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Characteristics of highly cross-linked polyethylene wear debris *in vivo*

Ryan M. Baxter¹, Daniel W. MacDonald¹, Steven M. Kurtz^{1,3}, and Marla J. Steinbeck^{1,2}

¹School of Biomedical Engineering, Science & Health Systems, Drexel University, Philadelphia, Pennsylvania

²College of Drexel Medicine, Drexel University, Philadelphia, Pennsylvania

³Exponent Inc, Philadelphia, PA, USA

Abstract

Despite the widespread implementation of highly cross-linked polyethylene (HXLPE) liners to reduce the clinical incidence of osteolysis, it is not known if the improved wear resistance will outweigh the inflammatory potential of HXLPE wear debris generated *in vivo*. Thus, we asked: What are the differences in size, shape, number, and biological activity of polyethylene wear particles obtained from primary total hip arthroplasty revision surgery of conventional polyethylene (CPE) versus remelted or annealed HXLPE liners? Pseudocapsular tissue samples were collected from revision surgery of CPE and HXLPE (annealed and remelted) liners, and digested using nitric acid. The isolated polyethylene wear particles were evaluated using scanning electron microscopy. Tissues from both HXLPE cohorts contained an increased percentage of submicron particles compared to the CPE cohort. However, the total number of particles was lower for both HXLPE cohorts, as a result there was no significant difference in the volume fraction distribution and specific biological activity (SBA; the relative biological activity per unit volume) between cohorts. In contrast, based on the decreased size and number of HXLPE wear debris there was a significant decrease in total particle volume (mm^3/g of tissue). Accordingly, when the SBA was normalized by total particle volume (mm^3/gm tissue) or by component wear volume rate (mm^3/year), functional biological activity of the HXLPE wear debris was significantly decreased compared to the CPE cohort. Indications for this study are that the osteolytic potential of wear debris generated by HXLPE liners *in vivo* is significantly reduced by improvements in polyethylene wear resistance.

Keywords

total hip replacement highly cross-linked polyethylene osteolysis wear debris biological activity

INTRODUCTION

Ultrahigh-molecular-weight polyethylene (hereafter, polyethylene) wear particle-induced osteolysis and, ultimately, implant loosening are recognized as major factors limiting the longevity of total joint replacement components.^{1–4} Osteolysis is complex, and while particles are the driving force, it is important to note that other contributing factors include component design and placement, access to the bone-implant interface, intracapsular

pressure, and patient disposition (e.g., tissue responses to wear debris). To improve implant wear resistance and decrease the incidence of osteolysis, first-generation highly cross-linked polyethylenes (HXLPEs) were introduced as an alternative to conventional, gamma inert-sterilized polyethylene [conventional polyethylene (CPE)].^{5–8} The first generation of HXLPE components were created by an initial phase of gamma irradiation followed by an annealing or remelting phase performed below or above the crystalline transition temperature, respectively, and then gamma-sterilized and packaged in an inert environment or sterilized using a nonionizing method (e.g., EtO gas sterilization or gas plasma sterilization).^{6,9,10} To date, both approaches have yielded improved clinical outcomes with regard to the reduction of osteolysis at early term (< 5 year)^{11–16} and midterm (5–10 year) follow-up.^{17–22} Despite these promising results, annealed polyethylene contains residual free radicals that are not eliminated by heating below melting temperature, leaving the potential for oxidation and component weakening *in vivo*.^{23–26} In contrast, remelted polyethylene contains no detectable (or few detectable) free radicals but has a lower crystallinity and consequently reduced mechanical (fatigue) properties.^{27–30} Moreover, the observation of comparable surface damage for both CPE and newer HXLPE components³¹ raises questions regarding the generation of inflammatory wear debris.^{32,33} Second-generation HXLPE materials containing antioxidants have been developed to eliminate residual radicals without changing the mechanical properties of the material⁶; however, the benefit of these modifications has not been established for longer implantation times.

