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Osseous and Soft Tissue Complications Associated With Foot and Ankle Surgery in Patients With Rheumatoid Arthritis Taking a Variety of Antirheumatic Medications

Colten D. Dougherty, DPM[1], Yun-Yi Hung, PhD, MPH[1], Miranda L. Ritterman Weintraub, PhD, MPH[2], Sandeep Patel, DPM, FACFAS[3], Christy M. King, DPM, FACFAS[4]

[1] *Third-Year Resident, Kaiser San Francisco Bay Area Foot and Ankle Residency Program, Kaiser San Francisco Bay Area Foot and Ankle Residency, San Francisco, CA*
[2] *Senior Research Project Manager, Graduate Medical Education, Kaiser Permanente Oakland Medical Hospital, Oakland, CA*
[3] *Attending Staff, Kaiser San Francisco Bay Area Foot and Ankle Residency Program, Department of Orthopedics, Kaiser Foundation Hospital, Walnut Creek, CA*
[4] *Residency Director, Kaiser San Francisco Bay Area Foot and Ankle Residency Program, Kaiser Foundation Hospital, Oakland, CA*

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ABSTRACT

There are multiple antirheumatic drug modalities available to patients with symptomatic rheumatoid arthritis (RA) that function to suppress the overactive immune system, but the inflammatory and immune suppression may contribute to postoperative complications. The purpose of this study was to determine if antirheumatic medications increased the risk of both soft tissue and osseous postoperative complications in patients with RA who underwent foot and ankle surgery. We reviewed patients with RA, aged 18 years and older, who underwent either an elective or a nonelective foot or ankle surgery involving an osseous procedure between 2009 and 2014. Chart review was conducted to document procedure type, active medications, and postoperative complications. Of the final 110 subjects meeting inclusion criteria, 31 (28%) patients had a postoperative complication (13 soft tissue, 9 osseous, and 9 both soft tissue and osseous). There was no statistically significant association between taking antirheumatic medications in the perioperative period and postoperative complications. Increased surgery duration and peripheral neuropathy were associated with a statistically significant increase in postoperative complications. Every 15 minutes of increased surgery time led to a 1.2-fold increase in complication risk. Nonelective procedures had a higher risk of soft tissue complications than did elective procedures (odds ratio 4.2, 95% confidence interval 1.1 to 16.0). Although there was no statistically significant association between the specific medication and complications, some medications trended toward statistical significance. When working with patients with RA, our findings suggest the importance of considering the risk of surgery duration and the potential risk of antirheumatic medications in the perioperative period.

Rheumatoid arthritis (RA) affects between 0.5% and 1% of adults in the developed world, with an annual incidence estimated between 5 and 50 per 100,000 population (1). RA is a chronic inflammatory disease that can affect multiple joints throughout the body by attacking bone and cartilage via an overactive immune system. To reduce joint destruction and to manage symptoms, multiple medications, often in combination, are prescribed. Treatment may suppress the inflammatory or immune response; however, it may also impede postoperative healing.

Medicinal treatment for RA includes nonsteroidal antiinflammatory drugs (NSAIDs), conventional disease-modifying antirheumatic drugs (DMARDs), corticosteroids, and, more recently, biologic DMARDs. NSAIDs, which are not recommended for long-term use, help by inhibiting the enzymes that synthesize prostaglandins in the inflammatory process. These medications can decrease the immune response, thereby increasing the risk for infection, producing negative effects on wound healing, and potentially interfering with bone healing pathways (2,3). Conventional DMARDs function to interfere with the body's inflammatory cycle. However, DMARDs can be cytotoxic and have been linked in the orthopedic literature to numerous complications, including postoperative complications such as skin healing after foot and ankle surgery (4-6). Corticosteroids, which are commonly used for bridge therapy and in rheumatoid flares uncontrolled by other medication, can lead to various complications such as infection and reduced bone formation and

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Address correspondence to: Christy M. King, DPM, FACFAS, Kaiser Permanente Oakland Medical Center, 275 MacArthur Boulevard, Oakland, CA 94611.

