

EXTENDED REPORT

Obesity is associated with a lower probability of achieving sustained minimal disease activity state among patients with psoriatic arthritis

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ABSTRACT

Aim To assess whether overweight and obese patients with psoriatic arthritis (PsA) are less likely to achieve sustained minimal disease activity (MDA) state compared to patients with normal weight.

Methods A cohort of patients was assessed at the University of Toronto PsA clinic at 6–12-month intervals according to a standard protocol from 2003 to 2012. Patients were categorised into the following groups according to their body mass index (BMI): normal (<25), overweight (25–30), and obese (>30). Sustained MDA was defined as achieving low disease activity state in five or more of the following domains for at least 1 year: skin, enthesitis, tender and swollen joint counts, pain, patient global assessment and function. Proportional odds discrete time to event analysis was used to investigate the association between BMI category and the achievement of sustained MDA.

Results Of the 557 patients included in the study, 36.2% were classified as overweight and 35.4% were obese. Overall, 66.1% of the patients achieved sustained MDA during the follow-up period. 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.

Conclusions Overweight and obese patients with PsA are less likely to achieve sustained MDA compared to those of normal weight.

INTRODUCTION

Psoriasis is a chronic immune mediated inflammatory skin disease affecting 2–3% of the population. Approximately 30% of the patients with psoriasis develop inflammatory arthritis, termed psoriatic arthritis (PsA).¹ Both psoriasis and PsA are strongly associated with obesity. Patients with PsA tend to have higher body mass index (BMI) than patients with psoriasis alone and the prevalence of obesity in psoriatic patients is higher than in the general population.² Obesity is a risk factor for psoriatic disease as it predicts the development of psoriasis and PsA in longitudinal prospective studies.^{3–6} Obesity is also associated with increased disease activity. The association between obesity and the severity of psoriasis has been reported by several

independent groups. Obese patients with psoriasis are more likely to suffer from widespread skin disease and respond less favourably to treatments, while weight reduction is associated with improvement in the skin disease.^{7–9}

Only a few studies assessed the relationship between obesity and the severity of arthritis in patients with PsA. Di Minno *et al*¹⁰ reported that increased BMI predicted less favourable response to TNF α blockers in patients with PsA who were followed for 24 months. The same group also showed that weight reduction was associated with improved response to treatment with TNF α blockers.¹¹ They hypothesised that under-dosing of medications may explain the poorer response of the obese patients to the treatment. An alternative cause may be related to the increased production of pro-inflammatory adipokines, by the adipose tissue. A number of these cytokines including TNF α , leptin and adiponectin, have been associated with disease activity among patients with psoriatic disease and may mediate the association between obesity and more severe manifestations of the disease in psoriatic patients.^{12–14} To date, no study has assessed the association between BMI and the likelihood of achieving minimal disease activity (MDA) state independently of drug treatment in patients with PsA. In the present study we aimed at assessing whether obesity is associated with a lower probability of achieving an MDA state among patients with PsA.

METHODS

Patients and setting

The University of Toronto PsA clinic serves as a primary, secondary and tertiary referral centre for PsA patients from the Greater Toronto Area and Southern Ontario. We consider a cohort of patients followed prospectively from 2003 to 2012. Since classification criteria for PsA were not available until 2006, the diagnosis of PsA was based on the presence of psoriasis and inflammatory arthritis and exclusion of other types of arthritis. However, 98% of the patients in the clinic satisfy the CASPAR criteria for classification of PsA.¹⁵ Patients who were followed in the clinic for less than a year were excluded since it was not possible for them to achieve the outcome. Written consent from all subjects was obtained according to the Declaration of Helsinki. The study has been approved by the University Health Network Ethics Board.



