Metabolic Syndrome and the Functional Outcomes of Hip and Knee Arthroplasty

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ABSTRACT. ***Objective.*** Patients with an elevated systemic inflammatory state are known to report greater pain with knee osteoarthritis (OA). We investigated the influence of risk factors of metabolic syndrome (MetS) on patient function before and after hip and knee replacement surgery.

Methods. A total of 677 consecutive patients with primary knee replacement and 547 consecutive patients with primary hip replacement with at least one MetS risk factor were reviewed from our joint registry. Demographic variables of age, sex, and comorbidity were retrieved. MetS risk factors were defined as body mass index (BMI) > 30 kg/m^2, diabetes, hypertension, and hypercholesterolemia. Baseline and 1-year Western Ontario McMaster University Osteoarthritis Index (WOMAC) scores were compared across patients by number of MetS risk factors, ranging from 1 to 4. Linear regression modeling was used to evaluate the effects of the MetS risk groups and the individual metabolic abnormalities on predicting baseline and 1-year WOMAC scores. Knee and hip patients were reviewed separately.

Results. The knee and hip patients showed a significant difference in sex distribution, BMI, and mean comorbidity across risk groups ($p < 0.05$). Unadjusted analysis showed that baseline and 1-year WOMAC scores, for both knee and hip patients, increased significantly with increasing number of MetS risk factors ($p < 0.05$). The linear regression model with the individual metabolic abnormalities was found to be more predictive of outcome than one with the number of MetS risk factors. Hypertension and obesity were the metabolic factors most predictive of a poorer outcome following hip surgery as compared to just obesity for knee patients.

Conclusion. Patient function following joint replacement surgery, particularly hip surgery, is negatively affected by metabolic abnormalities perhaps secondary to the systemic proinflammatory state. This knowledge should be used when counseling patients prior to surgery. (First Release July 15 2010; J Rheumatol 2010;37:1917–22; doi:10.3899/jrheum.091242)

Key Indexing Terms:
METABOLIC SYNDROME HIP ARTHROPLASTY KNEE ARTHROPLASTY
OUTCOMES OSTEOARTHRITIS

Risk factors defining the metabolic syndrome (MetS) are central adiposity, hypertension, elevated fasting glucose, and dyslipidemia defined as high triglyceride and low high-density lipoprotein (HDL) cholesterol[1,2]. Patients with MetS are known to have an elevated level of systemic inflammation that increases their risk for cardiovascular disease, thromboembolic disease, and colon cancer[1,3,4,5].

The relationship between MetS and systemic inflammation formed the basis for the hypothesis of this study. Adipose tissue has been shown to secrete mediators into the systemic circulation, such as tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and C-reactive protein (CRP), which induces a proinflammatory state and mediates insulin resistance[6,7,8,9]. Insulin resistance further promotes systemic inflammation through increased lipolysis and elevated systemic levels of free fatty acids. Moreover, adipocytes release the hormone leptin, which further promotes systemic inflammation[10,11]. Thus a negative cycle of obesity, insulin resistance, lipolysis, and systemic inflammation is created[12].

The orthopedic manifestation of this systemic inflammation has been examined in only a few studies. One group has shown that elevated systemic CRP is associated with increased knee joint inflammation[13]; others showed that elevated systemic CRP is associated with greater patient-reported pain with knee osteoarthritis (OA)[14]. The incidence of ongoing pain 1 year after joint replacement surgery ranges from 5% to 15% despite no clinical and radiographic abnormalities[15,16]. The question of whether this heightened inflammatory state and the MetS affect joint replacement outcomes has not been examined.

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Our primary objective was to determine if there was a relationship between 1-year functional outcome scores following knee and hip replacement surgery and the number of MetS risk factors. Our secondary objective was to determine which metabolic risk factors have the greatest influence on surgical outcomes. We hypothesized that those with the greatest number of MetS risk factors would demonstrate the poorest function at 1 year after surgery.