E-mail address: Christy.m.king@kp.org (C.M. King).

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strength (7,8). Biologic DMARDs, such as tumor necrosis factor alpha (TNF-α) inhibitors, suppress the immune system through the depletion of B cells and the inhibition of T-cell activation or cytokine inhibition. These medications have been associated with higher complication rates after orthopedic surgery (4). Although these treatment modalities work in varying ways to control the body's increased inflammatory or immune response, their cessation can trigger painful flare-ups. Among patients with RA, it is important to consider the potential impact of medication usage on postoperative complication risk during the perioperative period.

Much of the orthopedic literature concerning RA focuses on complications involving infection or wound healing issues in different anatomical locations of the body, including the knee and the hip (9-11). There is little within the foot and ankle literature and, more specifically, on potential osseous healing in patients with RA. Building on the work of Bibbo et al (12), who looked at wound healing and infection complications in patients with RA who were taking NSAIDs, steroids,

Table 1
Patient characteristics according to complications overall and by type*

Characteristics		Overall Complicationss		*p* Value	Soft Tissue Complications		*p* Value	Osseous Complications		*p* Value
	Total (N = 110)	No (n = 79)	Yes (n = 31)		No (n = 88)	Yes (n = 22)		No (n = 92)	Yes (n = 18)	
Demographic										
Age (y), mean (SD)	59.9 (11.9)	60.0 (12.8)	59.9 (9.6)	.9675	60.2 (12.3)	59.0 (10.4)	.6900	60.0 (12.3)	59.5 (9.8)	.8600
Sex, n (%)				.2511			.2500			.2100
Female	86 (78.2)	65 (81.0)	22 (71.0)		71 (80.7)	15 (68.2)		74 (80.4)	12 (66.7)	
Male	24 (21.8)	15 (19.0)	9 (29.0)		17 (19.3)	7 (31.8)		18 (19.6)	6 (33.3)	
Race/ethnicity, n (%)				.7100			.6300			.2700
White	62 (56.4)	42 (53.2)	20 (64.5)		46 (52.3)	16 (72.7)		51 (55.4)	11 (61.1)	
Black	11 (10.0)	7 (8.9)	4 (12.9)		10 (11.4)	1 (4.6)		7 (7.6)	4 (22.2)	
Asian/Pacific Islander	7 (6.4)	6 (7.6)	1 (3.2)		6 (6.8)	1 (4.6)		7 (7.6)	0 (0.0)	
Hispanic nonblack	24 (21.8)	19 (24.1)	5 (16.1)		21 (23.9)	3 (13.6)		21 (22.8)	3 (16.7)	
Other	6 (5.5)	5 (6.3)	1 (3.2)		5 (5.7)	1 (4.6)		6 (6.5)	0 (0.0)	
Clinical										
Body mass index, mean kg/m^2 (SD)	28.4 (7.3)	27.7 (7.0)	30.3 (7.7)	.0900	28.2 (6.9)	29.6 (8.5)	.4200	28.1 (7.4)	30.4 (6.1)	.2200
Body mass index, n (%)				.0859			.5400			.0300
< 25	35 (31.8)	30 (38.0)	5 (16.1)		30 (34.1)	5 (22.7)		34 (37.0)	1 (5.6)	
25 to 30	41 (37.3)	27 (34.2)	14 (45.2)		31 (35.2)	10 (45.5)		31 (33.7)	10 (55.6)	
