Obesity in Early Adulthood as a Risk Factor for Psoriatic Arthritis

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Objective: To study whether obesity increases the risk of psoriatic arthritis (PsA), given that obesity is a risk factor for psoriasis and is associated with more severe disease.

Design: Case series. We used Cox regression analysis to study the relationship between obesity and PsA while controlling for age at psoriasis onset, current body mass index (BMI), sex, family history of psoriasis, worst-ever body surface area (BSA) involvement, Koebner phenomenon, and nail involvement.

Setting: Dermatology clinics at the University of Utah School of Medicine.

Patients: Volunteer sample of patients with dermatologist-diagnosed psoriasis enrolled in the Utah Psoriasis Initiative from November 2002 to October 2008 (943 subjects; 50.2% women, 49.8% men).

Main Outcome Measures: Physician diagnosis of PsA from self-report questionnaire.

Results: In our subjects, we found that BMI at age 18 years was predictive of PsA (odds ratio [OR], 1.06) (P < .01) over and above control variables. Other variables that were predictors of PsA included younger age at psoriasis onset (odds ratio [OR], 0.98) (P < .01), female sex (OR, 1.43) (P = .01), higher worst-ever BSA involvement with psoriasis (OR, 1.01) (P = .04), Koebner phenomenon (OR, 1.59) (P < .01), and nail involvement (OR, 1.76) (P < .01). Current BMI and family history of psoriasis were not significant predictors of PsA.

Conclusions: This study suggests that obesity at age 18 years increases the risk of developing PsA. Adiposity is associated with higher levels of inflammatory cytokines known to be associated with psoriasis. This inflammatory milieu could increase the risk of PsA in predisposed subjects. Prevention and early treatment of obesity may decrease the risk of PsA.

Arch Dermatol. 2010;146(7):721-726
contrasts with RA, in which the BMI is inversely associated with RA vs psoriasis and PsA. In psoriasis, higher BMI is associated with increased cardiovascular risk. More recently it has become apparent that patients with PsA also show an increased frequency of cardiovascular diseases (ischemic heart disease, atherosclerosis, peripheral vascular disease, congestive heart failure, and cerebrovascular disease) and that their traditional cardiovascular risk factors (type 2 diabetes, hyperlipidemia, and hypertension) are also increased relative to controls.17 How- ever, there is a difference in the association between obesity and RA versus obesity and PsA. In psoriasis, higher BMI is generally associated with more severe disease, which contrasts with RA, in which the BMI is inversely associated with the severity of the RA.18

Our research group previously showed that patients with psoriasis in the Utah Psoriasis Initiative (UPI) cohort had an increased BMI compared with controls.19 With regard to the complex relationship between obesity and RA vs RA, we set out to study if obesity increases the risk of PsA in a large psoriasis cohort. We also studied the other clinical risk factors of PsA as well as the clinical features associated with obesity in this cohort.

METHODS

SUBJECTS

Detailed demographic and clinical data were obtained from participants with psoriasis enrolled in the UPI from 2002 to 2008. This study was approved by the University of Utah institutional review board and adheres to the principles of the Declaration of Helsinki. All subjects had a dermatologist-confirmed diagnosis of psoriasis, and all were consecutively recruited from the population of patients older than 18 years who attended Department of Dermatology clinics affiliated with the University of Utah. Over 95% of subjects with psoriasis attending our clinics have enrolled in the UPI. Enrollment includes completion of a structured questionnaire; clinical interview and detailed physical examination by a trained research physician; and collection of a peripheral blood sample for DNA extraction.

All eligible participants from the UPI were examined by 1 of the 2 faculty dermatologists (K.C.D. and G.G.K.) and were confirmed to have psoriasis. Patients were considered to have PsA if they reported that a rheumatologist had diagnosed PsA. Equivocal cases of PsA were excluded from the analysis. We determined the BMI of the patients on the basis of self-reported height and weight. At the time of enrollment in the UPI, subjects were asked to report their current height (in feet and inches), current weight (in pounds), and their weight at age 18 years (in pounds). All values were then converted into BMI. According to clinically accepted guidelines,20 BMI was categorized into 3 groups: BMI lower than 25, normal; BMI from 25 to lower than 30, overweight; and BMI of 30 or higher, obese. Koebner phenomenon was defined as a positive answer to the questionnaire question “has your psoriasis ever developed at the site of a skin injury, such as a scrape or a burn?”

