Risk Factors Associated With Increased Metal Sensitivity: A Retrospective Analysis Among 25,081 Patients With a Total Knee Arthroplasty

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INTRODUCTION: Total Knee Arthroplasty (TKA) is one of the most common orthopedic procedures, with >1 million cases performed annually in the United States, with a projected growth of 139% by 2040. Despite high success rates, patient (pt) reported dissatisfaction after TKA is as high as 10-20 % because of pre- and post-operative factors, often leading to revision TKA. The FDA acknowledges biological responses to metal implants including metal sensitivity as potential complications leading to poor clinical outcomes among TKA pts. Although in vitro metal sensitivity diagnostic tests are available and routinely performed to rule out metal sensitivity, it remains unknown what pt-specific demographics and clinical characteristics are associated with higher odd ratios (ORs) for positive metal sensitivity leading to a higher risk of implant failure. In this retrospective analysis of 25,081 all-comer primary and revision TKA pts suspected of metal sensitivity, we hypothesized that pt-specific demographic and clinical characteristics are associated with increased lymphocyte measures of metal sensitivity.
METHODS: Blinded, de-identified in vitro metal sensitivity bloodwork data (N=25,081) was reviewed retrospectively for n=11,903 TKA candidates pre-operatively and for n=13,178 TKA pts post-operatively dating from November 2009 to April 2023. Pt demographics and clinical characteristics such as gender, age, implant-referrable pain, implant time in situ, and history of drug or metal allergy were analyzed to identify OR with a 95% confidence interval (CI) associated with lymphocyte sensitization to implant metal(s) (ie, nickel). ORs for pt factors were calculated based on three levels of in-vitro metal sensitivity: a-Sensitive (stimulation index [SI]>4), b-Highly Sensitive (SI>8), and c-Extremely sensitive (SI>15) compared to non-metal sensitive pts (SI <2). Statistical significances were calculated with a student's t-test for demographic differences and Fisher's Exact Probability test for ORs differences.
RESULTS: General demographic data of N=13,178 post-operative TKA pts showed 35% of women exhibit statistically significant higher rates (*P*<.05) and severity (mean SI 6.7; *P*<.0001) of metal sensitivity vs. men, Table 1. Women with TKA post-operatively exhibited both higher implant-referrable pain and rates of history of metal allergy than males (6.5 vs. 6.0, *P*<.0001; 33% vs. 2%, *P*<.05, respectively), Table 1. Risk factors associated with increased metal sensitivity ORs among TKA patients included women for highly (OR 1.8; 95% CI 1.6–1.9) and extremely sensitive (OR 2.3; 95% CI 2.0–2.6; each, *P*<.005), Table 2, Figure 1. Pts with a TKA with a history of metal allergy also exhibited statistically significant ORs for highly (OR 1.7; 95% CI 1.6–1.9), and extremely sensitive (OR 2.2; 95% CI 2.0–2.5; each, *P*<.005), and pts post-operatively with high implant-referable pain for highly (OR 1.2; 95% CI 1.1–1.5) and extremely sensitive (OR 1.4; 95% CI 1.1–1.8; each, *P*<.05), Table 2, Figure 1. Other characteristics with slightly elevated ORs included history of drug allergies and taking anti-inflammatory medication at time of testing for both highly and extremely metal sensitive (*P*<.05). Overall, TKA patient age (<65 y) and implant time in situ did not show statistically significant higher ORs.
DISCUSSION: This extensive cohort data review spanning over a decade, 50 states, and a multitude of orthopedic practices show that specific demographic and clinical characteristics are associated with increased risk of implant metal sensitivity, such as female pts with a TKA, pts with a TKA and history of metal allergy, and pts with high TKA-referable pain.
SIGNIFICANCE/CLINICAL RELEVANCE: A diagnosis of metal sensitivity is not a diagnosis of current or future implant failure but rather a diagnosis of higher risk for implant failure due to a potential adverse biological response. Understanding which pt-specific characteristics have a higher probability of metal sensitivity is vital to help mitigate risks associated with metal sensitivity-related implant complications.
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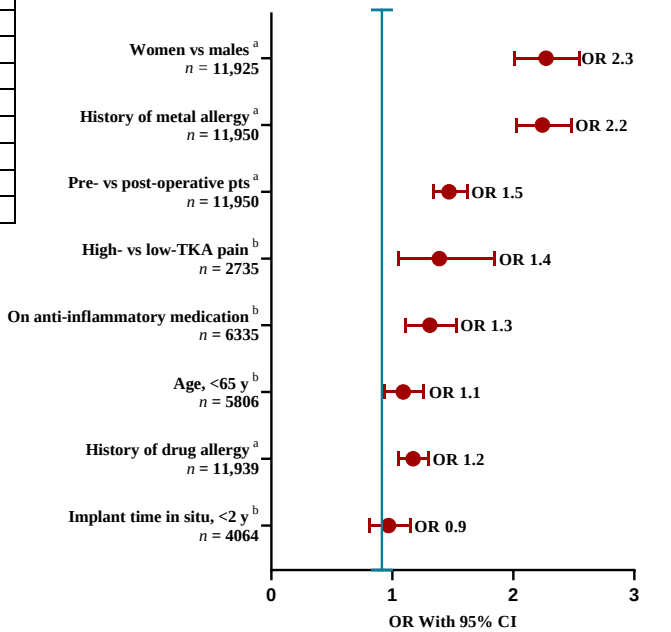
TABLE 1. Patient Demographics and Clinical Characteristics	**Men (*N* = 7350)**	**Women (*N* = 17,699)**	***P* Value**
Mean age, y [a]	63.4	63.4	0.94
History of metal allergy, n (%) [a]	147 (2.0%)	5802 (33%)	<0.05
History of drug allergy, n (%) [a]	590 (8.0%)	4927 (28%)	<0.05
Pre-operative (no implant), n (%)	2634 (36%)	9269 (52%)	0.87
Adults with TKA, n (%) [b]	4729 (64%)	8449 (48%)	0.90
Mean age of TKA, n	3.1	3.4	<0.05
Mean pain score, VAS (0-10)	6.0	6.5	<0.0001
LTT SI > 8 to Ni, Co, Cr, n (%)	563 (12%)	1582 (19%)	<0.05
LTT SI > 4 to Ni, Co, Cr, n (%)	1213 (26%)	2915 (35%)	<0.05
Median LTT SI to Ni, Co, Cr	4.3	6.7	<0.0001

