Metabolic Syndrome and the Incidence of Symptomatic Deep Vein Thrombosis Following Total Knee Arthroplasty

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ABSTRACT. ***Objective.*** We asked if patients with metabolic syndrome undergoing total knee replacement (TKR) have an increased risk for symptomatic deep vein thrombosis (DVT) at 3 months followup.

Methods. We reviewed 1460 patients from our joint registry undergoing primary, unilateral TKR between 1998-2006. Demographic variables of age, sex, comorbidity, and education were retrieved. Metabolic syndrome was defined as body mass index above 30 kg/m^2, diabetes, hypertension, and hypercholesterolemia. Logistic regression was used to examine the relationship of metabolic syndrome on the incidence of DVT.

Results. The overall incidence of symptomatic DVT was 4.4% (65/1460). Patients with metabolic syndrome had an increased incidence of DVT compared to those without metabolic syndrome (15.5% vs 3.4%). Adjusted analysis showed that the risk of symptomatic DVT in patients with metabolic syndrome was 3.2 times [odds ratio 3.2, 95% CI (1.0,15.4), p = 0.04] the risk in those without metabolic syndrome.

Conclusion. Hospital protocols developed for prophylactic anticoagulation following TKR should give special consideration to patients with metabolic syndrome. (First Release August 15 2009; J Rheumatol 2009;36:2298–301; doi:10.3899/jrheum.090282)

Key Indexing Terms:
METABOLIC SYNDROME DEEP VEIN THROMBOSIS KNEE ARTHROPLASTY

The incidence of asymptomatic deep vein thrombosis (DVT) following total knee replacement (TKR) ranges from 40 to 84% without prophylaxis[1]. Prophylaxis with low molecular weight heparin (LMWH) decreases that incidence to about 30% in TKR[2-5]. The incidence of symptomatic DVT following TKR is 2.1% with the use of thromboprophylaxis[6]. The incidence of fatal pulmonary embolus (PE) is estimated at 0.5-2.0%[7-12].

Prophylactic measures for DVT following joint arthroplasty include early ambulation, mechanical compression devices, and pharmacologic agents. Clinical risk factors for DVT include increasing age, immobility, a history of DVT/PE, obesity, congestive heart failure, and hypercoagulable states such as protein C and protein S deficiency[13,14].

Metabolic syndrome is defined as central adiposity, elevated fasting glucose level, hypertension, and dyslipidemia defined as high triglyceride and low high-density lipoprotein (HDL) cholesterol[15,16]. Patients having at least 3 of these 5 criteria are at 1.5 to 2-fold increased risk of cardiovascular disease[16]. The underlying etiology of the metabolic syndrome recognizes adipose tissue as an active endocrine organ that expresses tumor necrosis factor (TNF)-α, interleukin (IL)-6, and C-reactive protein (CRP), which together induce a proinflammatory state that mediates insulin resistance[17-20]. Moreover, metabolic syndrome is associated with a systemic prothrombotic state[15,21-23]. A few studies have shown that there is an increased incidence of DVT in those with metabolic syndrome; however, this has not been explored as a risk factor following TKR[24-26].

We asked if the incidence of symptomatic DVT following TKR is greater in those patients with metabolic syndrome compared to those without metabolic syndrome at 3 months followup.

MATERIALS AND METHODS

As part of our prospective total joint replacement registry, patients are recruited from a single Canadian academic institution, the Toronto Western Hospital, while on a waiting list for primary knee replacement surgery. All patients give informed consent to participate in the registry. Our inclusion criteria for this study were: age years 18 and above and diagnosis of primary or secondary osteoarthritis. The study protocol was approved by the Human Subject Review Committee.

All surgeries were performed by 1 of 3 fellowship trained arthroplasty surgeons between 1998-2006. Surgical technique was similar among the 3

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surgeons including use of tourniquet, operating room with laminar air flow, and implants used. All patients had a regional anesthetic. All patients received a standard protocol 14 days of LMWH for thrombosis prophylaxis started on the first postoperative day. No patients used mechanical compression devices. All patients were encouraged to begin ambulation on the first postoperative day.