Despite the introduction of HXLPE liners >10 years ago, the characterization of HXLPE wear debris is predominantly limited to wear simulations of total hip arthroplasty (THA)^{34–41} or total knee arthroplasty^{42–44} bearing designs *in vitro*. Although these studies have unfailingly shown a reduction in the wear volume of HXLPE when compared with CPE components, there is less agreement regarding a similar reduction in the number of HXLPE particles.^{35,41,45} Furthermore, *in vitro* studies have shown a reduction in particle size with increased cross-linking.^{35,40,46,47} Early *in vitro* studies demonstrated that exposure to polyethylene wear debris within a critical, biologically relevant size range (0.1–1 μm) resulted in enhanced monocyte activation and proinflammatory cytokine expression.^{48–50} More recently, HXLPE and CPE wear debris were isolated from a hip simulator and added to monocytes *in vitro*. At the highest particle concentration based on surface area ratio, the macrophage expression of tumor necrosis factor alpha (TNF α), a potent proinflammatory cytokine, was increased by 50% in response to HXLPE wear debris (mean size, 0.111 μm) compared to CPE wear debris (mean size, 0.196 μm).⁴⁷ These *in vitro* results highlight the importance of understanding whether the substantially improved wear resistance will outweigh the inflammatory potential of HXLPE wear debris generated *in vivo*. Thus, we asked: What are the differences in size, shape, number, and estimated potential biological activity of polyethylene wear particles obtained from primary THA revision surgery of CPE versus remelted or annealed HXLPE liners?

MATERIALS AND METHODS

Patient selection

Pseudocapsular tissue samples were collected from 14 patients undergoing revision arthroplasty of uncemented, metal-on-polyethylene hip components. Informed consent was obtained prior to tissue collection, and all procedures were performed in accordance with Institutional Review Board guidelines of the participating institutes. For the CPE gamma inert-sterilized cohort ($n = 4$, Howmedica Omnifit, Biomet Ringloc, Zimmer Trilogy), liners were revised after an average of 6.4 years (range 2.3–9.3 years) for polyethylene wear, loosening and osteolysis (Table I). For the highly cross-linked (HXLPE) cohort ($n = 5$ for each, remelted Zimmer Trilogy, annealed Stryker Trident), liners were revised after an

average of 3.3 years (ranges 1.7–6.6 years) for loosening or malposition (Table I). Implantation time was not significantly different between cohorts ($p = 0.333$, Kruskal–Wallis).

Component analysis

Twelve of the 14 patients with tissue samples had retrieved liners for penetration analysis. The polyethylene liners were cleaned using a 10% bleach solution and subsequently sonicated to remove any loose debris. Penetration was measured directly using a digital point-tipped micrometer (accuracy = 0.001mm). Volumetric penetration was calculated using a previously described method.⁵¹ Component information for all three polyethylene cohorts is provided in Table II, including head diameter, penetration (mm) and rate (mm/year), and calculated penetration volume (mm³) and rate (mm³/year).

Wear particle isolation

At the time of surgery, tissue samples were collected, fixed, dehydrated, and embedded in paraffin. Wear particle isolation was performed on paraffin-embedded tissues using methods modified from Margevicius et al.⁵² Tissues were removed from paraffin blocks, placed in 10 mL xylene overnight and then sequentially washed twice in xylene and twice in 100% ethanol for 3 min each. After drying for 2 h, 0.05 g of tissue was placed in a polypropylene tube and digested in 5 mL 65% HNO₃ at room temperature. After 24 h, tissues were agitated and left to digest for an additional 24 h. In a previous study, we compared tissue digestion by acids, bases, and enzymes and found HNO₃ to be the most complete without affecting wear particle morphology or size.⁵³

Following digestion, solutions were thoroughly mixed with a G560 vortex (Scientific Industries, Bohemia, NY) for three 30-s intervals then sonicated for 2 min to achieve uniform particle dispersion. Subsequently, the sample was vacuum filtered through a polycarbonate membrane with a 1.0 µm pore size (Whatman, Billerica, MA) and the filtrate containing submicron particles was collected. After filtration, the membrane was washed for 10 min with 10 mL of fresh 65% HNO₃ followed by methanol. To prevent particle agglomeration, the filtrate containing submicron particles was diluted with 15 mL of methanol containing 2% Nonidet P-40[®] (NP40 substitute; AppliChem GmbH, Darmstadt, Germany), a nonionic surfactant. The solution containing surfactant was mixed with a vortex for three 30-s intervals then sonicated for 2 min to reduce agglomeration. After sonication, the samples were filtered through a membrane with a 0.05 µm pore size. As before, the membrane was sequentially washed with 10 mL solutions of 65% HNO₃ and methanol. Based on the thorough digestion of tissue, centrifugation steps were not employed during wear particle isolation. Each membrane was then dried for 2 h at room temperature and prepared for imaging.

