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Lack of Association of High Body Mass Index with Risk for Developing Polymyalgia Rheumatica

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Abstract

Background—High body mass index (BMI) may have modulatory effects on the immune system.

Objectives—To determine the association between BMI and PMR as well as the influence of BMI on glucocorticoid treatment duration and development of giant-cell arteritis (GCA) in patients with PMR.

Methods—The BMI of 364 patients with PMR from a population-based incidence cohort was compared to the BMI of non-PMR subjects from the same population. High and low BMI were defined as ≥ 25 kg/m² and < 18.5 kg/m², respectively. The association between BMI and case status was determined. The association between BMI and the duration of glucocorticoid therapy as well as the development of GCA after accounting for relevant variables was also examined.

Results—The mean BMI at index was similar in both groups (PMR: 26 ± 5.4 kg/m²; non-PMR: 25.9 ± 4.0 kg/m²). There was no association between BMI and the duration of glucocorticoid therapy. No significant association was found between BMI and the development of GCA in patients with PMR.

Conclusions—Patients with high BMI (≥ 25 kg/m²) are not more likely to develop PMR. BMI did not influence the duration of glucocorticoid therapy nor the occurrence of GCA in patients with PMR.

Keywords

Polymyalgia Rheumatica; Body mass index; Giant Cell Arteritis

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INTRODUCTION

The growing epidemic of obesity and its threat to health is well recognized. As part of the effort to understand the effects of obesity, it has become apparent that adipocytes are immunologically active cells [1]. They are able to secrete many cytokines and other molecules that are not only involved in metabolic pathways, but have the capability to influence immune response [1, 2]. Metabolic surplus can lead to aberrant immune activity, and it is thought that this plays a key role in the state of 'low-grade' inflammation observed in obesity [2].

These observations have generated interest in the investigation of the influence of body mass index (BMI) on disease expression in various chronic inflammatory rheumatic conditions including rheumatoid arthritis, systemic lupus erythematosus, and psoriasis [3–5]. It is unknown, however, whether BMI is associated with polymyalgia rheumatica (PMR).

Polymyalgia rheumatica (PMR) is a relatively common inflammatory disorder of unknown etiology that develops in persons over the age of 50 years. The incidence of this condition in patients greater than 50 years is about 50 per 100,000 [6]. Approximately 16–21% of patients with PMR have giant cell arteritis (GCA) [7]. Standard treatment is glucocorticoids, which may be required for several years.

The objective of this study was to determine if patients with PMR have a higher BMI at disease incidence than those without PMR from the same population. We also sought to investigate whether higher BMI at disease incidence of PMR is associated with prolonged glucocorticoid treatment duration and the development of GCA. Recognition of the influence of BMI on PMR, its treatment course, and development of GCA could further knowledge of the pathophysiology and prognosis of this autoimmune disorder.

METHODS

Study Subjects

A population-based incidence cohort of PMR subjects was established using the Rochester Epidemiology Project and has been described previously [6],[8].

The cohort of PMR subjects contains patients diagnosed between January 1, 1970 and December 31, 1999. Inclusion required the fulfillment of three criteria: age $\geq$ 50 years; bilateral aching and morning stiffness (lasting 30 minutes or more) persisting for at least 1 month involving 2 of the following areas: neck or torso, shoulders or proximal regions of the arms, and hips or proximal aspects of the thighs; and an erythrocyte sedimentation rate (ESR) $>$ 40 mm/hour (Westergren method). Patients with response (definite improvement in symptoms within 24 hours) to low dose glucocorticoid therapy (20 mg prednisone per day or less) were also considered to have PMR. Other diseases that could explain symptoms, such as active rheumatoid arthritis, were excluded. The occurrence of GCA in PMR subjects was documented and based on the American College of Rheumatology (ACR) vasculitis classification criteria [9]. Demographic data available from the PMR cohort were age of

PMR at diagnosis and sex. Other clinical characteristics included ESR at diagnosis, number of rheumatology visits, and glucocorticoid treatment duration [6, 10–12].

A matched non-PMR group from the same population was also established. For each PMR subject, a control without PMR at the time of the subjects' PMR diagnosis was selected. Matching criteria were similar birth year (± 3 years), sex, and length of medical history. The index date for the control subjects corresponded to the PMR incidence date.

Data Collection

The BMI was ascertained by review of the complete medical record (inpatient and outpatient) for height and weight of the PMR and non-PMR subjects at the date of or closest to the incidence and index dates, respectively. A second BMI (BMI #2) was also recorded corresponding to the time preceding PMR diagnosis by up to 3 years, as the inflammatory effects of PMR at incidence may lead to weight loss. BMI #2 for the non-PMR cohort was taken in the time frame of up to 3 years prior to and after the index date. Missing data for BMI at incidence/index in the PMR and non-PMR cohorts was $<5\%$; however, there were 71/364 missing values (20%) for weight #2 in the PMR cohort and 42/364 missing values (12%) for weight #2 in the non-PMR cohort. High BMI (overweight) was defined as ≥ 25 kg/m² and low BMI (underweight) < 18.5 kg/m² [13].

