Published in final edited form as:

Spine (Phila Pa 1976). 2012 January 15; 37(2): 150–159. doi:10.1097/BRS.0b013e3182154c22.

Are periprosthetic tissue reactions observed after revision of total disc replacement comparable to the reactions observed after total hip or knee revision surgery?

Ilona M. Punt, MSc^{1,2}, Shennah Austen, BSc¹, Jack P.M. Cleutjens, PhD³, Steven M. Kurtz, PhD⁴, René H.M. ten Broeke, MD^{1,2}, Lodewijk W. van Rhijn, MD PhD^{1,2}, Paul C. Willems, MD^{1,2}, and André van Ooij, MD PhD⁵

¹Department of Orthopaedic Surgery, Maastricht University Medical Center, P.O. Box 5800, 6202 AZ Maastricht, the Netherlands ²Research School CAPHRI, Maastricht University, P.O. Box 616, 6200 MD Maastricht, the Netherlands ³Department of Pathology, Maastricht University, P.O. Box 616, 6200 MD Maastricht, the Netherlands ⁴Drexel University and Exponent Inc., 3401 Market Street, Suite 300, Philadelphia, PA 19104, USA ⁵Department of Orthopaedic Surgery, Viecuri Medical Centre, P.O. Box 1926, 5900 BX Venlo, the Netherlands

Abstract

Study design—Comparative study.

Objective—To compare periprosthetic tissue reactions observed after total disc replacement (TDR), total hip arthroplasty (THA) and total knee arthroplasty (TKA) revision surgery.

Summary of background data—Prosthetic wear debris leading to particle disease, followed by osteolysis, is often observed after THA and TKA. Although the presence of polyethylene (PE) particles and periprosthetic inflammation after TDR has been proven recently, osteolysis is rarely observed. The clinical relevance of PE wear debris in the spine remains poorly understood.

Methods—Number, size and shape of PE particles, as well as quantity and type of inflammatory cells in periprosthetic tissue retrieved during Charité TDR (n=22), THA (n=10) and TKA (n=4) revision surgery were compared. Tissue samples were stained with hematoxylin/eosin and examined by using light microscopy with bright field and polarized light.

Results—After THA, large numbers of PE particles <6 µm were observed, which were mainly phagocytosed by macrophages. The TKA group had a broad size range with many larger PE particles and more giant cells. In TDR, the size range was similar to that observed in TKA. However, the smallest particles were the most prevalent with 75% of the particles being <6 µm, as seen in revision THA. In TDR, both macrophages and giant cells were present with a higher number of macrophages.

Conclusions—Both small and large PE particles are present after TDR revision surgery compatible with both THA and TKA wear patterns. The similarities between periprosthetic tissue reactions in the different groups may give more insight in the clinical relevance of PE particles and inflammatory cells in the lumbar spine. The current findings may help to improve TDR design as

Address correspondence and reprint requests to: Ilona Punt, Department of Orthopaedic Surgery, Maastricht University Medical Center, P.O. Box 5800, 6202 AZ Maastricht, the Netherlands, Phone: + 31 43 3871317, Fax: + 31 43 3874893, i.punt@mumc.nl.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

applied from technologies previously developed in THA and TKA with the goal of a longer survival of TDR.

1. Introduction

Total disc replacement (TDR) has gained popularity since the early 1990s. In the development of TDR, researchers have used successful biomaterials and design principles that were developed in total hip arthroplasty (THA) and total knee arthroplasty (TKA).^{1–3} The SB Charité III TDR (Link, Germany) was the first prosthesis that was implanted extensively. This prosthesis is unconstrained and consists of two cobalt-chromium-molybdenum (CoCrMo) endplates and a mobile ultra-high-molecular-weight polyethylene (UHMWPE) core.⁴

Polyethylene (PE) wear is a well known phenomenon in THA and TKA that may ultimately lead to failure of the procedure, due to osteolysis and aseptic loosening.^{5–7} In this pathogenesis, clinical-, patient-, and implant-related factors are thought to play a role.⁸ PE bearing surfaces generate large numbers of biologically active wear particles which cause periprosthetic inflammatory reactions. Macrophages play an important role in this reaction, because these cells try to eliminate the foreign PE particles by phagocytosis.^{9,10} Small particles are easily phagocytosed, but cannot be digested. When particles are too large to be phagocytosed by macrophages, multinuclear giant cells are formed.¹⁰ The inability of macrophages and giant cells to degenerate the phagocytosed particles causes increased production of numerous inflammatory mediators and cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor α (TNF- α) and prostaglandin E2 (PGE2).^{7,11}

In THA, the periprosthetic inflammatory response is characterized by macrophages with diffuse cytoplasmatic birefringence, which indicates the presence of small PE particles.^{7,12} These PE particles are generally $<5 \mu\text{m}$.^{7,12} Giant cells and large extra-cellular particles which are commonly found after TKA, have been found in a lesser extent in the interface membranes after THA.⁷ PE particles in TKA have a broader size range, varying from 2–100 μm , than those after THA.^{7,12} Osteolysis and aseptic loosening are associated with macrophages containing many small PE particles as most frequently seen after THA.¹² Such small PE particles are generated by adhesion and abrasion, which are the main wear mechanisms in THA. In TKA, subsurface delamination, pitting and fatigue cracking release much larger and differently shaped pieces of PE.^{13–15}

Until recently, it was thought that it was unlikely that PE wear would pose a clinically relevant problem in TDR in the lumbar spine. It was hypothesized that there would be little formation of PE wear because of limited motions between the vertebral segments as compared to the hip and knee joint.⁴ Moreover, as the disc space is not a synovial joint, it was assumed that there would not be sufficient particle formation to induce early failure of TDR. However, recent studies documented comprehensive PE wear particles and inflammatory reactions in the periprosthetic tissue collected during TDR revision surgery.^{16–19} In a previous study we showed that PE wear particles $\geq 2.05 \mu\text{m}$ are extensively present in periprosthetic lumbar TDR tissue samples in 15 out of 16 symptomatic patients.¹⁸ The periprosthetic inflammatory reaction was characterized by the presence of mainly macrophages, giant cells and lymphocytes.¹⁸ However, osteolysis in TDR has been rarely reported.^{19–22} Therefore the clinical relevance of PE wear particles after lumbar TDR remains poorly understood.

