Risk Factors Associated with Increased Metal Sensitivity: A Retrospective Analysis of Over 25,000 Total Knee Arthroplasty Patients

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INTRODUCTION:

Total Knee Arthroplasty (TKA) is an effective intervention with over 1 million cases annually in the United States with a projected growth of 139% by 2040. Despite high success rates, patient-reported dissatisfaction after TKA is as high as 10-20% due to multiple, preoperative and postoperative factors. While in vitro metal sensitivity diagnostic tests are available and routinely performed to rule out metal sensitivity, it remains unknown what patient-specific demographics and clinical characteristics are associated with higher odd ratios for positive metal sensitivity leading to higher risk of implant failure. In this retrospective analysis of 25,081 all-comer primary and revision TKA patients suspected of metal sensitivity, we hypothesized that patient-specific demographic and clinical characteristics are associated with increased lymphocyte measures of metal sensitivity.

METHODS:

In-vitro metal sensitivity bloodwork data (N=25,081) was reviewed retrospectively for n=11,903 TKA candidates preoperatively and for n=13,178 TKA patients postoperatively dating from 2009 to 2023. Patient demographics and clinical characteristics were analyzed to identify Odd Ratios (OR) with 95% confidence intervals (CI) associated with lymphocyte sensitization to implant metals (i.e., nickel). ORs for patient 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-sensitive patients (SI <2). Statistical significances were calculated with student's t-test for and Fisher's Exact Probability test.

RESULTS:

Female patients exhibit higher rates (37.3%; $P<0.05$) and severity (mean SI 6.7; $P<0.001$) of metal sensitivity compared to males (25.7%; mean SI of 4.3, respectively). Postoperative TKA female patients exhibited higher implant-referable pain and higher rates of dermal sensitivity to jewelry than males (6.5 vs. 6.0, $P<0.0001$; 32.8% vs. 3.11%, $P<0.05$, respectively), Table 1. Females showed higher odd ratios for metal sensitivity (OR 1.8; 95% CI 1.6–1.9), (OR 2.3; 95% CI 2.0–2.6) for highly sensitive and extremely sensitive, respectively ($P<0.005$). TKA patients with a history of dermal sensitivity to jewelry also exhibited higher ORs (OR 1.7; 95% CI 1.6–1.9), (OR 2.2; 95% CI 2.0–2.5) ($P<0.005$) as well as postoperative TKA patients with high implant-referable pain (OR 1.2; 95% CI 1.1–1.5), (OR 1.4; 95% CI 1.1–1.8) for highly sensitive and extremely sensitive, respectively ($P<0.05$). Other characteristics with slightly elevated ORs included history of drug allergies, (OR 1.1; 95% CI 1.0–1.2), (OR 1.2; 95% CI 1.0–1.3) ($P<0.05$), and taking anti-inflammatory medication at the time of testing (OR 1.2; 95% CI 1.1–1.4), (OR 1.3; 95% CI 1.1–1.5) ($P<0.05$). TKA patient age (<65 years) and implant time in situ did not show statistically significant higher ORs. Table 2, Figure 1.
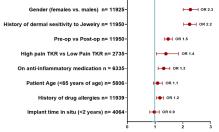
DISCUSSION AND CONCLUSION:

These data demonstrate that specific demographic and clinical characteristics are associated with elevated odd ratios for metal sensitivity in specific pre- and postoperative TKA patients. Female TKA patients, TKA patients with a history of dermal sensitivity to jewelry, and TKA patients with high implant-referable pain exhibited the highest ORs for metal lymphocyte sensitivity. In agreement with previous studies correlating high implant-referable pain to metal sensitivity, TKA patients with highly painful implants exhibited 50% higher odds of being highly metal sensitive compared to TKA patients with low implant pain—suggesting that metal sensitive, non-infected TKA patients may experience higher levels of pain due to the inflammatory effects of high metal lymphocyte reactivity. Also, in addition to having higher rates and severity of metal sensitivity, female TKA patients were 130% more likely than males to be extremely sensitized to metals (SI>15). This substantial difference is correlated to similar ORs (120% more likely) found for TKA patients with a history of dermal sensitivity to jewelry, which is frequently found in females, Fig.1. TKA patients with a history of drug allergies exhibited a slight, but significant ORs for metal sensitivity, which is likely due to these patients' ability to form drug-haptens in a similar way to metal-haptens inducing an immune response. Fig.1. This extensive cohort data review spanning over a decade, 50 states, and a multitude of orthopaedic practices, supports our hypothesis that specific demographic and clinical characteristics are associated with increased risk of implant metal sensitivity. It is important to distinguish that 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 patient-specific characteristics have a higher probability of metal lymphocyte sensitivity is vital to help mitigate risks associated with metal sensitivity-related implant complications.

