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Review

Impact of obesity on the clinical outcome of rheumatologic patients in biotherapy

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ABSTRACT

There is raising interest in the scientific community about the impact of body mass on different rheumatologic diseases. A growing body of evidence suggests that the effect of obesity on joint structure goes beyond the simply overload but is based on a complex interwinding of cytokines, hormones, growth factors, and intracellular regulators that at different stages can modify the course of a rheumatologic disease and the clinical response to biotherapies. In these settings, psoriatic arthritis (PsA) and rheumatoid arthritis (RA) have been the more extensively studied. Intriguing is the finding that the interaction between obesity and diseases seems different for PsA or RA. Concerning PsA, epidemiologic studies have provided robust data about the association between obesity and prevalence of psoriasis or PsA. Yet obesity is associated with an increase in degree of disability and poor clinical outcome on treatment with anti-tumor necrosis factor (TNF) drugs. Nevertheless, there are clues suggesting that weight reduction above 5% from baseline increases the probability of achieving a good clinical response in PsA patients on anti-TNF drugs. On the contrary, the epidemiological association between obesity and RA seems to be restricted to some categories of patients with peculiar demographic and autoimmune status. Furthermore, obesity definitely impairs the clinical response of RA patients to anti-TNF treatment, and this might be an effect limited to TNF-blocking agents, as preliminary studies are not confirming these findings for abatacept or tocilizumab. However, the most puzzling aspect of the impact of obesity on RA is that obese patients tend to have a more clinical active disease, an impaired response to biotherapies, and a less radiographically evident joint damage over time. The latter is a very stimulating issue and the knowledge of the underlying mechanisms should be an auspicious challenge for the researchers, which will provide further insights on the overall management of RA.

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1. Introduction

Obesity, defined as a body mass index (BMI, a ratio in which the weight in kilograms is divided by height in meters squared) above 30 kg/m^2, has become a public health emergency and its prevalence in the United States and in Western nations in general has greatly increased in the last years [1]. Obesity cannot be considered only as an

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overweight state with an enhanced fatty storage but as a very complex condition that exerts biological stress on multiple tissues and systems, including immune system [2]. Clinical and experimental evidence supports the hypothesis that obesity is a low-grade inflammatory condition possibly linking rheumatic diseases to insulin resistance and atherosclerotic cardiovascular diseases [3]. Thereby, high C-reactive protein levels in obese subjects are an expression of an inflammatory state that is induced by an increase in pro-inflammatory cytokines, such as monocyte chemoattractant protein-1 (MCP-1), interleukin-8 (IL-8), IL-1, IL-6, and tumor necrosis factor (TNF), being the visceral fat the main their main source [4]. Indeed, the increase of pro-inflammatory cytokines in obese subjects is directly related to a low-grade inflammation of adipose tissue and it is due to the proliferation of fat macrophages that synthesize cytokines and stimulate adipocytes to secrete the so-called "adipokines," the cytokines of adipocytes [5]. Among several adipokines, those more strictly correlating obesity to articular homeostasis are mainly leptin, which exerts pro-inflammatory e pro-catabolic effects and is found to increase in obesity [4], and adiponectin, which seems to promote bone resorption *via* osteoclast activation [6] and is decreased in obese subjects [4]. The role played by the adipokines in the pathophysiology of rheumatic diseases is currently under investigation, but there are several hints suggesting their involvement in modulating the course of diseases in obese patients affected with psoriatic arthritis (PsA) and rheumatoid arthritis (RA). Here, we reviewed the epidemiologic association of obesity with PsA and RA, the effect of high BMI on the disease course and activity, and the impact of obesity on clinical outcomes.

1.1. Epidemiology of obesity in PsA and RA

A first step in understanding the relationships between obesity and rheumatic diseases is the assessment of their epidemiology. In European countries, the prevalence of obesity is estimated around >10% of general population, psoriasis about 3%, and PsA roughly 1%. Thereby, it would be likely that the association of obesity with PsA might be casual. However, an Italian survey has shown that the prevalence of obesity in 511,532 individuals with incident diagnosis of psoriasis was 5.6% with an odds ratio (OR) of 1.30 (95% CI = 1.10–1.53) in comparison with healthy donors [7]. On the contrary, in a retrospective analysis performed in South Korea, there were no significant differences in the metabolic status between normal control and psoriasis patients. Also, there was no significant difference in the clinical response to cyclosporine between high BMI group and normal BMI group [8]. However, a large prospective study carried out over 12 years on an incident cohort of 121,700 US nurses has clearly demonstrated that a higher BMI and weight gain are risk factors for psoriasis in older women [9]. Recently, a novel cytokine, psoriasin, synthesized by keratinocytes, is selectively increased in psoriatic subjects [10]. Psoriasis and PsA share pathogenic pathways linking skin to joints [11]; thereby, it is conceivable that also PsA is significantly associated with obesity. A cohort study, representative of general UK population, was conducted between 1995 and 2010, and the exposure of interest was the first BMI measured after psoriasis diagnosis and end points were incident cases of physician-diagnosed PsA [12]. The authors estimated the adjusted risk ratio of PsA and of 75,395 individuals with psoriasis (43% male): 976 developed PsA, and its incidence rate increased with increasing BMI [12]. Likewise, a large prospective Nurses Health Study (NHS) has identified 146 incident PsA cases during 1,231,693 person-years of follow-up, and BMI was monotonically associated with an increased risk of new diagnosis of PsA [13].