> 30	34 (30.9)	22 (27.9)	12 (38.7)		27 (30.7)	7 (31.8)		27 (29.4)	7 (38.9)	
Smoker, n (%)				.6511			.9200			.5600
Former	32 (29.1)	21 (26.6)	11 (35.5)		25 (28.4)	7 (31.8)		26 (28.3)	6 (33.3)	
Never/not asked/unknown	66 (60.0)	49 (62.0)	17 (54.8)		53 (60.2)	13 (59.1)		57 (62.0)	9 (50.0)	
Yes	12 (10.9)	9 (11.4)	3 (9.7)		10 (11.4)	2 (9.1)		9 (9.8)	3 (16.7)	
Diabetes, n (%)				.2696			.3500			1.0000
No	92 (83.6)	68 (86.1)	24 (77.4)		75 (85.2)	17 (77.3)		77 (83.7)	15 (83.3)	
Yes	18 (16.4)	11 (13.9)	7 (22.6)		13 (14.8)	5 (22.7)		15 (16.3)	3 (16.7)	
Peripheral neuropathy, n (%)				.0410			.5300			.0800
No	91 (82.7)	69 (87.3)	22 (71.0)		74 (84.1)	17 (77.3)		79 (85.9)	12 (66.7)	
Yes	19 (17.3)	10 (12.7)	9 (29.0)		14 (15.9)	5 (22.7)		13 (14.1)	6 (33.3)	
Osteoporosis, n (%)				.4462			.7600			.5100
No	72 (65.5)	50 (63.3)	22 (71.0)		57 (64.8)	15 (68.2)		59 (64.1)	13 (72.2)	
Yes	38 (34.6)	29 (36.7)	9 (29.0)		31 (35.2)	7 (31.8)		33 (35.9)	5 (27.8)	
Peripheral vascular disease, n (%)				.7200			.6800			1.0000
No	100 (90.9)	71 (89.9)	29 (93.6)		79 (89.8)	21 (95.5)		83 (90.2)	17 (94.4)	
Yes	10 (9.1)	8 (10.1)	2 (6.4)		9 (10.2)	1 (4.6)		9 (9.8)	1 (5.6)	
Medication use										
NSAIDs, n (%)				.6117			.8400			.1000
No	68 (61.8)	50 (63.3)	18 (58.1)		54 (61.4)	14 (63.6)		60 (65.2)	8 (44.4)	
Yes	42 (38.2)	29 (36.7)	13 (41.9)		34 (38.6)	8 (36.4)		32 (34.8)	10 (55.6)	
Conventional DMARDs, n (%)				.8480			.7600			.2624
No	37 (33.6)	27 (34.2)	10 (32.3)		29 (33.0)	8 (36.4)		33 (35.9)	4 (22.2)	
Yes	73 (66.4)	52 (65.8)	21 (67.7)		59 (67.1)	14 (63.6)		59 (64.1)	14 (77.8)	
Biologic DMARDs, n (%)				.6116			.2900			1.0000
No	61 (55.5)	45 (57.0)	16 (51.6)		51 (58.0)	10 (45.5)		51 (55.4)	10 (55.6)	
Yes	49 (44.6)	34 (43.0)	15 (48.4)		37 (42.1)	12 (54.6)		41 (44.6)	8 (44.4)	
Steroids (prednisone), n (%)				.3502			.2900			.6000
No	61 (55.5)	46 (58.2)	15 (48.4)		51 (58.0)	10 (45.5)		50 (54.4)	11 (61.1)	
Yes	49 (44.6)	33 (41.8)	16 (51.7)		37 (42.1)	12 (54.6)		42 (45.7)	7 (38.9)	
Procedural										
Elective status, n (%)				.5600			.1000			.7300
Elective	93 (84.6)	68 (86.1)	25 (80.7)		77 (87.5)	16 (72.7)		77 (83.7)	16 (88.9)	
Nonelective	17 (15.5)	11 (13.9)	6 (19.4)		11 (12.5)	6 (27.3)		15 (16.3)	2 (11.1)	
Location, n (%)				.3700			.8099			.0700
Forefoot	30 (27.3)	23 (29.1)	7 (22.6)		24 (27.3)	6 (27.3)		28 (30.4)	2 (11.1)	
Midfoot	11 (10.0)	6 (7.6)	5 (16.1)		8 (9.1)	3 (13.6)		7 (7.6)	4 (22.2)	
Rearfoot	69 (62.7)	50 (63.3)	19 (61.3)		56 (63.6)	13 (59.1)		57 (62.0)	12 (66.7)	
Surgery duration (min), mean (SD)	131.1 (61.5)	117.7 (45.4)	163.6 (81.5)	< .001	120.5 (46.5)	173.8 (91.7)	< .0001	120.7 (53.5)	183.0 (73.5)	< .001