MATERIALS AND METHODS

As part of our prospective database, patients are recruited from a single Canadian academic institution, the Toronto Western Hospital, while on a waiting list for primary knee and hip replacement surgery. This registry was designed to track longitudinal patient outcomes of surgery. All patients give informed consent to have their data stored in a registry. Our inclusion criteria for this study were age at least 18 years with a diagnosis of primary or secondary OA, and unilateral joint replacement surgery. There were few patients with zero metabolic abnormalities in our study group; these patients were excluded. The study protocol was approved by the Human Subject Review Committee.

All surgeries were performed by one of 3 fellowship trained arthroplasty surgeons between the years 1998 and 2006. Surgical technique was similar among the 3 surgeons including use of tourniquet (knees), operating room with laminar air flow, and implants used. All patients were encouraged to begin ambulation on the first postoperative day.

Data collection. Baseline demographic data of age, sex, height, weight, and medical comorbidity are recorded in the database by patient self-report. Body mass index (BMI) was then calculated as weight (kg) divided by height (m^2). We defined comorbidity by the 14 categories of chronic illness taken from the Modified Cumulative Illness Rating Scale (CIRS)[17,18]. The CIRS comprises cardiac, vascular, hematological, respiratory, otorhinolaryngological and ophthalmological, upper gastrointestinal, lower gastrointestinal, hepatic and pancreatic, renal, genitourinary, musculoskeletal and tegumental, neurological, endocrine and metabolic, and psychiatric systems. Specifically, patients are asked if they have ever been diagnosed with diabetes, hypertension, or hypercholesterolemia.

The American Heart Association defines MetS as having 3 or more of the following[19]: increased waist circumference: men > 102 cm, women > 88 cm; elevated triglycerides > 150 mg/dl; reduced HDL cholesterol: men < 40 mg/dl, women < 50 mg/dl; elevated blood pressure > 130/85 mm Hg; and elevated fasting glucose > 100 mg/dl.

The World Health Organization (WHO) defines MetS as[20]: insulin resistance (type II diabetes, impaired fasting glucose), plus any 2 of the following risk factors: elevated blood pressure; plasma triglyceride > 150 mg/dl; HDL < 35 mg/dl (men), < 40 mg/dl (women); BMI > 30 and/or waist/hip circumference > 0.9 (men), > 0.85 (women); and urinary albumin > 20 mg/min; Alb/Cr > 30 mg/g.

As part of our registry, we did not routinely collect serum values of cholesterol, fasting glucose, blood pressure, or waist circumference measurements. We therefore classified MetS in our study based on BMI > 30 kg/m^2 and patient self-reported diagnosis of hypercholesterolemia, hypertension, and diabetes.

Patient functional status was assessed preoperatively and at 1-year followup with the Western Ontario McMaster University Osteoarthritis Index (WOMAC) score[21]; higher score on the WOMAC scale represents poorer function or greater pain. The psychometric properties of the WOMAC score including reliability, validity, and responsiveness are all well established in an OA population[21].

Statistical analysis. Continuous data such as age, BMI, and WOMAC scores were compared between multiple groups using analysis of variance (ANOVA) as all data were found to be normally distributed. Means and standard deviations are reported for all continuous variables. Categorical data such as gender are reported with frequencies and groups were compared with Fisher's exact test.

Linear regression modeling was used to examine the influence of the number of MetS risk factors on predicting preoperative and postoperative total WOMAC scores. Indicator variables were created for the ordinal predictor of the number of MetS risk factors. The group with 1 risk factor was taken as the reference group. The remaining variables entered into the models were age, sex, comorbidity, and baseline total WOMAC score when the 1-year WOMAC score was the dependent variable. Comorbidity was coded as the number of categories of the CIRS endorsed, excluding hypertension, hypercholesterolemia, and diabetes. The results of this model were compared to one predicting 1-year total WOMAC scores by the individual metabolic abnormalities. The predictive factors of interest were BMI, hypertension, hypercholesterolemia, and diabetes. BMI was coded as a binary variable in the model as obese (BMI > 30 kg/m^2) and nonobese (BMI < 30 kg/m^2). The model was adjusted for age, sex, baseline total WOMAC scores, and comorbidity. Comorbidity was again coded as the number categories of the CIRS endorsed, excluding hypertension, hypercholesterolemia, and diabetes. Separate analyses were conducted for the knee and hip patients.