TABLE 2

Patient risk factors associated with positive metal lymphocyte sensitization	# of TKA patients analyzed (n)	Sensitive (SI > 4) Odd Ratio (95% CI) * p value	Highly sensitive (SI > 8) Odd Ratio (95% CI) * p value	Extremely sensitive (SI >15) Odd Ratio (95% CI) * p value
Gender (females vs. males)	18308	**1.5** (1.4 - 1.6) **	**1.8** (1.6 - 1.9) **	**2.3** (2.0 - 2.6) **
History of dermal sesitivity to Jewelry	18285	**1.4** (1.3 - 1.5) **	**1.7** (1.6 - 1.9) **	**2.2** (2.0 - 2.5) **
Pre-op vs. Post-op	18310	**1.3** (1.2 - 1.3) **	**1.4** (1.3 - 1.5) **	**1.5** (1.3 - 1.6) **
High pain TKR vs. Low pain TKR	4134	**1.2** (1.0 - 1.5) *	**1.2** (1.1 - 1.5) *	**1.4** (1.0 - 1.8) *
On anti-inflammatory medication	9526	**1.1** (1.0 - 1.2) *	**1.2** (1.1 - 1.4) *	**1.3** (1.1 - 1.5) *
History of drug allergies	18286	**1.0** (1.0 - 1.1)	**1.1** (1.0 -1.2) *	**1.2** (1.0 - 1.3) **
Patient Age (<65 years of age)	8714	**1.1** (1.0 - 1.2) *	**1.0** (0.9 - 1.1)	**1.1** (0.9 - 1.3)
Implant time in situ (<2 years)	6084	**1.0** (0.9 - 1.1)	**1.0** (0.9 - 1.1)	**0.9** (0.8 - 1.1)

** p<0.005
* p<0.05

TABLE 1.	MALE	FEMALE	p value
TOTAL TESTED (n)	n= 7350	n= 17699	
AVG PATIENT AGE (years)	63.4	63.4	0.94
Pre- operative testing (no implant)	2634 (35.8 %)	9269 (52.4 %)	0.87
KNEE IMPLANTS (n)	4729 (64.2 %)	8449 (47.6 %)	0.9
AVG IMPLANT AGE AT TESTING (years)	3.1	3.4	<0.05
HISTORY OF METAL ALLERGY (n)	147 (3.11%)	5802 (32.8 %)	<0.05
HISTORY OF DRUG ALLERGY (n)	590 (12.47 %)	4927 (27.8 %)	<0.05
AVG PAIN SCORE (SCALE 0-10)	6.02	6.51	< 0.0001
POSITIVE LTT TO Ni, Co, Cr [SI > 8] (n)	563 (11.9 %)	1582 (20.23 %)	<0.05
POSITIVE LTT TO Ni, Co, Cr [SI > 4] (n)	1213 (25.7 %)	2915 (37.3 %)	<0.05
MAX LTT STIMULATION TO Ni, Co, Cr (SI)	4.3	6.7	< 0.0001

TKR PATIENTS RISK FACTORS ASSOCIATED WITH POSITIVE METAL SENSITIZATION

- Gender (females vs. males) n= 11925 — OR 2.3
- History of dermal sesitivity to Jewelry n= 11950 — OR 2.2
- Pre-op vs Post-op n= 11950 — OR 1.5
- High pain TKR vs Low Pain TKR n= 2735 — OR 1.4
- On anti-inflammatory medication n = 6335 — OR 1.3
- Patient Age (<65 years of age) n= 5806 — OR 1.1
- History of drug allergies n= 11939 — OR 1.2
- Implant time in situ (<2 years) n= 4064 — OR 0.9

ODD RATIOS WITH 95% CI