Abbreviations: DMARDs, disease-modifying antirheumatic drugs; NSAIDs, nonsteroidal antiinflammatory drugs; SD, standard deviation.
* Proportions may not sum to 100% due to rounding.

methotrexate, hydroxychloroquine, or gold, we hope to expand with a focus on both soft tissue and osseous postoperative complications among patients with RA who undergo foot and ankle surgery. In addition, there is limited research on complications after foot and ankle surgery because biologic DMARDs/TNF-α inhibitors have been more widely used. This study aimed to contribute to the limited research on the association between a variety of antirheumatic medications and various soft tissue and osseous complications among patients with RA who have undergone elective or nonelective foot and ankle surgery.

Patients and Methods

The Kaiser Permanente institutional review board approved this study with waiver of consent. A chart review was conducted on adult patients (18 years and older) with a diagnosis of RA for at least 1 year before surgery who underwent elective or nonelective foot or ankle surgery with at least 1 osseous procedure (osteotomy, arthrodesis, or open reduction internal fixation) between 2009 and 2014. Patients without a minimum of 12 months of continuous health plan membership and postoperative follow-up and with missing medication data were excluded. More than 200 charts were reviewed, and 110 patients met the inclusion criteria.

Medical charts, operative reports, and radiographs were reviewed by an author not directly involved in patient care (C.D.). Progress notes were reviewed to determine complications, including nonunion, delayed union, superficial skin infection (infection that required oral antibiotics), and deep infection (infection that required hospitalization, intravenous antibiotics, or incision and drainage). Antirheumatic medications that the patient was taking before the surgery were documented and categorized into the following groups: NSAIDs (ibuprofen, naproxen, etc.), conventional DMARDs (methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide), corticosteroids, and biologic DMARDs (etanercept, adalimumab, tocilizumab, tofacitinib, and infliximab). It was documented whether the patient continued the medication through surgery or stopped at least 2 weeks before surgery. The date, side of surgery, duration of surgery, type of procedure performed, procedure location (forefoot, midfoot, rearfoot/ankle), and elective status (elective vs nonelective) were documented. Elective procedures were separated further into type of surgery: osteotomy or arthrodesis. Nonelective procedures were categorized into open reduction internal fixation or primary arthrodesis.

The patients' demographic characteristics (age, sex, race) and clinical characteristics (body mass index [BMI], tobacco use at the time of surgery, peripheral neuropathy, and baseline comorbidities, including hypertension, diabetes mellitus, osteoporosis, cerebrovascular disease, and chronic kidney disease) were extracted from Kaiser Permanente Northern California comprehensive electronic medical records databases.

Statistical Analysis

We compared the demographic, clinical, medication use, and procedural characteristics between patients with and patients without complications. All analyses were performed by using SAS statistical software(version 9.3; SAS Institute, Cary, NC). Results were presented as proportions, means, medians, and standard deviations. Comparisons involving categorical variables were performed by using the χ^2 or Fisher's exact tests. Normally distributed continuous variables were compared by using the Student's t test or analyses of variance. Comparisons of non-normally distributed continuous variables were conducted by using the Wilcoxon rank-sum test or Kruskal-Wallis test. Multiple logistic regression analyses were conducted to examine the risk factors for complications overall and for soft tissue and osseous complications separately. Each multivariate model contained demographic characteristics and potential predictors that had values of $p \leq .10$ in bivariate analyses.

