds, UK

[2]Clinical Research Unit, Russells Hall Hospital, Dudley Hospitals NHS Foundation Trust,

DY12HQ, Dudley, UK

[3]Arthritis Research UK Centre for Epidemiology, University of Manchester, UK

*e-mail: george.kitas@nhs.net

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Competing interests

The authors declare no competing interests.

Figure 1: Potential interactions between exercise and IL-6 inhibition in Rheumatoid Arthritis