Co, cobalt; Cr, chromium; LTT, lymphocyte transformation test; Ni, nickel; SI, stimulation index; TKA, total knee arthroplasty; VAS, visual analog score. [a] Includes pre- and post-operative orthopedic patients. [b] Includes only post-operative patients with a TKA.

TABLE 2. Patient Risk Factors Associated With Metal Sensitivity	**Patients Analyzed, *N***	**Sensitive (LTT SI > 4) OR (95% CI), *P* value**	**Highly Sensitive (LTT SI > 8) OR (95% CI), *P* value**	**Extremely Sensitive (LTT SI > 15) OR (95% CI), *P* value**
Women vs males [a]	18,308	1.5 (1.4 –1.6) **	1.8 (1.6 – 1.9) **	2.3 (2.0 – 2.6) **
History of metal allergy [a]	18,285	1.4 (1.3 –1.5) **	1.7 (1.6 –1.9) **	2.2 (2.0 –2.5) **
Pre- vs post-operative pts [a]	18,310	1.3 (1.2 –1.3) **	1.4 (1.3 –1.5) **	1.5 (1.3 –1.6) **
High- vs low-TKA pain [b]	4134	1.2 (1.0 –1.5) *	1.2 (1.1 –1.5) *	1.4 (1.0 –1.8) *
On anti-inflammatory medication [b]	9526	1.1 (1.0 –1.2) *	1.2 (1.1 –1.4) *	1.3 (1.41 –1.5) *
Age, <65 y [b]	8714	1.1 (1.0 –1.2) *	1.0 (0.9 –1.1)	1.1 (0.9 –1.3)
History of drug allergy [a]	18,286	1.0 (1.0 –1.1)	1.1 (1.0 –1.2) *	1.2 (1.0 –1.3) **
Implant time in situ, <2 y [b]	6084	1.0 (0.9 –1.1)	1.0 (0.9 –1.1)	0.9 (0.8 –1.1)

***P*<.005, **P*<.05; LTT, lymphocyte transformation test; OR, odds ratio; Pt, patient; SI, stimulation index; TKA, total knee arthroplasty. [a] Includes pre- and post-operative orthopedic patients. [b] Includes only post-operative patients with a TKA.

Figure 1. Patient Risk Factors Associated With Extreme Metal Sensitivity SI>15



[a] Includes pre- and post-operative orthopedic patients. [b] Includes only post-operative patients with a TKA.