STATISTICAL ANALYSIS

To investigate the impact of BMI as an independent risk factor on PsA, we conducted hierarchical stepwise Cox proportional hazards modeling. A base model was first developed to control for factors with known or theoretically plausible association with PsA (sex, family history of psoriasis, age at onset of psoriasis, worst-ever body surface area [BSA] involvement with psoriasis, presence of Koebner phenomenon, and presence of nail involvement). Next, BMI at age 18 years and current BMI were added to the base model and tested for significance. In this manner, we were able to ascertain the impact of obesity on PsA independent of other contributing factors. Age at onset of PsA was used as the time-to-event variable. Patients who did not have PsA at the time of enrollment were considered right censored. We analyzed only patients that developed PsA after having psoriasis. All statistical analyses were conducted with SPSS statistical software, version 17.0 (SPSS Inc, Chicago, Ill). Variables with P<.05 were considered significant.
(P < .01), female sex (OR, 1.45) (P = .01), higher worst-ever body surface area involvement with psoriasis (OR, 1.01) (P = .04), Koebner phenomenon (OR, 1.59) (P < .01), and nail involvement (OR, 1.76) (P < .01). Current BMI and family history of psoriasis were not significant predictors of PsA (Table 2).

In the second block, BMI at age 18 years and BMI at enrollment were introduced into the model. Higher reported BMI at age 18 years was associated with increased risk of PsA (OR, 1.06) (P < .01) independent of the control variables mentioned in the first block, while current BMI was not associated with the risk of PsA (OR, 0.99) (P = .20).

At age 18 years, 14.1% of patients were considered overweight, and 5% were considered obese based on their retrospective self-reported height and weight. At the time of enrollment (mean [SD] patient age, 47.89 [16.69] years), 33.5% were overweight and 35.5% were obese. To illustrate the effect of obesity on PsA, Kaplan-Meier curves were developed for 3 categories of BMI at age 18 years (normal, overweight, and obese). Figure 2 shows the obese group having an earlier onset of PsA, followed by the overweight group, and finally the normal BMI group. Twenty percent of the overweight or obese group developed PsA by age 35 years. In the normal BMI group, 20% of the subjects develop PsA by age 48 years (x² = 14.36, P < .01).

**PHENOTYPIC CHARACTERISTICS OF OVERWEIGHT AND OBESITY IN PATIENTS WITH PSORIASIS**

Our research group previously showed that patients with psoriasis in the UPI who had a higher BMI also had a larger BSA covered with psoriasis. Severe psoriasis was defined a worst-ever BSA of 10% or more. These facts, in addition to the finding that obesity was a risk factor for PsA over and above other clinical features such as nail disease and higher BSA, prompted an assessment of the clinical characteristics associated with higher BMI in our cohort (Table 3). Female patients enrolled in the UPI tend to have a normal BMI at age 18 years, and male patients tend to report BMIs in the overweight or obese category at age 18 years (P < .01). There was no significant association between BMI at age 18 years and family history of psoriasis. Patients who were overweight or obese at age 18 years were more likely to report severe psoriasis (56.8% for obese vs 46.6% for overweight vs 38.7% for normal weight) (P = .02). The reported frequency of Koebner phenomenon tended to increase in overweight and obese patients, although the increase was not statistically significant (P = .36). Also, plaque thickness and plaque size tended to increase with BMI at age 18 years, but the difference did not reach statistical significance (P = .28 for thickness and P = .12 for size).

**COMMENT**

In the present study, we have built models that include clinical risk factors for development of PsA in patients with psoriasis. According to our first model, patients with younger age at onset of psoriasis, more severe psoriasis, nail lesions, and positive Koebner phenomenon are more prone to develop PsA. While some studies have pro-

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**Figure 1.** Time-to-event curve for development of psoriatic arthritis (PsA) in the study population.

**Figure 2.** Time-to-event curve for development of psoriatic arthritis (PsA) based on body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) at age 18 years in the study population.

