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ORIGINAL ARTICLE

Cross-linked Compared with Historical Polyethylene in THA

An 8-year Clinical Study

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Abstract Wear particle-induced osteolysis is a major cause of aseptic loosening in THA. Increasing wear resistance of polyethylene (PE) occurs by increasing the cross-link density and early reports document low wear rates with such implants. To confirm longer-term reductions in wear we compared cross-linked polyethylene (irradiation in nitrogen, annealing) with historical polyethylene (irradiation in air) in a prospective, randomized clinical study involving 48 patients who underwent THAs with a minimum followup of 7 years (mean, 8 years; range, 7–9 years). The insert material was the only variable. The Harris hip score, radiographic signs of osteolysis, and polyethylene wear were recorded annually. Twenty-three historical and 17 moderately cross-linked polyethylene inserts were analyzed (five patients died, three were lost to followup). At 8 years, the wear rate was lower for cross-linked polyethylene (0.088 ± 0.03 mm/year) than for the historical polyethylene (0.142 ± 0.07 mm/year). This reduction (38%) did not diminish with time (33% at 5 years). Acetabular cyst formation was less frequent (39% versus 12%), affected fewer DeLee and Charnley zones (17% versus 4%), and was less severe for the cross-linked polyethylene. The only revision was for an aseptically loose cup in the historical polyethylene group. Moderately cross-linked polyethylene maintained its wear advantage with time and produced less osteolysis, showing no signs of aging at mid-term followup.

Level of Evidence: Level I, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

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Each author certifies that his or her institution has approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

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Introduction

Wear particle-induced osteolysis is the major cause of aseptic loosening and (premature) revision in THA. The osteolytic effect of wear debris depends not only on particle size and shape but also mainly on the particle volume released into the surrounding tissue [14, 24]. Numerous authors have reported, with standard 28-mm heads, linear wear rates greater than 0.2 mm per year always produce wear particle-induced osteolysis, whereas this mostly is absent at annual wear rates less than 0.05 to 0.1 mm per year [1, 4, 10, 11, 20, 29, 32, 34, 35]. Therefore, increasing wear resistance of the PE for acetabular cups has been a major target. This can be achieved by increasing the cross-link density of the PE [41]. A wear simulator study suggested wear reduction of moderately cross-linked PE over historical PE is between 32% and 45% by volumetric wear rates [15].

Cross-linking is a process usually initiated by gamma irradiation whereby hydrogen atoms are removed from the PE molecules, creating free radicals, which recombine by linking with free radicals of neighboring PE molecule chains. This new network of cross-linked PE chains dramatically increases the wear resistance but also increases the stiffness of the PE and makes it more brittle [21, 28]. A PE that is too stiff or brittle may have reduced fatigue strength, which in clinical applications may lead to stress cracking and subsequent failure of the locking mechanism, or when impingement occurs, the insert rim may crack and delaminate [39].

However, not all free radicals created by the irradiation recombine to form cross-links. These residual free radicals are highly reactive and are responsible for early oxidation (aging) of the PE [12]. Oxidized PE exhibits accelerated wear and delamination. Free radicals can be removed using two postirradiation heat treatments, remelting or annealing. Remelted PE is more oxidation-resistant but has less mechanical strength than historical PE. In annealed PE, strength is maintained, but because of residual-free radicals, oxidation should appear, which could lead to accelerating long-term wear rates [12, 36].

Our primary study question was whether cross-linked PE could maintain its increased wear resistance with time up to 8 years when oxidation and aging effects may have affected the original properties. A secondary study question was whether the reduced wear rate of cross-linked PE led to reduced signs of osteolysis.