The purpose of this study was to determine and compare characteristics of PE wear particles and inflammatory reactions in periprosthetic tissue collected during revision surgery of TDR, THA and TKA.

2. Materials and methods

2.1 Patient demographics

Periprosthetic tissue samples were collected during TDR, THA and TKA revision surgery. From 2004 to 2009, in 22 patients a single level SB Charité III disc prosthesis (Link, Germany; DePuy, MA) was removed. The indications for revision surgery in this patient group were long-term TDR complications, such as pain and migration, subsidence, and/or facet joint degeneration. Retrieval of the TDR was thought necessary to remove one of the possible pain generators. After posterolateral instrumented fusion without TDR removal, the TDR and its surroundings could continue to give rise to pain due to continuous loading. The mean implantation time was 10 years (range: 4.1–16.3 years). The histological findings of these patients were compared with periprosthetic tissue samples of ten THA patients and four TKA patients, collected in 2009 and 2010. The mean implantation time was 13 years (range: 1.9–18.9 years) for the THA patients and 9 years (range: 3.0–21.8 years) for the TKA patients. Patients with a systemic disease, immune suppression or previous revision surgery involving the removal of an implant were excluded from analysis. All had negative intra-operative tissue cultures. An overview of the clinical patient data is shown in Table 1. The index surgeries were performed at various clinics.

2.2 Histological analyses

Periprosthetic fibrous tissue was collected from the interface membranes surrounding TDR, THA and TKA implants. The retrieved THA and TKA samples were highlighted with black ink to indicate which tissue side had been in contact with the implant.

The retrieved tissue samples were fixed in 10% phosphate buffered formalin for 24 hours and bony tissue was decalcified with TBD-1 Rapid Decalcifier (Thermo Shandon, Pittsburgh, USA) for one hour. After decalcification and embedding, the samples were kept in 70% ethanol. Paraffin sections of 4 μm thickness were cut with a microtome (Leica RM2245) and subsequently stained with hematoxylin and eosin (H&E).

Light microscopy (Leica DM5000B) was used with bright field and polarized illumination (magnification 100 $\times$). Bright field microscopy was used for examining the presence of periprosthetic inflammatory cells, and polarized light to detect PE particles. The cut-off level to detect PE particles was set at a length of 2.05 μm to distinguish between PE and dust particles.

2.3 Morphometric analysis of PE particles

From each H&E stained section a maximum of six regions containing the most PE particles were selected. For the histomorphometric analysis of PE particles a stereological software program was used (Leica Qwin software V3, Cambridge, UK). Analyzed parameters included number of PE particles per mm^2 of analyzed tissue, length (μm), width (μm), roundness of the PE particles and area fraction (%) of the PE particles versus total tissue area.

2.4 Periprosthetic inflammatory response

The tissue samples were examined, according to a modified Mirra classification, for the presence of chronic inflammatory cells (lymphocytes) and giant cells.²³ In addition to this classification, the number of mononuclear macrophages was counted (classified according to the same method as counting lymphocytes). For each tissue sample five microscopic fields were scored.

2.5 Statistical analysis

To compare PE wear particles characteristics and inflammatory reactions between TDR, THA and TKA a Mann-Whitney U test and a Kruskal-Wallis test were performed, using SPSS 16.0. Significance was indicated by $p < 0.05$.

3. Results

3.1 Comparison of quantity, size and morphology of PE particles

PE particles $\geq 2.05 \mu\text{m}$ were detected in the periprosthetic tissue samples of all patients, except one TDR patient (TDR-8), who did not reveal any PE particles. PE particles were mainly observed in macrophages and giant cells in the fibrous collagenous tissue but were also present in bone marrow (Figure 1).

The mean number of PE particles/ mm^2 ranged from 0 to 981, 1 to 1002 and 30 to 602 for TDR, THA and TKA, respectively (non significantly different number of PE particles/ mm^2 , $p=0.53$). An overview of the size and morphology of the PE particles per patient is shown in Table 2. For all groups, neither age nor gender were correlated with the mean number of PE particles/ mm^2 (TDR: $p=0.80$, $p=0.53$; THA: $p=0.42$, $p=0.95$; TKA: $p=0.27$, $p=\text{cannot be computed}$ (all cases are female); respectively).

The particle size frequency distribution of the THA patients showed that the smaller particles were the most numerous (Figure 2). Seventy-five percent of the particles were $< 6 \mu\text{m}$ and 94% of the particles were $< 12 \mu\text{m}$ in length. The TDR frequency distribution was comparable to THA, with 75% of the particles $< 6 \mu\text{m}$ and 90% of the particles $< 12 \mu\text{m}$ in length (Figure 2). In the TKA patients 71% of the particles were $< 6 \mu\text{m}$ and 86% of the particles were $< 12 \mu\text{m}$ (Figure 2). The TKA distribution peaked at the small particle length but there was another peak for particles $> 25 \mu\text{m}$. All individual cases showed a similar distribution in curve length per TDR, THA and TKA.