Also, for RA, a significant association between obesity and the development of the disease has been demonstrated, and the most meaningful data come from national health programs. Interestingly, this association seems to vary according with gender and autoimmunity and smoking status either. In a national case–control study on 515 patients recently diagnosed with RA, tobacco smoking was selectively associated with risk of anti-CCP-positive RA, whereas obesity was selectively associated with risk of anti-CCP-negative RA, with obese individuals being at more than 3-fold increased risk of this subtype compared with normal-weight individuals (OR = 3.45; 1.73–6.87) [14]. Similar findings have been reported by another case–control study on 2748 RA patients showing a strong association of high BMI >30/kg/m^2 with anti-CCP negative RA women OR = 1.6; 1.2–2.2) [15]. Even larger was the longitudinal study on 109,896 women enrolled in NHS-I and 108,727 in NHS-II, showing that risks of seropositive and seronegative RA were elevated among overweight and obese women, particularly among women diagnosed with RA at earlier ages [16].

1.2. Obesity and clinical outcomes in PsA

The first data on the possible impact of obesity on clinical outcomes in patients with psoriatic disease on biotherapy come from dermatology grounds. Some studies have shown a poor skin response to TNF blockers in obese psoriatic patients [17–19], and that weight loss ameliorates the skin response in formerly obese psoriatic patients [18]. The influence of high BMI on clinical response is somewhat controversial. A cross-sectional study conducted on 135 patients with active peripheral PsA (45 obese, 47 overweight, and 43 normal-weight) treated with adalimumab, etanercept, or infliximab did not show significant difference in rate of Disease Activity Score (DAS28) based remission among BMI classes, regardless of the TNF inhibitor prescribed [20]. In contrast, a prospective case–control study on 135 obese and 135 normal-weight PsA subjects has shown that BMI ≥ 30 kg/m^2 is a negative predictor of achieving and maintaining a state of minimal disease activity (MDA) [21]; MDA was achieved by 98 (36.3%) of the 270 PsA individuals. The prevalence of obesity was higher in those that did not achieve MDA than in those that did (64.0% *versus* 25.5%; $p < 0.001$). After adjusting for demographic and clinical variables, obesity was associated with a higher risk of not achieving MDA (hazard ratio (HR) = 4.90, 95% confidence interval (95% CI) = 3.04–7.87). A Canadian group [22] echoed these findings. Of the 557 patients included in the study, 36.2% were classified as overweight and 35.4% were obese. A dose–response association was found between obesity and the probability of achieving sustained MDA in the multivariate regression analysis. Patients in the higher BMI categories were less likely to achieve sustained MDA compared those in the lowest BMI category (overweight: OR = 0.66, $p = 0.003$; obese: OR = 0.53, $p < 0.0001$) after adjusting for potential confounding variables. The fact that obesity may impair the clinical response to TNF inhibitors seems to be corroborated by the improvement of response upon weight loss [23]. Among subjects with PsA starting treatment with TNF blockers, 138 overweight/obese patients received a concomitant dietary intervention (69 a hypocaloric diet (HD) and 69 a free-managed diet (FD)). At 6 months follow-up, MDA was more often achieved by HD than by FD subjects (HR = 1.85, 95% CI = 1.019 to 3.345). For increasing weight-loss categories (<5%, 5–10%, >10%), MDA was achieved by 23.1%, 44.8%, and 59.5%, respectively. The rate of MDA achievement was found to be double in subjects with >10% (OR = 6.67, 95% CI = 2.41 to 18.41) than in those with 5–10% (OR = 3.75, 95% CI = 1.36 to 10.36) weight loss.

1.3. Obesity and clinical outcomes in RA

The availability of predictive biomarkers may improve the efficiency of RA therapy [24]. Also, comorbid obesity may impact on RA course, although the association of high BMI and disease activity is controversial. Increased DAS28 in obese RA patients has been reported by some studies [25] but not confirmed by others [26–28]. A longitudinal survey from Sweden has shown that obesity was associated with worse RA disease outcomes and a higher prevalence of comorbidities. As BMI and obesity were independently associated with higher disease activity, fewer patients in sustained remission, higher HAQ score, more pain, and worse general health [29]. Despite the fact that RA in obese patients seems

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