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LETTER

Response to 'Infliximab therapy increases body fat mass in early rheumatoid arthritis independently of changes in disease activity and levels of leptin and adiponectin: a randomized study over 21 months'

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See related research by Engvall *et al.*, http://arthritis-research.com/content/12/5/R197

We read with great interest the study by Engvall and colleagues [1] in a recent issue of *Arthritis Research & Therapy*. The study showed that anti-tumor necrosis factor-alpha (anti-TNF-α) infliximab therapy is associated with an increase of body fat mass in early rheumatoid arthritis (RA) independently of changes in disease activity and levels of leptin and adiponectin.

With respect to this, we have prospectively followed a cohort of patients who had RA refractory to conventional disease-modifying antirheumatic drugs, including methotrexate, and who, owing to disease severity, underwent anti-TNF-α-infliximab therapy. Among them, a subgroup of 33 consecutive RA patients who were on periodical treatment with infliximab and who agreed to participate in the study was assessed to determine the short-term effect of this drug on insulin resistance, ghrelin, and adipokine profile. Besides noting a dramatic improvement of insulin resistance following infliximab administration [2], we observed that, upon administration of this drug, serum ghrelin concentrations (in picograms per milliliter) increased significantly (896.1 ± 314.8, median 861.2, interquartile range (IQR) 700.5 to 879.9 before infliximab at time 0 (baseline) and 976.3 ± 373.0, median 905.8, IQR 752.6 to 1,152.8 after infliximab infusion at 120 minutes; P <0.001) and that increases in ghrelin concentrations were associated with reductions in P-selectin concentrations (r = −0.513; P = 0.002) [3]. However, ghrelin concentrations were not related to the DAS28 (disease activity score using 28 joint counts), the mean erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) from disease diagnosis or the ESR, platelet count, CRP, or cumulative prednisone dose at the time of the study [3]. Moreover, we observed a significant correlation between leptin levels and body mass index [4].

Apart from stimulating growth hormone production, ghrelin regulates energy homeostasis through increasing food intake and decreasing fat utilization, leading to increased adiposity through growth hormone-independent mechanisms [5]. Ghrelin is further associated with metabolic syndrome features, and ghrelin administration has beneficial effects not only on cachexia in patients with heart failure and chronic obstructive pulmonary disease but also on insulin sensitivity in overweight patients and endothelial dysfunction in patients with metabolic syndrome [6]. Additionally, ghrelin has potent anti-inflammatory effects, including the inhibition of proinflammatory cytokine production by T lymphocytes and monocytes within the immune system and human endothelial cells [7]. Besides noting the rapid decrease of P-selectin, a biomarker of endothelial dysfunction [8], we observed a rapid and significant improvement of endothelial function following infliximab administration in these patients [9].

According to our observations, anti-TNF-α therapy increases serum levels of ghrelin. Since ghrelin has anti-inflammatory effects, increased levels presumably would be additive to the efficacious actions of infliximab [3].

Metabolic syndrome features are independently associated with atherosclerosis in RA [10]. However, in our

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series of patients with severe RA, in contrast to what was reported in non-RA subjects, metabolic syndrome features were not related to ghrelin concentrations [3]. It is possible that improvement of ghrelin metabolism through inhibition of cytokine production attenuates the cachexia in patients with RA. Additionally, in our series, we observed a significant increase of body mass index when values obtained before the onset of infliximab therapy were compared with those observed after 2 years of infliximab therapy (unpublished observations).

Considering all of these observations, we feel that, in patients with severe RA, the TNF-α blockade may improve the impaired production of ghrelin, a hormone that is implicated in RA-associated cachexia. This effect may lead to an increase of body mass index in RA patients undergoing TNF-α antagonist therapy.

Abbreviations

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; RA, rheumatoid arthritis; TNF-α, tumor necrosis factor-alpha.

Competing interests

The authors declare that they have no competing interests.

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