Imaging

Polycarbonate membranes with isolated polyethylene wear debris were fixed onto aluminum stubs with double-sided carbon tape. Membranes were sputter coated with a 5-nm-thick layer of platinum/palladium using a 208 HR vacuum sputter coater (Cressington, Watford, UK) in order to eliminate sample drift caused by the electron beam. Particles were visualized using a XL30 environmental scanning electron microscope (FEI/Phillips, Hillsboro, OR) at a working distance of 12 mm and a beam intensity of 5 kV. Imaging was performed in the Drexel University Centralized Research Facilities.

Membranes with a pore size of 1.0 µm were imaged at magnifications of 500× and 1000×; five and 10 images were collected, respectively. Membranes with a pore size of 0.05 µm were imaged at a magnification of 10,000×; 10 images were collected from three separate

regions, which did not include the true edge or center of the membrane to account for flow gradient effects during filtration. A minimum of 1000 particles was analyzed for each patient. For each polyethylene cohort, >1000 particles were analyzed. To validate the purity of polyethylene particles, multiple regions of polycarbonate membranes from two patient tissue digests were scanned using Fourier transform infrared (FTIR) Spectroscopy (Nicolet/Thermo Fisher Scientific, Waltham, MA) in transmission and compared with blank membranes. A comparison of the current FTIR findings with previous spectra showed agreement in the vibration peaks for polyethylene.⁵⁴

Wear particle analysis

Image analysis of environmental scanning electron micrographs was performed using a gray-scale level threshold in Adobe Photoshop (San Jose, CA). After analysis of the histogram, the threshold (grayscale value) corresponding to the right side of the main peak was chosen for all images. Subsequently, using a scale bar from each micrograph, particle areas and dimensions were determined using a custom macro in National Institutes of Health ImageJ. The resulting areas and dimensions were used to characterize particle number, size [equivalent circular diameter(ECD), Eq. (1), Table III] and shape [aspect ratio between debris height and width), Eq. (2); roundness, Eq. (3); form factor, Eq. (4)] based on the guidelines for wear particle analysis outlined in ASTM F1877 (Table III).⁵⁵

To characterize the particle biological activity, we used equations based on a model of cytokine secretion from cultured macrophages in response to varying doses of particle size and volume.^{56–58} The biological activity function, $B(r)$, which separately ranks the biological relevance of particles in <0.1–1, 1–10, and >10 μm size ranges, was assumed to be the same as previously published [Eq. (5)].⁵⁶ To determine particle volume in the current study, V_p [Eq. (6)], calculations were based on the work of Scott et al.⁵⁹ (Table III). Subsequently, the volume fraction distribution, $V(r)$ [Eq. (7)], was determined for the <1, 1–10, and >10 μm size ranges (Table III).⁵⁶ For each component, volumetric penetration rate was determined using measured linear penetration along with the geometric diameter of liner [Eq. (8)]. To determine the relative biological activity per unit volume [specific biological activity (SBA); Eq. (9)], the product of $B(r)$ and $V(r)$ was evaluated over each size range (Table III). The highest predicted value of SBA, 1, would be obtained if particle volumes were all in the <1 μm size range. Finally, to determine functional biological activity, FBA [Eq. (10)], SBA was normalized by the total particle volume (mm^3/g of tissue, or by component wear volume rate [mm^3/year ; Eq. (11)] as suggested by Fisher et al.⁵⁶ (Table III).

Inflammatory response

Brightfield images were scored for the presence of macrophages and giant cells using a modified Mirra classification.⁶⁰ For each tissue sample five microscopic fields (500 $\times$) were scored for macrophages based on a 0–3+ scale: 1+ equaled 1–9, 2+ equaled 10–49, and 3+ $\geq$ 50 macrophages/field. For giant cells, five fields were scored at 250 $\times$; 1+ equaled 1–2, 2+ equaled 3–8, and 3+ equaled $\geq$ 9 giant cells/field.

