Plasma Adipokine Levels and Their Association with Overall Burden of Painful Joints among Individuals with Hip and Knee Osteoarthritis

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ABSTRACT. ***Objective.*** To investigate the association between plasma adipokine levels and the burden of painful joints among individuals with hip and knee osteoarthritis (OA).

Methods. Adipokines (leptin, adiponectin, adipsin, resistin) were determined by ELISA (n = 78). Individuals reported painful joints on a homunculus. Associations were examined by sex-stratified Poisson analyses.

Results. Adjusted for age, body mass index, and hip/knee OA, higher leptin and adiponectin and lower adipsin levels were associated with greater painful joint burden (i.e., counts) among women ($p < 0.01$). Among men, higher resistin levels were associated with lower counts ($p = 0.03$).

Conclusion. Findings support the likelihood of a systemic-dependent sex-specific pain burden among individuals with OA. (J Rheumatol First Release Dec 15 2013; doi:10.3899/jrheum.130709)

Key Indexing Terms:
OSTEOARTHRITIS ADIPOKINES HIP KNEE JOINTS

While the etiology of osteoarthritis (OA) is not well understood[1], obesity has long been recognized as an important risk factor. Although the underlying mechanisms in this case are not fully known, mechanical factors are viewed as a likely important link for weight-bearing joints[2]. Findings of positive associations between obesity and OA in non-weight-bearing joints have suggested systemic links as well[1,3,4]. Finally, the common presence of multiple symptomatic joints (weight-bearing and otherwise) among individuals with late-stage OA in at least 1 joint[5,6] further contributes to a broader view that there are systemic components to OA[7].

White adipose tissue has been recognized as an important endocrine organ that secretes a wide variety of biologically active adipokines[8,9]. Thus, the metabolic link between obesity and OA has focused predominantly on adipokines. However, the focus has nearly exclusively been on associations with single joints. The association between joint pain, the primary symptom of OA, and adipokines also has been examined to some extent[10,11,12]. Again, however, the focus has been on individual joints; the extent of overall symptomatic joint burden has not been considered. We investigated the association between plasma levels of adipokines and the extent of painful joint involvement among patients with endstage hip and knee OA. Because differential associations between obesity and OA have been reported between men and women[13,14], our investigation was carried out separately in men and women.

MATERIALS AND METHODS

Subjects. Seventy-eight patients with late-stage hip or knee OA scheduled for joint replacement surgery were consecutively recruited from an academic hospital in Toronto, Canada. Eligibility criteria included being ≥ 18 years of age and having the ability to read and comprehend English. Individuals with inflammatory arthritis, those being treated for inflammatory conditions, or those with posttraumatic arthritis were ineligible. Participants were identified and diagnosis confirmed radiographically by participating surgeons.

The study was approved by the University Health Network Research Ethics Board. Written informed consent was obtained from all patients. A study health survey was completed prior to surgery.

Study outcome. Patients were asked to indicate on a homunculus all joints that were painful on most days for at least a month in the past 12 months. A count score was developed of symptomatic *regions* (e.g., no distinction between 1 and 2 hips; neck, spine, shoulders, elbows, wrists, hands, hips, knees, ankles, feet) not including the surgical joint (possible range of regional symptomatic joint count, 0–9).

The questionnaire also included height and weight, used to calculate body mass index (BMI; kg/m^2), and demographic characteristics including age and sex. An indicator variable reflecting presence of knee/hip OA was retained.

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Laboratory methods. Fasting blood was obtained from all patients prior to surgery, stored at –80°C, and analyzed in batch. Plasma concentrations of adipokines were quantitated by ELISA kits according to manufacturers' instructions (human leptin multiplex ELISA Adipokine Panel 2, Bio-Rad, and adiponectin, resistin, and adipsin multiplex ELISA Adipokine Panel 1, Bio-Rad). Samples were diluted as appropriate and assayed in duplicate in the same run.

Analysis. Analyses were sex-stratified. Mean age and median values of BMI and adipokines are presented for the sample. Bivariable associations between BMI and adipokine levels were examined using Spearman's correlation coefficient. Poisson regression analysis for count data (i.e., regional painful joint count) was used to assess the multivariable adjusted (age, BMI, knee/hip, adipokines) association between each adipokine concentration level and regional joint count. For comparative interpretability of regression estimates, the effects for leptin, adiponectin, and resistin represent effects for every 5-unit increase in concentration, while for adipsin it is for every unit increase. This was based on the average range of each adipokine concentration distribution, such that the estimates on average represent the effect of a decile increase over the respective concentration range.

