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Serum Inflammatory Markers for Periprosthetic Knee Infection in Obese Versus Non-Obese Patients

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ABSTRACT

Accurate diagnosis of periprosthetic joint infection (PJI) is challenging. Most infection diagnosis criteria define elevated serum C-reactive protein (CRP) as >1.0 mg/dL and erythrocyte sedimentation rate (ESR) as >30 mm/hour. Obesity has been reported as a pro-inflammatory state with elevated baseline CRP values. We hypothesized that higher cut-off values would be more accurate to diagnose PJI in obese patients due to their elevated baseline CRP. BMI, serum inflammatory markers, and synovial fluid were collected for 102 revision total knee arthroplasty patients, and analyzed for the highest area under the curve. We found a CRP of 3.6 mg/dL was more accurate to diagnose PJI in obese patients versus traditional values. Clinicians should be judicious and use additional criteria when diagnosing PJI in obese patients.

Total knee arthroplasty (TKA) is a highly successful procedure performed over 600,000 times annually in the United States, and its use continues to rise [1]. The reported rate of periprosthetic joint infection (PJI) following TKA is 1.5% for the first 2 years after surgery with an additional 0.45% increased risk between post-operative years 2 and 10 [2]. PJI is currently the top cause for revision TKA [3]. Diagnosis of PJI is often difficult due to the lack of a single biomarker and gross variability among patients and bacterial profile. The current reference standard for PJI diagnosis comes from the Musculoskeletal Infection Society (MSIS) definition criteria [4]. This diagnostic criterion examines elevated serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), synovial fluid values, presence of draining sinus, purulence and synovial fluid cultures.

The current standard for inflammatory markers cut-off value is set at a CRP of 1.0 mg/dL and an ESR of 30 mm/hour [4]. Reported sensitivity and specificity of these cut-off values are variable with suboptimal accuracy [5,6]. Due to concerns about the poor specificity of these values, many authors have begun to examine their sensitivity and specificity in well-defined patient populations and have suggested higher cut-off levels for these markers [5,7–9]. While many studies have examined cut-off values for serum inflammatory markers of PJI, none of them have specifically targeted cohorts defined by body mass index (BMI). Obesity (i.e., BMI >30) has been found to increase both the risk of requiring TKA and for undergoing TKA at a younger age [10,11]. It is also a well-recognized risk factor for infection following TKA, with a 6.7-fold increase in infection risk reported for obese patients as opposed to non-obese patients [12].

In addition to being a risk factor for PJI, obesity has also been recognized as an inflammatory state. A study published in 1999 found that a higher number of overweight and obese patients had elevated CRP levels (>0.22 mg/dL) compared with their normal-weight counterparts [13]. Additional research has supported the association between elevated baseline CRP and heart disease, diabetes mellitus, stroke, metabolic syndrome, and cancer [13–15]. In osteoarthritis research specifically, studies have implicated inflammation in the pathogenesis of the disease in obese patients beyond just load-bearing effects [16,17]. One group found an increased risk of radiographic progression in the knee associated with increased serum CRP [16]. It is hypothesized that the adipose tissue itself is responsible for activating these pro-inflammatory pathways [14]. The relationship between obesity and CRP is further strengthened with the finding that CRP decreases following weight loss [18].

Since obesity has long been recognized as a pro-inflammatory state with an elevated baseline CRP, we hypothesized that a higher cut-off value may be more accurate for PJI diagnosis in obese patients. Obese patients without PJI may experience more false positive diagnoses due to their elevated baseline CRP. The work-up for PJI in this population can be highly confusing given the number of co-morbidities they frequently present with. Additionally, there are several instances when CRP and ESR may be relied on heavily to guide diagnosis. For example, if knee aspiration cannot be obtained or if cultures are false positive or contaminated, the serum inflammatory markers are used for diagnosis and potentially treatment. This study aimed to identify the most appropriate CRP and ESR cut-off values to be used to diagnose PJI in obese versus non-obese patients.

Conflict of Interest statement associated with this article can be found at http://dx.doi.org/10.1016/j.arth.2014.07.005.

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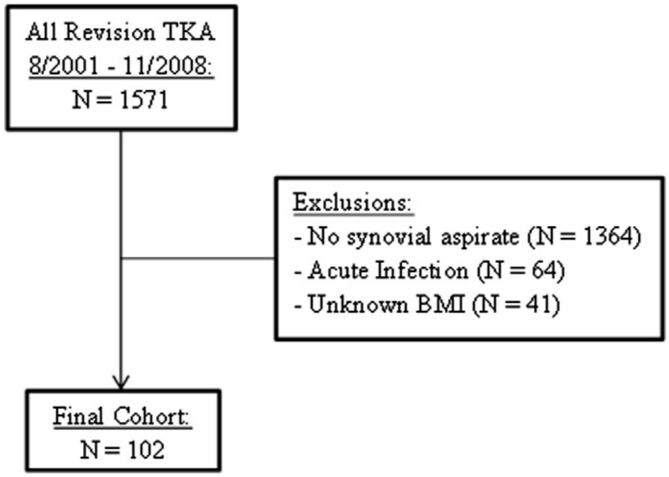

Fig. 1. Sample selection flow diagram.