**Table 2.** Hierarchical Cox Regression Model Predicting Time to Developing PsA

<table>
<thead>
<tr>
<th>Analysis Characteristic</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block 1 (χ² change, 85.15)</td>
<td></td>
</tr>
<tr>
<td>Age at psoriasis onset</td>
<td>0.984 (0.96-0.98)</td>
</tr>
<tr>
<td>Family history of psoriasis</td>
<td>0.84 (0.62-1.15)</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.45 (1.09-1.94)</td>
</tr>
<tr>
<td>Severity, worst-ever BSA</td>
<td>1.01 (1.00-1.01)</td>
</tr>
<tr>
<td>Nail involvement</td>
<td>1.76 (1.25-2.47)</td>
</tr>
<tr>
<td>Koebner phenomenon</td>
<td>1.59 (1.17-2.14)</td>
</tr>
<tr>
<td>Block 2 (χ² change, 8.72)</td>
<td></td>
</tr>
<tr>
<td>BMI at age 18 y</td>
<td>1.06 (1.02-1.10)</td>
</tr>
<tr>
<td>BMI today</td>
<td>0.99 (0.96-1.01)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BSA, affected body surface area; CI, confidence interval; OR, odds ratio; PsA, psoriatic arthritis.

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posed a positive correlation between the severity of skin disease and the risk of PsA, others have not found any association between skin lesions and activity, severity, and functional status of the arthritis.\textsuperscript{21} Psoriatic nail lesions are seen more frequently in patients with PsA, the frequency being 40% to 45% in uncomplicated forms of psoriasis and 87% in PsA.\textsuperscript{15} The observed association between Koebner phenomenon and PsA in our study could be explained by the microtrauma theory, which proposes that the ligament and tendon insertion points are subject to repeated microtrauma and that this contributes to development of PsA.\textsuperscript{22} Microtrauma theory could be the equivalent of Koebner phenomenon in the skin. Similarly, microtrauma to the nail unit could lead to psoriatic nail changes. Patients with active disease are thus more prone to showing a positive isomorphic response in the skin (Koebner phenomenon), nail (psoriatic nail changes), and joints (PsA).

We found a significant association between lower age at onset of psoriasis and risk of developing PsA, similar to the known association between lower age at psoriasis onset and severity of disease. Patients with a younger age at onset of psoriasis may have a different burden of genes or different types of triggers that put them at increased risk for PsA. Furthermore, a lower age at onset of psoriasis means that the autoimmune inflammatory cascade driving psoriasis has been in effect for a longer period and could push the genetically predisposed patient to be at an increased risk for PsA.

The present study suggests that increased BMI in early adulthood increases the risk of PsA in patients with psoriasis and is independent of other risk factors. Each unit increase in BMI at age 18 years was associated with a 5.3% increase in the risk of PsA. Thus, patients who report having been obese at age 18 years are 3 times more likely to develop PsA in the course of their psoriasis than patients with normal BMI at age 18 years. These results coincide with findings of a previous study showing that patients with PsA are more likely to have a BMI higher than 25 than controls (72.5% vs 53.6%) (\(P<.01\)).\textsuperscript{23} Obese patients are at especially higher risk for PsA if they have other risk factors, including early onset of psoriasis, nail involvement, and positive Koebner phenomenon. These data support a growing concept that patients more prone to PsA might benefit from more frequent and meticulous screening measures for early detection and treatment of PsA, ie, before the development of irreversible joint destruction.

Previously, our group\textsuperscript{19} reported that the prevalence of obesity in the UPI is higher than in the general population in Utah. This retrospective patient-reported assessment of body image before and after development of psoriasis suggested that obesity usually followed, rather than preceded, psoriasis, implying that psoriatic inflammation contributed to the obese state. However, the Nurses’ Health Study II (NHSII),\textsuperscript{24} which prospectively examined the relationships between BMI, weight change, waist circumference, hip circumference, waist-hip ratio, and incident psoriasis in 78,626 women over a 14-year period, found a graded positive association between BMI measured at multiple time points and the risk of incident psoriasis, which suggests that obesity is a risk factor for future development of psoriasis.