RESULTS

Forty-five women and 33 men were enrolled. Sample descriptions are presented in Table 1. Regional symptomatic joint count (not including surgical joint) ranged from 0 to 8 among women, and from 0 to 5 among men. For adiponectin, resistin, adipsin, and leptin, the intraassay coefficients of variation were < 11.7%, < 10.1%, < 5.2%, and < 5.4%, respectively.

Significant Spearman's correlations were found between BMI and adipokine levels. Among women: leptin ($\rho = 0.58$, $p < 0.001$), adiponectin ($\rho = -0.15$, $p = 0.34$), adipsin ($\rho = 0.38$, $p = 0.011$), and resistin ($\rho = 0.37$, $p = 0.013$); and among men: leptin ($\rho = 0.68$, $p < 0.001$), adiponectin ($\rho = 0.06$, $p = 0.73$), adipsin ($\rho = 0.14$, $p = 0.44$), and resistin ($\rho = 0.31$, $p = 0.045$).

Results from adjusted analyses are presented in Table 2. The fit of the models was tested by way of goodness-of-fit chi-square test. For both women and men, the Poisson model form fit the data reasonably well ($p = 0.0604$ and 0.1462, respectively). Sex-stratified analyses were justified on the basis of finding significant interactions (data not shown) between sex and each adipokine level (all $p < 0.04$) except adipsin. Overall model fit was poor when interactions were not considered (goodness-of-fit test: chi-square = 113.4454, df = 67, $p = 0.0003$).

Among women, adjusted for age, BMI, and knee/hip OA, each 5 ng/ml increase in leptin and 5 μg/ml increase in adiponectin was significantly associated with a 15% and 18% increase, respectively, in regional symptomatic joint count. On the other hand, for each μg/ml increase in adipsin, regional symptomatic joint count was significantly reduced by 15%. Among men, only resistin was significantly associated with regional symptomatic joint count in adjusted analyses. Each 5 ng/ml increase in resistin was associated with a 15% decrease in regional symptomatic joint count.

Table 1. Sample description.

	Female, n = 45	Male, n = 33
Age, yrs, mean (± SD), range	64.7 (10.1), 43.9–82.8	61.4 (11.3), 43.7–88
	Median (range)	Median (range)
BMI	32.5 (21.1–52.4)	28.7 (20.2–48.5)
Leptin, ng/ml	26.3 (4.4–66.7)	7.1 (2–38.9)
Adiponectin, μg/ml	18 (4.5–54.7)	12.4 (2.5–47.6)
Adipsin, μg/ml	3.9 (2.6–15.2)	3.5 (0.8–6.5)
Resistin, ng/ml	26.6 (14.4–47.4)	26.1 (8.7–52)

BMI: body mass index.

DISCUSSION

Findings from our present study suggest that among individuals with hip and knee OA, there may be a "dose-response" association between overall painful joint burden and plasma levels of adipokines. However, differences in association were found between women and men.

Adipokines are emerging as modulators of rheumatic diseases by promoting and perpetuating inflammatory responses. While it is unknown whether the joint pain reported by our study participants is OA-related, other than for their hip or knee, leptin levels have been shown to be associated with pain severity among individuals with hand OA[15]. As well, leptin has been shown to act as a proinflammatory agent[16] with catabolic effects in joints affected by OA[17]. In recent work, serum leptin has been shown to be associated with prevalent and incident knee OA among women[18], and found to be positively correlated with the severity of knee OA[19]. In cross-sectional analyses, Ding, *et al* reported a negative association between serum leptin levels and knee cartilage volume, and Stannus, *et al* reported a positive association between serum leptin and hip joint space narrowing[20,21]. In both studies, the associations were more notable among women. Within the present sample, composed wholly of individuals with severe hip and knee OA, higher plasma leptin level was associated with overall greater painful joint burden among women. Among men, associations trended toward being negative, though not significantly.