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Data collection and outcome measures

Patients were evaluated according to a standard protocol at 6–12-month intervals.¹⁶ At each visit a physical examination was conducted, a complete musculoskeletal examination was carried out along with an assessment of psoriasis severity, laboratory tests were conducted and a medication history was taken. The resulting data along with information on symptoms were recorded and entered into a computerised database. BMI was calculated at each visit and patients were categorised into the following groups: normal (BMI<25), overweight (BMI 25–30) and obese (BMI>30). Since only 27 (4.9%) patients were classified as underweight (BMI<20), these patients were included in the ‘normal’ BMI category. The presence of joint tenderness and/or swelling was assessed in 68 and 66 joints, respectively. Psoriasis severity was assessed using the Psoriasis Activity and Severity Index (PASI) and body surface area (BSA) involvement. The assessment of enthesitis is based on the Spondyloarthritis Research Consortium of Canada (SPARCC) score but any additional tender enthesal sites are also recorded. Patient reported outcomes including Health Assessment Questionnaire (HAQ), severity of pain and global assessment of disease activity were obtained.

The primary outcome of the study was the achievement of MDA for at least 1 year (sustained MDA). MDA was defined as fulfilling at least five of the following seven criteria: tender joint count ≤ 1 , swollen joint count ≤ 1 , PASI ≤ 1 or BSA ≤ 3 , patient pain Visual Analogue Scale (VAS) of ≤ 15 , patient global disease activity VAS score of ≤ 20 , HAQ ≤ 0.5 , and tender enthesal points ≤ 1 .¹⁷ The last observation carried forward was used to handle missing data.

Statistical analysis

Baseline descriptive statistics were computed with continuous variables summarised by their means and SDs and categorical variables summarised by proportions. Comparisons between the three BMI categories were made using the Cochran–Armitage trend test for categorical variables and analysis of variance (ANOVA) for continuous variables. The principal outcome considered was the achievement of sustained MDA. Explanatory variables included BMI category (primary predictor), sex, age, duration of PsA, non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying antirheumatic drugs (DMARDs) and TNF α blockers. Additional regression models were constructed for each of the seven criteria comprising MDA. Each of these criteria was separately considered as the outcome using the same explanatory variables as outlined before. The association of these variables and the probability of achieving each of the outcomes were examined in proportional odds discrete time to event regression analysis. The dataset used for the discrete time to event model was structured as discrete time units of 6 months up to and including the patient’s time record of achieving sustained MDA or censoring. The interaction terms BMI \times DMARDs and BMI \times TNF α blockers were introduced as additional explanatory factors into separate regression models to assess whether the association between BMI and sustained MDA was modified by treatment.

RESULTS

Of the 831 patients who visited the PsA clinic between 2003 and 2012, 557 were included in the study. A total of 274 patients were excluded due to missing data or short follow-up period. These patients were not significantly different from the study sample with respect to their demographics, BMI, duration

of PsA, and tender and swollen joint count; however they had a higher PASI score at baseline and were less likely to use NSAIDs or DMARDs. Of the patients who were included in the analysis, 58.7% were male and their mean age and PsA disease duration at baseline were 48.6 ± 13.1 and 11.5 ± 10.4 years, respectively. The mean follow-up duration from baseline until the last assessment or achievement of sustained MDA was 3 ± 2.6 years.

Two hundred patients (36.2%) were classified as overweight and 196 (35.4%) were obese. Their characteristics at baseline are presented in table 1. Overweight and obese patients were older at baseline ($p=0.04$) compared to patients with normal weight. In addition NSAID use was also more frequent in obese and overweight patients ($p=0.003$).

Overall, 368 (66.1%) patients achieved sustained MDA while 189 patients (33.9%) did not achieve sustained MDA. High pain score, HAQ and tender joint counts were the items most frequently associated with failure to achieve MDA (criterion was not achieved in 79.4%, 59.4% and 48.1% of the observations, respectively).