Materials and Methods

We compared the first-generation moderately (≤ 50-kGy total irradiation dose) cross-linked PE (Duration™; Stryker Orthopaedics, Mahway, NJ) with PE gamma-sterilized in air, a clinical standard at the time the study began but now considered and in the following referred to as historical PE. We enrolled 48 patients (48 hips) after informed consent and ethical approval in a randomized, prospective clinical study. Patients were included who had primary THAs who had a diagnosis of osteoarthritis, rheumatoid arthritis, avascular necrosis of the femoral head, or post-traumatic arthritis of the hip. The patients were between 48 and 74 years of age on enrollment. Patients were excluded if they had prior reconstructive procedures, such as surface replacement arthroplasty or fracture fixation, or hemiarthroplasties. We also excluded patients if they had active infections or if they had a malignancy in the area of the involved hip. We obtained the patients' medical histories, including demographics, joint disease diagnosis, and concurrent diseases. Included patients were assigned to either the historical PE insert (26 hips) or the moderately cross-linked PE insert (22 hips) by double-blind block randomization. Five patients died of unrelated causes and three were lost to followup, leaving 40 patients (23 historical, 17 Duration™) for clinical and wear analyses. The historical PE and Duration™ PE groups were similar in terms of gender distribution (13 males/10 females versus 11 males/six females), average age (64 years), body mass index (28 kg/m^2 versus 29 kg/m^2), preoperative (40 versus 39) and postoperative (93 versus 95) Harris hip scores [19], stem size (4 versus 4), average cup diameter (54 mm versus 54 mm), cup inclination (47° versus 48°), liner thickness (8 mm versus 8 mm), and average followup (8 years). The randomization process resulted in good matching, leaving the insert material as the only variable of the study (Table 1). A priori power analysis (G*Power 3; Düsseldorf University, Düsseldorf, Germany) [13] was performed, assuming an annual wear rate of 0.15 mm per year for the historical PE based on published values [11] and a wear rate of 0.09 mm per year for the Duration™ PE based on the 45% reduction in linear wear rate predicted from a simulator study [15]. Assuming conservative standard deviations for the wear rate measurement (± 0.07 mm/year) based on a pilot study and standard values for alpha ($\alpha = 0.05$) and power ($\beta = 80\%$), a total sample size of 46 was calculated. After loss to followup (n = 40), post hoc analysis confirmed a power of $\beta = 92\%$, benefiting mainly from the lower than assumed standard deviations.

Table 1. Patient demographics, surgical and implant parameters, and wear

Variable	Historical PE	Duration™ PE
Total/available	26/23	22/17
Age (years)	64 (54–72)	64 (48–74)
Body mass index (kg/m^2)	28 (23–49)	28 (24–36)
Male/female	13/10	11/6
Harris hip score preoperatively	40 ± 19	39 ± 16
Stem size	4 (2–5)	4 (3–5)
Head diameter (mm)	28	28
Cup diameter (mm)	54 (48–62)	54 (48–60)
Cup inclination (degrees)	47 ± 7	48 ± 6
Liner thickness (mm)	9 (7–11)	9 (6–12)
Followup (years)	8 (7.2–8.8)	8 (6.9–9.0)
Harris hip score postoperatively	93 ± 14	95 ± 12
Wear rate (mm/year)	0.142 ± 0.07	0.088 ± 0.03*

Values are expressed as mean or mean ± standard deviation, with range in parentheses; *p = 0.01; PE = polyethylene.

Both of the acetabular cup inserts used were of the same hemispheric design and were mated to an ABG® II hydroxyapatite-coated hemispheric acetabular shell made of titanium alloy (Stryker) and matching press-fit hydroxyapatite-coated ABG® II stem (Stryker). All femoral heads were of CoCr alloy and measured 28 mm in diameter. Both inserts were manufactured from ram-extruded rods converted from Hoechst GUR 415 resin by Poly Hi Solidur, Inc (Reading, PA) with a molecular weight between 5 and 6 million g/mol. The historical PE inserts were packaged and sealed in a double-plastic blister surrounded by air and the package then was irradiated at a dose of 30 kGy. The moderately cross-linked PE inserts were placed in two sealed blisters, which were evacuated and then flushed with nitrogen before sealing. The oxygen concentration in the inner blister was less than 0.5% (v/v) and the concentration in the outer blister was less than 5% (v/v) at the time of packaging. The completed package then was gamma-irradiated with a dose of 30 kGy. After irradiation, packages were placed in an oven for annealing at a temperature of 50°C for 144 hours density by promoting free radical recombination. The elevated cross-link density of moderately cross-linked PE was verified using a small punch test [37]. Additional mechanical tests showed strength, stiffness, and elongation to break as a measure of brittleness were not affected by the moderately cross-linked PE process.

