Published in final edited form as:

J Arthroplasty. 2017 July ; 32(7): 2289–2300. doi:10.1016/j.arth.2017.01.047.

PERI-IMPLANT DISTRIBUTION OF POLYETHYLENE DEBRIS IN POSTMORTEM RETRIEVED KNEE REPLACEMENTS: can polyethylene debris explain loss of cement-bone interlock in successful Total Knee Arthroplasties?

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Abstract

Background—Loss of mechanical interlock between cement and bone with *in vivo* service has been recently quantified for functioning, non-revised, cemented Total Knee Arthroplasties (TKA). The cause of interlocking trabecular resorption is not known. The goal of this study was to quantify the distribution of PE debris at the cement-bone interface and determine if polyethylene (PE) debris is locally associated with loss of interlock.

Methods—Fresh, non-revised, postmortem-retrieved TKAs (n=8) were obtained *en bloc*. Lab-prepared constructs (n=2) served as negative controls. The intact cement-bone interface of each proximal tibia was embedded in Spurr's resin, sectioned, and imaged under polarized light to identify birefringent PE particles. PE wear particle number density was quantified at the cement-bone interface and distal to the interface, then compared to local loss of cement-bone interlock.

Results—The average PE particle number density for postmortem retrieved TKAs ranged from 8.6 (1.3) to 24.9 (3.1) particles/mm² (SE) but was weakly correlated with years in service. The average particle number density was twice as high distal (> 5mm) to the interface compared to at the interface. The local loss of interlock at the interface was not related to presence, absence, or particle density of PE.

Conclusions—PE debris can migrate extensively along the cement-bone interface of well-fixed tibial components. However, the amount of local bone loss at the cement-bone interface was not correlated with the amount of PE debris at the interface, suggesting that the observed loss of trabecular interlock in these well-fixed TKAs may be due to alternative factors.

Keywords

UHMWPE; polyethylene debris; total knee arthroplasty; aseptic loosening; postmortem retrieval

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Introduction

Cemented total knee arthroplasty (TKA) is a highly successful procedure that relieves pain and improves functionality for patients with multi-etiological arthritis. Recent arthroplasty registry data report that the 10 year revision rate is between 4.9 and 7.8% [1] with aseptic loosening reported as the most common reason for late revision [2, 3]. However, the lifetime risk of revision has been estimated to be 14.9% for males and 17.4% for females in the US [4]. This high lifetime risk of revision is particularly alarming given the current projections of 3 million primary knee arthroplasties in the US per year by 2030 [5]. The cause of aseptic loosening of cemented TKAs is multifactorial with component alignment, kinematic function, surgical approach to achieve good cement fixation, implant design, patient factors, and polyethylene (PE) wear debris considered to be important contributing factors.

Progressive radiolucencies at the cement-bone interface [6] have been associated with aseptic loosening, and components with greater initial interlock between cement and bone have a lower incidence of radiolucency [6, 7]. Recent work using *en bloc* postmortem retrievals that were not clinically loose demonstrated substantial loss of mechanical interlock between the cement layer and trabecular bone adjacent to the tibial tray [8]. This loss of trabecular interlock with the cement was not visible on plain film X-rays, but could represent an initial stage of the loosening process, eventually leading to clinical radiolucency. It is known that with trabecular resorption, these interfaces become mechanically weaker [9], suggesting that there is reduced fixation strength of the tibial component. However, the mechanism responsible for this loss of interlock is not known.

Studies of failed total hip and knee arthroplasties have been used to definitively link polyethylene (PE) wear debris and osteolysis. Peri-implant fibrous tissue was found to contain a heavy burden of particles observable by polarized light [10]. In addition to PE debris, authors noted copious amounts of acrylic material and metal debris [11–14] in these failed implants, though PE represented 80% of all particulate debris [14]. The wear particles were observed in both histiocytic and foreign body giant cell reactions; the former characteristic of the hip, and the latter of the knee [13, 15]. The resultant pro-inflammatory cytokine release from these innate immune cells is thought to be a predominant cause of osteolytic defects on the periphery of the devices [16], as well as progressive radiolucency in both TKA and total hip arthroplasty (THA) [16]. The breadth of data shows a clear relationship between polyethylene wear rate [17] or debris burden [18] and osteolysis in loosened prostheses. However, because nearly all of these studies were performed on failed joint replacements, the relationship between PE debris and the loss of mechanical interlock between cement and trabecular bone in *functioning* TKAs is uncertain. To date, the extent to which PE debris accumulates in marrow spaces around well-fixed TKA components, particularly at the cement-bone interface, is not well understood.

In this study, we used postmortem–retrieved tibial components of TKA to examine the distribution of PE debris in the vicinity of the cement-bone interface and also measure the loss of cement-bone interlock at the cement-bone interface. We asked three research questions: **1)** what is the particle number density (#PE debris/mm²) and anatomical (spatial) distribution of PE debris adjacent to the cement-bone interface and in the trabecular spaces

distal to the cement? **2)** does PE debris in the peri-implant bone accumulate proportionally with years in service and with the amount of articular surface wear? **3)** are areas of high particle number density locally associated with trabecular resorption in regions that initially interlocked with PMMA cement?

