Sex Differences Associated with Th17/IL-17 Serum Biomarker Expression in Orthopedic Populations

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Introduction: Previous reports indicate that sex discrepancies exist with respect to perioperative complications and implant failures for some types of implants[1]. It remains unknown however, what biological mechanisms cause this discrepancy. Do female orthopedic patients exhibit a more excessive immune inflammatory profile compared to male orthopedic patients? We hypothesize that female patients will show quantitively different patterns of inflammatory protein serum expression vs. male patients.

Methods: Metal-LTT[1] and cytokine serum markers from de-identified individuals using Luminex Multi-Analyte Assay was approved by Rush University IRB. Group 1= Male No TJR; n=8, Group 2= Female No TJR; n=9, Group 3= Male TJR; n=13 (77% TKA; mean implant time in situ 1.2 yr.), Group 3= Female TJR; n=13 (69% TKA; mean implant time in situ 1.5 yr.). Statistical differences were determined using unpaired t-test at statistical significance at $p \leq 0.05$ using Graphpad Prism 6.0.

Results: Male and female TJR patients exhibit increased serum expression of Th17-cell dependent cytokines: IL-17A, IL-23, and IL-22 compared to respective non-TJR group (Fig 1). However, in general, female TJR patients exhibit the greatest expression of Th17-cell inflammatory cytokines. While male non-TJR group exhibit a Th2 cell based immune profile due to pronounced levels of Th2-cell cytokines: IL-5, IL-9, and IL-2, which are known to suppress the differentiation/expression of Th17 cells. Increased immune inflammatory profile may account in part, for increased metal sensitivity as exhibited among female patients.

Conclusion: These results indicate that females have higher levels of Th17 immune inflammatory biomarkers post-operatively, which may be in part, the underlying biological mechanism responsible for sex discrepancies associated with implant complications e.g. Type IV metal sensitivity. This retrospective study was not able to determine if these results are due to a pre-existing condition prior to TJR, immune responses were triggered post TJR or a combination of both these elements. It is likely that a larger study of pre-op patients would yield statistical increases female Th17 reactivity over males. In conclusion, our findings suggest targeting Th17/IL-17 and/or skewing the immune response to Th2-cell based reactivity, may be an effective strategy to combat peri-implant inflammation and/or diagnose those predisposed to experience problems.

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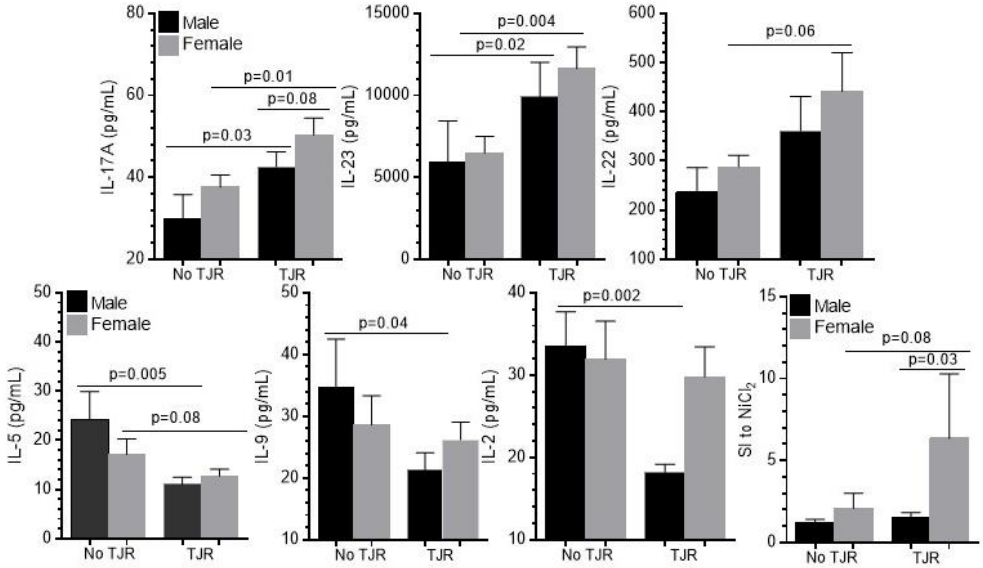

Figure 1. Serum levels of prototypical CD4+ Th17 (IL-17A, IL-23 and IL-22) and Th2 cell cytokines (IL-5, IL-9 and IL-2) among age-matched male and female non-TJR individuals compared to male and female TJR patients and rates of in vitro metal reactivity to nickel via LTT (metal-reactive stimulation index; SI>4). Note: Black bar=Male and Dark grey bar=Female.