Statistical analysis

For each polyethylene cohort, we evaluated the size, shape, number, and biological activity of polyethylene wear debris from periprosthetic tissues. Initial statistical analysis revealed that there were no differences in penetration rates, particle characteristics, or inflammatory responses among the highly cross-linked groups (annealed and remelted cohorts), thus the cohorts were combined for the purposes of this study. To determine whether particle characteristics varied by polyethylene cohort (conventional vs. remelted or annealed HXLPE), differences were determined by Kruskal–Wallis analysis of variance. Subsequent

statistical comparisons using Wilcoxon Mann–Whitney were performed when the original Kruskal–Wallis tests were significant. Based on a previous analysis of particle biological activity from revised total disc replacement components, the sample size in the current study was sufficiently powered (>90%) to detect a significant difference in functional biological activity. Statistical analysis was performed using JMP 9.0 (SAS Institute, Cary, NC).⁵⁸

RESULTS

Differences in penetration volume and number of wear debris particles CPE and HXLPE cohorts

As expected, the volumetric penetration rates were significantly lower for the highly cross-linked liners when compared with conventional polyethylene ($p = 0.013$; Table II). The HXLPE cohorts also had a lower number of particles per gram of tissue compared to the CPE cohort [$p = 0.005$; Figure 1(A)]. However, for the HXLPE cohort tissues submicron particles represented ~95% of the total wear debris, which was significantly higher than the 90% found in CPE cohort tissues [$p = 0.016$; Figure 1(B)].

Differences in particle size and shape between CPE and HXLPE cohorts

Differences in the size of the particles were observed between conventional- and highly cross-linked-polyethylene cohorts; however, the shape of the particles for all three cohorts was similar (Table IV). Specifically, the mean ECD was 26% larger for the CPE cohort when compared with the HXLPE cohort [mean difference = $0.11 \mu\text{m}$; $p = 0.016$; Figure 1(C)]. For particle shape, >90% of the particles were granular or ellipsoidal for all three groups, and no detectable differences were observed with respect to aspect ratio (mean difference = 0.13 ; $p = 0.396$), roundness (mean difference = 0.023 ; $p = 0.435$), or form factor (mean difference = 0.092 ; $p = 0.056$; Table IV). The percentage of fibrils represented >10% of the total debris in all patient tissues and no significant difference was detected between cohorts (mean difference = 1.5% ; $p = 0.396$; Figure 2).

Differences in wear volume and estimated potential biological activity between CPE and HXLPE cohorts

To determine the SBA per unit volume, particles were separated by size ranges that represent high ($<0.1\text{--}1 \mu\text{m}$), intermediate ($1\text{--}10 \mu\text{m}$), and low ($>10 \mu\text{m}$) biological activity. Initially comparing the percentages of particle volume (mm^3) in each size range revealed no significant differences between cohorts (Table IV). The volume percentage in each size range was then normalized by a ranked biological activity scalar to determine particle SBA, which was also comparable between cohorts [$p = 0.135$; Figure 3(A)].

On the contrary, major differences were observed between cohorts when total particle volume (mm^3) was normalized per gram of tissue or normalized by volumetric penetration rate of the implant to obtain FBA. Specifically, the CPE cohort had a >90% increase in particle volume (mm^3)/g compared to the HXLPE cohort wear debris ($p = 0.005$). Thus, after normalizing SBA by the total particle volume (mm^3 /g) to obtain functional biological activity (FBA), significant increases were observed for particles from the CPE cohort compared to the HXLPE cohort [$p = 0.005$; Figure 3(B)]. Similarly, using component volumetric penetration rates (mm^3/year) to calculate FBA as suggested by Fisher et al.,⁵⁶ the FBA values of particles from the CPE cohort were higher [$p = 0.013$; Figure 3(C)].

For HXLPE cohort tissues, a mild inflammatory response (1+) to the presence of wear particles was observed in 7 of 10 patient tissues (Table I). On the contrary, the macrophage responses for the CPE cohort tissues were significantly higher ($p = 0.002$), and giant cells were only observed in this group. When considering all three cohorts, macrophage scores

were positively correlated with the FBA calculated using particle volume per gram and volumetric penetration rate (Spearman's $Rho = 0.74$ and 0.78 ; $p = 0.002$ and 0.003 , respectively). Similar, but weaker positive correlations were observed between FBA (calculated using particle volume per gram and volumetric penetration rate) and giant cell scores (Spearman's $Rho = 0.57$ and 0.88 ; $p = 0.035$ and 0.114 , respectively).

