Rheumatol Ther (2020) 7:447–456
https://doi.org/10.1007/s40744-020-00215-6

REVIEW

Obesity and Psoriatic Arthritis: A Narrative Review

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Received: April 24, 2020 / Published online: June 3, 2020

ABSTRACT

Patients with psoriatic arthritis (PsA) have a higher burden of cardio-metabolic comorbidities like obesity, hypertension, diabetes, and cardiovascular disease compared to the general population. Adipose tissue is thought to promote a chronic low grade inflammatory state through inflammatory mediators like tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), leptin, and adiponectin. A higher body mass index (BMI) is a risk factor for development of PsA and affects disease activity and response to therapy including both disease-modifying antirheumatic drugs (DMARDs) and tumor necrosis factor inhibitors (TNFi). Obesity has an impact on the morbidity in PsA, particularly cardiovascular and/or metabolic. Patients with PsA have a higher cardiovascular risk and obesity may have an additive impact on morbidity and mortality. This review explores the relationship between obesity and PsA.

Keywords: Body mass index (BMI); Cardiovascular risk; Obesity; Psoriatic arthritis (PsA)

Key Summary Points

Obesity is an important comorbidity in patients with psoriatic arthritis (PSA).

Obesity increases the risk of PsA, possibly related to a higher level of pro-inflammatory mediators.

Patients with a higher body mass index (BMI) are less likely to achieve minimal disease activity (MDA).

A weight reduction strategy has been shown to improve PsA disease activity along with its other beneficial effects of reducing diabetes, hypertension, and coronary artery disease.

Digital Features To view digital features for this article go to https://doi.org/10.6084/m9.figshare.12370133.

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INTRODUCTION

Psoriasis is a common immune-mediated condition with primary manifestations in the skin. Psoriatic arthritis (PsA) is a chronic inflammatory disease that is associated with psoriasis and affects approximately 10–30% of patients with

psoriasis [1]. PsA shares clinical, genetic, and etiopathogenic features with other forms of spondyloarthritis (SpA) including axial spondyloarthritis (axSpA), reactive arthritis, and inflammatory bowel disease (IBD)-associated arthritis. Features of PsA include peripheral arthritis, enthesitis, dactylitis, skin and nail psoriasis, inflammatory back pain (IBP), and extra-articular features like uveitis and inflammatory bowel disease. Beyond extra-articular features, PsA is associated with multiple comorbidities, particularly metabolic comorbidities, including obesity, diabetes, and increased cardiovascular risk [2, 3]. In fact, patients with PsA have a higher prevalence of cardiovascular comorbidities like obesity, hypertension, and hyperlipidemia compared to patients with psoriasis without PsA [4] and compared to the general population [5]. More than 50% of patients with PsA have at least one comorbidity and around 40% of patients can have three or more comorbidities [6, 7]. Obesity is among the most prevalent comorbidities in PsA. This may be particularly important as adipose tissue plays a role not only in metabolism but also in immune and inflammatory processes [8].

This narrative provides a review of the burden of obesity in patients with PsA and the relationship between PsA, obesity, and outcomes. In conducting a review of the literature, we searched the Pubmed database using the following terms: "psoriatic arthritis", "obesity", "body mass index", and "cardiovascular disease", and relevant literature was selected for review. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

BURDEN OF OBESITY: INCREASED PREVALENCE OF OBESITY IN PSORIATIC DISEASE

The World Health Organization (WHO) defines obesity as a condition of abnormal or excessive accumulation of fat in the adipose tissue, to the extent that health may be impaired [9]. The estimated prevalence of obesity (BMI $\geq$ 30 kg/m^2) in US adults is 39.8% according to the Centers for Disease Control and Prevention (CDC) [10]. Available evidence suggests that obesity is a common problem in PsA, even compared to other chronic diseases. A number of studies have reported a higher prevalence of obesity in PsA [5, 11–13]. A claims-based study reported higher prevalence of obesity in PsA compared to rheumatoid arthritis (RA) or psoriasis (6.0% vs 4.4% vs 3.8%) and incidence rates per 1000 patient-years of 32.9 vs 24.4 vs 26.4, respectively [13]. A cross-sectional study of patients with PsA and patients with RA enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) Registry showed a higher prevalence of obesity in PsA compared to RA (45% vs 39%) [12]. Likewise, the mean $\pm$ SD BMI of the PsA group was higher than in RA (30.6 ± 6.8 kg/m^2 vs 29.3 ± 6.9 kg/m^2; $P = 0.004$) [12]. A population-based incidence cohort from Olmstead County reported that 44% of patients with PsA were obese [11]. The large difference in the prevalence across studies is related to the study design, setting (i.e., claims-based study vs registry-based study vs population-based medical records) and outcome definitions used (i.e., codes vs physician diagnoses). Similarly, Bhole et al. reported that patients with PsA have higher BMI values than those with psoriasis or RA [14].

