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Orthopedic Surgery among Patients with Rheumatoid Arthritis: A Population-based study to Identify Risk factors, Sex differences, and Time trends

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Abstract

Objective—To identify risk factors for large joint (LJS) versus small joint surgery (SJS) in rheumatoid arthritis (RA) and evaluate trends in surgery rates over time.

Methods—A retrospective medical record review was performed of all orthopedic surgeries following first fulfillment of 1987 ACR criteria for adult-onset RA among residents of Olmsted County, Minnesota, USA in 1980–2013. Risk factors were examined using Cox models adjusted for age, sex and calendar year of RA incidence. Trends in incidence of joint surgeries were examined using Poisson regression models.

Results—A total of 1077 patients with RA (mean age 56 years, 69% female, 66% seropositive) were followed for a median of 10.7 years during which 112 (90 women) underwent at least one SJS and 204 (141 women) underwent at least one LJS. Risk factors included advanced age, rheumatoid factor and anti-CCP antibody positivity for both SJS and LJS, and BMI 30 kg/m^2 for LJS. Risk factors for SJS and LJS at any time during follow-up included the presence of radiographic erosions, large joint swelling, and methotrexate use. SJS rates decreased by calendar year of incidence (hazard ratio 0.53; $p=0.001$), with significant decline in SJS after 1995. The cumulative incidence of SJS was higher in women than men ($p=0.008$).

Conclusion—In recent years, there has been a significant decline in rates of SJS but not LJS in patients with RA. The incidence of SJS is higher among women. Traditional RA risk factors are strong predictors for SJS and LJS. Increasing age and obesity are predictive of LJS.

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INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic inflammatory disease with a clinical course that can vary widely from a mild, self-limiting illness to a severe, rapidly progressing, destructive process that can lead to permanent joint damage and functional disability within a few years of disease onset. Despite treatment to target strategies and aggressive medical management utilizing disease modifying anti-rheumatic drugs (DMARDs), there remains a subset of patients that eventually require joint surgery to improve overall function and quality of life. The need for orthopedic surgery is now considered an indicator of disease severity, failure of medical therapy, and often a marker of poor prognosis. [1] Joint reconstruction procedures in particular have been associated with an increased mortality in patients with RA.[2]

The goal of orthopedic procedures is to reduce pain, improve function and reduce disability. These may include interventions on large joints and small joints besides soft tissues and cervical spine. The predictors of future large joint replacement surgery have been studied and include elevated inflammatory markers (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) at diagnosis, high health assessment questionnaire (HAQ) scores at inclusion, rheumatoid nodules, and radiographic damage early in the course of disease. [3]

Factors predicting long term risk of small joint surgeries (SJS) are not as well understood. Moreover, it is unclear whether predictors for surgical interventions are the same among men and women. Several studies have already suggested that the advances in medical therapy for RA have led to a significant decline in orthopedic procedures in these patients. [4, 5] The extent to which RA related factors versus non RA related factors are associated with need for joint surgery is not well delineated.

PATIENTS AND METHODS

Study population and data collection

A population-based cohort of Olmsted County, Minnesota residents aged 18 years and older with incident RA between January 1, 1980, and December 31, 2013, was assembled using the resources of the Rochester Epidemiology Project. [6] All patients met the 1987 American College of Rheumatology classification criteria for RA and were followed longitudinally until July 1, 2016; death; or migration out of the county. [7]

For each patient, the entire inpatient and outpatient medical records from all providers in Olmsted County were reviewed to obtain data on orthopedic procedures and potential risk factors. The date and type of each procedure after the RA incidence date were recorded along with the involved joints. Surgeries involving the following joints were included: shoulders, elbows, wrists, thumbs [base, metacarpophalangeal joint (MCP), interphalangeal joint (IP)], other fingers [MCP, proximal interphalangeal joint (PIP), distal interphalangeal joint (DIP)], hips, knees, ankles, first toes [metatarsophalangeal joint (MTP) and IP] and MTP 2–5, toes 2–5 (PIP, DIP). Procedures were stratified further into the following categories (1) Large joint surgery (LJS): Hip, knee, ankle, shoulder and elbow (2) SJS: Hand, wrist, foot.

Data on smoking status at RA incidence (never, current, former), height, weight, and results of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) tests were also collected by medical record review. Body mass index (BMI) at RA incidence was calculated and obesity was defined as BMI ≥ 30 kg/m². Data on use of DMARDs and glucocorticoids were also collected. DMARDs other than methotrexate included hydroxychloroquine, sulfasalazine, leflunomide and azathioprine.

Statistical methods

Descriptive statistics were used to summarize the demographic characteristics of the cohort. The cumulative incidence of first surgery adjusted for the competing risk of death was estimated for both SJS and LJS. This method censored patients who were still alive at last follow-up and accounted for those who died before experiencing surgery to avoid overestimation of the rate of occurrence of surgery. Risk factors for SJS and LJS were examined using Cox models adjusted for age, sex and calendar year. Time-dependent covariates were used to model risk factors that developed during follow-up, such as treatment whereby treated patients were modeled as unexposed until the time they started a treatment and exposed thereafter.