DISCUSSION

Despite the widespread implementation of HXLPE liners to reduce the clinical incidence of osteolysis, it is unknown if the substantially improved wear resistance will outweigh the inflammatory potential of HXLPE wear debris generated *in vivo*. Thus, we asked: What are the differences in size, shape, number and estimated potential biological activity of polyethylene wear particles obtained from primary THA revision surgery of CPE versus remelted or annealed HXLPE liners?

We acknowledge the limitations of our study. First, the analysis of wear debris from pseudocapsular tissues may represent a conservative estimate of the total number of particles in the environment surrounding the joint. However, by selecting the same tissue region for all three polyethylene cohorts, we do not bias the current comparison of wear particle characteristics. Second, the lower size limit of wear debris was determined using polycarbonate membranes with a pore size of $0.05 \mu\text{m}$. However, this pore size is only expected to exclude a small percentage ($\sim 2.8\%$) of particles whose biological activity is still under investigation *in vitro*.^{61–64} Third, the limited availability of tissues resulted in both the inclusion of a small number of patients and the use of implants from different manufacturers for the CPE group. As more samples become available, additional studies will be undertaken. Finally, we used a previously published model to estimate the functional biological activity of wear debris that was based on the amount of TNF α released by cultured macrophages in response to wear debris of various sizes.⁵⁶ In the current *in vivo* study, we correlated macrophage and giant cell responses to wear debris characteristics, rather than relying on TNF α measurements in tissue.

The current study showed that both remelted and annealed first-generation HXLPE liners used in THA generated significantly fewer and smaller particles than CPE liners.⁶⁵ Our findings additionally show HXLPE wear particle volume was reduced and resulted in a significant decrease in FBA regardless of method used to calculate the FBA. These findings suggest that careful particle recovery based on proper filtration and isolation techniques may allow particle volume to serve as a surrogate for calculating FBA in the absence of component volumetric wear information. Other investigations of HXLPE wear debris *in vivo* are limited to two case studies of THA liners, both of which were revised after the development of severe wear conditions.^{32,33} In the first study, rerevision of a cemented THA was performed after 4 years following the collapse of a hydroxyapatite (HA) impaction graft. Scanning electron microscopy (SEM) analysis showed a mean particle size of $0.66 \mu\text{m}$, which was more than twofold larger than in our current study ($0.31 \mu\text{m}$). This size difference may be attributed to their methodological exclusion of $<0.2 \mu\text{m}$ particles, the effect of HA granules embedded in the acetabular liner and/or the effect of using tissue samples from rerevision THA. In addition, their summary of particle shape showing a maximum aspect ratio of 2.4 was considerably different than the current findings, which identified aspect ratios as large as 10 in both HXLPE cohorts. In the second study, revision of a cemented THA was performed after 2 years due to osteolysis and impingement of the acetabular rim. Polarized light and SEM analysis of periprosthetic tissue sections indicated that particle size ranged from 1 to $5 \mu\text{m}$, but a full particle characterization was not performed.⁵³

In agreement with our current findings, *in vitro* studies evaluating differences in wear debris from CPE and HXLPE liners have shown decreased HXLPE particle size and a concomitant increase in the percentage of submicron particles for these liners.^{35,39,66} Overall, the mean HXLPE particle size in the current study, 0.31 μm , falls within the ranges reported for the articulation of HXLPE against smooth (0.08–0.26 μm)^{36,39,45,47} and artificially roughened counter-faces (0.39–0.50 μm).^{41,67}

Similar to *in vitro* characterizations of particle shape, we observed predominantly granular or ellipsoidal particles with fibrils occurring at a frequency of approximately 5% in both HXLPE cohorts.^{41,47} In a separate *in vitro* study, the incidence of fibrils (aspect ratio >4) decreased with increased cross-linking, whereas we did not detect a difference in the percentage of fibrils between polyethylene cohorts.³⁵ In an extensive study of wear by Wang,⁶⁸ the formation of fibrillar extensions was observed on the bearing surface along the predominant direction of wear, which could potentially be released during multidirectional motion. Thus, fibrillar debris observed in our study may represent the liberation of these surface extensions due to cross-shear and multidirectional loading *in vivo*. These findings are concerning given studies showing increased gene expression of IL-1 β and TNF- α in response to fibrils in a murine model of osteolysis.^{69,70}