The design of our study did not allow us to confirm a causal relationship between obesity and PsA. Furthermore, if a causal relationship exists, the direction is not known. The same dilemma remains to be solved regarding the association between obesity and psoriasis.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>&lt;25</th>
<th>25-30</th>
<th>&gt;30</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>347 (47.7)</td>
<td>82 (64.6)</td>
<td>18 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>381 (52.3)</td>
<td>45 (35.4)</td>
<td>27 (60.0)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Age at onset of psoriasis, mean (SD), y</td>
<td>27.3 (16.7)</td>
<td>28.6 (15.9)</td>
<td>20.1 (12.7)</td>
<td>.01</td>
</tr>
<tr>
<td>Family history of psoriasis</td>
<td>461 (63.3)</td>
<td>77 (60.6)</td>
<td>31 (68.9)</td>
<td>.61</td>
</tr>
<tr>
<td>Worst-ever BSA, mean (SD)</td>
<td>21.2 (27.4)</td>
<td>25.5 (30.0)</td>
<td>28.6 (29.3)</td>
<td>.09</td>
</tr>
<tr>
<td>Psoriatic arthritis\textsuperscript{b}</td>
<td>193 (26.5)</td>
<td>45 (35.4)</td>
<td>18 (40.0)</td>
<td>.03</td>
</tr>
<tr>
<td>Age at onset of PsA, mean (SD), y</td>
<td>38.3 (14.7)</td>
<td>33.4 (12.9)</td>
<td>33.8 (15.6)</td>
<td>.12</td>
</tr>
<tr>
<td>Nail lesions</td>
<td>421 (57.8)</td>
<td>90 (70.9)</td>
<td>26 (57.8)</td>
<td>.02</td>
</tr>
<tr>
<td>Koebner phenomenon</td>
<td>295 (40.5)</td>
<td>54 (42.5)</td>
<td>23 (51.1)</td>
<td>.36</td>
</tr>
<tr>
<td>Thin plaques</td>
<td>186 (26.1)</td>
<td>26 (23.2)</td>
<td>7 (17.1)</td>
<td></td>
</tr>
<tr>
<td>Thick plaques</td>
<td>196 (29.7)</td>
<td>42 (37.5)</td>
<td>15 (36.6)</td>
<td>.27</td>
</tr>
<tr>
<td>Small plaques</td>
<td>288 (40.2)</td>
<td>35 (31.0)</td>
<td>10 (24.4)</td>
<td></td>
</tr>
<tr>
<td>Large plaques</td>
<td>158 (23.7)</td>
<td>31 (27.4)</td>
<td>14 (34.1)</td>
<td>.12</td>
</tr>
<tr>
<td>Severe psoriasis\textsuperscript{c}</td>
<td>271 (38.7)</td>
<td>55 (46.6)</td>
<td>25 (56.8)</td>
<td>.02</td>
</tr>
<tr>
<td>Smoking</td>
<td>266 (36.5)</td>
<td>48 (37.8)</td>
<td>18 (40.0)</td>
<td>.87</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BSA, affected body surface area; PsA, psoriatic arthritis.

\(a\) Unless otherwise indicated, data are reported as number (percentage) of patients.

\(b\) Ninety-one cases with an equivocal diagnosis of PsA were excluded from the analysis.

\(c\) Severe psoriasis was defined as BSA involved with psoriasis at worst-ever involvement higher than 10%.
a time. Obese patients were more likely to report that arthritis impeded their physical activity. Also, patients with PsA in the UPI had a higher prevalence of mood disturbances, especially depression, than patients with no evidence of arthritis (prevalence of depression, 26.6% vs 18.7%) \( (P = 0.02) \), and the presence of depression or other mood disturbances could decrease physical activity and fitness. In this sequence of events, PsA would precede obesity.

In the other sequence, obesity would precede PsA. In the present study, the mean (SD) age at onset of PsA was 37.09 (14.66), and the association with obesity was focused on BMI at age 18 years, i.e., 2 decades before the mean age at onset of PsA. This sequence suggests that at least in some cases, obesity preceded PsA and might have acted as a predisposing factor to the condition.