METHODS

TKA Procurement and Radiographic Assessment

Eight fresh-frozen, *en bloc* postmortem retrievals with cemented Total Knee Arthroplasties (TKAs) were obtained from BLINDED Anatomical Gift Program. Information regarding TKA functionality for the donors prior to time of death was obtained from next of kin, but patient charts were not available. Donor age, weight, height, BMI, time in service, and implant specifics were recorded for all specimens (Table 1).

Plain radiographs were used to determine the degree of radiographic loosening at time of death according to standard technique [19, 20] and were scored by a board certified orthopaedic surgeon with extensive experience performing TKAs (BLINDED). Five components were rated “well-fixed” with incomplete radiolucency of <2 mm thickness around the implant at the cement-bone interface. Three were rated as “possibly loose,” with incomplete radiolucency of <2 mm thickness around the implant with focal lucency of >2 mm at the cement-bone interface. Two of the possibly loose components were noted to have small/focal osteolytic lesions on the periphery of the device (Figure 1). “Probably loose,” would have been assigned after identification of 1) radiographic evidence of cement fracture; 2) complete circumferential radiolucency at the cement-bone interface; 3) lucency at the cement-metal interface; and/or 4) extensive lucency around the keel or post of an implant. None of the donors were considered “probably loose”.

Two fresh tibiae from anatomical donors without previous history of total joint replacement were used to create lab-prepared (negative) controls for cement interdigitation without any bony remodeling or production of PE debris. For these two cases, the proximal tibiae were prepared for cementation using standard methods including transverse sectioning of bone, lavage to clean the bone bed, and application of PMMA cement (Simplex, Stryker Orthopaedics, Mahwah, NJ). A mock metal tray was used to pressurize the doughy PMMA cement into the bone bed.

Polyethylene Tray Wear Score

The Hood Wear Score [21] was used to semi-quantitatively determine the amount of surface and backside wear for each PE insert. Briefly, the PE insert was examined by BLINDED for deformation, pitting, cement debris, scratching, burnishing, abrasion and delamination for 10 regions of each insert (front and back, separately), graded on a scale of 0–3, and added.

Tibial Plateau Sectioning and Embedding

An undecalcified sectioning procedure was developed to create resin embedded samples containing cement, the cement-bone interface, and trabeculae/marrow distal to the cement-bone interface. While this procedure necessitated use of water irrigation for the major cuts

prior to embedding, care was taken to not disturb the interior contents, including any existing debris, of the specimens. The metal tibial tray component was removed by heating the metal while applying slight tension, preserving the cement-bone interface [22]. The proximal 15 cm of the tibiae were frozen at -80°C , and then sectioned every 10 mm from the sagittal midline using a water-irrigated diamond blade (IsoMet 2000; Buehler Inc, Lake Bluff, IL, USA). An axial cut was made 20 mm below the plateau to separate the sagittal sections containing the cement-bone interface from the distal bone. The sagittal sections were fixed in 10% neutral buffered formalin for 48 hours, and then dehydrated in graded ethanol (70–100%) over a course of 6–8 weeks. Sagittal sections were cut into smaller segments and were embedded in Spurr's Resin (SPI-chem, West Chester, PA, USA) under vacuum according to manufacturer's protocol.

The embedded sagittal tissues were sectioned in the coronal plane, using the same water-irrigated diamond blade saw. Between one and three coronal sections (Figure 2A) were taken for anterior periphery, interior, and posterior periphery regions for each sagittal section, depending on the medial-lateral position. The circumferential 10 mm of the tibiae was designated as "periphery" (associated with the cortex), while any interior area was designated as "interior" (associated with the post and/or keel). Coronal sections were ground and polished using a water-irrigated polisher (EcoMet 6; Buehler Inc) to a thickness of 0.1–0.5 mm. The number of coronal sections obtained per donor bone ranged from 34 to 53, averaging 45.

Polarized Light Microscopy and Polyethylene Wear Determination

Each coronal section was imaged under polarized light (Nikon Eclipse E800M, Tokyo, Japan) to identify PE wear particles at $100\times$ magnification. Micrographs were taken of 6 Regions of Interest (ROI, 1 mm^2 at $0.76\text{ }\mu\text{m}/\text{pixel}$): 3 ROIs at the cement-bone interface, and 3 deep ($\sim 5\text{ mm}$ distal) to the interface, yielding an average of 270 discrete ROIs imaged per donor specimen (Figure 2B). Each micrograph was examined by BLINDED for quantification of birefringent polyethylene wear particles. The PE particles we included in the final analysis of PE particle number density ($\# \text{PE particles}/\text{mm}^2$ or ρ_N) were defined as those that met four conditions: 1) birefringent under polarized light, 2) not visible under standard transmitted white light microscopy, 3) in focal plane, and 4) area larger than 10 px^2 ($5.62\text{ }\mu\text{m}^2$). For images with PE ρ_N exceeding $20/\text{mm}^2$, the ImageJ (U. S. National Institutes of Health, Bethesda, Maryland, USA) particle count function was used automate the counting process. The micrograph image was converted to 8-bit format, inverted, a manual threshold was applied, and particles were counted using an overlay mask (Figure 2C). A comparative analysis of 10 representative ROIs was performed to determine potential differences in identification of particles between direct visual counting and image processing via ImageJ; the difference in particle counts obtained manually versus those using ImageJ was less than 5% (test fields for validation contained 10–39 particles). Particle size (area), major and minor axis, aspect ratio, and circularity were determined using ImageJ for micrographs containing the upper quartile count of particles per donor.