Trends in incidence of first joint surgeries over time by sex were examined using Poisson regression models with quasipoisson methods to account for overdispersion. Smoothing splines were used to allow for non-linear time trends. A *p* value of less than 0.05 was considered statistically significant for all analyses. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The study cohort includes 1077 patients with RA. Clinical characteristics of this cohort are displayed in Table 1. The majority were women (69%) and the mean age at RA incidence was 56 years (SD 15.7). RF was positive in 66%. At RA incidence, men had a slightly higher incidence of large joint swelling (49.1% vs. 41.5%, *p*=0.02), but there were no significant sex differences in obesity or RF and/or CCP positivity. The median follow-up for the entire cohort was 10.7 years.

A total of 189 patients underwent at least 1 or more joint surgeries during the follow-up period. Ninety women and 22 men underwent at least one SJS and 141 women and 63 men underwent at least one LJS. The cumulative incidence of first SJS was significantly higher in women (14.4% by 15 years after RA incidence; 95% confidence interval [CI]: 11.3–17.4%) than men (7.6% at 15 years; 95% CI: 4.3–10.8%; *p*=0.008), but no sex differences were noted in the cumulative incidence of first LJS (20.2% at 15 years among women; 95% CI: 16.8–23.6% and 18.8% among men; 95% CI: 13.8–23.5%; *p*=0.55).

Table 2 shows risk factors for first joint surgery at RA incidence. Significant risk factors for both LJS and SJS included advanced age, seropositivity (RF and/or anti-CCP), radiographic erosions, large joint swelling, and methotrexate use. Risk factors for SJS alone included rheumatoid nodules and use of DMARDs other than methotrexate. Radiographic erosions

and seropositivity were the strongest risk factors for SJS (Hazard ratio 4.55 and 2.47, respectively). Obesity and the use of glucocorticoids were risk factors for LJS.

Figure 1 shows the calendar years trends in first LJS and SJS rates. There was a significant decline in the rate of SJS, but the rate of LJS remained unchanged. SJS were more common among women than men and declined in both sexes from 2000 forward. LJS rates were similar among women and men, and there was no evidence of a trend over time ($p=0.87$).

DISCUSSION

This study aimed to describe the risk factors, sex differences, and time trends in orthopedic surgery for RA. Our findings confirmed that clinical and laboratory markers of severe articular disease are also the risk factors for joint surgery. Women had a higher incidence of SJS compared to men but there were no differences in LJS, and there was a decline in the rate of SJS for both sexes over the study period. By the end of the study less than 1% of patients per year underwent SJS.

There is a strong link between disease activity, medically refractory disease, and the risk for joint surgery. In addition to the risk factors identified here, disease activity score has been correlated with risk for orthopedic surgery in large RA cohorts. [8] This was shown for both LJS and SJS. Previous studies have also revealed similar time trends in joint surgery rates, with SJS declining sharply and LJS remaining relatively stable. [9] While many LJS could be a consequence of degenerative disease rather than chronic inflammation, the risk factors identified here for LJS, specifically large joint swelling, radiographic erosions, and methotrexate use, suggest that RA is an underlying factor in at least some of these procedures. Further, LJS in RA is associated with worse primary disease outcomes. [10]

A significant percentage of patients who underwent an orthopedic procedure during the study interval began treatment for RA prior to the widespread use of DMARDs. Lack of exposure to effective DMARDs has been correlated to risk for joint surgery in other studies. [11] Even moderate disease activity within the first five years of RA diagnosis has been shown to increase the long term risk of joint surgery. [8] Longer exposure to DMARDs within the first year after RA diagnosis has also been correlated to a longer time to joint surgery, suggesting that patients derive benefit from early and sustained remission or low disease activity, observations which provide indirect support for the current treat to target strategy. [12] Interestingly, biologic medications have not been shown to have any effect on the need for orthopedic procedures, which is likely due to the fact that the joint destruction necessitating joint replacement occurs prior to starting biologics in most cases. [13]

Time trends among men and women have not been well described previously. The higher rate of SJS among women may reflect higher rates of medically refractory disease or predisposition to joint damage compared to men. In a large, multinational cohort, women were found to have lower remission rates and higher disease activity scores compared to men. [14] However, both sexes had similar and stable rates of LJS throughout the study period. This contrasts to the trend amongst the general population. A population-based study from Olmsted County suggested that the rates of total hip and knee arthroplasty have

increased steadily from 1969 to 2008 and continue to increase for all age groups, with higher rates among women than men. [15] The stable rate of LJS observed in the current study likely reflects a combination of the increase in procedures performed for degenerative joint disease with the declining incidence of large joint destruction due to RA. A study focusing on specific surgical indications would be required to further investigate this hypothesis.

