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Editorial

Is fat that bad in rheumatoid arthritis?

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There is considerable interest, within the rheumatologic community, in the links between rheumatoid arthritis (RA) and obesity.These two conditions share some common features. Both are characterized by increased cardiovascular risk, systemic inflammation and overall increased morbidity and mortality compared to general population. There is also a tendency to consider obese people as a fragile population in RA. This is somehow encouraged by studies showing that obese RA patients, compared to those with lower body mass index (BMI), have persistently higher disease activity and are less likely to achieve remission on treatment. Moreover, there is some evidence that weight reduction, can ameliorate function, reduce disease activity and the need for DMARD treatment. As such, weight reduction is frequently advised to obese RA patients as a means to ameliorate quality of life, reduce handicap and increase survival.

Should we then consider those patients as a subgroup of more severe patients deserving particular attention in RA? When a closer look to obese RA patients is taken, there is concordant evidence that, despite a supposed longstanding sustained clinical activity, those patients have lower progression of structural damage, which is an apparent paradox [1–3]. Actually, when synovitis was searched for at ultrasonography or MRI, clinical synovitis was a bad predictor of synovitis at imaging in obese patients [4,5]. This somehow supports the concept that clinical examination overestimates synovitis in this subset of patients.

The other components of the most used global index of disease activity in RA, DAS28, are patient evaluation of general health (GH) and biological markers of acute-phase response (like C-reactive protein, CRP, or erythrocyte sedimentation rate, ESR). Both components may be affected in obese patients independent of disease activity. Obesity is, per se, associated with lower quality of life, which may impact GH [6]. Moreover, CRP is increased in obese people independent of any other inflammatory condition [7,8], possibly due to the peculiar profile of cytokines associated with increased visceral fat. This all suggests that obese people may have a falsely increased disease activity and that, in reality, their disease may be actually milder compared to nonobese patients.

Different explanations have been proposed to justify the lower radiological progression in obese patients. On one side, overestimated disease activity may lead to a more aggressive therapeutic attitude, with consequent overtreatment [9]. The role of adipokines has also been evoked, in particular that of adiponectin, which may be involved in radiological damage and whose serum levels are reduced in obesity [10].

Whatever the mechanistic explanations, the data suggest that when obesity is present, the severity of RA is milder. Conversely, when RA patients are thin their disease is more aggressive. This may be evident when this apparent paradox is considered in the wider perspective of body composition. RA is a systemic disease that leads to loss of muscle mass, which is replaced by fat. This is the so-called rheumatoid cachexia. As such, body weight being equal, RA patients have lower muscle and higher fat compared with healthy people. Moreover, it seems that in RA the relationship between fat mass and BMI is non-linear [11,12]. Thus, the differences in body composition between RA patient and general population are more marked for patients with low BMI, while for progressively higher BMIs the differences attenuate, being the lowest for obese RA patients. This is reflected by the fact that low-BMI RA patients are those with the most severe erosive disease [1] and also those with the highest mortality[13].

Conversely, even if RA patients have lower muscle compared to healthy subjects, the relation between muscle mass and BMI seems to be more linear [12]. Hence, obese patients have high fat mass but also high muscle, and their body composition is not deeply affected by RA. This means that there are no major differences in body composition between obese RA patients and obese subjects without RA. To further support the concept of milder disease in obese RA patients, apart from lower radiographic progression, this subset of patients has also lower total and cardiovascular mortality compared to patients with lower BMI [14,15].

The difficulty in determining real disease activity, and the better prognosis (at least at the group level) are then of paramount relevance when it comes to define therapeutic strategy and assess treatment response in this subset of patients.

In a recent article of *Joint Bone Spine*, Juan et al. [16] report the results of a meta-analysis exploring the impact of obesity on clinical response to biologic agents in several chronic inflammatory diseases. They found that obese RA patients have lower odds of achieving good EULAR response and DAS28-based remission on anti-TNF treatment. A similar tendency was found for rituximab, but this conclusion was based on the results of a subgroup analysis of a single study involving patients who had failed a first anti-TNF

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agent. Moreover, another study that did not find any difference between obese and nonobese RA patients in clinical response to rituximab [17], was excluded from the metaanalysis. Conversely, the efficacy of both tocilizumab and abatacept in RA seems to be independent of patient BMI.

The mechanism underlying these findings is unclear, in particular why obesity impacts response only to TNF inhibition. A first consideration is that these conclusions are supported by a limited number of studies, none of high-standard methodological quality.

Moreover, in this work, anti-TNF agents are analysed as a class while, in fact, they are a heterogeneous group of drugs comprising monoclonal antibodies vs. soluble receptor, intravenous vs. subcutaneous drugs, fixed vs. tailored dosage. In the only prospective study on anti-TNF included, only infliximab showed a differential effect between obese and nonobese patients, while this was not the case for both etanercept or adalimumab.

The intravenous route may not explain this result, as in the included studies both abatacept and tocilizumab – whose effect was not affected by obesity – were given intravenously. Hence, before concluding to a class effect, each anti-TNF agent should be analysed separately. This seems important as, at present, there is no mechanistic background to suggest that a given cytokine or pathway should be preferentially targeted in obese patients.

On the other side, one may argue that, if obese patients have only falsely increased disease activity, this should impact the perceived efficacy of all agents, indistinctly. That was not the case, as said of both tocilizumab and abatacept.

Although all the involved studies with the latter two agents had a prospective design – and several were randomised double blind studies – the outcome measures were nevertheless the same as those for anti-TNF.

Moreover, although proper metaanalyisis could not be performed, Juan et al. found a similar BMI-dependency of anti-TNF-agents also in psoriasis, psoriatic arthritis and Crohn's disease

These findings are then intriguing and highlight the need for further studies, of appropriate design and quality, as the impact on clinical practice may be a major one.While waiting for further data to be available, current evidence suggests that when it comes to decide whether to start a biologic in obese RA patients, clinicians should first of all focus on assessing the real disease activity and establish prognosis.

For this purpose and in this subgroup of patients, simple clinical examination may be insufficient and imaging tools like ultrasonography or MRI may provide additional benefit.

The same suggestions apply for treatment monitoring.When the indication for biologic treatment is retained, and the choice is not imposed by patient co-morbidity or non-medical reasons, the result of this study may provide some elements that can be pondered for the choice of the targeted treatment.

Disclosure of interest

The authors declare that they have no competing interest.

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Gaëlle Clavel[a,b]
Johanna Sigaux[a,c,d]
Luca Semerano[a,c,d,*]
[a] *Inserm UMR 1125, 1, rue de Chablis, 93017 Bobigny, France*
[b] *Fondation Rothschild, department of internal medicine, 75019 Paris, France*
[c] *Sorbonne Paris Cité, université Paris 13, 1, rue de Chablis, 93017 Bobigny, France*
[d] *Assistance publique–Hôpitaux de Paris (AP–HP), groupe hospitalier Avicenne – Jean-Verdier–René-Muret, service de rhumatologie, 125, rue de Stalingrad, 93017 Bobigny, France*

[*] Corresponding author at: Assistance publique–Hôpitaux de Paris (AP–HP), groupe hospitalier Avicenne – Jean-Verdier–René Muret, service de rhumatologie, 125, rue de Stalingrad, 93017 Bobigny, France.
E-mail address: luca.semerano@aphp.fr
s(L. Semerano)

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