Lymphocyte Reactivity to Metals in Subjects with Metal-On-Metal Hip Arthroplasty

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INTRODUCTION: Some patients with total joint arthroplasties can tolerate large debris burdens for long periods of time (>8 years) with relatively little peri-implant reactivity, whereas other patients with similar particulate and ionic burdens demonstrate pronounced osteolysis or soft tissue problems within 2-7 years, such as metal debris induced pseudotumours.[1,2] Immunologic responses (e.g. cell-mediated hypersensitivity) associated with metal components may be partly responsible for differential reactivity. Previous reports have indicated that patients with metal-on-metal total hip arthroplasty over the long term (>10years) have elevated levels of immune reactivity to metals in proportion to the amount of circulating metal.[1] Thus, we hypothesized that patients with metal-on-metal total hip arthroplasty will acquire elevated metal-reactivity responses over time in proportion to metal exposure. We tested this hypothesis using a prospective longitudinal study of subjects receiving metal-on-metal hip arthroplasty (surface replacement) and comparing metal specific reactivity (e.g. proliferation responses) of primary lymphocytes to soluble metal challenge (Al^{+3}, Co^{+2}, Cr^{+3}, Fe^{+3}, Mo^{+5}, Nb^{+5}, Ni^{+2}, Zr^{+2}, and V^{+3} chloride solutions) at 0.01mM and 0.1mM at 3 time points: pre-operatively, 2-4 months and 1-2 years.

MATERIALS AND METHODS: Two groups of subjects totaling 27 were used in this investigation: Group 1-healthy controls (n=8, 4 male, 4 female, average age 30 yrs, range 23-63 yrs), Group 2-subjects with THA (n=19, 8 male, 9 female, average age 68, range 55-80, all ConservePlus, Wright Medical). Human primary lymphocytes were isolated from 30 mls of blood (15-30 x 10^6 cells per subject) and incubated with DMEM and 10% autologous serum with either no metal (plain media) as a negative control, 0.01 mg/ml phytohemagglutinin (PHA) as a positive control and Al^{+3}, Co^{+2}, Cr^{+3}, Fe^{+3}, Mo^{+5}, Ni^{+2}, Zr^{+2}, and V^{+3} chloride solutions at 0.01mM and 0.1mM at 3 time points: pre-operatively, 2-4 months and 1-2 years. The amount of lymphocyte proliferation was normalized to that of the negative "control" (no challenge agent), and this stimulation index, SI was used for inter- and intra-group comparison. Statistical comparisons used students t-test for SI data and Kruskil-Wallis for metal ion data, where an "*" on the graphs indicates $p<0.05$ when compared to pre-op conditions/controls.

RESULTS: To date, all subjects are doing well with no radiographic signs of lysis and no clinical signs of soft tissue problems. *Metal Ion Concentrations:* Subjects with surface replacements demonstrated >20x increase in serum Cr and >8x increase in serum Co at 2-4 months and 1-2 years post-op (Fig 1). Average metal ion concentrations did not increase from 2-4 months to 1-2 years, and they have not been determined to be "dangerously" elevated, from a clinical perspective. Group 2 subjects with metal-metal bearings demonstrated a linear correlation between serum Cr and serum Co levels (Fig 2). Levels of ions are in the "acceptable range" in most cases. *Lymphocyte Reactivity:* There was an increase in the incidence in metal reactivity over the course of 2 years from 7/19 (37%) reactive pre-op to 10/19 (53%) reactive at 2-4 months post-op to 7/9 (78%) reactive at 2-4 years, where an SI>2 to any metal was used as an "+" indication of metal reactivity.[1] This increase in incidence of metal reactivity also reflected in the average levels of metal reactivity over time (Fig 3), where 1-2 years Group 2 samples tested at 0.01mM were statistically elevated over 2-4 months, pre-op, and controls levels of reactivity to Al, Co, Cr, and Ni. The highest levels of metal reactivity were to Ni at 1-2years post-op. *Lymphocyte Reactivity vs Serum Metal Concentrations:* None of the groups at any time point demonstrated a correlation between metal ion levels and lymphocyte reactivity (SI). There was a linear correlation between Co reactivity and Cr reactivity at 2-4 months post-op (Fig 4).

DISCUSSION: There was a statistically significant increase in metal reactivity in subjects with metal-on-metal surface replacement THA implants from pre-operative to 1-2 years post operatively. This finding only partially supports our hypothesis. This pre to post operative increase was shown for Co and Cr metal ion levels and metal LTT reactivity to Al, Co, Cr, and Ni. However, these prospective results only partially support our hypothesis and previous assertions of a direct linkage between in vivo metal ion exposure and lymphocyte reactivity[1] because in the short term (0 to 2 years) we did not find a correlation (significant or otherwise) between serum metal ion levels and levels of metal reactivity as measured by LTT. Linear correlations between Co and Cr serum metal ion levels suggest that released metal and resulting dissemination results from wear mechanisms and corrosion where Cr tends to be preferentially released. Linear correlations between Co and Mo reactivity at SI<2 levels in only Group 2 at post-op intervals implies acquired cross-reactivity. However, it remains unknown how high Mo levels can be in the peri-implant area and whether they are relevant. Whether elevated lymphocyte reactivity to metal is predictive of early or eventual revision arthroplasty remains undetermined and is currently the subject of continued follow-up study.

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Reference List

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2. Pandit H, Glyn-Jones S, McLardy-Smith P, et al. Pseudotumours associated with metal-on-metal hip resurfacings. J Bone Joint Surg Br 2008; 90:847-51.

Figure 1.

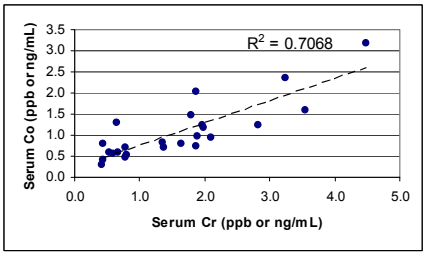

Figure 2.

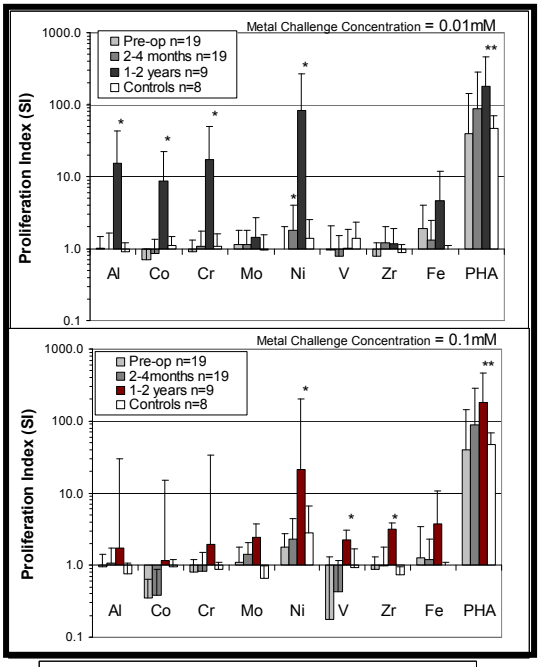

Figure 3.