In vitro studies have consistently reported a decrease in component wear of HXLPE liners compared to CPE.^{36,39,67} However, our result showing a reduced number of HXLPE particles lacks a clear consensus *in vitro*, with studies reporting increased, similar and decreased particle numbers for HXLPE liners compared to CPE.^{35,41,45} On the other hand, our findings for particle number more consistently agree with *in vitro* studies showing an increased percentage of submicron particles generated from HXLPE liners compared to CPE liners.^{34,39,66}

For particle volume distribution, several *in vitro* studies have shown an increase in the submicron volume percentage of wear debris generated by HXLPE components.^{34,39} However, our findings most closely agree with a recent study investigating the biological activity of wear debris generated from HXLPE and CPE liners *in vitro*.⁷¹ In their study and our own, neither the distribution of particle volume nor the relative biological activity per unit volume of wear debris (SBA) was significantly different between polyethylene cohorts. Others have also observed similar values of SBA after testing HXLPE and CPE liners against artificially roughened counterfaces.^{41,66} Mean values of SBA in the current study, 0.31 for both HXLPE cohorts, were again within the range of values (0.08 and 0.86) previously reported for articulation of HXLPE against smooth and artificially roughened counterfaces, respectively.^{41,71}

In the current study and others, increases in the level of cross-linking resulted in a significant reduction in the total volume of HXLPE wear debris.^{41,71} Thus, despite an increased percentage of submicron particles in both HXLPE cohorts, our assessment of wear debris from periprosthetic hip tissues revealed a significant decrease in FBA for both HXLPE cohorts. Of note, the largest value of FBA_{particle} for either HXLPE cohort (0.37) was from an annealed HXLPE liner revised for malposition after 5.2 years. The increased particle volume contributing to the FBA was predominantly due to an increase in overall particle size. Overall, the current data provide a direct confirmation that the osteolytic potential of HXLPE wear debris *in vivo* is outweighed by a significant improvement in wear resistance. The lack of agreement previously shown between gravimetric wear and particle number *in vitro*⁴⁶ highlights the importance of evaluating the particle characteristics and their potential biological activity of wear debris from revision tissues.

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FIGURE 1.

Particle number and size comparisons for the HXLPE and conventional cohorts. (A) Particle number. There were significantly fewer particles in tissues from the HXLPE cohort compared to the CPE cohort ($p = 0.005$). (B) Particle number percentage based on size. The number of particles in the submicron range ($0.05\text{--}0.99\text{ }\mu\text{m}$) was significantly increased for the HXLPE cohort ($p = 0.016$). (C) Particle size. The average particle size based on equivalent circular diameter was smaller for the HXLPE cohort ($p = 0.016$). The column labeled “HXLPEs” represents the combined data from remelted and annealed HXLPE cohorts. Provided are medians with a boxed range of 25–75th percentile data and whiskers showing the 10th and 90th percentile data. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FIGURE 2.

Representative environmental scanning electron microscopic images of polyethylene wear debris from CPE and HXLPE. (A) CPE, (B) annealed, and (C) remelted cohorts. Based on aspect ratio and roundness, the majority of particles in the CPE cohort and both HXLPE cohorts were either granular or ellipsoidal. For wear particles generated *in vivo* and isolated from periprosthetic tissues, the percentage of fibrils represented >10% of the total wear debris, and were only found in the CPE cohort.

FIGURE 3.

Specific biological activity and functional biological activity measurements for the HXLPE and CPE cohorts. (A) SBA comparisons. No difference was detected in the SBA values between the two cohorts. (B) FBA comparisons based on particle volume. After normalizing SBA by the total particle volume (mm^3/g of tissue), FBA was significantly lower for the HXLPE cohort compared to the CPE cohort. (C) FBA comparisons based on implant wear rate. Similarly, normalizing SBA using volumetric penetration rate (mm^3/year) of the implant resulted in a FBA value that was significantly lower for the HXLPE cohort compared to the CPE cohort. Provided are medians with a boxed range of 25–75th percentile data and whiskers showing the 10th and 90th percentile data. Outliers are shown as open circles. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE I