Cement-Bone Interdigitation Depth

A protocol to quantify the depth of estimated initial and current (after *in vivo* use and possible trabecular resorption) interlock of trabecular bone in the cement layer was developed in our lab [8]. The initial interdigitation was deduced using a “trace fossil” methodology: the cured, pressurized cement preserved a mold of the original trabecular architecture even after bone resorbed, forming a negative space of where bone once existed (Figure 2D). Using high-resolution micrographs (0.8 $\mu\text{m}/\text{px}$) of the cement-bone interface for each interface section, a segmented line was drawn at the most distal extent of the cement into the bone (Line 1). A second segmented line was drawn at the most proximal extent of trabecular structures into the cement (Line 3). Current interdigitation was defined as the extent of remaining bone interlock with cement at time of death, and another segmented line was drawn here (Line 2). Initial Interdigitation Depth (inID) was calculated using a local minimum point-to-point measurement algorithm in Image Pro Plus (Media Cybernetics, Rockville, MD, USA) between Lines 1 and 3. Current Interdigitation Depth (curID) was calculated using the same algorithm, but between Lines 1 and 2. The difference between inID and curID was defined as the Loss of Interdigitation Depth, or lossID. The estimated error in determining the inID was reported as 0.06 mm with lab-prepared constructs and the absence of *in vivo* resorption [8].

Soft Tissue Interposition

Organized, fibrous tissue between the cement-bone interface was identified on coronal sections via light microscopy. An image mask was created of the area of the soft tissue (Photoshop CS5, Adobe, San Jose, CA). The area of the mask was divided by the width of the coronal section in ImageJ. The amount of soft tissue interposition was reported as “average height (mm).”

Peri-Implant Soft Tissue Histology

Soft tissue specimens from the synovial capsules of donors with the lowest PE ρ_N (Donor B), and longest time in service and most PE surface wear (Donor H) were embedded in paraffin and sectioned in 20 μm sections using a microtome (Leica 2155, Leica Biosystems, Buffalo Grove, IL, USA). Sections were stained with Harris’s Hematoxylin and Eosin Y/Phloxine B, and then were imaged under transmitted white light for tissue architecture, and polarized light to identify of wear debris. Because tissue specimens had been frozen and thawed multiple times due to the nature of the Anatomical Gift Program, definitive identification of individual cell types (i.e., foreign body giant cells and macrophages) was not attempted.

Statistical Methods

Descriptive PE ρ_N statistics including the average, median, % PE positive ROIs, and frequency distribution of the ~270 sample points was determined for each donor bone. One-way Analysis of Variance (ANOVA) was used to compare PE ρ_N based on location for anterior/central/posterior regions. Paired t-tests were used to compare lateral and medial compartments, and interfacial versus distal grouped ROIs. To correlate local trabecular resorption of each coronal section and local PE wear, the median PE ρ_N for the interfacial

and distal ROIs was calculated per mm^2 and compared to LossID in the same section. Linear regression was used to explore the relationship between the median PE ρ_N (in total, or per compartment, i.e., interface, distal, etc) and loss of cement-bone interdigitation (lossID) and time in service. Linear regression was also used to evaluate the relationship between articular and backside surface wear (Hood Wear Score) and time in service and presence of PE debris (% PE positive ROIs). Finally, an Analysis of Covariance (ANCOVA) was used to determine if the presence or absence of PE debris at the interface of each section influenced the amount of bone resorption (lossID) that occurred at the cement-bone interface. Because the amount of initial interdigitation (inID) was not controlled, it was used as a covariate in the ANCOVA. All statistical analyses were conducted using JMP 9.0 (SAS Institute, Cary, NC, USA).

RESULTS

Morphology, Count and Spatial Distribution of PE debris

For our first research question, we determined the PE particle density (ρ_N) and spatial distribution of birefringent PE wear debris particles for each donor using polarized light microscopy. We examined regions at the interface between PMMA cement and bone, and distal (>5 mm) to the interface (Figure 3). As has been reported by other groups [10, 12, 14, 23], the morphology of these particles included filaments and lenticular shapes, which were visible as individual particles or in clumps (Figure 4A–C). Due to the thickness of the sections, particles that appeared smaller or rounder may have been oriented out of plane. Overall average particle size (area) was $29 \mu\text{m}^2$, with an aspect ratio of 2.11 (Table 2). The average equivalent circle diameter (ECD) was $4.55 \mu\text{m}$, and minimum ECD was $2.67 \mu\text{m}$. Additionally, while it was common to visualize a small group of particles in isolation, often there were trabecular reservoirs of hundreds of particles that were aggregated together. Importantly, PE debris was found in every donor specimen at both the cement-bone interface and in the trabecular spaces distal to the interface, despite no evidence of an incomplete cement mantle.