The association between BMI and the probability of achieving sustained MDA

An inverse dose–response association was found between BMI and the probability of achieving sustained MDA in univariate regression analysis. Patients in the higher BMI categories were less likely to achieve sustained MDA compared to those in the lower BMI category (BMI 25–30: OR 0.65, $p=0.002$; BMI>30: OR 0.52, $p<0.0001$). This inverse association remained statistically significant in a multivariate regression model (BMI 25–30: OR 0.65, 95% CI 0.50 to 0.85, $p=0.002$; BMI>30: OR 0.52, 95% CI 0.40 to 0.67, $p<0.0001$; table 2). In addition, female gender (OR 0.71, $p=0.0003$), older age (10-year increase, OR 0.87, $p=0.003$), longer duration of PsA (10-year increase, OR 0.88, $p=0.03$) and the use of DMARDs (OR 0.77, $p=0.03$) and NSAIDs (OR 0.55, $p<0.0001$) were associated with lower probability of achieving sustained MDA. No statistically significant interaction was found between BMI category and the use of DMARDs ($p=0.82$) or anti-TNF α agents ($p=0.35$), therefore no additional sub-group analysis was performed involving these treatments.

Association between BMI and the probability of achieving the criteria for each of the individual items of MDA

We further assessed the association between BMI category and the probability of fulfilling each of the individual items comprising MDA for at least a year using multivariate regression analysis (see table 3). BMI category was associated with a lower probability of achieving sustained MDA in the following domains: tender joint count (OR 0.77, $p=0.003$), psoriasis activity (by PASI or BSA, OR 0.29, $p<0.0001$), pain score (OR 0.43, $p<0.0001$), patient global assessment (OR 0.35, $p<0.0001$) and HAQ (OR 0.61, $p<0.0001$). Swollen joint count and enthesitis were not associated with BMI category.

DISCUSSION

A significant proportion of our cohort of PsA patients was overweight or obese. Increased BMI was associated with a less favourable outcome as patients who were overweight were less likely to achieve sustained MDA compared those with normal weight and the likelihood of achieving sustained MDA in obese patients was even lower. This association was independent of the use of DMARDs and biological medications.

Obesity has a negative impact on psoriatic disease. Obese patients with psoriasis tend to suffer from more severe skin

Table 1 Characteristics of the study population by BMI category at baseline

Variable	BMI category			p Value
	Normal (N=180)	Overweight (N=200)	Obese (N=197)	
Age (years)	50.7±14.9	52.3±13.2	53.2±10.1	0.04
Gender: male	81 (51.6%)	138 (69%)	107 (54.6%)	0.74
Age at diagnosis of PsA (years)	36.8±14.1	35.1±11.6	38.2±12.4	0.002
Age at diagnosis of psoriasis (years)	28.9±15.1	26.3±13.4	30.1±14.3	0.002
Smoker: current	25 (16.1%)	24 (12.1%)	29 (15%)	0.25
Smoker: past	26 (16.8%)	29 (14.7%)	42 (21.7%)	
Alcohol consumption: none	63 (40.7%)	82 (41.4%)	84 (43.1%)	0.63
Swollen joint count	3.8±3.7	4.1±3.8	4.3±4.2	0.74
Tender joint count	6.4±7.2	7.5±7.2	8.0±7.8	0.26
Damaged joint count	12.3±13.3	14.1±15.5	12.6±13.6	0.63
PASI	4.2±6.6	4.8±6.2	5.7±9.0	0.15
CRP (mg/L)	17.3±29.0	11.8±12.2	15.9±14.6	0.90
ESR (mm/hr)	21.5±22.0	20.1±18.8	19.3±16.3	0.75
HAQ	0.87±0.76	0.91±0.71	0.96±0.64	0.10
Pain score	4.3±2.8	4.7±2.5	4.9±2.5	0.72
Patient global score	2.6±1	2.6±0.9	2.8±0.8	0.09
Use of NSAIDs	104 (66.2%)	146 (73%)	157 (80.1%)	0.003
Use of DMARDs	90 (58.1%)	122 (61.6%)	125 (63.8%)	0.28
Use of anti TNF α agents	23 (14.7%)	21 (10.6%)	34 (17.4%)	0.40

BMI, body mass index; CRP, C-reactive protein; DMARDs, disease modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; NSAIDs, non-steroidal anti-inflammatory drugs; PsA, psoriatic arthritis; PASI, Psoriasis Area and Severity Index.