TDR and THA particles generally had a round to oval shaped morphology. The shape of TKA particles was highly variable with also larger fibrils and flakes. The area fraction (%) of the PE particles versus total tissue area had a size range from 0.03–2.98, 0.00–1.41 and 0.01–0.26 for TDR, THA and TKA, respectively.

The single osteolysis case in the TDR group, does not effect the significance of the outcomes.

3.2 Comparison of the inflammatory cells

An overview of the number and type of inflammatory cells according to a modified Mirra classification is shown in Table 3. Lymphocytes were scored $I+$ in 8 of 22 TDR patients, but were scored $2+/3+$ in most THA and TKA patients. In the TDR group, macrophages were $0/I+$ in 8 patients and $2+/3+$ in 14 patients. Macrophages were scored $2+/3+$ in all THA patients, except for one patient. There were significantly fewer macrophages in the TDR group compared to THA ($p < 0.01$). In TKA patients macrophages were scored $I+$ in 2 patients and $3+$ in the other two patients. The number of giant cells was $0/I+$ in 14 TDR patients and $2+/3+$ in 8 patients. In the THA group they were $0/I+$ in four patients, and $3+$ in all other samples. Giant cells were scored $2+/3+$ in all TKA samples.

4. Discussion

TDR surgery is increasingly performed as a treatment for degenerative disc disease, with similar success rates at two and five year post-operatively compared to fusion surgery.^{24,39} Recently, it has been demonstrated that PE particles and periprosthetic inflammation can

occur after TDR.^{19,20} Nevertheless its clinical relevance is still poorly understood as osteolysis has been rarely observed after TDR.^{19,20} The present study shows that wear mechanisms are comparable to those found in TKA and THA. The observed wear characteristics and histological findings after THA and TKA in this study were consistent with findings from literature.^{7,12–15,25} THA samples showed high numbers of particles <6 µm, mainly contained in macrophages. Particles >12 µm were less prevalent and therefore, less giant cells were observed. PE particles after TKA had a broad size range, with larger PE particles like fibrils and flakes. As a result, more giant cells were present in TKA compared to THA. In TDR, the size range was comparable to TKA, but the smaller particles predominated, as in THA. In other words, in TDR both macrophages and giant cells were present with relatively higher numbers of macrophages.

Differences in quantity, size and shape of PE particles between TDR, THA and TKA are presumably due to differences in loading and wear mechanisms.^{26–29} Submicron particles in THA appear to be generated by adhesion and abrasion mechanisms, whereas wear conditions in TKA generate larger particles through subsurface delamination, pitting and fatigue cracking.^{26–29} Kurtz et al.¹⁷ described wear and damage mechanisms in PE cores from TDRs similar to those observed in both THA and TKA. In the central, spherical dome region of the TDR cores, microscopic multidirectional scratches were found, comparable to the wear mechanisms observed after THA.¹⁷ Around the rim, extensive plastic deformation and fractures were often observed, produced by endplate impingement and resulting in fatigue damage and fracture, as has been reported in retrieved TKA components. In contrast, the prevailing wear mechanisms in the central dome region were adhesion and abrasion.¹⁷ The similarity with TKA wear patterns at the rim, may explain the broad size range of TDR particles. However, small particles were the most prevalent, probably because the prevailing wear mechanisms at the dome, compared to THA patterns.

Periprosthetic osteolysis after TDR appears to be a rare phenomenon as it was only seen in one patient in the present study (TDR-10), as described in more detail by van Ooij et al.¹⁹ This single TDR osteolysis patients, does not have an effect on any of the outcomes. To our knowledge, only three other cases of osteolysis potentially attributable to PE wear debris after TDR have been reported.^{20–22} This is in contrast with the clinical experience with vulcanized rubber in a one-piece TDR design known as the Acroflex, which exhibits short-term clinical failure, frequently associated with osteolysis.²¹ In the case of THA and TKA, osteolysis due to PE particles (in metal-on-polyethylene bearings) and cobalt chromium particles (in metal-metal bearings) are well recognized as potential reasons for revision.^{5–7} Scanning electron microscopy (SEM) showed high concentrations of submicron PE particles in TKA and THA specimens.^{5,13,25,30} These submicron sized particles are known to be the most potent for inducing osteolysis.^{9–11,31} Possibly, submicron sized PE particles are not present in sufficient concentrations to cause osteolysis after TDR. Future research should determine whether submicron sized particles are present after TDR.

Another possible explanation regarding the low frequency of osteolysis in TDR is the osteolysis threshold. The risk of osteolysis appears to increase when the wear penetration rate reaches a critical level.^{17,32} In a review on the association between the PE wear rate and osteolysis, an osteolysis threshold of 0.1 mm/year PE wear in THA was suggested.³² The one patient with osteolysis from the TDR group had a wear penetration rate of 0.14 mm/year, which exceeded the suggested osteolysis threshold in THA.¹⁷ Nevertheless, as this is the only analyzed wear penetration rate of a TDR patient with osteolysis, it will obviously require many more cases of TDR patients to support this hypothesis of an osteolysis threshold in the spine as suggested in the hip. Another theory of osteolysis is the concept of the effective joint space in THA as postulated by Schmalzried et al.³³ This theory states that PE particles generated during wear of the THA, disseminate in the synovial fluid.³³

Depending on the bone-implant contact, the joint fluid and thereby the particles enter the interfaces, the periprosthetic soft tissue and the bone during movement. These areas accessed by the joint fluid become part of the joint space and are then called the effective joint space.³³ When periprosthetic inflammation and bone resorption occur, the effective joint space extends and the process of osteolysis progresses.³³ The absence of a synovial membrane in the intervertebral disc could explain the rarity of osteolysis. It is important to note that the aforementioned osteolysis mechanisms, hypothesized to explain PE particle reactions, may not be relevant to other TDR design and biomaterials. As noted previously, short-term Acroflex failures were frequently associated with osteolysis due to generation of vulcanized rubber debris²¹ and alternative, metal-on-metal artificial discs have been shown to generate metal-ions, which enter the blood stream and circulate systemically.^{34,35} Thus, the findings for osteolysis and particle response in the present study are limited to mobile bearing TDRs containing PE and should not be generalized to TDR designs incorporating other biomaterials.