Clinical followup parameters were assessed at patient visits postoperatively at less than 6 weeks and at 1, 2, 3, 5, and 8 years postoperatively. Standard standing radiographs were obtained for subsequent wear measurement (5 and 8 years). Two of us (AJT, WV, blinded to PE insert used) identified migration, loosening, and potentially wear-related phenomena, such as osteolytic cyst formation and radiolucent lines, in the femur and acetabulum. Migration was defined as a change in distance between the proximal tip of the hip stem and trochanter major on anteroposterior radiographs reaching or exceeding 3 mm or greater than 3 mm displacement of the cup in any direction. Findings were located according to the seven zones of Gruen et al. [18] for the femur and the three zones of DeLee and Charnley [6] for the acetabulum. On the femur and acetabulum, osteolytic cysts or radiolucent lines were rated as present or nonpresent. On the acetabulum, where multiple cysts were seen, also the number, size, and shape (affected bone-implant interface) of cysts were evaluated and scored in a composite severity index. In the absence of a gold standard rating system, the following classification was used: one point was given to one small cyst covering a small proportion of the bone-implant interface; two points were given for either two such small cysts or one medium-sized cyst affecting approximately ½ the bone-implant interface of the zone under investigation; two points also were given for a large cyst extending from a neighboring zone into the investigated zone affecting approximately ½ the bone-implant interface; three points were given when two medium-sized cysts or a large cyst affected all or most of the bone-implant interface of the zone under investigation. With three acetabular zones, the total severity index ranged from 0 (no cysts) to 9 (extensive cysts in all three zones). A similar rating of radiolucent lines was not applied, as they were present in only one patient.

Wear was measured by one blinded observer (WV) on standard anteroposterior standing digital radiographs (5-MPix resolution) determining femoral head penetration [27] using the Roman V 1.70 software (Institute of Orthopaedics, Oswestry, UK). Accuracy, intraobserver and interobserver reliability of this method, and software reportedly are equal or superior to other common methods [16].

We statistically compared the linear wear rates of both groups using the nonparametric two-tailed Mann-Whitney test. Proportions of patients with wear rates greater or less than clinically relevant thresholds were compared using Fisher's exact test. Also, the proportions of patients showing cysts as a sign of osteolysis were compared using Fisher's exact test.

Results

At 8 years' followup, the linear wear rates were less ($p = 0.007$) for the moderately cross-linked PE (0.088 ± 0.03 mm/year) than for the historical PE (0.142 ± 0.07 mm per year). More patients ($p = 0.006$) with the historical PE had annual wear rates greater than 0.1 mm per year than did patients with the moderately cross-linked PE insert (17 of 23 versus five of 17, respectively) (Fig. 1). More patients ($0 = 0.2$) in the historical PE group also had high wear rates (greater than a threshold value of 0.2 mm per year) than in the moderately cross-linked PE group (four of 23 versus 0 of 17, respectively). At 5 years, the annual wear rate also was less ($p = 0.02$) for the cross-linked PE (0.106 ± 0.037 mm/year) than for the historical PE (0.152 ± 0.062 mm/year) group. The average reduction in wear rate with cross-linked PE at 8 years (38%) did not decrease when compared with the rate at the 5-year followup (30%).

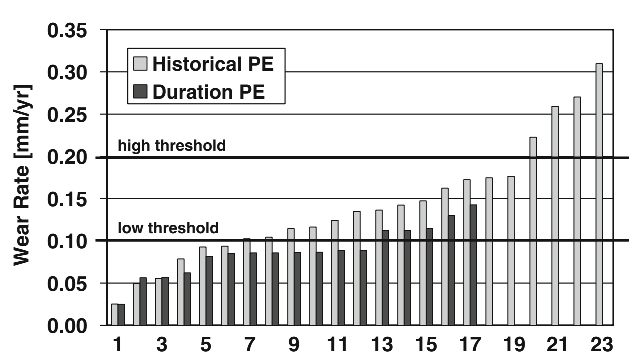

Fig. 1 A histogram shows annual linear wear rates for each patient measured at 8 years.