A very plausible link between obesity and PsA is the chronic inflammatory state in obese subjects. It has been repeatedly observed that expansion of adipose tissue during weight gain is associated with recruitment of inflammatory macrophages through chemokines such as CC-chemokine ligand 2 (CCL2). Adipocytes and recruited macrophages produce cytokines such as tumor necrosis factor (TNF) and interleukin 6 (IL-6) and adipokines such as adiponectin, leptin, and resistin, which are thought to be associated with obesity, insulin resistance, and related inflammatory disorders.\(^\text{25} \) Adiponectin is primarily anti-inflammatory, and leptin and resistin are proinflammatory.\(^\text{26} \) The effect of leptin on both naïve and adaptive immunity could potentially be responsible for worsening of psoriasis. Leptin acts on naïve T cells, increasing their IL-2 secretion and proliferation. It also increases interferon-γ production by memory T cells.\(^\text{27} \) More interestingly, leptin inhibits the proliferation of regulatory T cells, which were recently found to be defective in function in psoriasis.\(^\text{28} \) In case-control studies, serum leptin levels\(^\text{29-31} \) and tissue leptin and leptin receptor expression\(^\text{29} \) were significantly higher in patients with severe psoriasis than in those with mild to moderate psoriasis and controls. Serum leptin levels showed a positive correlation with the Psoriasis Area Severity Index (PASI).\(^\text{29} \) In vitro, leptin and resistin could induce CXCL8 and TNF production by blood monocytes, both of which are implicated in the pathogenesis of psoriasis. In addition, leptin could induce IL-1β and IL-1 receptor antagonist production and secretion of amphiregulin, which in vivo cultured lesional psoriasis skin upregulates epidermal proliferation.\(^\text{32} \) Serum levels of adiponectin are lower in patients with psoriasis than in controls and inversely correlate with PASI score.\(^\text{31} \) These observations argue for obesity and its associated inflammatory cytokines as adding to genetic susceptibility factors, perhaps increasing the probability of expression of both psoriasis and PsA.

Psoriatic arthritis has several features in common with RA. Both diseases are associated with an increased cardiovascular risk.\(^\text{33,34} \) However, there are important differences between PsA and RA. Although RA is also associated with increased prevalence of cardiovascular risk factors including obesity, severe disease is associated with lower BMI.\(^\text{18} \) In psoriasis, however, severe disease is associated with higher BMI.

A possible link between obesity and psoriasis and/or PsA could be driven by a genetic variation that predisposes the patients to both conditions. Several recent genome-wide association studies have revealed an association of genes (eg, \( FTO \), \( INSIG2 \), \( MTMR9 \), \( MCR4 \), \( SLC6A14 \), \( GAD2 \), \( ENPP1 \)) with obesity. It is not known whether these genetic variations are seen more frequently in patients with psoriasis. A small study of 109 patients with psoriasis and 125 healthy controls did not show any association between G-2548A polymorphism of the leptin gene and psoriasis in a Turkish population.\(^\text{35} \) Further studies are needed to investigate a genetic relationship between obesity and psoriasis and/or PsA.

There are several limitations to our study. First, the diagnosis of PsA in all participants was self-reported as having been diagnosed by a rheumatologist. We did not have a rheumatologist independently confirm the diagnosis; however, all patients were seen by dermatologists trained in assessing PsA, and equivocal cases were excluded from the study. Second, no data were collected on disease severity, joints affected, or subclassification of PsA. Furthermore, BMI at age 18 years was based on self-reported height and weight data and was not directly measured in the study. Patients might have underestimated or overestimated their weight at age 18 years. However, we believe that this bias nondifferentially affects patients with and without PsA and is unlikely to have distorted the association between PsA and BMI.

In summary, the present findings suggest that the presence of obesity at age 18 years increases the risk of developing PsA later in life. This increased risk is over and above other risk factors for PsA, including younger age at onset of psoriasis, having more severe psoriasis based on the worst-ever PASI involved, Koebner phenomenon, and nail involvement. Evaluation of additional sample sets in an attempt to replicate these results is imperative for strong conclusions to be drawn. Prospectively enrolled databases of patients with psoriatic disease with detailed clinical information, including rheumatologic examination, are needed to confirm these data.

Accepted for Publication: November 26, 2009.
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Financial Disclosure: Dr Soltani-Arabshahi, Wong, Callis Duffin, and Krueger has received fees as a consultant or advisory board member for Abbott, Almirall, Alza, Amgen, Anacor, Astellas, Barrier Thera-
REFERENCES