Table 2 Association between BMI category and the probability of achieving sustained MDA among patients by discrete time proportional odds analysis

	Univariate model			Multivariate—reduced model		
	OR	95% CI	p Value	OR	95% CI	p Value
Gender: female	0.70	0.56 to 0.88	0.002	0.71	0.56 to 0.89	0.003
Age*	0.84	0.77 to 0.92	0.0002	0.87	0.79 to 0.95	0.003
Duration of PsA*	0.84	0.75 to 0.92	0.0005	0.88	0.78 to 0.99	0.03
BMI category†						
Overweight versus normal	0.65	0.50 to 0.85	0.002	0.66	0.50 to 0.87	0.003
Obesity versus normal	0.52	0.40 to 0.67	<0.0001	0.53	0.41 to 0.69	<0.0001
DMARDs use	0.74	0.59 to 0.93	0.009	0.77	0.61 to 0.97	0.03
TNF α blockers	1.07	0.85 to 1.35	0.54			
NSAIDs	0.59	0.47 to 0.74	<0.0001	0.55	0.43 to 0.70	<0.0001

*10-year increase.

†Overweight (BMI 25–30), obesity (BMI > 30).

BMI, body mass index; DMARDs, disease modifying anti-rheumatic drugs; MDA, minimal disease activity; NSAIDs, non-steroidal anti-inflammatory drugs; PsA, psoriatic arthritis.

Table 3 Association between BMI category and the probability of fulfilling the individual MDA items by proportional odds discrete time analysis*

	Overweight versus normal			Obesity versus normal		
	OR	95% CI	p Value	OR	95% CI	p Value
Tender joint count \leq 1	0.88	0.73, 1.06	0.17	0.79	0.66 to 0.93	0.006
Swollen joint count \leq 1	1.11	0.88, 1.40	0.38	1.19	0.95 to 1.48	0.13
PASI \leq 1 or BSA \leq 3	0.43	0.31, 0.61	<0.0001	0.28	0.21 to 0.39	<0.0001
Patient pain (VAS \leq 5)	0.56	0.43, 0.73	<0.0001	0.45	0.34 to 0.58	<0.0001
PGA (VAS \leq 20)	0.44	0.36, 0.55	<0.0001	0.35	0.29 to 0.43	<0.0001
HAQ \leq 0.5	0.84	0.68, 1.03	0.10	0.62	0.51 to 0.75	<0.0001
Tender enthesal points \leq 1	0.90	0.64, 1.25	0.52	0.96	0.70 to 1.32	0.81

*Multivariate model adjusted for age, gender, duration of PsA, use of DMARDs and anti-TNF α .

BMI, body mass index; BSA, body surface area; HAQ, Health Assessment Questionnaire; MDA, minimal disease activity; PASI, Psoriasis Activity and Severity Index; PGA, Patient Global Assessment; VAS, Visual Analogue Scale.

involvement and have poor response to TNF α blockers while weight loss improves the response to treatment.^{7-9 18} Similarly, obese patients with PsA respond less favourably to TNF α blockers¹⁰ while weight loss is associated with improved outcome.¹¹ Our results are in line with previous reports in the field and reinforce the tight link between obesity and the severity of psoriatic disease. Overall, 35.4% of the patients in our cohort suffered from obesity; this estimate is higher than the reported prevalence of obesity in the general population in Canada (25.3%).¹⁹ In addition, we have found that the inferior outcome among overweight and obese patients was independent of DMARDs or anti-TNF α blockers use. This association was noted among patients who were using non-biological DMARDs and TNF α blockers, but also among patients who were not using any medications. Additionally, no interaction was found between BMI and either DMARDs or TNF α blockers, suggesting that this association may not necessarily be explained by under-dosing of medications.