One patient in the historical group had osteolysis with acetabular radiolucencies in all three DeLee and Charnley zones. This patient also had aseptic acetabular loosening and underwent revision surgery. The annual wear rate of this patient was at the higher end of the distribution at 0.22 mm per year. Acetabular radiolucencies or loosening were absent in the moderately cross- linked PE. Radiographic appearance of one or more osteolytic cysts in the acetabulum was greater ($p = 0.057$) in patients in the historical PE (nine of 23) group than in patients in the cross-linked PE (two of 17) group. When the number of affected DeLee and Charnley zones was counted, the proportion of zones showing cyst formation also was greater ($p = 0.022$) with historical PE (12 of 69, 17%) than with cross-linked PE (two of 51, 4%). When cyst formation was weighted by size using the 0- to 9-point severity index, the higher level of cyst formation for the group with historical PE became even more pronounced (14.5% versus 2.9%) ($p = 0.021$). Although there were no femoral radiolucencies seen in either group, femoral osteolysis was noted in similar numbers ($p = 0.489$) of patients in both groups (four of 23 for the historical PE group and two of 17 for the moderately cross-linked PE group).

Discussion

Wear particle-induced osteolysis is a major cause of aseptic loosening in THA. Wear resistance of PE may be enhanced by increasing the cross-link density. Simulator studies and short- to midterm clinical studies with as much as 6 years followup [1–3, 7–9, 15, 17, 21, 22, 25, 30, 31] document reduced wear. However, aging may influence the material as in vivo oxidation may start to degrade the beneficial properties of cross-linked PE with its higher residual amount of free radicals, especially in material that is annealed and not remelted. We therefore asked whether cross-linked PE could maintain its increased wear resistance with time up to 8 years when oxidation and aging effects may have affected the original properties. Our secondary question was whether the reduced wear rate of cross-linked PE led to reduced osteolysis. This relationship is being scrutinized because wear particles of cross-linked PE have been suspected to have a higher osteolytic potential, and it can be investigated only when followups are long enough for development and radiographic diagnosis of cyst formation.

Our study is limited by the relatively small group size, which nonetheless was sufficiently powered to investigate the first question regarding wear rate reductions but weakly powered to draw conclusions on the second question regarding effective reduction of osteolysis with cross-linked PE. Quantifying osteolysis in an objective and reliable manner generally is difficult and was not well described before the study by Dumbleton et al. [11] in 2002. Our two experienced observers tried to classify size, number, and position in a composite severity index. However, periacetabular cyst formation can be evaluated only partially from anteroposterior radiographs, as approximately ½ the periacetabular cyst is covered by the insert and projected in the anteroposterior plane [5, 26, 43]. A set of oblique radiographs or three-dimensional CT may resolve this problem but poses ethical issues. As in any study trying to link wear rates to wear debris-induced osteolysis, the highly individual response of periprosthetic tissue to particle load (responders and nonresponders) probably confounds studies on wear and osteolysis unless joint register-sized databases can be used. Although accurate and reliable digital wear-measurement software was used on high-resolution radiographs, the prospective nature of the study would have allowed radiostereometric analysis (RSA) to be used. This would have further increased accuracy and improved analysis of the wear angles and creep or liner settling.

Our study also is limited by the fact that the wear analysis was performed only at 5 and 8 years but not after short followup, so we have no information regarding whether both materials differed regarding creep or liner settling was completed after 6 to 24 months. Studies such as those of Digas et al. [7, 8] showed highly cross-linked PE has not only reduced steady-state wear rates at 5 years but also less creep and liner settling, which also tends to be completed earlier. If this would apply to a lesser degree also to the moderately cross-linked PE used in our study, the reduction in steady-state wear rate measured at 5 or 8 years could still be larger. However, with creep and liner settling measuring less than 0.1 mm [9], the effect size is smaller than the pixel of a standard digital radiograph and thus hardly can be captured with conventional radiographic wear measurement but with RSA only.