Summary of Patient Clinical Information

Tissue/Explant #	Implant Model	Revision Reason	Implantation Time (year)	Gender	Age at Revision (year)	Radiographic Osteolysis	Macrophage/Giant Cell (0-3+ range)
Gamma inert cohort							
RIH346/645	Howmedica Omnifit	Loose (fem.)	2.3	F	78	Y	3/3
RIH280/591	Biomet Ringloc	PE wear, instability	5.1	F	63	N	3/1
RIH400/692	Biomet Ringloc	Loose (acet. and fem.)	8.8	F	66	Y	2/0
RIH286/595	Zimmer Trilogy	Loose (fem.)	9.3	F	66	Y	3/0
Remelted HXLPE cohort							
RIH107/451	Zimmer Trilogy	Loose (acet. & fem.)	1.7	F	66	N	1/0
RIH658/878	Zimmer Trilogy	Loose (fem.)	1.7	F	56	N	1/0
RIH254/570	Zimmer Trilogy	Malposition	2.9	F	58	N	1/0
RIH656/876	Zimmer Trilogy	Loose (fem.)	3.6	M	59	N	0/0
CWH007/766	Zimmer Trilogy	Dislocation	6.6	F	67	N	0/0
Annealed HXLPE cohort							
RIH199/520	Stryker Trident	Loose (fem.)	2.0	M	55	N	0/0
RIH413/702	Stryker Trident	Loose (acet.)	2.7	F	57	N	1/0
RIH194/515	Stryker Trident	Loose (acet.)	5.2	F	57	N	1/0
RIH460/736	Stryker Trident	Malposition	5.2	F	71	N	1/0
RIH450/729	Stryker Trident	Loose (fem.)	5.9	M	63	N	1/0

Fem., femoral; acet., acetabular; macrophage and giant cells scores: 1+, 1–9 macrophages/high power field (500×) and 1–2 giant cells/medium power field (250×); 2+, 10–49 macrophages/high power field and 3–8 giant cells/medium power field; 3+, 50 macrophages/high power field, and 9 giant cells/medium power field.

The combined chronic inflammatory response (macrophage and giant cells) was positively correlated with FBA Particle ($\rho = 0.74$; $p = 0.002$).

TABLE II

Summary of Component Information

Tissue/Explant #	Head Diameter (mm)	Penetration (mm)	Calculated Penetration Volume (mm ³)	Penetration Rate (mm/year)	Calculated Volumetric Penetration Rate (mm ³ /year)
Gamma inert cohort					
RIH346/645					
RIH280/591	22	1.45	2202	Liner not received from institution 0.28	432
RIH400/692	32	0.58	1869	0.07	212
RIH286/595	28	0.89	2191	0.10	236
Remelted HXLPE cohort					
RIH107/451	32	0.05	166	0.03	98
RIH658/878	32	0.05	171	0.03	100
RIH254/570	32	0.06	207	0.02	71
RIH656/876	32	0.06	177	0.02	49
CWH007/766	32	0.01	30	0.00	5
Annealed HXLPE cohort					
RIH199/520					
RIH413/702	32	0.07	232	Liner not received from institution 0.03	86
RIH194/515	28	0.04	100	0.01	19
RIH460/736	28	0.03	79	0.01	15
RIH450/729	32	0.05	155	0.01	26

TABLE III

Calculations Used to Determine Wear Particle Characteristics: Size, Shape, Volume, and Biological Activity

Equation #	Parameter	Equation	Definition
1	ECD (μm)	$\sqrt{\frac{4 \cdot A_p}{\pi}}$	Diameter of a circle with an area equivalent to the particle area (A_p) ³
2	AR	$\frac{L_p}{W_p}$	Ratio of particle length to particle breadth ³
3	R	$\frac{4 \cdot A_p}{\pi \cdot (L_p)^2}$	Length-based measure of circularity ranging from zero to one (perfect circle) ³
4	FF	$\frac{4 \cdot \pi \cdot A_p}{(\text{perimeter})^2}$	Perimeter-based measure of circularity ranging from zero to one (perfect circle) ³
5	$B(r)$	$\left\{ \begin{array}{c} \text{Scalar} \\ 1.00 \\ 0.20 \\ 0.04 \end{array} \right\} \left\{ \begin{array}{c} \text{Particlerange} \\ ECD < 1 \text{ mm} \\ 1 \text{ mm} < ECD < 10 \text{ mm} \\ ECD > 10 \text{ mm} \end{array} \right\}$	Biological activity scalars for individual size ranges
6	V_p	$1 \text{ sol}; 18 \cdot \pi \cdot ECD^3$	Individual particle volume
7	$V(r)$	$\left\{ \begin{array}{c} \sum V_{p(ECD < 1 \mu\text{m})} \\ \sum V_{p(1 \mu\text{m} < ECD < 10 \mu\text{m})} \\ \sum V_{p(ECD > 10 \mu\text{m})} \end{array} \right\} \cdot \frac{1}{\sum V_{p(\text{Total})}}$	Volume fraction distribution
8	V_{PR}	$\pi \cdot d^2 \cdot L_{PR}$	Volumetric penetration rate calculated using measured linear penetration rate and the diameter of the liner
9	SBA	$\sum V(r) \cdot B(r)$	Specific biological activity (SBA) per unit volume of wear debris ²
10	FBA_{particle}	$SBA \cdot V_{\text{Total}}$	Functional biological activity (FBA), SBA scaled by V_{Total} ²
11	FBA_{implant}	$SBA \cdot V_{PR}$	Functional biological activity (FBA), SBA scaled by V_{PR}

