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## ***Stronger Relationship than Subtitle Suggests***

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I read the article by Yang et al. with great interest. The study is a needed link between histopathological studies, diagnosis of patient-specific in-vitro metal hypersensitivity reactions, and clinical outcomes in painful aseptic TKA patients.

The findings indicate that metal sensitization can be a predictor of a potential immune response (i.e. ALVAL) around the bone-implant interface, given that among 27 patients with a wide range of confounding factors such as age, BMI, time of revision, and Knee Society Score, there was identifiable peri-implant lymphocyte accumulations in 22 of 27 (81%) TKA patients with positive metal-LTT scores.

However, the authors glossed over the relationship between moderate ALVAL scores (5 to 8) and the level of in-vitro metal hypersensitivity found in this cohort. According to the authors' own Appendix data, 12.5% of patients with mild in-vitro sensitivity exhibited moderate ALVAL, 25% of patients with moderate in-vitro sensitivity exhibited moderate ALVAL, and 27% of patients with high in-vitro metal sensitivity exhibited moderate ALVAL scores confirmed by histopathology. Furthermore, as acknowledged in the manuscript, the authors failed to include a control group (nonsensitive patients) to compare their metal-sensitive group to. In our view, a control group should be a requisite to making any meaningful clinical comparison. Despite the study's conclusion that there is little relationship between in-vitro metal sensitization, histopathological findings, and revision outcomes, the data shows that 100% of the in-vitro metal sensitive cohort (n=27) exhibited ALVAL scores varying from low to moderate, including 22% with a moderate ALVAL score.

This publication is a much-needed study of the relationship between in-vitro metal sensitization and clinical outcomes in painful TKR patients. We find that the results, when viewed from an incidence level, may not support the conclusion. In-vitro metal sensitivity testing is not meant to provide a diagnostic result related to a clinical outcome, but rather a diagnostic result related to a condition (lymphocyte metal sensitization) that should be considered a risk factor for poor implant performance. In the case of this study, 22% of the metal-sensitive group with a wide range of confounding factors presented with a moderate ALVAL score at the time of revision surgery and 78% presented with mild ALVAL ranging from 1 to 4.

We thank the authors for an excellent study; however, we contend that there should be more attention paid to the higher incidence of poor implant performance (i.e. aseptic pain, ALVAL) in patients with diagnosed in-vitro metal sensitivity, rather than to trying to draw a direct correlation between a diagnosed condition and a clinical outcome.

**Conflict of Interest:**

Marco S. Caicedo, Ph.D is COO/Senior Scientist at Orthopedic Analysis, LLC.