Mean PE ρ_N ranged from 8.6 (Donor B, 3.5 years in service) to $24.9 \text{ particles/mm}^2$ (Donor D, 4 years in service), as seen in Table 1. The donors with the shortest and longest time in service possessed an average of 13.4 and $19.7 \text{ particles/mm}^2$, respectively. The population of PE debris had a positive skew, with retrieval donor bones exhibiting few or no PE particles in the majority of sample locations, with a large number of particles in a few locations (Figure 4D). This is reflected in the median PE count, which ranged from 0 to 4 particles/mm^2 . Some false positives were found in the two control specimens. However, the mean PE particle density ($0.19\text{--}0.24 \text{ particles/mm}^2$) for the controls was much smaller than the retrievals (0.8 to 2.3% of the retrieval levels). The spatial distribution of PE wear debris was not significantly different for medial versus lateral regions ($p=0.44$) or anterior, posterior, and interior regions ($p=0.28$) of the tibial components (Table 3). We found that 2.2 fold more debris accumulated distally (>5 mm) than at the interface ($p<0.008$) when mean PE ρ_N was compared per donor at those locations.

PE Debris Accumulation and Loss of Fixation with Years in Service

We next examined the accumulation of PE debris in the bone compartment in relation to years in service. Median PE ρ_N of the 34–53 coronal sections per donor for both interfacial and distal regions were used for each donor instead of mean count, because of the general positive skew of the data. There was a positive correlation between median PE ρ_N and years in service for the distal location ($r^2 = 0.67$, $p=0.013$) (Figure 5A). At the interface, there was a weaker correlation ($r^2=0.33$, $p=0.144$). The loss of interdigitation depth (lossID) also had a weak positive correlation with time in service ($r^2 = 0.30$, $p=0.10$, Figure 5B). Consistent with other postmortem retrieval studies [8, 24] the increase in lossID appears to occur early (~5 years), prior to the generation of significant deposits of wear debris at the interface. Neither the quantity nor presence of PE (% PE positive ROIs) wear debris, nor increasing time service, corresponded to the presence of osteolytic lesions in this study. Additionally, we found no association between the amount of organized fibrous tissue at the cement-bone interface and any metric, including the amount of PE debris. PE debris was rarely present in this soft tissue lining using our methodology.

PE Insert Surface Wear

The Hood Wear Scoring system [21] was used to semi-quantitatively rate the amount of surface wear on the articular and the back side of the PE inserts. Total wear increased ($r^2=0.64$, $p=0.006$) with time in service (Figure 5C), ranging from a total score of 31 to 109 for those with *in vivo* service. The wear on Donor H was noted to be extensive, to the effect of the post having been ground nearly completely away (Figure 1A). Constructs with higher wear scores also had greater median PE ρ_N ($r^2=0.57$, $p=0.012$). This suggests that there is a proportional relationship between PE burden produced at the articulating surface and the burden of debris present in the bone or at the interface.

PE Debris and Local Bone Resorption

For our third major research question, we examined if the presence or absence of PE debris at the interface influenced the amount of bone resorption that occurred at the cement-bone interface. Via polarized light microscopy, we found evidence of particles in close proximity to trabecular bone that were not associated with any resorption pits along the trabecular surface, even with a relatively high PE ρ_N in the same ROI (Figure 6A). At the cement-bone interface, we found examples of resorbed or resorbing trabeculae without evidence of PE debris (Figure 6B). It was however, not uncommon to observe fields devoid of trabecular bone in both distal and interface regions, but full of polyethylene debris, and these fields often represented the upper limits of PE counts for each donor specimen.

An ANCOVA with loss of interdigitation (lossID) as the dependent variable, presence/absence of debris at the interface as the independent variable, and initial interdigitation depth (inID) as a covariate was used (Figure 7). LossID was greater with larger inID ($p<0.0001$), which would be expected considering the greater the initial interdigitation depth, the greater the measurable potential of resorption. Importantly, there was no significant difference ($p=0.4$) between the lossID versus inID relationship (slope) for specimens with debris at the interface and those without debris. However, it should be noted that this analysis assumes the presence/absence of PE debris and amount of resorption at a particular location

represents independent data points that are not influenced by either donor bone or position in bone.

Survey of Peri-Prosthetic Soft Tissue Histology

Peri-prosthetic soft tissue is often taken at the time of revision as a material source to investigate PE particle count and size distribution. Soft tissue sections from the donor with the least average PE ρ_N in the peri-implant bone (Donor B) had no visible PE particles ($n=3$ tissue samples, data not shown). In contrast, Donor H, with the longest time in service and highest Hood Wear Score, had substantial PE wear debris that was evident in multiple soft tissue sections (Figure 8A–D). These findings suggest that high PE burden in the peri-implant soft tissue may be indicative of high PE burden in the peri-implant bone. Future work could focus on the correlation between PE ρ_N in peri-implant soft tissue and the peri-implant bone.