The PE cores of the Charité TDR have been sterilized by gamma radiation. During this process radicals are being formed, which react slowly with oxygen over time which may have compromised the PE stability.^{2,36} Since 1997, the Charité PE cores were gamma sterilized in first generation barrier packages (N-Vac). Before 1997, the PE cores were gamma sterilized using historical, air permeable packaging by Waldemar Link. The manufacturing of Charité was transferred to DePuy Spine in 2004, and since then the PE cores were sterilized in a vacuum sealed foil pouch (GVF).³⁷ The PE cores in our study have been sterilized by using gamma air or N-Vac, and all were manufactured by Link. No foil pouch barrier packaging PE cores were available in this study. *In vivo* oxidation is a long-term concern in gamma sterilized PE. After implantation the PE comes into contact with oxygen dissolved in body fluids and tissue.³⁷ This amount of oxygen has been proven to be capable of causing oxidation of THA and TKA in less than one decade after implantation.³⁸ In THA, the exposed rims of acetabular liners show frequently oxidation *in vivo*, because the metallic components protect the other areas of the PE bearings.³⁸ Kurtz et al. showed a similar mechanism occurring in TDR, which may explain why oxidation was significantly higher at the rim.³⁷ In these patients oxidation was observed to the same extent in both gamma air and N-Vac sterilized cores.³⁷ Therefore, from the perspective of oxidation, the PE properties of all of the TDRs evaluated in this study can be considered to come from the same population.

One of the limitations of this study is that the cut-off level to detect PE particles was set at a length of 2.05 μm to distinguish between PE and dust particles at the light microscopical level. As a result we were unable to detect submicron sized PE particles, which may be the most bioactive.^{11,31} Therefore, additional research should be performed on submicron sized PE particles. Another limitation is the small number of patients with their relatively high variance. Due to heterogeneity within the groups, it is difficult to correlate patient characteristics and revision reasons with PE wear characteristics and inflammatory reactions. Nevertheless, this is the largest published series worldwide of retrieved TDR prostheses.

The majority of the patients who underwent primary TDR surgery were between 30–50 years old at the time of implantation. This implies that a long life span of the TDR is essential. Charité TDRs show an overall success rate of 57.8% after five years.^{24,39} However, longer follow-up complications are increasingly becoming apparent now.^{19,40} New technologies developed to improve survival of THA and TKA, should also be applied to TDR to create a longer life span. Highly cross linked PE (HXLPE), stabilized by thermal treatments and by vitamin E, has been used with promising initial results in THA and could

be promising for wear reduction in TDR, provided concerns regarding *in vivo* oxidation, impingement and rim fracture can be successfully mitigated.⁴¹

5. Conclusion

The present study showed the presence and similarities between PE wear particles and periprosthetic inflammatory cells in TDR, THA and TKA. Both small and large particles are present after TDR revision surgery due to combined THA and TKA wear patterns. The broad range of the length of these PE particles is comparable to TKA. Nevertheless, small particles contained in macrophages were most numerous in TDR, due to domination of wear patterns similar to THA. Although PE wear-related osteolysis is an important cause of revision and reduced longevity in THA and TKA, osteolysis has been rarely observed thus far after TDR. Detailed histomorphologic and radiographic research of future osteolytic TDR patients is necessary to find an explanation for this phenomenon. The similarities between periprosthetic tissue reactions in the different groups may give more insight in the clinical relevance of PE particles and inflammatory cells in the lumbar spine. Future TDR retrieval cases with an index surgery after 2004 are necessary to establish insight in PE wear particles and periprosthetic tissue reactions of Charité TDR PE components stored within second generation (GVF) barrier packaging.

Acknowledgments

Institutional support was received in part from the National Institutes of Health, AR 56264.

References

1. Bono CM, Garfin SR. History and evolution of disc replacement. *Spine J.* 2004; 4:145S–150S. [PubMed: 15541659]
2. Kurtz, SM. UHMWPE Biomaterials Handbook, Second Edition: Ultra High Molecular Weight Polyethylene in Total Joint Replacement and Medical Devices. New York: Academic Press; 2009.
3. Sakalkale DP, Bhagia SA, Slipman CW. A historical review and current perspective on the intervertebral disc prosthesis. *Pain Physician.* 2003; 6:195–198. [PubMed: 16883380]
4. Link HD. History, design and biomechanics of the LINK SB Charite artificial disc. *Eur Spine J.* 2002; 11 Suppl 2:S98–S105. [PubMed: 12384729]
5. Hirakawa K, Bauer TW, Stulberg BN, Wilde AH, Borden LS. Characterization of debris adjacent to failed knee implants of 3 different designs. *Clin Orthop Relat Res.* 1996;151–158. [PubMed: 8895632]
6. Hirakawa K, Bauer TW, Stulberg BN, Wilde AH, Secic M. Characterization and comparison of wear debris from failed total hip implants of different types. *J Bone Joint Surg Am.* 1996; 78:1235–1243. [PubMed: 8753716]
7. Horikoshi M, Macaulay W, Booth RE, Crossett LS, Rubash HE. Comparison of interface membranes obtained from failed cemented and cementless hip and knee prostheses. *Clin Orthop Relat Res.* 1994:69–87. [PubMed: 7994979]
8. Tsao AK, Jones LC, Lewallen DG. What patient and surgical factors contribute to implant wear and osteolysis in total joint arthroplasty? *J Am Acad Orthop Surg.* 2008; 16 Suppl 1:S7–S13. [PubMed: 18612018]
9. Gallo J, Kaminek P, Ticha V, Rihakova P, Ditmar R. Particle disease. A comprehensive theory of periprosthetic osteolysis: a review. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2002; 146:21–28. [PubMed: 12572890]
10. Gallo J, Raska M, Mrazek F, Petrek M. Bone remodeling, particle disease and individual susceptibility to periprosthetic osteolysis. *Physiol Res.* 2008; 57:339–349. [PubMed: 17465692]