Glucocorticoid treatment duration for this cohort was updated to March 31, 2009 [10].

As smoking has been related to lower body weight, this variable was abstracted for cases and controls. The status was determined as never, former (quit prior to incidence/index date), or current (at incidence/index date). Data was missing in $< 5\%$ for this variable.

Statistical Analysis

Data was summarized as percentages and continuous variables as mean $\pm$ standard deviation. Comparison between groups was based on t-tests for continuous variables and Pearson's chi-square test for categorical variables. Conditional logistic regression models were used to assess the association between BMI and case status. Analyses were performed using BMI at incidence/index date and also for BMI #2. BMI was examined continuously using both linear and quadratic effects, and was also categorized as <18.5 kg/m² and ≥ 25 kg/m².

Cox proportional hazards models were used to examine the association between BMI and the duration of steroid therapy as well as the development of GCA; the endpoints were discontinuation of glucocorticoid therapy and the development of GCA, respectively. Patients were censored if they were still on glucocorticoid therapy at death or date of last follow-up for analysis of the association between BMI and duration of glucocorticoid therapy. Data from patients who had not yet developed GCA were censored at death or date of last follow-up for the analysis of the association between BMI and the development of GCA. Multivariable models were used to examine the associations of interest after adjusting for relevant variables. In the analysis of discontinuation of glucocorticoid therapy, adjustment for the development of GCA, which occurred during follow-up, was performed using a time-dependent covariate.

RESULTS

There were 364 patients in both the PMR and non-PMR cohorts. Characteristics of these patients are described in Table 1. Though the cohorts were not matched on smoking status, no differences were apparent for this variable.

Association between BMI and PMR patients

The mean BMI at incidence/index and BMI #2 was similar in both groups (Table 2); however, the PMR cohort had significantly fewer patients with BMI <18.5 kg/m² at incidence/index (2% in PMR vs. 5% in non-PMR cohort, $p=0.021$). BMI #2 values were also examined and the association with the presence of PMR was similar although not quite as strong ($p=0.14$ for BMI <18.5 kg/m²).

Logistic regression analyses revealed no association between BMI at incidence as a continuous measure and the presence of PMR (Table 3). However, BMI < 18.5 kg/m² was significantly protective for the development of PMR (odds ratio [OR] 0.39, 95% confidence interval [CI] 0.16 – 0.98). The association between both BMI < 18.5 kg/m² and BMI ≥ 25 kg/m² at PMR incidence was similar for females and males, although not statistically significant (data not shown).

Influence of BMI on glucocorticoid requirements

There was no association between BMI measured continuously either at incidence (hazards ratio (HR) [14] 1.01; 95% CI 0.98–1.05) or preceding incidence (BMI #2, data not shown). Similarly, there was no association of BMI with glucocorticoid requirements when BMI was assessed as a categorical variable (HR for BMI < 18.5 kg/m² = 0.40; 95% CI 0.10–1.62; HR for BMI ≥ 25 kg/m² = 0.96; 95% CI 0.73–1.26). The results were similar after adjustment for ESR at index, smoking status, calendar year, number of ESR measurements during follow-up and development of GCA.

Association between BMI and the development of GCA

Seventeen patients developed GCA at or before PMR diagnosis and were excluded from this analysis. Of the remaining 347 PMR patients, 49 developed GCA during follow-up. No significant association between the BMI at incidence or prior to incidence and the development of GCA in patients with PMR was found (HR 0.95; 95% CI 0.88–1.02 for BMI at index; HR 0.92; 95% CI 0.85–1.00 for BMI #2). Categorization of BMI did not reveal a significant association with subsequent development of GCA (HR for BMI < 18.5 kg/m² = 1.58; 95% CI 0.37–6.67; HR for BMI ≥ 25 kg/m² = 1.41; 95% CI 0.78–2.54). Analyses adjusting for smoking, ESR at index and number of ESR measurements during follow-up did not reveal these factors to influence the development of GCA.

DISCUSSION

In this population based cohort, patients with high BMI (≥ 25 kg/m²) were not more likely to develop PMR. BMI did not influence the duration of glucocorticoid therapy or the occurrence of GCA.

To date, most of the studies of obesity and rheumatic disorders have not revealed an increased risk for rheumatic disease occurrence. Results from a cohort of patients with undifferentiated arthritis failed to demonstrate increased risk for developing rheumatoid arthritis in obese patients [3]. Indeed, elevated BMI was found to be protective from the presence of radiographic joint damage in the patients who did develop rheumatoid arthritis [3]. A case control study of systemic lupus erythematosus (SLE) revealed no difference in the BMI between patients with SLE versus controls [15], and there has been conflicting data about the correlation between elevated BMI and increased disease activity in these patients [4, 16]. Conversely, there have been several studies suggesting that obesity is an independent risk factor for the development of psoriasis [5, 17].