Psoriasis (without PsA) is also associated with a higher prevalence of obesity. A systematic review aggregating data from 2.1 million study participants (201,831 patients with psoriasis) concluded that patients with psoriasis have greater pooled odds ratio (OR) for obesity [1.66 and 95% confidence interval (CI) 1.46–1.89] compared with those without psoriasis [15]. Additionally, this review found that the prevalence of obesity increases as the severity of psoriasis increases with an OR (compared with the general population) from 1.46 for patients with mild psoriasis to 2.23 for severe psoriasis [15]. Obesity often precedes the diagnosis of psoriasis. In fact, obesity is an established risk factor for development of psoriasis in the general population [16, 17].

WHY IS PSA ASSOCIATED WITH OBESITY?

The association between obesity and PsA is complex and possibly bidirectional. While obesity has been demonstrated to be a risk factor for the development of PsA [18], studies have also suggested that weight gain may be a consequence of these inflammatory conditions as patients with joint dysfunction may be less inclined to be physical active [19, 20]. Additionally, we know that enthesitis can be associated with repetitive joint trauma, in particular micro-trauma [21, 22]. Obesity may lead to more weight on the joints, altered mechanics, and repetitive micro-trauma. While this can lead to osteoarthritis (OA), it may also stimulate an inflammatory process [23].

OBESITY AND INFLAMMATION

Obesity is characterized by chronic inflammation promoting a low grade inflammatory state [24]. There is increasing evidence to suggest that adipose tissue, composed of adipocytes, functions as an active endocrine organ, releasing adipocytokines and pro-inflammatory mediators. Adipokines have diverse physiological functions including regulation of the immune system and inflammatory response [24, 25]. Leptin promotes pro-inflammatory cytokines (interleukin-1α (IL-1α), IL-12, tumor necrosis factor alpha (TNFα), IL-17, IL-6) and suppresses anti-inflammatory cytokines (i.e., transforming growth factor (TGFβ), IL-10) [26]. On the contrary, adiponectin, adipokine, is believed to have anti-inflammatory effects, especially its low molecular weight iso-form [24]. Lower levels of adiponectin and higher levels of leptin have been reported in patients with psoriasis compared to healthy controls [27, 28]. Additionally, leptin was positively associated and adiponectin was negatively associated with the severity of psoriasis [29]. Beyond these two adipokines, adipose tissue is a source of pro-inflammatory cytokines such as IL-6, TNFα, and IL-8 [30]. Finally, there may be certain pathways that are more easily activated in obese patients than non-obese patients. In SpA mouse models, endoplasmic reticulum (ER) induces the cellular inflammatory cascade through the c-Jun N-terminal kinase (JNK) pathway [31]. The JNK pathway has been shown to be upregulated in the adipose tissue of obese individuals, leading to immuno-inflammatory responses [32]. Apart from low grade inflammation from adipose tissue, increased mechanical loading on the joints, and a possible link with obesity-related dyslipidemia as suggested in OA are hypothesized as risk factors for PsA [33]. Trauma is a known factor in psoriatic skin lesions and a similar phenomenon has been hypothesized in the development of PsA. The weight load of obesity leads to both increased mechanical stress and risk of local micro-damage. PsA is characterized by enthesitis and obesity is associated with pathology of enthesis in the general population [34]. Patients with psoriasis who are exposed to repeated trauma are at a higher risk of developing inflammatory arthritis [35]. A prospective longitudinal cohort study showed that physical trauma was independently associated with an increased risk of PsA compared with controls (multivariate hazard ratio HR of 1.32 (95% CI 1.13–1.54) [36]. In summary, adipose tissue is associated with inflammation. There is increased risk and prevalence of autoimmune disease with obesity with the strongest levels of evidence for RA, PsA, psoriasis, and multiple sclerosis [37, 38]. This may lead to interactions that are associated with the development or management of inflammatory disorders, such as PsA. Similarly biomechanic stress might be another factor linking obesity to PsA which has led to increasing interest in understanding the relationship between obesity and chronic inflammatory diseases like PsA.