Results

The mean age of the 110 patients was 59.9 years, 86 (78.2%) were female, and 62 (56.4%) were white (Table 1). Overall, 31 (28%) patients had a complication. Thirteen (12%) patients had only a soft tissue complication, 9 (8%) patients had only a osseous complication, and 9 (8%) patients had both soft tissue and osseous complications. Of the 22 (20%) soft tissue complications, 14 (12.7%) were superficial only and 8 (7.3%) were superficial and deep infections. There were 18 (16.4%) osseous complications (Table 2). Of the osseous complications, there were 9 (8.2%) nonunions and 9 (8.2%) delayed unions. Use or pattern of use of antirheumatic medications was not associated with having specific complications (Table 1). Patients with a BMI of 25 to 30 kg/m^2 and >30 kg/m^2 were significantly more likely to have a osseous complication than were patients with a BMI of <25 kg/m^2 ($p = .03$). Patients with complications were more likely to have peripheral neuropathy ($p = .041$) and longer surgery duration ($p < .001$) (Table 1).

Table 2
Complications (N = 110)

Complication	No. of Patients (%)
Soft tissue	22 (20.0)
Superficial infection only	14 (12.7)
Both superficial and deep infection	8 (7.3)
Osseous	18 (16.4)
Nonunion	9 (8.2)
Delayed union	9 (8.2)

Table 3 reports the medication use according to complication type. Although there were some trends toward a relationship, there were no statistically significant variations in complication rates between patients who took medications and patients who stopped taking medications before surgery or between patients who were not taking medications and patients who either stopped taking medications before surgery or who continued to take their medications.

Table 4 shows the multivariate analyses results. For every 15-minute increase in surgery duration, there was a 1.21-fold (1.07- to 1.37-fold) increased risk of complications overall. A similar pattern of association was seen for both soft tissue and osseous complications. Compared with elective procedures, nonelective procedures were associated with a higher risk for soft tissue complications (adjusted odds ratio [OR] 4.23, 95% confidence interval [CI] 1.12 to 16.00). Looking at some notable trends with the overall complication rates, there was a trend in the NSAID and biologic DMARD groups toward a complication when taking the medication and did not stop compared with patients who were taking medication and stopped prior to surgery. There was a trend toward soft tissue complications for patients taking biologic DMARDs and continuing them through surgery compared with patients who were not taking the medication at all. Those taking conventional DMARDs trended toward experiencing soft tissue complications when taking the medication and not stopping before surgery compared with patients who stopped taking the medication before surgery. Looking at osseous complications, there was a trend toward complications in the NSAID and conventional DMARD groups if a patient was taking the medication and did not stop compared with patients who had never been taking the medication. Furthermore, there was a trend for osseous complications when the patient continued biologic DMARDs through surgery compared with patients who stopped taking the medication before surgery.

Discussion

Overactive immune system suppression is the primary target for antirheumatic medications; however, this can lead to concern for potential increased postoperative complications. Overall, we found that 31 (28%) of 110 patients had either soft tissue or osseous complications: 13 had soft tissue complications only, 9 had osseous complications only, and 9 had both soft tissue and osseous complications. These results are comparable to the results of a study by Bibbo et al (12), who showed a 32% complication rate in patients with RA undergoing foot and ankle surgery and taking NSAIDs, steroids, methotrexate, hydroxychloroquine, or gold. There was no significant relationship between those patients who sustained a complication and their active medication. Increased surgical time and peripheral neuropathy were associated with an increased risk of complications in our study.

In addition to minimizing the risk of postoperative complications, the perioperative management of medications must be balanced to reduce the risks of a painful RA flare. When patients stop their typical antirheumatic regimen before surgery, there is a risk of postoperative RA flare (13,14). In some cases, these flares are not controlled with the