11. Green TR, Fisher J, Stone M, Wroblewski BM, Ingham E. Polyethylene particles of a 'critical size' are necessary for the induction of cytokines by macrophages in vitro. *Biomaterials*. 1998; 19:2297–2302. [PubMed: 9884043]
12. Schmalzried TP, Jasty M, Rosenberg A, Harris WH. Polyethylene wear debris and tissue reactions in knee as compared to hip replacement prostheses. *J Appl Biomater*. 1994; 5:185–190. [PubMed: 10147443]
13. Hirakawa K, Bauer TW, Stulberg BN, Wilde AH. Comparison and quantitation of wear debris of failed total hip and total knee arthroplasty. *J Biomed Mater Res*. 1996; 31:257–263. [PubMed: 8731215]
14. Kobayashi A, Freeman MA, Bonfield W, Kadoya Y, Yamac T, Al-Saffar N, Scott G, Revell PA. Number of polyethylene particles and osteolysis in total joint replacements. A quantitative study using a tissue-digestion method. *J Bone Joint Surg Br*. 1997; 79:844–848. [PubMed: 9331048]
15. Mabrey JD, Afsar-Keshmiri A, Engh GA, Sychterz CJ, Wirth MA, Rockwood CA, Agrawal CM. Standardized analysis of UHMWPE wear particles from failed total joint arthroplasties. *J Biomed Mater Res*. 2002; 63:475–483. [PubMed: 12209890]
16. Kurtz SM, Peloza J, Siskey R, Villarraga ML. Analysis of a retrieved polyethylene total disc replacement component. *Spine J*. 2005; 5:344–350. [PubMed: 15863092]
17. Kurtz SM, van Ooij A, Ross R, de Waal Malefijt J, Peloza J, Ciccarelli L, Villarraga ML. Polyethylene wear and rim fracture in total disc arthroplasty. *Spine J*. 2007; 7:12–21. [PubMed: 17197327]
18. Punt IM, Cleutjens JP, de Bruin T, Willems PC, Kurtz SM, van Rhijn LW, Schurink GW, van Ooij A. Periprosthetic tissue reactions observed at revision of total intervertebral disc arthroplasty. *Biomaterials*. 2009; 30:2079–2084. [PubMed: 19155064]
19. van Ooij A, Kurtz SM, Stessels F, Noten H, van Rhijn L. Polyethylene wear debris and long-term clinical failure of the Charite disc prosthesis: a study of 4 patients. *Spine (Phila Pa 1976)*. 2007; 32:223–229. [PubMed: 17224818]
20. Licina P, Thorpe PLPJ. Osteolysis and complications associated with artificial disc replacement. *J Bone Joint Surg Br*. 2004; 86-b:460–461.
21. Fraser RD, Ross ER, Lowery GL, Freeman BJ, Dolan M. AcroFlex design and results. *Spine J*. 2004; 4:245S–251S. [PubMed: 15541673]
22. McAfee PC, Geisler FH, Saiedy SS, Moore SV, Regan JJ, Guyer RD, Blumenthal SL, Fedder IL, Tortolani PJ, Cunningham B. Revisability of the CHARITE artificial disc replacement: analysis of 688 patients enrolled in the U.S. IDE study of the CHARITE Artificial Disc. *Spine (Phila Pa 1976)*. 2006; 31:1217–1226. [PubMed: 16688035]
23. Mirra JM, Amstutz HC, Matos M, Gold R. The pathology of the joint tissues and its clinical relevance in prosthesis failure. *Clin Orthop Relat Res*. 1976:221–240. [PubMed: 776484]
24. Guyer RD, McAfee PC, Banco RJ, Bitan FD, Cappuccino A, Geisler FH, Hochschuler SH, Holt RT, Jenis LG, Majd ME, Regan JJ, Tromanhauser SG, Wong DC, Blumenthal SL. Prospective, randomized, multicenter Food and Drug Administration investigational device exemption study of lumbar total disc replacement with the CHARITE artificial disc versus lumbar fusion: five-year follow-up. *Spine J*. 2009; 9:374–386. [PubMed: 18805066]
25. Schmalzried TP, Campbell P, Schmitt AK, Brown IC, Amstutz HC. Shapes and dimensional characteristics of polyethylene wear particles generated in vivo by total knee replacements compared to total hip replacements. *J Biomed Mater Res*. 1997; 38:203–210. [PubMed: 9283965]
26. Collier JP, Mayor MB, McNamara JL, Surprenant VA, Jensen RE. Analysis of the failure of 122 polyethylene inserts from uncemented tibial knee components. *Clin Orthop Relat Res*. 1991:232–242. [PubMed: 1959276]
27. McKellop HA, Campbell P, Park SH, Schmalzried TP, Grigoris P, Amstutz HC, Sarmiento A. The origin of submicron polyethylene wear debris in total hip arthroplasty. *Clin Orthop Relat Res*. 1995:3–20. [PubMed: 7634588]
28. Shanbhag AS, Jacobs JJ, Glant TT, Gilbert JL, Black J, Galante JO. Composition and morphology of wear debris in failed uncemented total hip replacement. *J Bone Joint Surg Br*. 1994; 76:60–67. [PubMed: 8300684]