Materials and Methods

This study retrospectively examined a continuous series of 1571 patients who underwent revision TKA at our institution between 8/7/2001 and 11/20/2008. Patients who did not have synovial fluid aspiration taken within 40 days before a one-stage revision or the first stage of a two-stage procedure were excluded ($n = 1364$). Patients who did not have a BMI within 6 months prior to surgery ($n = 41$) were also excluded. Patients with acute post-operative infection (within 6 weeks of index surgery) were excluded ($n = 64$) due to the use of different inflammatory markers cut-off values. This resulted in a cohort of 102 patients to be analyzed (Fig. 1). Variables collected included age, gender, BMI, diagnosis indication for primary knee arthroplasty, diagnosis of inflammatory arthropathies, use of immunosuppressive medications, type of revision, history of previous infection, synovial fluid aspirate values, serum inflammatory markers CRP and ESR, complete blood count (CBC) with differential values, presence of purulence during revision, sinus tract at revision, and synovial fluid and soft tissue microbiologic culture results.

Using MSIS criteria to diagnose PJI, patients were classified first into infected versus non-infected [4]. Patients were then classified as obese with BMI >30 and non-obese with BMI <30. This left four groups for analysis: 1. non-obese, non-infected ($n = 10$), 2. non-obese, infected ($n = 28$), 3. obese, non-infected ($n = 19$), and 4. obese, infected ($n = 45$) (Fig. 2).

The Student's t-test was utilized to determine statistically significant differences between demographic factors, serum values, and synovial aspirate values. Receiver operating characteristic curves (ROC) for the CRP and ESR values were plotted as true-positive results (sensitivity) and false-negative results (1-specificity). An area under the curve equal to 1 shows an ideal test with 100% sensitivity and 100% specificity, whereas an area of less than 0.5 exhibits a poor diagnostic test. This analysis provided the level with the highest sensitivity and specificity for CRP and ESR. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were then calculated for the two serum markers in both groups utilizing the cut-off values for obese patients found in the study as well as the traditional values. A P-value ≤0.05 was considered statistically significant. All statistical analyses were performed using SPSS 16.0™ (Chicago, IL, USA).

Table 1
Patient Demographics.

Variable	Non-Obese Patients ($n = 38$)	Obese Patients ($n = 64$)	P-value
Average age (years)	64 (±13.1)	64 (±11.3)	0.84
Gender			
Male	15 (39.5 %)	33 (51.5%)	0.24
Female	23 (60.5%)	31 (48.4%)	
Use of immunosuppressive medication	5 (13.2%)	7 (10.9%)	0.74
Indication for index surgery			
Osteoarthritis	34 (89.5%)	56 (87.5%)	0.47
Rheumatoid arthritis	3 (7.9%)	3 (4.7%)	
Other	1 (2.6%)	5 (7.8%)	
Indication for revision surgery			
Infection	28 (73.7%)	45 (70.3%)	0.72
Aseptic	10 (26.3%)	19 (29.7%)	
Type of revision procedure			
1-Stage	19 (50.0%)	38 (59.4%)	0.36
2-Stage	19 (50.0%)	26 (40.6%)	
History of previous prosthetic joint infection	13 (34.2%)	22 (34.9%)	0.94
Mean CRP (mg/dL)	7.0 (±8.9)	9.9 (±12.8)	0.23
Mean ESR (mm/hour)	59.6 (±43.0)	56.2 (±39.8)	0.69

CRP—C-reactive protein; ESR—erythrocyte sedimentation rate.

Results

Obese and non-obese patients did not differ with regards to age, gender, prevalence of inflammatory arthropathy, or use of immune modulating medications (Table 1). No significant differences were found between the main demographics and surgical variables between obese and non-obese patients. The t-test did not reveal any differences in serum CRP and ESR (Table 1) or synovial values between obese and non-obese patients. This may be due to the small sample size or to the wide range of values in each group (CRP 0.3 mg/dL to 26.4 in non-obese patients and 0.1 to 55.5 mg/dL in obese-patients).

Using ROC curves, a higher CRP cut-off value for diagnosing PJI in obese patients was found (3.6 vs. 1.4 mg/dL) (Table 2A). A smaller difference in ESR cut-off was also found (36.5 mm/hour in obese patients and 32.5 mm/hour in non-obese patients). The AUC in all four groups was greater than 0.80 (0.887–0.906) and accuracy was between 86.2 and 89.5% for all cut-off values (Figs. 3 and 4). This suggested cut-off value for CRP performed better than the traditional value in every category in non-obese patients, while being equal in sensitivity (Table 2A and B). In obese patients, the suggested CRP cut-off value achieved higher accuracy, specificity, and positive predictive value, but with inferior sensitivity and negative predictive value. Suggested cut-off ESR values performed similarly to the traditional ESR value, with slight improvements in specificity.

Discussion

Obese patients have been found to have higher baseline CRP and ESR, but little research has been done to clarify this difference in the

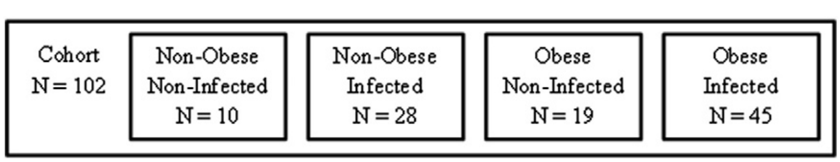

Fig. 2. The cohort was classified into four groups for analysis.