ECD, equivalent circular diameter; A_p , particle area; AR, aspect ratio; L_p , particle length; W_p , particle width; R , roundness; FF, form factor; $B(r)$, biological activity scalars by size range; V_p , particle volume; $V(r)$, volume fraction distribution; SBA, specific biological activity; FBA, functional biological activity; V_{Total} , particle volume (mm^3)/g as determined by penetration rate.

TABLE IV

Summary of Wear Particle Characteristics

Category	Parameter	Remelted HXLPE (<i>n</i> = 5), Mean ± 1 SD (Median)	Annealed HXLPE (<i>n</i> = 5), Mean ± 1 SD (Median)	Conventional (CPE; <i>n</i> = 4), Mean ± 1 SD (Median)	HXLPE Compared to CPE, <i>p</i>
Size	ECD (μm)	0.32 ± 0.37 (0.20)	0.31 ± 0.39 (0.20)	0.43 ± 0.53 (0.26)	0.005
Shape	AR	2.00 ± 1.06 (1.66)	2.01 ± 1.07 (1.70)	2.15 ± 1.13 (1.80)	0.396
	<i>R</i>	0.59 ± 0.19 (0.60)	0.58 ± 0.19 (0.59)	0.55 ± 0.19 (0.56)	0.435
	FF	0.63 ± 0.25 (0.66)	0.61 ± 0.24 (0.64)	0.52 ± 0.26 (0.53)	0.056
	Fibril, AR > 4 (%)	4.5 ± 1.7 (4.4)	4.6 ± 2.5 (4.3)	6.1 ± 2.9 (5.8)	0.396
Number	Total estimated number/g (×10 ⁸)	1.23 ± 0.54 (1.09)	1.45 ± 0.45 (1.72)	5.14 ± 3.37 (3.78)	<0.005
	Submicron number (%)	94.8 ± 0.7 (95.3)	94.8 ± 0.2 (94.6)	90.5 ± 3.6 (91.0)	<0.016
Volume	Total estimated volume (mm ³)/g (×10 ⁻³)	0.36 ± 0.05 (0.35)	0.62 ± 0.60 (0.27)	6.47 ± 4.83 (5.73)	<0.006
	Submicron volume (%)	13.4 ± 5.0 (11.5)	12.8 ± 6.2 (12.3)	8.3 ± 5.1 (9.5)	0.156
	Total estimated volume (mm ³)/year	36.5 ± 33.3 (22.5)	64.6 ± 39.4 (71.0)	293.3 ± 120.7 (236.0)	0.013
Biological activity	SBA _{Particle}	0.31 ± 0.04 (0.29)	0.30 ± 0.05 (0.30)	0.26 ± 0.05 (0.28)	0.135
	FBA _{Particle} (×10 ⁻³)	0.11 ± 0.03 (0.10)	0.17 ± 0.13 (0.08)	1.51 ± 0.93 (1.49)	0.005
	FBA _{Component}	12.1 ± 12.7 (6.9)	20.5 ± 14.1 (18.5)	77.1 ± 46.2 (59.4)	0.013

SD, standard deviation; ECD, equivalent circular diameter; AR, aspect ratio; *R*, roundness; FF, form factor; SBA, specific biological activity; FBA, functional biological activity. The bold numbers indicate when comparisons were significantly different between HXLPE and CPE.