DISCUSSION

In this study, we documented the distribution of polyethylene (PE) wear debris in marrow spaces adjacent to the cement-bone interface in non-revised, cemented total knee arthroplasties (TKA) that were functional at time of death. The median and mean PE particle number density (ρ_N) increased with time in service, and there was more debris distal to the interface (>5 mm) compared to regions directly adjacent to the cement-bone interface. The debris was not evenly distributed, with many sample areas having no debris and other (few) areas with large particle counts. In addition to quantifying the distribution of PE debris, a primary goal of this study was to determine if there was a relationship between PE presence and the loss of interdigitation between cement and bone that has previously been observed in *en bloc* retrievals. Overall, donors with more time in service lost more interdigitation and had more debris. However there was no difference in local resorption for sections with or without debris.

Previous studies have identified PE wear debris in the knee or hip through various methods, whether through polarized light microscopy of intact tissue [12, 13, 25, 27] or through tissue digestion protocols [14, 18, 23, 28–32]. The approach taken in the current study was unique in that the goal was to examine native, unprocessed PE debris in close proximity to an intact cement-bone interface of non-revised knees. We chose a sectioning and light microscopy imaging procedure that allowed a precise mapping of the location of PE debris in relation to remaining trabecular bone fixation. Use of *en bloc* postmortem retrieval knees rather than intra-operative revision retrievals permitted the investigation of both interface morphology and PE distribution for intact interfaces, prior to any clinical loosening. Further, processing of undecalcified bone embedded in Spurr's resin—which approximates the stiffness of PMMA cement and bone—maintained an intact cement-bone interface throughout all procedures. This facilitated quantification of initial and current trabecular interdigitation. To the authors' knowledge, this is the first detailed attempt to examine the PE debris in TKA at the location where loss of interlock occurs, at the cement-bone interface (rather than synovial fluid or peri-implant soft tissue), while also comparing the extent of fixation in the same compartment.

The Relevance of PE Particle Size, Quantity, and Presence in TKA

Polarized light microscopy was used as our primary tool to identify PE debris. While the wavelength of visible light (0.4–0.7 μm) prohibits clear identification of submicron particles, it has been documented that TKAs generate larger particles than total hip arthroplasty (THA) [15, 28, 32]. The greater incidence of particles $>1\ \mu\text{m}$ in the knee may be due to the wear mechanisms of poorly conforming surfaces of the knee which generate larger particles due to fatigue failure, rather than abrasion and adhesive wear that produce submicron debris in THA [15, 28, 32]. In turn, the larger debris may be less effective at eliciting an inflammatory response, making the debris less biologically relevant [28, 32]. However, Hirakawa et al [28] demonstrated that the majority of PE debris for both THA and TKA remains $<2\ \mu\text{m}$ in diameter.

While it was not possible to quantify submicron debris using our embedding and light microscopy approach, multiple authors have examined the size and shape distribution of submicron debris using SEM [14, 18, 23, 28–32]. SEM was not compatible with our embedding approach because it would not have been possible to differentiate embedded PE debris from the epoxy resin, as both materials would appear identical under chemical analysis.

Regarding the focal osteolysis as seen on plain X-ray for Donors A and H at the periphery of the implant, we found no association between the osteolytic defects and the PE ρ_N or presence of debris at the defect site. There are a few possible explanations. First, at the initiation of bone resorption, PE debris could have been co-located in high volume, and as the defect enlarged, fluid pumping from normal joint use could have removed the original deposit, leaving a defect without PE debris. Second, if the PE debris was retained in the defect, our generous dehydration steps prior to embedding may have rinsed away any loose debris, and our choice of methodology was not suitable to assessing the quantity of PE debris in a void. Third, the cause of the osteolysis in these clinically successful components may be something other than PE debris, as we never observed any fibrous tissue with encapsulated debris inside the defects. One possible alternative cause may include an incomplete cement mantle, which was clearly seen in the posterior region of Donor A. Poor cement coverage and/or fractures in the cement mantle are well associated with osteolytic defects [11, 33], potentially due to fluid pumping along the cement-bone interface facilitated by the interposition of soft tissue, especially in the chronic setting of aseptic loosening [34]. In the absence of debris, clinically relevant levels of fluid flow were demonstrated to cause peri-prosthetic osteolytic lesions when these forces were transmitted through fibrous tissue, which resulted in flow velocities ten times greater than physiologic levels [34]. Therefore, osteolytic defects may be driven by processes different from that causing trabecular resorption at the cement interface. Whereas osteolytic lesions are strongly associated with PE debris, the mechanisms regulating resorption of interdigitated trabeculae have yet to be fully elucidated.