The diagnosis of DVT was made after the patient was assessed by a physician, who ordered a Doppler ultrasound based on the clinical symptoms of excessive pain and swelling that did not suggest infection or simple hematoma. We recorded the incidence of symptomatic DVT within the first 3 months of knee replacement surgery.

A positive Doppler study was one demonstrating a complete filling defect in a noncompressible deep vein. We report only proximal DVT defined as proximal to the trifurcation of the popliteal artery. Clots found distal to the trifurcation are considered not clinically significant in our orthopedic practice and so they are not treated with chemical anticoagulation.

Collection of data. Baseline demographic data of age, sex, body mass index (BMI), and medical comorbidity are recorded in the database by patient self report. Education was recorded as either higher education level (university or above) or low education level (high school or below). Medical comorbidity was scored on the Charlson Comorbidity Illness Index[27]. The Charlson Index was first developed in 1987 and encompasses 19 medical conditions weighted on a scale from 1–6. A higher score represents a poorer state of health. Given the low frequency of comorbidity in this sample, the data was collapsed in 4 categories, a score of 0, 1, 2, or > 3.

The World Health Organization (WHO)[28] defines metabolic syndrome as insulin resistance (type 2 diabetes, impaired fasting glucose, impaired glucose tolerance) plus any 2 of the following: 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.

The American Heart Association defines metabolic syndrome as those with 3 or more of the following[29]: 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. Our patients with metabolic syndrome had a BMI ≥ 30 kg/m^2, diabetes, hypertension, and hypercholesterolemia.

Functional status and pain level were assessed pre-operatively with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) function and pain scores, respectively[30]. A greater score on the WOMAC scale represents poorer function or greater pain. The WOMAC score has been well validated for use in an osteoarthritis population[30].

Statistical analysis. Continuous data such as age, BMI, and WOMAC pain and function scores were compared between groups using t-tests as all data were found to be normally distributed. Means and standard deviations are reported for all continuous variables. Categorical data such as sex, education, and incidence of symptomatic DVT are reported as frequencies, and groups were compared with Fisher's exact test.

Multivariable logistic regression modeling was performed to determine the effect of metabolic syndrome on the incidence of symptomatic DVT. The covariates entered into the model were age, sex, education, BMI, Charlson Index, and diagnosis of metabolic syndrome.

All statistical analysis was performed with SPSS version 13.0 (Chicago, IL, USA). Odds ratios (OR) for regression modeling and their 95% confidence intervals (CI) are reported. All reported p values are 2-tailed with an alpha of 0.05.

RESULTS

In our registry, we had complete outcomes data on 1460 out of 1625 (89.8%) patients that comprised our study cohort. Responders were not significantly different from non-responders in age, BMI, sex, or comorbidity.

At the time of surgery, there were no differences between groups for age, sex, or baseline functional status ($p > 0.05$). The patients with metabolic syndrome had a significantly greater BMI at 32.8 kg/m^2 compared to 30.4 kg/m^2 in those without metabolic syndrome (Table 1).

The symptomatic DVT rate was 66/1470 (4.5%) overall, 21/135 (15.5%) in the metabolic syndrome group and 45/1325 (3.4%) in the patients without metabolic syndrome ($p < 0.001$). There were no differences in WOMAC scores between groups at 1-year followup ($p > 0.05$).

Logistic regression modeling showed that metabolic syndrome was a significant predictor of symptomatic DVT after joint replacement surgery, adjusted for age, sex, BMI, Charlson Index, and education [OR = 3.2, 95% CI (1.0, 15.4), p = 0.04; Table 2].

DISCUSSION

Our study shows that patients with metabolic syndrome, defined as hypertension, hypercholesterolemia, diabetes, and obesity, are at a 3-fold increased risk for symptomatic DVT following knee replacement surgery compared to those without metabolic syndrome. Previous work examining the patient level predictors for DVT following joint replacement identified elevated BMI[31,32], comorbidity as measured by the American Society of Anesthesiologists scale[32], and sex[31]. Other investigators, however, failed to identify any patient characteristics predicting breakthrough DVT[33]. In our model, we adjusted for BMI and medical comorbidity and therefore there is an independent effect of metabolic syndrome over and above the individual risk factors of the syndrome.