All statistical analyses were performed with SPSS version 13.0 (SPSS, Chicago, IL, USA). Unstandardized beta coefficients and 95% confidence intervals are reported for regression modeling. All reported p values are 2-tailed with alpha = 0.05.

RESULTS

In our registry, we had complete outcomes data on 1596 out of 1915 (83.3%) patients that comprised our study cohort. There were data for 889 knees and 707 hips for analysis. Responders were not significantly different from nonresponders in age, sex, BMI, or comorbidity ($p > 0.05$).

At the time of surgery, there were significant differences between risk groups for sex, BMI, and comorbidity for both the knee and hip patients ($p < 0.05$). There were no differences in mean age across risk groups (Tables 1 and 2).

For the knee cohort, the baseline total WOMAC scores showed significant differences between groups, with increasing scores for increasing number of MetS risk factors. Postoperatively, there was a similar trend in all categories of WOMAC scores, with the highest scores in the group with all 4 MetS risk factors ($p < 0.05$; Table 3).

The hip cohort demonstrated a pattern similar to the knee cohort, with increasing WOMAC scores with a greater number of MetS risk factors, both preoperatively and postoperatively (Table 4).

Linear regression modeling showed that prior to knee surgery, those patients with 3 MetS risk factors demonstrated significantly higher total WOMAC scores adjusted for age, sex, and comorbidity, compared to those with 1 MetS risk factor: odds ratio 3.5 (95% CI 1.1, 8.2; $p = 0.03$; Table 5). Postoperatively, the number of MetS risk factors was not predictive of total WOMAC scores ($p > 0.05$; Table 5).

For the hip cohort, prior to surgery those patients with all 4 MetS risk factors demonstrated significantly higher total WOMAC scores compared to the reference group (1 MetS risk factor): 16.1 (95% CI 1.9, 30.8; $p = 0.04$; Table 5). After surgery, patients with 2 and 4 MetS risk factors had significantly higher WOMAC scores than the reference group,

Table 1. Demographic data compared across number of MetS factors for patients with knee OA.

Characteristic	1 MetS Factor, n = 349	2 MetS Factors, n = 240	3 MetS Factors, n = 165	4 MetS Factors, n = 135	p
Mean age, yrs (SD)	65.9 (13.6)	67.0 (10.7)	67.5 (10.1)	67.2 (6.5)	0.68
Male, %	46	38	23	43	0.005
BMI, kg/m^2 (SD)	25.5 (3.2)	30.8 (6.1)	34.4 (6.0)	38.5 (6.1)	0.0001
Mean comorbidity (SD)	2.1 (1.1)	2.9 (1.5)	3.5 (1.7)	4.9 (1.6)	0.0001

BMI: body mass index.

Table 2. Demographic data compared across number of MetS factors for patients with hip OA.

Characteristic	1 MetS Factor, n = 265	2 MetS Factors, n = 212	3 MetS Factors, n = 141	4 MetS Factors, n = 89	p
Mean age, yrs (SD)	64.8 (12.5)	65.5 (11.1)	66.1 (12.0)	66.2 (11.7)	0.74
Male, %	39	34	46	41	0.04
BMI, kg/m^2 (SD)	22.0 (3.3)	23.3 (4.8)	29.1 (6.9)	36.6 (4.0)	0.0001
Mean comorbidity (SD)	1.8 (1.2)	3.4 (1.5)	3.7 (1.4)	5.2 (2.1)	0.0001

BMI: body mass index.

Table 3. Baseline and 1-year Western Ontario McMaster University Osteoarthritis Index (WOMAC) scores (SD) compared across number of MetS risk factors for patients with knee OA.

Characteristic	1 MetS Factor, n = 349	2 MetS Factors, n = 240	3 MetS Factors, n = 165	4 MetS Factors, n = 135	p
WOMAC baseline					
Pain	10.3 (4.0)	10.5 (3.9)	11.3 (4.4)	15.3 (15.4)	0.04
Function	41.8 (14.6)	41.7 (14.2)	46.0 (15.7)	55.8 (15.4)	0.04
Total	52.0 (17.9)	52.2 (17.6)	57.1 (19.6)	67.2 (16.1)	0.03
WOMAC 1-year					
Pain	2.8 (1.4)	3.1 (2.6)	4.2 (4.0)	5.8 (4.7)	0.02
Function	14.1 (13.1)	16.5 (13.9)	19.1 (17.9)	28.7 (18.9)	0.006
Total	16.9 (15.9)	19.7 (16.8)	23.4 (20.7)	34.5 (23.5)	0.006

Table 4. Baseline and 1-year Western Ontario McMaster University Osteoarthritis Index (WOMAC) scores (SD) compared across number of MetS risk factors for patients with hip OA.