Comparison to Similar Studies

In comparison to our study, Massin et al. [12] examined postmortem retrieved THA femoral components, using polarized light microscopy to identify PE wear debris at both the metal-

cement and cement-bone interfaces. They too found birefringent debris within marrow-filled trabecular structures adjacent to the implant, and additionally demonstrated a “reservoir” of debris distal to the component, but remarked on the lack of published material demonstrating distal osteolysis in THA. In the present study, more debris was found distal (>5 mm) to the cement-bone interface than at the interface. The more distal concentration of debris may be due to either: 1) the cement-bone interface creating a barrier to debris transport or 2) local fluid pumping from during knee loading [35] causing migration of particles between trabecular structures, where the debris then remains. Libouban et al [36] found similar migration in their *ex vivo* study of the effect of trabecular architecture on PE migration. This phenomenon may be analogous to the deposition and accumulation of man-made debris on beaches and tide pools. Without adequate fluid pressure or flow to move the particles back into the effective joint space, they remain in the trabecular spaces. This also raises the possibility that PE wear debris may migrate much further down the tibial canal. It has been previously documented that PE debris may migrate to lymph nodes, liver, and spleen [37, 38], and in femurs, distal to the hip prosthesis [12]. Some authors expect submicron particles to migrate the slowest [36], however, if the trabecular structures act like a sieve, potentially the smallest particles migrate the fastest and farthest [39]. Regardless, it seems likely based on our findings and others that PE debris migration would progress further distally in the marrow spaces.

Limitations

There were several limitations to this study. Use of postmortem retrievals allowed us to examine clinically successful components, but in the absence of detailed pre-mortem donor information such as activity level or functional outcome measurements with which to further contextualize our results. Additionally, postmortem retrievals of TKA are relatively rare, and this necessitated a small sample size, which precluded the ability to perform subgroup analyses. Expanding the donor population to include cases with larger osteolytic lesions would be helpful to relate PE burden magnitude with focal lysis. A larger, prospective study would be necessary to properly address the effects of pre-mortem activity level, surgical technique, BMI, and other factors on the accumulation of PE debris and trabecular bone resorption.

We took several precautions to minimize disruption of the resident PE debris during processing including bulk sectioning of frozen constructs, followed by careful dehydration and infiltration of smaller specimens with resin. It is possible that PE debris could have migrated during the embedding process within these smaller specimens, although care was taken to limit any agitation, and image analysis was performed on embedded sections away from free edges of the small specimens. Three-dimensional imaging would be ideal to do this, but polyethylene is radiolucent, so micron-level CT imaging would likely not be able to detect PE debris.

Next, our methodology, while designed to assess both local PE debris distribution and interfacial bone resorption, relied upon the use of polarized light microscopy that cannot resolve submicron particles due to the inherent physical limitation of the visible light wavelength. Polarized light microscopy has been used to document the presence of

submicron debris through diffuse cytoplasmic birefringence in peri-prosthetic soft tissue specimens [25]. However, diffuse birefringence was not identified in our bone specimens, potentially because 1) submicron debris was not concentrated intracellularly, but rather was loose in the trabecular spaces, or 2) the freeze-thaw cycles caused cellular lysis and loss of intracellular PE deposits. To address this limitation, an SEM study of PE debris isolated from trabecular bone at the cement-bone interface and compared to peri-implant debris would be useful in determining the potential resorptive effect of submicron debris in different compartments.

Further, there was a possibility that our preparation and imaging methods could lead to false positive birefringence. Negative controls were prepared from lab-prepared specimens using postmortem retrieved tibiae without a history of total joint replacement. While the negative controls had the occasional false positive, these were one to two orders of magnitude below the experimental group in debris count, demonstrating that the embedding and sectioning methodology were sound, and the polarized light microscopy analysis was capable of identifying PE debris. The false positives seen in the two control specimens were likely the result of 1) internal refraction due to incomplete permeation of the embedding medium, 2) fragmented birefringent particles of bone from the sagittal sectioning, or even 3) environmental exposure to PE through contaminated water supplies or common household products [40]. The high correlation between articular surface wear score and microscopic PE debris further supports the approach used to prepare and identify the PE debris in this study. Ideally, a clinical negative control using TKAs in which there is no PE debris would be informative to definitely rule out PE-induced resorption of the interlocked bone.

The results of the current study show that even with an intact cement layer, PE debris can and will migrate along the interface and also into the trabecular spaces. However, there is longstanding evidence that cementing techniques resulting in 2–3 mm of cement-bone interdigitation have improved clinical outcomes [41, 42]. In addition to providing a stable fixation environment, the cement layer is thought to serve as a seal against migration of articular debris along the peri-implant interface and trabecular bone bed [43]. It is possible that even a visually complete mantle still has small gaps through which PE debris may be transported, especially on the periphery of the mantle. This would not be particularly surprising given that there are small gaps (14 μm thick for lab prepared constructs, 40 μm for postmortem retrievals) along the cement-trabecular bone interface [35] that could serve as a conduit for debris migration. Further, loading of the joint results in micromotion along the trabeculae-cement interface, which could serve as an active mechanism to transport debris. Therefore a complete cement mantle does not inhibit all debris migration, but is very likely to slow the process.