29. Wright TM, Rimnac CM, Stulberg SD, Mintz L, Tsao AK, Klein RW, McCrae C. Wear of polyethylene in total joint replacements. Observations from retrieved PCA knee implants. *Clin Orthop Relat Res.* 1992;126–134. [PubMed: 1537143]
30. Lee JM, Salvati EA, Betts F, DiCarlo EF, Doty SB, Bullough PG. Size of metallic and polyethylene debris particles in failed cemented total hip replacements. *J Bone Joint Surg Br.* 1992; 74:380–384. [PubMed: 1587882]
31. Ingham E, Fisher J. The role of macrophages in osteolysis of total joint replacement. *Biomaterials.* 2005; 26:1271–1286. [PubMed: 15475057]
32. Dumbleton JH, Manley MT, Edidin AA. A literature review of the association between wear rate and osteolysis in total hip arthroplasty. *J Arthroplasty.* 2002; 17:649–661. [PubMed: 12168184]
33. Schmalzried TP, Jasty M, Harris WH. Periprosthetic bone loss in total hip arthroplasty. Polyethylene wear debris and the concept of the effective joint space. *J Bone Joint Surg Am.* 1992; 74:849–863. [PubMed: 1634575]
34. Zeh A, Becker C, Planert M, Lattke P, Wohlrab D. Time-dependent release of cobalt and chromium ions into the serum following implantation of the metal-on-metal Maverick type artificial lumbar disc (Medtronic Sofamor Danek). *Arch Orthop Trauma Surg.* 2009; 129:741–746. [PubMed: 18592257]
35. Zeh A, Planert M, Siegert G, Lattke P, Held A, Hein W. Release of cobalt and chromium ions into the serum following implantation of the metal-on-metal Maverick-type artificial lumbar disc (Medtronic Sofamor Danek). *Spine (Phila Pa 1976).* 2007; 32:348–352. [PubMed: 17268267]
36. Costa L, Bracco P, Brach del Prever EM, Kurtz SM, Gallinaro P. Oxidation and oxidation potential in contemporary packaging for polyethylene total joint replacement components. *J Biomed Mater Res B Appl Biomater.* 2006; 78:20–26. [PubMed: 16470814]
37. Kurtz SM, MacDonald D, Ianuzzi A, van Ooij A, Isaza J, Ross ER, Regan J. The natural history of polyethylene oxidation in total disc replacement. *Spine (Phila Pa 1976).* 2009; 34:2369–2377. [PubMed: 19789469]
38. Kurtz SM, Hozack W, Marcolongo M, Turner J, Rimnac C, Edidin A. Degradation of mechanical properties of UHMWPE acetabular liners following long-term implantation. *J Arthroplasty.* 2003; 18:68–78. [PubMed: 14560414]
39. Guyer RD, McAfee PC, Hochschuler SH, Blumenthal SL, Fedder IL, Ohnmeiss DD, Cunningham BW. Prospective randomized study of the Charite artificial disc: data from two investigational centers. *Spine J.* 2004; 4:252S–259S. [PubMed: 15541674]
40. Punt IM, Visser VM, van Rhijn LW, Kurtz SM, Antonis J, Schurink GW, van Ooij A. Complications and reoperations of the SB Charite lumbar disc prosthesis: experience in 75 patients. *Eur Spine J.* 2008; 17:36–43. [PubMed: 17929065]
41. Manning DW, Chiang PP, Martell JM, Galante JO, Harris WH. In vivo comparative wear study of traditional and highly cross-linked polyethylene in total hip arthroplasty. *J Arthroplasty.* 2005; 20:880–886. [PubMed: 16230239]

Fig. 1. H&E stained sections containing characteristic histological features of the retrieved periprosthetic fibrous tissue from one patient of each study group. A) Section of a TDR patient observed with bright field microscopy, B) Section of a TDR patient observed with polarized light, C) Section of a THA patient observed with bright field microscopy, D) Section of a THA patient observed polarized light, E) Section of a TKA patient observed with bright field microscopy, F) Section of a TKA patient observed with polarized light. For further explanation see text.

Fig. 2.
PE particle size frequency distribution. Bars represent percentage of particles for each size range and the lines represent the cumulative percentage of the particles.

Table 1

Clinical data of the SB Charité III TDR patients.