The underlying mechanism linking obesity and psoriasis is largely unknown. In the present study the association between increased BMI and active disease was observed in several domains including pain, function (by HAQ), tender joint count, patient global assessment and skin activity. Overlapping inflammatory pathways may be potential biological links underlying the association between obesity and psoriatic disease. Obesity is characterised by low level chronic inflammation that is driven by pro-inflammatory cytokines such as TNF α produced by adipocytes. This cytokine is a primary mediator of pro-inflammatory pathways in psoriatic disease. Thus bi-directional relationship may explain the association where pro-inflammatory cytokines produced in the adipose tissue increase the susceptibility and severity of psoriatic disease and in turn the same cytokines produced by the inflamed skin and synovial tissues perpetuate obesity-related co-morbid conditions frequently found in psoriatic patients such as the metabolic syndrome.²⁰⁻²² Other mechanisms unrelated to the immune system may also explain the link between obesity and poor outcome in PsA. Obesity may be associated with biomechanical abnormalities in the joint, particularly in the lower limbs, that may result in increased micro-damage in these sites. McGonagle *et al*²³ suggested that microscopic damage and associated aberrant inflammatory response in the entheses may be the initial lesion in the evolution of PsA. The predilection of PsA to the lower limbs supports this hypothesis. Another mechanism may be related to altered pain threshold. Obesity has been associated with higher reported levels of generalised pain among healthy individuals and in patients with rheumatoid arthritis.²⁴⁻²⁶ This may contribute to the lower likelihood of achieving the MDA criteria in the pain and tender joint count domains among obese patients. Lastly, obesity is associated with osteoarthritis and other non musculoskeletal co-morbid conditions that may lead to physical disability independently of inflammatory arthritis.²⁷ It has been shown that HAQ score is highly influenced by co-morbidities in addition to the effect of arthritis.²⁸

We did not observe any association between BMI and swollen joint count or enthesitis, nor did we find a difference in inflammatory markers and damaged joint count across the BMI categories. Obesity may affect the accuracy of joint and enthesal assessment. However, to the best of our knowledge this topic has not been investigated in PsA patients. Thus, in the present study most of the negative impact of obesity on disease outcome was related to patient-reported outcome, pain and the skin domain. The higher proportion of NSAID use in obese patients may also indicate higher pain levels in that group. Furthermore, in a recent

analysis of our cohort we did not find an association between obesity and radiographic progression of joint damage.²⁹ This is similar to recent reports in rheumatoid arthritis showing that obesity is associated with less progression of radiographic damage.^{30 31} Thus, currently, there is no data linking obesity to more destructive forms of PsA. It is possible that obesity-related mechanical overload could explain some of the difference in pain scores and other patient reported outcomes.

In this article we fit univariate and multivariate models to examine the response to treatment as a function of patient BMI. The multivariate model included a modest number of factors which, to some degree, enhances our confidence in the causal inferences. More sophisticated approaches to causal inference involving the use of inverse probability of treatment weighted estimating functions for fitting marginal structural models^{32 33} are warranted. In the present setting these are challenging to implement because the time varying variables which might lead to confounding by indication are only measured intermittently. This challenge is a topic of future research which will give insight into the robustness of the findings reported herein.

This study was limited in several aspects. First, its observational nature does not allow determination of a causal relationship between BMI and MDA; since this is not an inception cohort it is possible that worst disease has led to accelerated weight gain and higher BMI at baseline. Second, not all potential confounding variables could be adjusted for (eg, physical activity).

Lastly, a significant proportion of patients were excluded due to missing data or short follow-up period. However, these patients were not significantly different in most aspects from the study population. The strengths of the study include the large number of patients, the long observation period and the accurate and detailed phenotyping of the patients. To the best of our knowledge this is the first study assessing the effect of BMI on disease outcome irrespective of medications used for arthritis.

In summary, the present results indicate that overweight and obesity are associated with lower probability of achieving MDA among patients with PsA. This association was independent of the use of biological and non-biological DMARDs. This effect is probably mediated through various pathogenic mechanisms. Weight loss may improve the long-term outcome and overall health of the patients and increase their chances of achieving disease remission.

Contributors All authors were involved in the preparation and drafting of the article or revising it critically for important intellectual content, and all authors approved the final version to be published. All authors were likewise involved in the study conception and design, acquisition of data as well as analysis and interpretation of data. AT and RJC performed the statistical analysis. DDG had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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