OBESITY AS A RISK FACTOR FOR DEVELOPMENT OF PSA

Several studies have found that obese patients with psoriasis and obese patients in general have an increased risk for the development of PsA [39]. A case control study showed that a higher reported BMI at age 18 years was associated with higher odds of PsA compared to normal-weight individuals independent of control

variables (OR 1.06, $P < 0.01$) [40]. Another prospective study reported borderline association between obesity and development of PsA (relative risk (RR) 2.02, 95% CI 0.97–4.24) [41]. In a cohort of US Nurses Health Study II, BMI and central obesity were associated with an increased risk of incident PsA. Compared with BMI less than 25.0, the RR was 1.83 for BMI 25.0–29.9 kg/m^2 (95% CI 1.15–2.89), 3.12 for BMI 30.0–34.9 kg/m^2 (95% CI 1.90–5.11), and 6.46 for BMI over 35.0 kg/m^2 (95% CI 4.11–10.16) [18]. The UK population-based study of more than 75,000 patients with psoriasis showed that the risk of development of PsA was higher in patients with psoriasis and obesity (BMI $\geq$ 25.0 kg/m^2) or morbid obesity (BMI $\geq$ 35.0 kg/m^2) as compared with psoriasis and BMI < 25 kg/m^2. Compared with patients with psoriasis and BMI < 25 kg/m^2, the RR for developing PsA was 1.09 (0.93–1.28) for BMIs from 25.0 to 29.9 kg/m^2, 1.22 (1.02–1.47) for BMIs from 30.0 to 34.9 kg/m^2, and 1.48 (1.20–1.81) for BMIs $\geq$ 35.0 kg/m^2 [42].

IMPACT OF OBESITY ON PSA CHARACTERISTICS, DISEASE ACTIVITY AND SEVERITY OF PSA

Patients with PsA who are obese frequently have higher disease severity. Among 314 patients with PsA, obese patients tended to have a longer time to diagnosis compared to patients with a normal BMI [43]. In a study from the UK, patients who were obese were found to have higher joint counts, C-reactive protein (CRP), Health Assessment Quality-Disability Index (HAQ-DI), and composite measures including Clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA). Additionally, obese patients with PsA are less likely to be in a patient acceptable symptom state as measured by the PsA Impact of Disease (PSAID) [22]. A USA-based study similarly found that obesity was associated with higher PSAID and Routine Assessment of Patient Index Data (RAPID3) scores [44]. Eder et al. reported a higher consumption of non-steroidal anti-inflammatory drugs in patients with obesity than in normal-weight patients but no significant difference in the swollen and tender joint count and joint damage [45]. An Italian study did not find any difference in the baseline disease characteristics of obese and non-obese patients but the obese group of patients did have higher comorbidities like hypercholesterolemia and hypertriglyceridemia [46]. A dietary intervention study showed significant improvement in disease activity measures like DAS28-CRP, DAPSA, and HAQ-DI [47]. Weight reduction correlated in a dose–response manner with higher ACR 20 response rate and greater reductions in DAS28-CRP and HAQ. On the contrary, a registry-based observational study comparing 1900 obese and non-obese patients with PsA did not show a statistically significant difference in the DAS28 and CRP values but did show a significant difference in the percentage of patients achieving a EULAR good or moderate (EGOM) [48].

IMPACT OF OBESITY ON RESPONSE TO THERAPY

Patients with obesity have poorer response to treatment, but poorer response to TNF inhibitors in particular [49]. In one cohort study, after adjustment for all the other variables, obesity was associated with a higher risk of not achieving Minimal Disease Activity (MDA) (hazard ratio [HR] 4.90, 95% confidence interval [95% CI] 3.04–7.87; $P < 0.001$) [46] (Table 1). Patients on infliximab were on a dose of 5 mg/kg which was not adjusted and might have hampered an optimal response. The findings were similar in a cohort of 557 patients that showed obese patients with PsA are less likely to achieve sustained MDA compared to those of normal weight [45]. Additionally, when identifying predictors of response to TNF inhibitors, Ogdie et al. reported that obesity was among the strongest predictors with OR 0.51 (0.33–0.81) for not achieving Clinical Disease Activity Index (CDAI) remission [50]. Furthermore, beyond establishing obesity as a risk factor for non-response to therapy, there is good data to suggest that weight loss can have a significant impact on response. Among obese patients with PsA initiating a TNFi, patients with 5–10% weight loss had a higher odds of

Table 1 Impact of obesity on response to therapy

Research article first author	Number of subjects	Obese (%)	Outcome	Effect size (OR)	95% CI	*P* value
Di Minno et al. (2013)	270	135 (50%)	Probability of not achieving MDA in obese vs normal patients	4.9	3.04–7.87	<0.001
Eder et al. (2014)	557	197 (35.4%)	Probability of achieving MDA in obese vs normal patients	0.52	0.4–0.67	<0.001
Ogdie et al. (2019)	774	428 (55%)	Predictor of CDAI remission in BMI > 30 vs ≤ 30	0.51	0.32–0.81	
Di Minno et al. (2014)	126	126 (100%)	Probability of achieving MDA with 5–10% vs < 5% weight loss	3.75	1.36–10.36	0.011

OR odds ratio

achieving MDA compared to patients who lost less than 5% of their body weight (OR 3.75). The OR of achieving MDA with greater than 10% weight loss was 6.67 [51]. This study further supports the causal association of obesity with response to therapy. It is possible that some of this improvement is driven by the patient-reported outcomes (PROs) as patients generally feel better after weight loss. However, regardless of why the improvement in achievement of MDA occurs, there is a need for weight reduction strategies to improve clinical outcomes for our patients [52, 53].