Patient number	Age at implantation (years)	Gender	Level	Year at index surgery	Implantation time at revision (years)	Type PE sterilization	Revision reason(s)
TDR-1	37	M	L4-5	1992	13.5	Air	Pain, broken metal wire, subsidence, facet joint degeneration
TDR-2	39	F	L5-S1	1995	9.2	Air	Pain, flattening PE core, broken metal wire, subsidence
TDR-3	33	F	L4-5	1995	10.6	Air	Pain, disc degeneration L3-4 above a successful posterior fusion L4-S1
TDR-4	34	F	L5-S1	1997	8.5	Unknown	Pain, facet joint degeneration L5-S1
TDR-5	46	F	L4-5	2001	5.3	Unknown	Pain, height loss posteriorly at core, facet joint degeneration L4-5, L5-S1, disc degeneration L3-4
TDR-6	33	F	L3-4	1992	12.7	Air	Pain, instability/retrolisthesis L1-2, L2-3, pseudoarthrosis L4-5, anterior migration
TDR-7	46	M	L4-5	1998	6.2	Unknown	Pain, subsidence
TDR-8	47	M	L4-5	2001	4.2	Unknown	Pain, subsidence, facet joint degeneration
TDR-9	39	M	L4-5	1995	10.2	Air	Pain, facet joint degeneration L4-5, degeneration disc L1-2, L3-4
TDR-10	45	F	L5-S1	1998	6.5	Unknown	Pain, broken prosthesis with osteolysis in the sacrum, endplate loosening, facet joint degeneration
TDR-11	34	F	L4-5	1999	4.9	Inert	Pain, subsidence
TDR-12	56	F	L4-5	1990	16.1	Air	Pain, anterior migration, pressure against aorta, facet joint degeneration
TDR-13	44	M	L4-5	1989	16.0	Air	Pain, subsidence, multiple disc and facet joint degeneration
TDR-14	42	F	L4-5	2000	6.2	Unknown	Pain after posterior pedicle screw fixation and fusion L4-L5, L5-S1
TDR-15	42	F	L4-5	1993	13.7	Unknown	Pain, broken marker wire
TDR-16	42	F	L4-5	1996	10.7	Air	Pain
TDR-17	49	F	L3-4	2003	4.1	Unknown	Pain in lower back and both legs, no bony fusion, prosthesis in excessive extension
TDR-18	51	M	L5-S1	1991	16.3	Air	Pain, pseudoarthrosis L5-S1, subsidence
TDR-19	52	F	L5-S1	1993	15.0	Air	Pain back and left leg pain
TDR-20	50	M	L5-S1	2002	6.4	Unknown	Pain, facet joint degeneration L5-S1, lateral migration of the endplate, disc degeneration L3-4
TDR-21	43	F	L5-S1	2000	8.4	Unknown	Pain, facet joint degeneration L5-S1
TDR-22	47	F	L4-5	1993	16.0	Air	Pain, degeneration disc L1-3, facet joint degeneration L5-S1, oblique implantation of prosthesis

Clinical data of the THA and TKA patients.

Patient number	Age at implantation (year)	Gender	Year at index surgery	Implantation time (year)	Type of implant	Cement	Type PE sterilization	Revised component	Revision reason(s)
THA-1	51	F	1990	18.9	Charnley stem Charnley cup	Yes	Air	Cup+Stem	Pain, aseptic loosening, radiolucent lines around the stem and cup, eccentric position due to wear
THA-2	64	F	1990	18.9	Osteonics Omniflex Osteonics PE cup	Yes	Air	Cup	Pain, aseptic loosening, radiolucent lines around the stem, displacement of the head in the cup due to wear
THA-3	39	M	1994	15.0	Osteonics Omnifit Osteonics MCI cup	Yes, hybride	Air	Cup	Pain, aseptic loosening, radiolucency around the cup, bone loss of the acetabulum
THA-4	78	F	2004	5.4	Osteonics Omnifit SHP cup	Yes	Inert	Stem	Pain, aseptic loosening, increased activity on scintigraphy around stem
THA-5	66	M	1995	14.3	Osteonics Omnifit Osteonics PE cup	Yes	Air	Cup	Pain, aseptic loosening, radiolucency around the cup, progressive cup migration
THA-6	44	F	1992	17.3	Osteonics Omniflex Dual Radius cup	No	Air	Cup+Stem	Pain, aseptic loosening after trauma, radiolucent lines around the stem, eccentric position due to wear
THA-7	79	F	1998	11.1	Muller straight stem Osteonics PE cup	Yes	Unknown	Cup	Pain, aseptic loosening, radiolucent lines around the cup, broken marker wire, eccentric position due to wear
THA-8	62	F	1994	15.8	Osteonics Omnifit Dual Radius Cup	No	Air	Cup	Pain, eccentric position of the head due to wear
THA-9	49	M	1994	15.4	Osteonics Omnifit Dual Radius Cup	No	Air	Cup	Pain, eccentric position of the head, radiolucent lines around the cup
THA-10	77	F	2008	1.9	Omnifit HA stem SHP cup	Yes, hybride	Inert	Cup	Pain, aseptic loosening, bone loss acetabulum
TKA-1	65	F	1987	21.8	Kinemax	Yes	Air	Both components	Pain, aseptic loosening of the tibial and femoral component with advanced wear
TKA-2	65	F	2000	8.9	Kinemax Plus CR insert	Yes	Inert	Both components	Persisting anterior knee pain, aseptic loosening of both components, advanced wear of the tibial insert
TKA-3	55	F	2007	3.0	Nexgen Flex Nexgen LPS insert	No	Inert	Both components	Pain, aseptic loosening both components
TKA-4	46	F	2005	4.7	Richard Genesis Insert 11 DD	Yes	Inert	Both components	Persisting anterior knee pain, aseptic loosening both components

All THA and TKA patients showed intra-operatively negative tissue cultures to rule out a concomitant infection.

Table 2

Quantitative analysis of retrieved PE wear debris in periprosthetic tissue obtained during TDR, THA and TKA revision surgery.