The lack of any correlation between presence of PE debris at the interface and loss of interlock suggests that there may be other factors that contribute to the loss of mechanical interlock. Stress shielding of the interdigitated trabecular struts may result in bone resorption in accordance with Wolff's Law [35, 44, 45]. Fluid flow through micro-gaps at the cement-bone interface may result in increased osteoclastic activity through mechanotransduction of supraphysiologic shear stress [46] and/or pressure [47, 48]. Ischemic-reperfusion injury resulting from both the initial surgery, oxygen consumption during inflammatory responses

to particle debris, and a large, avascular implant can directly and indirectly damage bone [16]. It may also be possible that none of the postmortem retrievals reached the minimum threshold of PE ρ_N necessary to initiate increased trabecular resorption despite the extensive wear recorded from some tibial inserts.

The decreasing trend of revisions due to wear debris clearly indicates that improvements in PE manufacturing, sterilization, and design were key to increasing the device survival [49]. However, this study demonstrates that PE debris in and of itself may not be responsible for the loss of cement-bone interlock in functioning TKAs. Considering the rates of revision are now at ~5% for 10 years post implantation for some devices [49], looking beyond PE debris to other potential causes of aseptic loosening may be necessary to further improve the longevity of TKA. Note that all of implants in this study were unrevised, clinically successful implants at time of death. Yet, the average loss of trabecular bone interlock with cement was over 70%, even for devices with less than 5 years in service. Though neither quantity nor the simple presence of PE debris was associated with trabecular bone loss, the loss of interlocking bone may contribute to eventual clinical loosening in some patients.

Conclusions

Polyethylene debris from the articulating surface of total knee replacements can migrate extensively along the cement-bone interface, and in the supporting trabecular bone of well-fixed tibial components. More debris was found in the supporting trabecular bone compared to the interlocked regions of the cement-bone interface. The amount of local bone loss at the cement-bone interface was not correlated with the amount of PE debris at the interface, suggesting that the observed loss of trabecular interlock in these well-fixed TKAs may be due to alternative factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Research reported in this publication was supported by the National Institute for Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under award numbers R01AR42017 and F30AR067570. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Figure 1.

PE inserts from donor TKAs (A and B) and associated osteolytic lesions at the cement-bone interface (C and D, arrows). Frank delamination, deformation, and pitting damage can be noted for Donor H (A). Burnishing and scratching was noted for Donor A by using graphite to identify damage (B, asterisk).

Figure 2.

Methods for analysis of PE wear debris and loss of fixation. Axial schematic of the tibial plateau, where the outer region within 10mm of the cortex was designated “periphery” and the inner region as “interior” (A). Red lines indicate a representative collection of coronal sections for further analysis. Illustration of a coronal section of the cement-bone interface (B). The interfacial region was considered within 5mm of the distal extent of the cement. Boxes represent ROIs. Polarized light microscopy analysis via image processing (C). Under light microscopy, PE debris is not visible. Under polarized light, the bone is birefringent on a black background. The inset demonstrates native PE particles, which are also birefringent. The final threshold image demonstrates what particles were counted. Analysis of Interdigitation Depth and Contact Fraction (D). At time of surgery, bone is interdigitated with cement (inID). With in vivo service, bone resorbs (curID). $\text{LossID} = \text{inID} - \text{curID}$

Figure 3. Polarized light microscopy examples of PE debris

Reflected white light microscopy (**A**) and polarized light microscopy (**B**) of the same cement-bone interface (Donor B). Zirconium dioxide particles are clearly visible in the cement, as noted by the opaque specks. Reflected white light (**C**) and polarized light microscopy (**D**) of a small cluster of shards or spindles of PE debris (circle), demonstrating the marrow cavities appear dark, while PE debris is birefringent/bright (Donor F). Representative image of PE particles present (**E**, **inset**, **arrows**) and absent (**F**) in the marrow space (Donor D). Scale bar = 100 μ m.

Figure 4. The morphology (A–C) and frequency (%) distribution of PE wear particles (D)
 PE debris appeared as larger filaments (A), as lenticular or lens shapes (B), and clumped as a mix of the two (C). Scale bar = 100um.

Figure 5. Wear debris accumulation with years in service

Median PE Particle Number Density per ROI at the cement-bone interface (circles) and distal (~5mm, squares) from the interface (A), average loss of interdigitation depth (LossID) (B), and total Hood Wear Score (C) as a function of years in service. Lab-prepared controls represent time 0. Donors are noted with letters corresponding to Table 1. TKAs rated “possible loose” are noted by darkened data points.

Figure 6. PE debris without resorption; resorption without PE debris

PE wear debris in close proximity to a trabeculum (A) without evidence of resorption (A, inset, arrows). A trabecular strut interdigitated with bone cement (B). In the absence of discernible PE debris, there is bone resorption evident by the cavity in cement that had formed around the shape of the original strut. The boundary of the PMMA (no radio-opacifier) cement is marked with a dashed line (B, inset). *= resorbed bone area. Scale bar = 100um.