To date, most clinical trials have not found a significant difference in the primary outcome when stratifying by obesity, in contrast with real-world studies, and thus most of the therapies available for PsA are not dose adjusted by weight. However, there are three exceptions: ustekinumab (IV), infliximab (IV), and golimumab (IV) are dosed by body weight [54].

MANAGEMENT OF OBESITY AS A CARDIOVASCULAR RISK FACTOR IN PSA

We know that a significant portion of patients with PsA are obese and that obesity is a risk factor for PsA. It is crucial to recognize and address comorbidities associated with PsA, such as obesity, because of their implications for disease activity, quality of life, and therapy. Obesity reduction has multiple benefits. In fact, among patients with psoriasis, a reduction in BMI may reduce the risk of PsA. A large PsA cohort study found that reducing BMI over a 10-year period was associated with a reduction in the risk of developing PsA compared with BMI remaining constant over the same period [55]. Patients with PsA are at a higher risk for cardiovascular disease including myocardial infarction and major adverse cardiovascular events (MACE) after accounting for traditional cardiovascular risk factors [3, 56, 57]. The most recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the primary prevention of cardiovascular disease have now included psoriasis and other chronic inflammatory conditions as "risk-enhancing factors" for cardiovascular disease as is an elevated C-reactive protein [58]. Clinicians are encouraged to first calculate the 10-year cardiovascular risk (i.e., through use of Framingham Risk Score). Among patients with borderline or intermediate risk, presence of a risk-enhancing factor (i.e., psoriasis, RA, lupus, or other chronic inflammatory disorders) should be managed more aggressively (such as earlier initiation of a statin) [59]. While obesity is not directly named as a risk factor, obesity is often associated with other cardio-metabolic conditions (i.e., dyslipidemia, hypertension, diabetes, metabolic syndrome) which are named risk

factors [60]. This makes cardiovascular risk assessment (as well as assessment for these associated conditions) that much more important. Improving cardiovascular risk assessment techniques in patients with inflammatory arthritis is challenging and has been a topic of ongoing research [61, 62].

MANAGE OBESITY IN PATIENTS WITH PSA

In this paper, we have summarized the impact of obesity on disease activity, response to therapy, cardiovascular risk, and patients' general well-being. However, there are currently relatively few resources for rheumatologists and dermatologists to help patients lose weight. Access to nutritionists to guide dietary interventions is desirable but not always available [53]. Physical activity recommendations for patients with inflammatory arthritis are the same as for the general population [63]. However, physical activity alone tends to have lower effectiveness for weight loss than dietary strategies [64]. Additionally, diets are hard to adhere to and exercise programs are challenging to initiate and maintain [52]. Pharmacological treatment options for obesity are limited. Bariatric surgery is the treatment of choice when all other interventions have failed. Regardless of the type of bariatric surgery performed, its effects on weight loss and associated comorbidities are superior when compared with non-surgical interventions [65] and initial evidence suggests there is some benefit in psoriasis and PsA [66–68]. However, further studies are needed, specifically, pragmatic interventions to address obesity need to be developed and tested for application in clinical practice.

CONCLUSION

Obesity and PsA share a complex relationship which is likely bidirectional. Obesity has been demonstrated as a known risk factor for development of PsA in multiple studies. Adipose tissue is metabolically active and produces a chronic low grade inflammation in obese individuals. This chronic low grade inflammation may be responsible for the increased risk for PsA, increased disease burden, and poor response to therapy, but there may be other confounders in this relationship as well (e.g., micro-trauma, general functional impairments from obesity, and worse PROs). Weight loss has been demonstrated to improve the achievement of MDA in patients with obesity initiating a TNFi. Diet and exercise still form the crux of obesity treatment, which can be challenging for our patients. Weight reduction strategies should be encouraged to improve outcomes related to PsA but also to promote the overall health of our patients. Further studies are needed to develop weight reduction strategies that can be applied in clinical practice.

ACKNOWLEDGEMENTS

We acknowledge the support of Dr. Chaim Putterman, Professor of Medicine, Albert Einstein College of Medicine.

Funding. No funding or sponsorship was received for this study or publication of this article. Dr. Ogdie is supported by NIH/NIAMS R01 AR072363.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Anand Kumthekar has nothing to disclose. Alexis Ogdie reports Grants from Novartis (to Penn), Pfizer (To Penn), Amgen (To Forward/NDB); Consulting for AbbVie, Amgen, Bristol-Myers Squibb, Celgene, Corrona, Eli Lilly and Company, Janssen, Novartis, Pfizer, UCB, and Takeda.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human

participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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