Table 3
Medication use according to complication type

Medication	Overall Complications		Soft Tissue Complication		Bone Complication	
	No. of Patients (%)	*p* Value*	No. of Patients (%)	*p* Value*	No. of Patients (%)	*p* Value*
NSAIDs						
Not taking medication	18/68 (27)	1.00	14/68 (21)	.785	8/68 (12)	.221
Taking medication, did not stop before surgery	5/12 (42)	.4635	3/12 (25)	.668	3/12 (25)	1.000
Taking medication, stopped before surgery	8/30 (27)		5/30 (17)		7/30 (23)	
Biologic DMARDs						
Not taking medication	16/61 (26)	1.00	10/61 (16)	.408	10/61 (16)	.764
Taking medication, did not stop before surgery	7/17 (41)	.2422	4/17 (24)	1.000	4/17 (24)	.420
Taking medication, stopped before surgery	8/32 (25)		8/32 (25)		4/32 (13)	
Conventional DMARDs						
Not taking medication	10/37 (27)	1.00	8/37 (22)	.502	4/37 (11)	.2977
Taking medication, did not stop before surgery	15/49 (31)	.6188	11/49 (22)	.360	9/49 (18)	1.000
Taking medication, stopped before surgery	6/24 (25)		3/24 (13)		4/24 (21)	
Steroids						
Not taking medication	15/61 (25)	.639	10/61 (16)	1.00	11/61 (18)	1.00
Taking medication, did not stop before surgery	14/43 (33)	1.000	11/43 (26)	1.000	6/43 (14)	1.000
Taking medication, stopped before surgery	2/6 (33)		1/6 (17)		1/6 (17)	

Abbreviations: DMARDs, disease-modifying antirheumatic drugs; NSAIDs, nonsteroidal antiinflammatory drugs.
* χ^2 tests, with the first *p* value comparing complication rates between patients who were not taking the medication with patients who were taking the medication and did not stop before surgery, and the second *p* value comparing patients who stopped taking the medication with patients who did not stop taking the medication.

patient's baseline medications and may require escalation to a stronger immune suppressive regimen. Continuing certain medications perioperatively can help prevent flare-ups of RA and help with the postoperative pain rehabilitation process (13,14).

NSAIDs are common medications that function to reduce prostaglandin synthesis, which decreases inflammation, thus reducing rheumatoid symptoms. Bibbo et al (12) found that of 104 patients with RA, 64% were taking an NSAID; however, there was no statistically significant result to conclude that NSAIDs were responsible for increased postoperative complications. In our study, 42 (38%) patients were taking NSAIDs. Thirty (71%) of the patients taking NSAIDs stopped at least 2 weeks before surgery, which is typically recommended to reduce bleeding risk in surgery. Studies in animals have shown that NSAID use inhibits the bone formation pathway; however, there is conflicting evidence within in vivo human research, and NSAID use and nonunions cannot be conclusively linked (13,15). A systematic literature review by Kurmis et al (16) suggests that short-term NSAID use is a safe and effective supplement to multimodal pain management without significantly increasing the risk of complications in healing. Blending the available evidence across specialties, the short-term use of NSAIDs in the postoperative period should be balanced between the potential risks in healing and the benefits in pain management. Furthermore, NSAIDs should be withheld at least 5 half-lives before surgery to decrease bleeding risk (8).

First-line medications in the defense of symptoms of RA typically include DMARDs, with most literature referencing methotrexate. Kawakami et al (17) assessed variations in postoperative complication rates among patients with RA undergoing total joint surgery and taking either DMARDs or TNF-α medications, and found only a 2% risk of surgical site infection and a 26% risk of deep vein thrombosis in the DMARD group. Grennan et al (18) looked at patients undergoing orthopedic surgery and did not find an increased risk of infection or wound healing in patients who continued methotrexate use before and after surgery. In patients who continued the methotrexate, the risk of flare was 0% compared with 8% in patients who stopped methotrexate preoperatively. Bibbo et al (12) found that taking DMARDs in the perioperative period did not have a direct association with complications after foot and ankle surgery. Similar to previous studies, DMARDs used in our study were not correlated with postoperative complications. This suggests the continued use of DMARDs throughout the perioperative period is safe and may help decrease the risk of a rheumatoid flare.