Our findings do not support the hypothesis that a high BMI may contribute to the development of the inflammatory condition, PMR. Elevated BMI also did not have an impact on the disease course as assessed by subsequent development of GCA or glucocorticoid treatment requirements as reflected in duration of therapy. Our study, like many others, used BMI as a surrogate marker for overall fat mass. The validity of BMI for this purpose has been questioned, as body composition and distribution of types of adipose tissue may be different in those with similar BMIs, a factor which should be taken into consideration when interpreting results [18]. Other measures of total body fat such as dual x-ray absorptiometry (DXA) or waist circumference may be more accurate when assessing the effect of adiposity on disease states [14].

Interestingly, although the numbers of patients were small, being underweight ($< 18.5 \text{ kg/m}^2$) was associated with a lower likelihood of developing PMR. This may be a chance finding, but it is possible that these patients may have a more favorable milieu of inflammatory mediators that inhibit the development of PMR. Low weight patients may have had other chronic illness and therefore were less likely to enter the cohort because their symptoms may not have been recognized as PMR; however, previous work with this particular cohort did not show an increased risk for chronic medical conditions such as malignancy, renal or liver disease [11].

To our knowledge, the effect of BMI on glucocorticoid requirement has not been examined. Continuous treatment for PMR in a population-based cohort over a defined period of greater than one year in most circumstances made this investigation possible. The lack of effect of BMI on glucocorticoid treatment duration may imply that any low grade inflammation associated with a high BMI in conjunction with an inflammatory condition like PMR has no bearing on glucocorticoid treatment requirements. This lack of effect would seem to suggest no association between BMI and a heightened inflammatory state. We did not however, assess the effect of BMI on total cumulative glucocorticoid doses used. Regardless, even after controlling for several variables, including ESR at index, smoking status, calendar year, number of ESR measurements during follow-up and development of GCA no association could be detected. Other factors such as variation in treatment practices between providers may play a role in total glucocorticoid duration.

The main strength of this study is the utilization of the Rochester Epidemiology database, which allows the ascertainment of complete medical data for a defined population (Olmsted

County, Minnesota). The PMR cohort is a large population-based incident cohort derived over a time period of 30-years.

Limitations of this study include the use of BMI as a surrogate marker for adiposity. Additionally, this is a retrospective study, which relies on data recorded in the medical record. There was a portion of weights missing, particularly in the PMR cohort preceding diagnosis (BMI #2). Analysis of the available data did show that BMI #2 was similar to the BMI at incidence (on average patients gained 0.23 kg/m² of BMI prior to the diagnosis of PMR), thus it is unlikely that there would be a significant impact of missing data on our primary findings of lack of association of BMI and risk of developing PMR. In addition, due to the small number of patients who developed GCA during follow-up, this study may not have adequate power to detect small associations between BMI and development of GCA.

As reflected in our findings of lack of association of high BMI and an increased risk for PMR, the effects of elevated BMI on rheumatic inflammatory conditions are complex and incompletely understood. The use of other measures for total body fat and molecular studies may help to clarify these relationships.

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Table 1

Characteristics of 364 Patients with Polymyalgia Rheumatica (PMR) and 364 non-PMR subjects

Variable	Non-PMR (N=364)	PMR (N=364)	P-value
Age, years	73.3 ± 8.5	73.4 ± 8.6	0.93
Female (%)	245 (67%)	244 (67%)	0.94
Length of follow-up, years	10.6 ± 7.4	11.9 ± 6.7	--
Smoking (%)			0.96
Never	198 (56%)	202 (56%)	
Current	55 (16%)	53 (15%)	
Former	101 (29%)	103 (29%)	

Table 2

BMI in PMR patients and non-PMR subjects

Variable	Non-PMR (N=364)	PMR (N=364)	P-value
BMI at index, kg/m ²	26.0 ± 5.4	25.9 ± 4.0	0.83
BMI #2 [*] , kg/m ²	26.2 ± 5.5	26.1 ± 4.1	0.66
BMI < 18.5 kg/m ² at index (%)	18 (5%)	7 (2%)	0.021
BMI ≥ 25 kg/m ² at index (%)	185 (53%)	200 (56%)	0.47
BMI #2 < 18.5 kg/m ² (%)	12 (4%)	5 (2%)	0.14
BMI #2 ≥ 25 kg/m ² (%)	175 (53%)	166 (57%)	0.39

^{*} BMI #2 corresponds to the value in the time preceding PMR incidence date by up to 3 years and ±3 years from index date in the non-PMR cohort.

[†] BMI #2 values were not available for 71 (20%) in the PMR cohort and 42 (12%) in the non-PMR cohort.

Table 3

Association between Body Mass Index (BMI) and Occurrence of Polymyalgia Rheumatica

Variable	Odds ratio	95% CI
BMI at index, kg/m ²	1.00	0.96 – 1.03
BMI<18.5 kg/m ² at index (%)	0.39	0.16 – 0.98
BMI ≥ 25 kg/m ² at index (%)	1.04	0.76 – 1.43

* adjusted for age, sex, calendar year of PMR incidence/index and smoking (never vs. former vs. current) – all adjustors were insignificantly associated with the presence of PMR.