The importance of adiponectin in the pathogenesis of OA has been supported by clinical observations. In patients with OA, plasma adiponectin levels have been reported significantly higher as compared to healthy controls[22], and were also higher among women with erosive hand OA as compared to those with nonerosive OA[23]. Nevertheless, the literature is inconsistent in this regard[15]. We report that among women with severe hip and knee OA, plasma levels of adiponectin were associated with overall greater painful joint burden. The differences in findings between studies are likely consequences both of varying study designs and of

Table 2. Multivariable adjusted associations between regional painful joint count (outcome) and adipokines; Poisson analysis.

Predictors	Count Ratio	Lower 95% CL	Upper 95% CL	p
Women				
Age	1.03	1.01	1.06	0.020
BMI	1.01	0.97	1.05	0.541
Knee vs hip	1.25	0.76	2.05	0.373
Leptin (per 5 ng/ml)	1.15	1.05	1.28	0.002
Adiponectin (per 5 μg/ml)	1.18	1.06	1.31	0.003
Adipsin (per 1 μg/ml)	0.85	0.75	0.96	0.009
Resistin (per 5 ng/ml)	1.06	0.93	1.20	0.361
Men				
Age	1.02	0.98	1.05	0.402
BMI	1.03	0.93	1.14	0.533
Knee vs hip	0.92	0.43	1.95	0.818
Leptin (per 5 ng/ml)	0.86	0.67	1.11	0.249
Adiponectin (per 5 μg/ml)	0.87	0.72	1.05	0.156
Adipsin (per 1 μg/ml)	0.96	0.79	1.18	0.719
Resistin (per 5 ng/ml)	0.85	0.74	0.99	0.031

CL: confidence limits; BMI: body mass index.

variability in disease stages across samples[15]. As well, the association between adiponectin and pain specifically is not well understood.

Serum resistin levels have been shown to be higher among individuals with severe knee OA as compared to controls with no OA[24]. In that study, female sex was associated with higher leptin and adiponectin serum levels, but no association was found between sex and resistin levels. Similarly, in our present study, serum levels of leptin and adiponectin were higher in women, although little difference was observed between sexes for resistin and adipsin. We found that serum resistin level was significantly associated with regional symptomatic joint count only in men, with higher levels associated with a lower overall count. While previous work has not examined serum levels as they relate to overall symptomatic joint burden, among women, higher serum resistin levels have been reported to be associated with radiographic changes in hand OA[25]. Nevertheless, the role (or lack thereof) of resistin in OA pathogenesis and its association with pain is not clear[15]. The differences we identify between sexes may explain some of the inconsistencies in the literature, particularly where samples are comprised and analyzed considering men and women together. Finally, minimal work has examined the role of adipsin in OA. Among patients scheduled to undergo knee replacement, adipsin in the synovial fluid has been characterized as antiinflammatory[26], and serum levels have been shown to be higher among individuals with OA compared to those without[27].

These study results further support the view that systemic effects may be operational among individuals with OA. Unlike previous studies focused exclusively on single joints, this work suggests that overall symptomatic joint burden among individuals with established OA in the hip or knee may reflect an underlying metabolic systemic phenotype, and further suggests that the characteristics of this phenotype may be sex-specific. Interestingly, with adipokine levels considered, BMI did not exhibit an independent effect on symptomatic joint count. We note, however, that height and weight were self-reported. The extent to which individuals overestimate their height and/or underestimate their weight influences BMI estimates downward. Nevertheless, this is unlikely to affect estimates relating adipokine levels and symptomatic joint count.

The number of patients in our study was relatively small, precluding the drawing of definitive conclusions on the association between circulating levels of adipokines and the extent of symptomatic joint burden. Despite the small size, statistically significant associations were observed, and thus further investigations are warranted. While all patients had severe hip or knee OA, duration of disease was not assessed, and thus uncontrolled for in adjusted analyses. These were cross-sectional findings, and thus causality could not be determined; higher or lower adipokine concentrations can be the cause or the result of OA and/or joint pain (number of joints reported on a homunculus as painful does not mean these joint regions are necessarily affected by the disease). Finally, adipokines have isoforms, and different isoforms may have different biological properties. However, in our study we assessed only totals.

Joint pain in OA as a systemic disorder entails a need to reevaluate OA treatment and management strategies, with consideration for multimodal approaches. Systemic factors may also help explain high levels of comorbidity in OA populations and may be targets for comorbidity prevention.

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