Patient number	Region tissue	Mean number of PE particles/mm ²	Number of regions containing PE	Length, median (μm)	Length, range (μm)	Width, median (μm)	Roundness, median	Area fraction (%)
TDR-1		599	6	3.58	2.05–943.73	2.05	1.35	2.53
TDR-2		657	6	4.10	2.05–165.44	2.05	1.50	1.22
TDR-3		54	4	3.07	2.05–24.93	1.62	1.35	0.06
TDR-4		53	6	3.07	2.05–167.78	1.42	1.50	0.07
TDR-5		15	3	3.07	2.05–21.29	1.02	1.35	0.00
TDR-6		323	6	3.07	2.05–135.49	1.78	1.50	0.42
TDR-7		90	2	3.07	2.05–162.14	2.20	1.50	0.25
TDR-8		0	0	-	-	-	-	-
TDR-9		50	6	3.58	2.05–40.17	2.05	1.35	0.06
TDR-10		981	6	4.97	2.05–171.35	2.24	1.48	2.98
TDR-11		2	1	9.04	2.31–45.36	2.31	1.54	0.01
TDR-12		299	6	4.61	2.05–157.39	2.05	1.47	0.98
TDR-13		139	6	3.70	2.05–247.25	1.78	1.50	1.07
TDR-14		16	3	2.31	2.05–5.90	1.02	1.35	0.00
TDR-15		683	6	4.10	2.05–116.46	2.05	1.43	1.26
TDR-16		146	6	3.70	2.05–129.06	1.69	1.50	0.28
TDR-17		26	6	4.10	2.05–30.45	1.69	1.51	0.03
TDR-18		344	6	3.07	2.05–45.78	1.42	1.35	0.29
TDR-19		244	6	3.07	2.05–30.54	1.42	1.35	0.17
TDR-20		20	2	4.10	2.05–20.72	2.05	1.37	0.02
TDR-21		111	6	3.07	2.05–45.07	2.31	1.35	0.15
TDR-22		229	6	3.70	2.05–575.07	1.87	1.50	1.13
THA-1	F	373	6	4.10	2.05–227.46	1.63	1.51	0.03
THA-2	A	300	6	3.07	2.05–45.38	1.42	1.40	0.27
THA-3	A	239	6	3.70	2.05–145.48	2.05	1.50	0.50
THA-4	F	3	5	4.10	2.05–11.05	2.31	1.35	0.00
THA-5	A	526	6	3.58	2.05–65.37	1.81	1.42	0.04

Patient number	Region tissue	Mean number of PE particles/mm ²	Number of regions containing PE	Length, median (μm)	Length, range (μm)	Width, median (μm)	Roundness, median	Area fraction (%)
THA-6	A	441	6	3.07	2.05–43.67	1.62	1.35	0.31
THA-7	A	215	6	2.31	2.05–45.71	2.31	1.35	0.26
THA-8	A	1002	6	2.31	2.05–311.44	2.31	1.20	1.41
THA-9	A	277	6	3.70	2.05–120.08	2.19	1.47	0.03
THA-10	A	1	1	2.05	2.05–9.28	1.02	1.35	0.00
TKA-1	Unknown	201	6	4.10	2.05–2265.04	2.05	1.56	0.02
TKA-2	T	602	6	4.10	2.05–539.40	2.05	1.60	0.05
TKA-3	T	40	6	3.22	2.05–214.17	2.05	1.50	0.26
TKA-4	F	30	6	2.31	2.05–15.48	1.02	1.35	0.01

A = acetabulum, F = femur, T = tibia

Table 3

Histological classification of retrieved periprosthetic tissue after TDR, THA and TKA revision surgery according to the modified Mirra classification.

Patient number	Chronic inflammatory cells (lymphocytes) ^a	Macrophages ^b	Giant cells ^c
TDR-1	1+	2+	2+
TDR-2	1+	3+	2+
TDR-3	0	1+	0
TDR-4	0	2+	1+
TDR-5	0	2+	1+
TDR-6	1+	2+	3+
TDR-7	0	2+	1+
TDR-8	0	0	0
TDR-9	1+ ^d	3+	0
TDR-10	0	3+	2+
TDR-11	0	0	0
TDR-12	1+ ^d	2+	3+
TDR-13	0	2+	2+
TDR-14	1+ ^d	0	0
TDR-15	1+	3+	2+
TDR-16	0	0	0
TDR-17	2+ ^d	2+ ^d	0
TDR-18	0	1+	0
TDR-19	0	0	0
TDR-20	0	3+ ^e	1+ ^d
TDR-21	0	0	0
TDR-22	1+	2+	2+
THA-1	3+	3+	3+
THA-2	2+	3+	1+
THA-3	2+	3+	3+
THA-4	1+	1+	0
THA-5	2+	3+	3+
THA-6	1+	3+	3+
THA-7	2+	3+	3+
THA-8	2+	3+	3+
THA-9	3+	3+	1+
THA-10	2+	2+	0
TKA-1	2+	3+	3+
TKA-2	3+	3+	3+
TKA-3	3+	1+	2+
TKA-4	3+	1+	2+ ^e

^a 1+: 1–9 cells/high power field (×500) and/or 1 lymphoid follicle/low power field (×100), 2+: 10–49 cells/high power field (×500) and/or 2–3 lymphoid follicles/low power field (×100), 3+: ≥50 cells/high power field (×500) and/or ≥4 lymphoid follicles/low power field (×100).

^b 1+: 1–9 macrophages/high power field (×500), 2+: 10–49 macrophages/high power field (×500), 3+: ≥50 macrophages/high power field (×500).

^c 1+: 1–2 cells/medium power field (×250), 2+: 3–8 cells/medium power field (×250), 3+: ≥ 9cells/medium power field (×250).

^d Histology only found in one microscopic field.

^e Histology only found in two microscopic fields.