Characteristic	1 MetS Factor, n = 265	2 MetS Factors, n = 212	3 MetS Factors, n = 141	4 MetS Factors, n = 89	p
WOMAC baseline					
Pain	10.1 (3.9)	10.7 (3.6)	11.7 (3.3)	11.8 (3.6)	0.001
Function	41.6 (15.3)	42.7 (14.7)	44.0 (15.1)	48.9 (14.1)	0.001
Total	49.7 (17.9)	50.9 (17.1)	52.9 (17.9)	58.1 (16.6)	0.001
WOMAC 1-year					
Pain	4.3 (2.4)	4.8 (3.4)	5.2 (3.8)	6.6 (3.6)	0.06
Function	19.1 (10.8)	21.8 (14.0)	22.1 (14.3)	27.1 (13.7)	0.03
Total	22.7 (13.0)	26.4 (17.0)	26.5 (17.6)	33.5 (16.7)	0.01

adjusted for age, sex, comorbidity, and preoperative total WOMAC score: 3.1 (95% CI 0.3, 5.1; p = 0.03) and 15.0 (95% CI 1.4, 28.1; p = 0.04; Table 5), respectively.

For the models where the individual metabolic factors were entered, obesity (2.4, 95% CI 1.4, 4.2; p = 0.03; Table 6) and hypertension (7.3, 95% CI 2.4, 13.2; p = 0.006; Table 6) were found to be significant predictors of less functional improvement at 1 year following hip replacement surgery. For the knee cohort, only obesity (3.6, 95% CI 0.02, 7.2; p = 0.04; Table 6) significantly predicted diminished 1-year outcome.

Comparing the 2 regression models, one with the number of metabolic abnormalities entered and one with the individual metabolic abnormalities entered, the latter was found

Table 5. Linear regression modeling predicting preoperative and postoperative total Western Ontario McMaster University Osteoarthritis Index (WOMAC) scores for knee and hip patients by number of metabolic abnormalities, adjusted for age, sex, and comorbidity. Postoperative WOMAC scores are also adjusted for preoperative WOMAC scores.

	Beta Coefficients (95% CI) Predicting Preoperative WOMAC Scores	p	Beta Coefficients (95% CI) Predicting 1-year WOMAC Scores	p
Knees				
MetS 2 risk factors	3.0 (–1.3, 7.9)	0.69	3.3 (–0.8, 7.5)	0.12
MetS 3 risk factors	3.5 (1.1, 8.2)	0.03	0.3 (–4.7, 5.2)	0.93
MetS 4 risk factors	3.2 (–1.2, 9.4)	0.29	7.6 (–0.8, 16.0)	0.08
Hips				
MetS 2 risk factors	0.6 (–2.8, 2.7)	0.63	3.1 (0.3, 5.1)	0.03
MetS 3 risk factors	2.7 (–3.9, 9.1)	0.86	0.4 (–6.1, 5.3)	0.24
MetS 4 risk factors	16.1 (1.9, 30.8)	0.04	15.0 (1.4, 28.1)	0.04

Postoperative model R^2 knees: 0.29; hips: 0.32. MetS: metabolic syndrome.

Table 6. Linear regression modeling predicting postoperative total Western Ontario McMaster University Osteoarthritis Index (WOMAC) scores for knee and hip patients by metabolic abnormalities, adjusted for age, sex, preoperative total WOMAC scores, and comorbidity.