Although many factors possibly confounding this comparative wear study were controlled or matched, activity level as a major factor affecting wear [32] was not measured or controlled. Whereas demographics (gender, age, body mass index) and postoperative clinical outcome as measured using the Harris hip score were the same between groups, these provide only slight indication regarding functional capacity and overall activity level. With the advance of activity-monitoring technologies, wear studies such as this would benefit from information about activity.

Finally, a minimum of 7 years' followup is still too short to analyze and draw conclusions regarding long-term effects. However, PE intentionally cross-linked to reduce wear over PE gamma-irradiated solely for the purpose of sterilization was introduced for widespread clinical use in the mid- to late 1990s and thus clinical evidence from 8 to

10 years followup is the longest that can be reported at this stage. Although newer generations of highly cross-linked PE inserts reportedly have promising low wear rates, from 59% to greater than 95% wear reduction compared with rates of historical PE inserts in simulator or short-term clinical studies, the longest published followup of these studies is only 6 years, and prospective randomized comparisons between alternative PE inserts are scarce [2, 3, 7–9, 17, 22, 31].

We found the wear rates of the moderately cross-linked PE at 8 years were less than than those of historical PE. The reduction of 38% correlated well with reductions of 33% to 45% reported for comparisons of these materials in hip simulator studies [8]. The absolute wear rate of the historical PE compared well with the rate in another wear study that measured penetration rates for PE not intentionally cross-linked for wear reduction (eg, 0.16 mm/year) [33]. The reduction of this first-generation cross-linked PE is less than the clinically reported wear rate reductions observed at 5 years for highly cross-linked PE, ranging between 59% [30] and 95% [7]. Highly cross-linked PE inserts of newer generation than the Duration™ PE used in our study have been exposed to much higher irradiation doses in the order of 100 kGy and thus have a much higher cross-link density and consequently wear resistance. The relative reduction also depends on which PE is used in the control group. The 38% reduction in wear rate observed at 8 years is not less than the 30% reduction measured at the 5-year followup in our patients or the 33% reduction reported for larger groups comparing the same materials [15]. It seems more that the benefit of using a cross-linked PE over historical PE may increase with time. Fears that cross-linked PE, especially the annealed versions such as Duration™ that have more free residual radicals prone to oxidation than the remelted alternatives [42], may degrade in vivo so that wear accelerates beyond the 5-year point cannot be supported based on our results. The fact that absolute annual wear rates decreased for both materials between 5 and 8 years may be attributable to lower activity levels as patients are aging during followup.

Cysts suggesting wear debris-driven osteolysis reportedly occur more frequently on the acetabulum than the femur [23]. This can be expected because the acetabular bone-implant interface is closer to the origin of wear debris and because the interface between the proximal femur and hydroxyapatite-coated stem probably is better sealed against particle migration [40]. It also may be a hint that the osteolysis observed is wear particle driven and not bone resorption owing to other effects such as stress shielding. Cysts on the acetabular side were observed less frequently, affected fewer zones, and were smaller for the cross-linked PE at good evidence level. The trend toward less osteolysis also was visible on the femoral side, although without statistical evidence. The only acetabular revision attributable to aseptic loosening was in a patient in the control group with one of the highest wear rates. Although strong correlations between wear rates and osteolysis were reported in a literature review [11], such findings could be expected, as smaller particle volumes are released into the periprosthetic tissue triggering less cytotoxic response. However, a cell culture study [38] suggested wear particles of cross-linked PE can be smaller and shaped differently from those of alternative PE and thus may have a higher cytotoxicity (functional osteolytic potential). As a result, cross-linked PE may produce equal or higher levels of osteolysis despite reduced wear volumes. The results of our study do not support this concern.

Moderately cross-linked PE reduced in vivo wear rates compared with historical PE at 8 years. The reduced wear was accompanied by reduced signs of osteolytic cyst formation. The wear reduction was maintained and even augmented between 5 and 8 years, indicating no oxidation effects had yet degraded the material at clinically noticeable levels. The wear rate reduction correlated well with simulator predictions, providing confidence in predictions for newer generations of cross-linked PE. Cross-linked PE seems to be a superior choice over historical material, even after longer times in vivo, therefore, cross-linked PE may deserve to become the new standard.

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