Perioperative corticosteroid use can contribute to a variety of postoperative complications, most notably soft tissue complications. These complications include impaired wound healing, increased friability of

Table 4
Logistic regression results for experiencing a postoperative complication by demographic, clinical, medication use, and procedural characteristics

Characteristic	Model 1 Overall Complications OR (95% CI)	Model 2 Soft Tissue Complications OR (95% CI)	Model 3 Bone Complications OR (95% CI)
Demographic			
Age (every 10-y increase)	1.03 (0.67 to 1.53)	0.9 (0.57 to 1.43)	0.93 (0.56 to 1.54)
Sex (reference = female)	1.85 (0.63 to 5.37)	2.94 (0.90 to 9.64)	2.96 (0.79 to 11.09)
White race (reference = nonwhite)	2.06 (0.76 to 5.57)	2.34 (0.75 to 7.29)	1.62 (0.45 to 5.93)
Clinical		—	
Body mass index (continuous)	1.04 (0.97 to 1.11)	—	—
Peripheral neuropathy (reference = no)	2.48 (0.73 to 8.45)		2.54 (0.61 to 10.65)
Medication use			
NSAIDs (reference = no)	—	—	2.14 (0.64 to 7.15)
Procedural			
Nonelective (reference = elective)	—	4.23 (1.12 to 16.00)	—
Location (reference = forefoot)			
Midfoot	—	—	4.17 (0.48 to 36.17)
Rearfoot	—	—	2.09 (0.36 to 12.16)
Surgery duration (every 15-min increase)	1.21 (1.07 to 1.37)	1.28 (1.11 to 1.46)	1.22 (1.05 to 1.42)

Abbreviations: CI, confidence interval; NSAIDs, nonsteroidal antiinflammatory drugs; OR, odds ratio.
Models adjust for demographic characteristics and variables with a value of $p \leq 1.000$ in the respective bivariate analyses in Table 1.

skin and blood vessels, hyperglycemia, and fluid retention (19). It is widely documented in the orthopedic literature that high-dose steroids continued through the perioperative period lead to an increased risk of infection (1,19-21). Looking at the relationship between steroids and bone healing, Lems (7) found that glucocorticoid use in patients with RA reduced bone formation, whereas bone resorption was unchanged or elevated. This led to increased osteoclast activity and reduced bone strength. These negative effects on bone healing were dose dependent (7). Khanna et al (20) evaluated spinal fusion with various antirheumatoid medications and found that patients taking higher-dose steroids (>7.5 mg daily) had smaller improvements in Nurick scores. Although they found that all the medications were safe for fusions, Khanna et al (20) suggested decreasing prednisone to <7.5 mg daily and decreasing biologic DMARD use. Akkara Veetil and Bongartz (8) suggested that an adrenocorticotropic hormone stimulation test can help clarify if steroids should be stopped before surgery. They recommended using <10 mg/daily and to use a stress dose of steroids only if the adrenocorticotropic hormone stimulation test shows impairment (8). Our study did not find a significant relationship between steroid use and complication rates; however, this may be owing to the low number of patients taking steroids in our cohort.

Biologic DMARDs have shown improvement in controlling RA symptoms and decreasing the progression of the disease. Despite the frequent use of the medication, there are no clear guidelines on the perioperative use of these medications, especially within the foot and ankle literature. The generalized use of TNF-α inhibition agent etanercept revealed an increase in the general rate of infection throughout the patient treatment course (12). Bibbo and Goldberg (22) compared a group of patients who were taking biologic DMARDs with a group of patients who were not. They found that it was safe to continue etanercept and infliximab throughout the perioperative period without an increased risk for postoperative soft tissue complications (22). Den Broeder et al (5) did not find that TNF-α inhibitors increased surgical infections in 1219 elective orthopedic procedures (odds ratio [OR] 1.5, 95% confidence interval [CI] 0.43 to 5.2). Conversely, Kawakami et al (17) found that patients with RA undergoing total joint replacement had a 12.5% incidence of surgical site infection if they were taking an anti–TNF-α agent compared with 2% in the DMARD group ($p = .36$, OR 21.80). Additionally, in this group taking TNF blockers, 51% had a positive deep vein thrombosis result compared with 26% in the DMARD group ($p = .03$, OR 2.83) (17).