Figure 7. ANCOVA comparing the effect of the presence of PE debris on the loss of fixation
 The presence of PE debris at the interface did not alter the relationship (slope, $p=0.4$)
 between lossID and inID. inID= initial interdigitation depth; lossID = loss of interdigitation
 depth. $n=321$ sample measurements across 8 postmortem donors.

Figure 8. Periprosthetic soft tissue histology

Donor H had copious amounts of PE wear debris in soft tissue as seen by comparison of light microscopy (A, C) and polarized light microscopy (B, D, arrows). Possible foreign body giant cells can be seen in C (horizontal arrows), coinciding in location with debris in D. Diffuse cytoplasmic birefringence indicative of submicron PE debris [10, 25, 26] was observed (B,D), however, large, shard-like particles encased in fibrous tissue measuring over 4mm in length were also seen. Scale bar = 200um.

Table 1

Postmortem retrieved TKAs for donor (A–H) and lab-prepared constructs (1, 2).

Donor	Sex	Age	Weight	BMI	Time in Service (years)	Implant manufacturer/model	PE type	CR/PS	Radiographic Score	Total Hood Wear Score	Median pN	Avg pN	Interface Avg pN	Distal Avg pN	% PE Positive ROIs	Mean PG Size (mm ²)	Avg Soft Tissue Height (mm)	inID (mm)	curID (mm)	lossID (mm)
1	M	64	56	23.9	0	N/A	N/A	N/A	N/A	N/A	0	0.19	0.0	0.4	27	100.61	N/A	1.54	1.43	0.11
2	F	54	95	33.3	0	N/A	N/A	N/A	N/A	N/A	0	0.24	0.5	2.2	11	67.25	N/A	0.47	0.29	0.18
A	M	85	89	24.9	2.25	Stryker/Traillon	UHMWPE	CR	Possibly Loose *	46	0	13.42	11.1	15.6	44	122	0.28	0.61	0.23	0.38
B	M	67	69	23.1	3.5	Zimmer/Nexgen	UHMWPE	PS	Well Fixed	41	0	8.65	3.2	48.0	37	52.21	0.44	1.16	0.59	0.57
C	M	92	101	29.2	3.75	Stryker/Traillon	HXLPE	CR	Well Fixed	35	0	13.48	8.3	18.6	39	61.92	1.14	1.06	0.4	0.66
D	F	91	87	33.2	4	Stryker/Traillon	HXLPE	CR	Possibly Loose	31	0	24.89	13.4	35.2	39	67.3	0.17	1.36	0.4	0.96
E	F	85	77	25.1	4.4	Zimmer/Nexgen	UHMWPE	PS	Well Fixed	70	2	12.38	17.1	7.6	54	70.55	0.36	1.3	0.55	0.75
F	M	74	97	32.8	6.75	Zimmer/Nexgen	UHMWPE	PS	Well Fixed	32	1	8.84	12.9	40.1	56	79.68	0.09	0.96	0.57	0.39
G	F	88	42	18.2	14	Stryker/Scorpion	UHMWPE	PS	Well Fixed	47	1	22.71	23.5	21.7	54	87.03	0.26	2	0.76	1.24
H	F	91	55	20.4	20	Zimmer/IB II	UHMWPE	PS	Possibly Loose *	109	4	19.72	8.7	27.9	70	197.21	0.87	0.95	0.24	0.71

PE = polyethylene; CR = cruciate retaining; PS = posterior stabilized; inID = initial interdigitation depth; curID = current interdigitation depth; lossID = loss of interdigitation depth (inID-curID);

UHMWPE = ultra high molecular weight polyethylene; HXLPE = highly cross-linked polyethylene; Total Hood Wear Score = frontside + backside wear; pN = particle number density (#PE particles/mm²);

ROI=Region of Interest;

*=identification of osteolytic lesions on radiograph.

Table 2

Particle size analysis for all retrieved specimens.

	Mean	Median	SD	Min	Max
Area (µm ²)	28.94	16.31	42.73	5.62	745.29
ECD (µm)	6.06	4.55	2.81	2.67	30.8
Major Axis (µm)	7.76	6.49	4.6	2.71	57.98
Minor Axis (µm)	3.38	3.22	2.11	1.23	27.69
Aspect Ratio	2.11	1.89	0.86	1	7.89
Circularity	0.76	0.78	0.19	0.14	1

No significant differences were found between donors based on time in service or articular wear burden. As such, the data was pooled. ECD= equivalent circle diameter.

Table 3

The anatomical distribution of PE debris.

Compartments			#PE/mm ²		
M/L	Ant/Int/Post	Distal/Interface	Mean	Median	SD
L	Anterior	Distal	16.9	2	36.32
		Interface	14.68	0	38.46
	Interior	Distal	19.17	0	39.03
		Interface	13.88	1	25.27
	Posterior	Distal	12.62	1	35.27
		Interface	4.25	0	12.41
M	Anterior	Distal	23.2	2	47.01
		Interface	10.27	0	27.36
	Interior	Distal	22.64	1	45.82
		Interface	13.47	0	30.96
	Posterior	Distal	20.5	1	44.02
		Interface	9.4	0	25.19

L=lateral; M=medial.