	Beta Coefficients (95% CI) Predicting 1-year WOMAC Scores	p
Knees		
Hypertension	–3.1 (–8.4, 2.5)	0.29
Obesity	3.6 (0.02, 7.2)	0.04
Hypercholesterolemia	3.1 (–2.3, 8.4)	0.18
Diabetes	4.4 (0.5, 7.2)	0.07
Hips		
Hypertension	7.3 (2.4, 13.2)	0.006
Obesity	2.4 (1.4, 4.2)	0.03
Hypercholesterolemia	4.5 (–0.2, 8.9)	0.08
Diabetes	–2.3 (–8.3, 3.7)	0.46

Model R^2 knees: 0.34. Model R^2 hips: 0.41.

to better predict postoperative joint replacement outcomes, based on the model R^2 values given in Tables 5 and 6.

DISCUSSION

Investigators have recently suggested that OA is not simply an isolated joint disease but may be related to a systemic, proinflammatory state. The proposed pathologic mechanisms involve the associations of insulin resistance[22], adipokines such as leptin and adiponectin[23,24,25], serum lipid balance[26], and atheromatous vascular disease[27]. In our study, we found that WOMAC scores showed a trend to increasing joint pain and dysfunction with a higher number of MetS risk factors in both knee and hip patients, pre and postoperatively. After adjustment for relevant covariates, patients with all 4 MetS risk factors who presented for knee and hip replacement surgery had significantly higher total WOMAC scores than patients with only 1 MetS risk factor. The presence of all 4 MetS risk factors also predicted a poorer outcome following hip replacement surgery, driven largely by obesity and hypertension.

Those with MetS are known to have elevated circulating levels of proinflammatory markers such as IL-6 and CRP[12]. The elevated systemic inflammatory state in MetS has been shown to be associated with prevalent myocardial infarction[28], stroke[28], and the incidence of cognitive decline[29]. This inflammation has also been linked to increased joint pain in patients with knee OA[13,14]. Our study suggests that the elevated systemic inflammation associated with these metabolic risk factors may affect the outcomes of joint replacement surgery. Much attention has been focused on patient dissatisfaction following joint replacement surgery[30,31,32]; however, no research has examined the relationship between systemic and joint inflammation as a predictor of ongoing pain.

There are conflicting reports discussing the influence of each MetS risk factor in predicting outcomes of joint replacement surgery. Some authors suggest that higher BMI predicts poorer outcome following surgery[33], while most have found no negative association with short-term outcomes[34,35], longterm outcomes[36,37], or implant survivorship[34,36]. We found that higher BMI predicted a diminished functional improvement following both hip and knee replacement surgery. Reports on the effect of comorbidity on functional outcomes also show no consensus[38,39,40]. No studies have specifically looked at the influence of hypertension or hypercholesterolemia on outcomes. Surgical outcomes in diabetic patients have not been well investigated, but these patients have been shown to obtain the same relative benefit from joint replacement surgery as those without diabetes[41,42]. This supports our finding that hypertension, but not diabetes or high cholesterol, predicted less functional improvement following hip replacement surgery. Klein, *et al* performed a stratified analysis similar to our study, examining the risk of cardiovascular disease with an increasing

number of MetS risk factors[43]. Similar to our study, they found a graded risk with an increasing number of risk factors, with the greatest difference in patients having all 4 MetS risk factors[43].

One potential limitation of our study is how we have defined MetS. We did not measure patient blood pressure or serum HDL and triglyceride levels; instead, we used patient report of a history of diagnosis of hypertension and hypercholesterolemia. Our definition may overlook those with undiagnosed comorbidity at the time of surgery; however, we believe that any systematic misclassification resulting in a selection bias was minimal. Second, we studied a patient population from a high-volume tertiary care joint arthroplasty hospital and thus our results are only directly generalizable to a similar population. Third, although we adjusted for relevant factors that may confound the relationship between the metabolic factors and joint function, there was still potential for residual confounding from unmeasured factors. We believe the association we found is likely clinically relevant as a predictor of surgical outcomes.

In summary, patients with MetS who present for knee and hip replacement surgery have greater pain and dysfunction. The regression model with the individual metabolic abnormalities was found to be more predictive of outcome than one with the number of risk factors present. Obesity and hypertension are important predictors for hip surgery outcomes, compared to just obesity for knee surgery. This knowledge should be used in counseling patients prior to surgery to set appropriate expectations. Further work should be directed to understanding the relationship between systemic and joint inflammation and pain following joint replacement surgery.

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