There is sparse literature evaluating biologic DMARD use in relation to bone healing. Although overexposure of TNF-α leads to local bone and cartilage loss in patients with RA, it also serves as an important regulator for fracture healing. In a mouse model study by Timmen et al (23), it was found that high levels of TNF-α inhibitors negatively influenced fracture healing, reduced cartilage production, and created more soft tissue callus instead of bone, thus decreasing overall the biomechanical bone stability. They suggested that TNF-α inhibitors could slow bone healing by lowering the biomechanical stability and increasing the flexibility of the callus, which could, in turn, increase the chance of nonunion (23). Peter et al (24) gave beagles alendronate before, after, or both before and after fracture. Those that received the medication developed 2 to 3 times as much bone callus and had slower bone healing but did not inhibit complete bone healing (24). In this study, no statistically significant association was found between taking biologic DMARDs and postoperative risks, but it is generally recommended to hold at least 1 dose before surgery, usually about 1 month preoperatively (8).

Longer duration of surgery had a significant increase in complication risks in our patient population. It is appreciated in the orthopedic literature that a prolonged operative time has been found to have an increased risk of postoperative infection (18). Peersman et al (25) reviewed 6489 total knee arthroplasties and found that as operative time increased, the patient was at a statistically significantly increased risk for postoperative infection. They also found that BMI was directly correlated to operative time. In our study, we found that increased BMI trended toward an increase in complications in foot and ankle surgery. Taking an even closer look at surgical time, we found that for every 15-minute increase in surgery, there was a 1.2-fold increased risk of complication. In addition, nonelective cases were associated with a higher risk for soft tissue complications compared with elective cases. The nonelective patient population was included to capture more of the patients whose medications were not stopped before surgery. It is difficult to elucidate if this is because of the increase in energy associated with trauma, longer potential surgical times, or the medication itself. A larger cohort of patients undergoing nonelective traumatic surgery would be needed to further define this relationship more clearly.

Peripheral neuropathy had a significant increase on overall and osseous complications. The effects of peripheral neuropathy are well documented in patients with diabetes and Charcot arthropathy (26). This is likely because of the inability to feel pain and potential noncompliance with postoperative non-weightbearing, which increases the chance of a delayed union or nonunion.

This study design had some inherent limitations. There are a variety of antirheumatic medications available for the treatment of RA, and it was challenging to capture the true relationship of certain medications when the number of patients taking a medication was low. This study included only surgery involving at least 1 osseous procedure while excluding isolated soft tissue or metatarsal head resection, which may have limited the amount of soft tissue infections seen in the RA population. However, the available literature has well documented the potential of soft tissue complications and has not highlighted the potential for bone healing issues, thereby providing an impetus for this research study. Looking at the procedure types, arthrodesis of various joints in the foot carries varying inherent nonunion rates. Sixty-five percent of the procedures in this study involved an arthrodesis, mostly involving the rearfoot, with the documented nonunion rates varying from 5% to 15% in the literature. The nonunion rate of 8% in our study is within the recognized risk of nonunion. Expanding the number of patients may help define the relationship between the antirheumatic medications and soft tissue and bone healing complications.

In conclusion, increased surgical duration and peripheral neuropathy conferred statistically higher rates of postoperative complications. The various types of antirheumatic medication did not seem to have an influence on the risk of soft tissue or osseous complications. However, for NSAID, conventional DMARD, and biologic DMARD drug classes, there seems to be a trend toward higher complication rates in patients actively taking the medication. For some medication types, patients who discontinued their medication generally had rates of complications like those patients who were not ever taking the medication. This suggests a possible benefit from holding medications; however, the decision to hold antirheumatic medication should be weighed against the risk of the patient developing a rheumatoid flare. When working with patients with RA, our study findings suggest the importance of considering the risk of surgery duration and the potential risk of antirheumatic medications in the perioperative period. Future research on antirheumatic medications in the perioperative period with larger sample sizes is needed.

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