There are several limitations to this study. Since findings relied on medical record documentation to identify risk factors for surgery, it was not possible to account for individual patient factors such as disease activity, functional impairment, or specific indication around the time of surgery. This, along with the retrospective study design, cautions against making a causal link between disease severity and orthopedic procedures. Further, the patients were drawn from Olmsted County which is predominantly Caucasian with a high percentage of the population working in the healthcare field. This is relevant to the orthopedic surgery rates reported here since higher socioeconomic status, white ethnicity, and rural residence have been associated with an increased likelihood of undergoing arthroplasty among patients with RA. [16]

Despite advances in treatment for RA, there still remains a population of patients that require orthopedic surgery to optimize function. The risk factors and time trends identified in this study may help with risk stratification and assist clinicians in counseling patients about prognosis and treatment decisions. Future studies should focus on individual patients and specific surgical indications to determine who could benefit from orthopedic surgery. Finally, this study highlights the effect of disease-modifying therapies on the long-term outcomes in RA and emphasizes the critical importance of early diagnosis and treatment.

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Significance and Innovation

1. There has been a significant decline in the rate of small joint surgery but not large joint surgery in patients with rheumatoid arthritis.
2. Women are more likely than men to undergo small joint surgery for rheumatoid arthritis.
3. Strong risk factors for joint surgery include seropositivity, radiographic erosions, and large joint swelling.

Figure 1. Calendar year trends in first small (top) and large (bottom) joint surgeries among women (solid line) and men (dashed line) with rheumatoid arthritis.

Table 1

Clinical characteristics at rheumatoid arthritis (RA) incidence of patients with incident RA in 1980–2013.

Characteristic	Females (N=739)	Males (N=338)	Total (N=1077)	p value
Age, years				0.001
Mean (SD)	54.9 (16.1)	58.2 (14.1)	55.9 (15.6)	
Median	54.7	59.5	55.9	
Length of follow-up, years				--
Mean (SD)	12.3 (8.5)	11.9 (7.8)	12.2 (8.3)	
Median	10.9	10.4	10.7	
Smoking Status				<0.001
Never	396 (53.6%)	111 (32.8%)	507 (47.1%)	
Current	137 (18.5%)	79 (23.4%)	216 (20.1%)	
Former	206 (27.9%)	148 (43.8%)	354 (32.9%)	
BMI, kg/m²				0.002
Mean (SD)	28.0 (6.8)	28.6 (4.6)	28.2 (6.2)	
Median	26.9	28.0	27.3	
Obese (BMI ≥ 30 kg/m²)	240 (32.5%)	110 (32.5%)	350 (32.5%)	0.982
RF and/or CCP positive	479 (64.8%)	230 (68.0%)	709 (65.8%)	0.300
ESR, mm/1 hr				0.025
Mean (SD)	25.0 (20.3)	23.8 (22.2)	24.6 (20.9)	
Median	20.0	17.0	20.0	
Large joint swelling	307 (41.5%)	166 (49.1%)	473 (43.9%)	0.020

SD: standard deviation, BMI: body mass index, RF: rheumatoid factor, CCP: anti-cyclic citrullinated peptide, ESR: erythrocyte sedimentation

Table 2

Risk factors for first small and large joint surgery at rheumatoid arthritis incidence and during follow-up

Characteristics at RA incidence	Small joint surgery		Large joint surgery	
	Hazard ratio* (95% CI)	P value	Hazard ratio* (95% CI)	P value
Age (per 10 year increase)	0.84 (0.74, 0.96)	0.009	1.29 (1.17, 1.42)	<0.001
Sex, female	1.87 (1.17, 2.99)	0.008	1.06 (0.79, 1.43)	0.683
Calendar year (1994–2013 vs 1980–1993)	0.53 (0.36, 0.78)	0.001	0.94 (0.70, 1.26)	0.671
ESR (per 10 mm/1 hr)	1.02 (0.92, 1.13)	0.560	1.07 (1.00, 1.14)	0.069
RF and/or CCP positive	2.47 (1.52, 4.01)	0.001	1.54 (1.12, 2.10)	0.008
Current smoker	1.18 (0.77, 1.83)	0.168	0.97 (0.69, 1.37)	0.880
Ever smoking	1.43 (0.97, 2.11)	0.069	1.18 (0.89, 1.57)	0.253
Obesity (BMI 30 kg/m ²)	0.77 (0.49, 1.20)	0.254	2.03 (1.53, 2.70)	<0.001
Time-dependent Characteristics				
Rheumatoid Nodules	3.32 (2.27, 4.87)	<0.001	0.98 (0.71, 1.35)	0.920
Erosions/ destructive changes	4.55 (2.93, 7.05)	<0.001	1.68 (1.26, 2.23)	<0.001
Large joint swelling	1.61 (1.01, 2.58)	0.047	2.10 (1.42, 3.11)	<0.001
Methotrexate	1.64 (1.08, 2.48)	0.019	1.97 (1.44, 2.68)	<0.001
Other DMARD	1.87 (1.18, 2.98)	0.008	1.28 (0.94, 1.76)	0.119
Glucocorticoids	1.32 (0.87, 2.01)	0.196	1.95 (1.37, 2.78)	<0.001

* adjusted for age, sex and calendar year of RA incidence. p <0.05 considered statistically significant.

SD: standard deviation, BMI: body mass index, RF: rheumatoid factor, CCP: anti-cyclic citrullinated peptide, ESR: erythrocyte sedimentation, DMARD: disease modifying anti-rheumatic drug