INTRODUCTION  Cross-linking of ultra-high molecular weight polyethylene (UHMWPE), with it’s associated alterations in the physico-chemical characteristics, has markedly improved wear resistance (1,2). Hip simulator studies have demonstrated 80-100% decreases in wear rates using these new materials (1,2), potentially decreasing UHMWPE debris generation and resulting clinical sequelae. While alterations in cross-linking induced material characteristics are well studied, information regarding potential changes in the biological response is limited. Thus the purpose of this study was to characterize the cellular response to cross-linked UHMWPE (XLPE) surfaces using clinically relevant in-vitro models. We used human peripheral blood monocytes and murine macrophages as surrogates for cells mediating peri-implant inflammation, and evaluated gene expression and release of bone resorbing cytokines after culture onto material surfaces. These investigations will provide essential insight into the inflammatory properties of XLPE before the onset of wear and degradation.

MATERIALS AND METHODS  Lipped culture disks were designed to isolate cells on the material and prevent contact with the tissue culture dish (Fig 1, inset). Disks were fabricated from cross-linked UHMWPE (XLPE, electron beam irradiated @ 100 KGy, Zimmer), conventional UHMWPE (CPE), titanium-alloy (TiAlV), and cobalt-chrome alloy (CoCr). Surfaces were characterized using an optical stereomicroscope and surface profilometer. XLPE disks were sterilized by plasma glow discharge, while other disks were irradiated in an inert environment.

**Human peripheral blood monocyte** were from peripheral blood donated by healthy volunteers (n=5) and purified by sequential discontinuous Percoll gradients (3). Monocytes were cultured in Macrophage/ Serum-Free (M-SFM, GibcoBRL) supplemented with 1% penicillin/streptomycin. **Murine macrophages** (RAW 264.7, ATCC) were plated at 2x10^6 cells/disk and each experimental condition was conducted in triplicate for each disk type and the entire experiment was repeated four times. Cells were characterized using an optical stereomicroscope and surface profilometer. XLPE disks were sterilized by plasma glow discharge, while other disks were irradiated in an inert environment.

RESULTS  Non-stimulated macrophages in both in-vitro models released basal levels of IL-1, TNF-α and IL-6, while cells cultured with LPS were stimulated to release up to 45 times basal levels. In human and murine models, cells cultured on the two PE surfaces released similar levels of mediators, which were also similar to cytokine release on control tissue culture surfaces. Among the human volunteers, while the trends in cytokine release were similar, there were differences in the actual levels of cytokines released. To highlight the variability among donors, the data was not pooled and individual donor data is plotted (Fig 1, Donor #2). In 4/5 cases, CoCr surfaces were most stimulatory to the human monocytes and elicited a 5-15 fold increase in IL-1β levels over NS-controls. TiAlV disks also stimulated the human monocytes significantly, but at levels not as high as CoCr. This was also observed in the murine macrophage model (Fig 2). Increasing culture time from 24h to 48h only increased the magnitude of cytokine levels and the trends in material response were not altered. Qualitative analysis of RT-PCR data correlates well with cytokine release data and suggests that cytokine levels seen were due to de-novo cytokine gene transcription initiated by material interactions.

DISCUSSION  While it is well documented that cross-linking of UHMWPE reduces the crystallinity and alters the material properties (1,2), our investigations demonstrate that these changes did not affect cytokine release by human monocytes or RAW macrophages. Both XLPE and CPE surfaces elicited similar levels of bone resorbing cytokines. The heightened stimulation of macrophages cultured on metallic disks demonstrates the sensitivity of the model system in recognizing and responding to different biomaterial surfaces. The variability in individual donor responses to TiAlV and CoCr surfaces may reflect how individuals respond differently to similar stimuli and perhaps reveal a predisposed sensitivity to particular materials. Variations in host response is believed to be an important reason why total joint replacements fail in only a small number of patients, whereas wear of components occurs in all patients. In the future, it may be beneficial to determine a patient’s tolerance to different biomaterials in an attempt to modulate the inflammatory response and consequent implant failure.

Acknowledgements: Authors are grateful to Dale Swarts and William Clarke (Zimmer) for providing materials and Zimmer for supporting the study.

References

48th Annual Meeting of the Orthopaedic Research Society
Poster No: 1082