INTRODUCTION:
Recent efforts to reduce the incidence of osteolysis after total hip arthroplasty include the introduction of highly crosslinked polyethylenes (HXPE). While much is known regarding the improved biomaterial properties of HXPE, there is little information regarding the relative biologic activity of the wear particles generated. The net biologic response to wear debris is affected by many factors including the volume of wear debris, the relative inflammatory potential of the generated particulate debris, and the presence or absence of endotoxin. It is clear that endotoxin is capable of stimulating an inflammatory response and that removing endotoxin from particles substantially reduces this activity under some conditions. Endotoxin has been shown to have a high affinity for polyethylene and can increase the inflammatory response to conventional polyethylene (CPE). However, the relative affect of endotoxin on the biologic response to CPE and HXPE is not clear. Any differential affects of endotoxin on the inflammatory response to HXPE or CPE wear debris could substantially effect predictions regarding improved outcomes after total hip replacement due to improved wear behavior for HXPE compared with CPE. The goal of this study was to test the hypothesis that endotoxin will have similar stimulatory effects on the inflammatory response to HXPE and CPE particles using an in vivo murine model.

METHODS:

**Particle Preparation**

Ceridust 3615 high density polyethylene (CD) was crosslinked via e-beam irradiation at 10 MRad and 40 MRad. CD particles were characterized by Densitometric Scanning Calorimetry (DSC), Fourier Transform Infrared spectroscopy (FTIR) and Transvinylene Index (TVI). Size distribution profiles were determined using scanning electron microscopy (SEM) and a commercial particle analyzer. LPS was added to polyethylene debris using a recently published protocol demonstrating greater efficacy than previous methods.

**Endotoxin Testing**

A standardized LAL endotoxin detection test (QCL-1000, Cambrex, Inc) was modified to detect both bound and soluble endotoxin levels in all samples. In Vivo Osteolysis Experiments

The inflammatory response to crosslinked and non-crosslinked CD debris was quantified using an established murine calvarial model. Endotoxin-spiked titanium was used as a positive control. Eight mice (C57BL/6) were used in each treatment group.

**Statistical Analysis**

ANOVA was used to analyze differences between treatment groups. An unpaired T-test was used to compare endotoxin-free to LPS-positive particles at each crosslinking dose. When comparing the percent change relative to control, a paired T-test was used.

RESULTS:

DSC and FTIR characterization of GUR 1050 and CD demonstrated the anticipated decrease in melting point and increase in TVI associated with increased crosslinking. The mean diameter of particles was 6.98 microns. Endotoxin levels were undetectable (<0.005 EU/ml) for all endotoxin-free groups. All endotoxin-positive and endotoxin-negative groups had more osteolysis than the vehicle-only SHAM groups (p<0.0001). All LPS-positive particle groups elicited a higher biologic response than the endotoxin-negative groups (p<0.07).

DISCUSSION:
Endotoxin increases the inflammatory response to conventional polyethylene and titanium wear debris in vitro and in vivo. The effect of endotoxin on the relative inflammatory response to conventional compared with highly crosslinked polyethylene had not been studied to date. Significant differences in the relative affinity of endotoxin for HXPE and CPE could affect the prediction that the improved wear noted for HXPE compared with CPE will result in reduced rates of osteolysis.

Figure 1: Dose-Response to Crosslinking in presence and absence of LPS (endotoxin).

Our study demonstrates that endotoxin increased the inflammatory response to both conventional and highly crosslinked polyethylene to a similar degree (Figure 1). This suggests that crosslinking polyethylene at clinically relevant levels (10MRads) or even at higher levels (40MRads) did not substantially change the affinity of endotoxin compared with non-crosslinked (conventional) polyethylene.

Some limitations exist in our study. First, we used a well characterized high density polyethylene (Ceridust) rather than highly crosslinked ultra-high molecular weight polyethylene (UHMWPE). This decision was based on the large volumes of particles needed for in vivo analysis and the limited amounts of highly crosslinked UHMWPE generated due to its improved wear properties. Second, the in vivo murine model used in this study is well established and has been used previously to study the inflammatory response to wear debris. However, it is possible that subtle differences could exist between endotoxin positive and negative HXPE and CPE that are below the detection limits of this model.

In conclusion, our data supports the hypothesis that endotoxin binds with similar affinity to crosslinked and conventional polyethylene. The improved wear noted for some HXPEs compared with CPE suggests reduced long-term rates of osteolysis using these new materials if the particles generated have similar inflammatory response profiles. Our data supports the hypothesis that the presence or absence of endotoxin will not negatively effect the prediction that the improved wear noted for HXPE compared with CPE will result in reduced rates of osteolysis.

Long-term clinical analysis is needed to confirm these predictions.

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ACKNOWLEDGEMENTS:
We’d like to acknowledge grant support from the OREF. Microradiographs were graciously performed by Vicki Kalscheur at the UW School of Veterinary Medicine, Comparative Orthopedic Research Laboratories.

THE EFFECT OF ENDOTOXIN ON THE RELATIVE BIOREACTIVITY OF CONVENTIONAL AND HIGHLY CROSSLINKED POLYETHYLENES
Ilgen, R I; Hotuje, D; Bauer, I M.; Forsythe, T M
University of Wisconsin, Madison, WI
illgen@orthorehab.wisc.edu

Poster No: 1792

53rd Annual Meeting of the Orthopaedic Research Society