Patients with metabolic syndrome have been shown to be in a chronically elevated systemic inflammatory state and prothrombotic state[21-23]. Through both genetic and acquired characteristics, metabolic syndrome has been linked to other diseases such chronic kidney disease, cholesterol gallstones, polycystic ovary disease, and sleep apnea[15,16,34]. Parvizi, *et al*[35] showed that patients with metabolic syndrome were at a 1.5 times greater risk for PE following hip and knee replacement surgery[35]. In the medical literature, patients with metabolic syndrome have been shown to be at a 2-fold increased risk of venous thromboembolism (VTE) compared to those without metabolic syndrome[24-26]. This is an important area of study as joint arthroplasty patients are known to be at a very high risk for DVT following surgery.

The ideal VTE prophylactic regimen following joint arthroplasty is not clear as the selection of an appropriate agent is a balance between efficacy, the risk of bleeding, patient compliance, cost, and ease of administration. Lieberman and Hsu wrote that they believe patients should be stratified according to risk to select the most appropriate agent and duration of prophylaxis[36]. We believe that patients with metabolic syndrome should be considered at a greater risk for VTE following TKR and this should be considered when deciding on an appropriate prophylactic regimen.

Table 1. Unadjusted analysis comparing demographic and baseline functional outcome scores between patients with and without metabolic syndrome.

	Metabolic Syndrome, n = 135	Without Metabolic Syndrome, n = 1325	p
Mean Age (SD)	66.1 (9.2)	66.6 (9.9)	0.85
% Male	33.0	36.5	0.57
Mean BMI, kg/m^2 (SD)	32.8 (2.1)	30.4 (6.8)	0.02
Preoperative WOMAC scores			
WOMAC total	55.8 (15.2)	53.4 (17.9)	0.16
WOMAC pain	15.3 (15.4)	10.5 (3.8)	0.63

SD: standard deviation; BMI: body mass index; WOMAC: Western Ontario and McMaster Universities osteoarthritis Index.

Table 2. Logistic regression model predicting incidence of symptomatic DVT by age, sex, education, metabolic syndrome, diabetes, hypertension, hypercholesterolemia, comorbidity, and BMI.

	Odds Ratio (95% CI)	p
Age	0.9 (0.87, 1.0)	0.32
Sex	3.4 (0.4, 18.5)	0.78
Education	4.1 (0.8, 20.6)	0.14
Metabolic syndrome	3.0 (1.1, 12.4)	0.04
Diabetes	3.1 (0.4, 21.9)	0.26
Hypertension	2.3 (0.6, 32.2)	0.63
Hypercholesterolemia	1.6 (0.2, 33.5)	0.72
Body mass index (BMI)	1.1 (0.9, 1.3)	0.35
Comorbidity	1.3 (0.9, 2.2)	0.19

DVT: deep vein thrombosis; CI: confidence interval.

One potential limitation of our study is that we have not measured patient blood pressure or serum HDL and triglyceride levels; instead, we used patient reported history of a diagnosis of hypertension and hypercholesterolemia. Measuring these values in patients receiving pharmacotherapy would give a false profile of the patients' risk, and thus we believe that relying on patient self report for a past diagnosis preserves the validity and generalizability of our findings. Second, we did not perform routine venography on all patients to measure the asymptomatic DVT rate in both groups. Our study better represents clinical practice — venography is not routinely performed and we tested only those with clinical symptoms. We rely on Doppler ultrasound for the diagnosis of DVT in our patient population; however, this again represents routine clinical practice and has been shown to be a reliable diagnostic tool in this population[37-39]. Moreover, a consistent relationship has been shown between venography proven asymptomatic DVT and symptomatic DVT diagnosed by Doppler ultrasound in TKR[40]. It should be noted that we are not reporting on the total incidence of VTE following TKR, but rather the symptomatic proximal DVT rate.

Patients with metabolic syndrome demonstrated a 3-fold greater risk for symptomatic DVT following TKR in our study. We believe that protocols developed for DVT prophylaxis should give special consideration to patients with metabolic syndrome.

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