

Figure 3. Surface characteristics with or without PMPC graft layer before (pre) and after (post) 20 million cycles. (A) 3D morphometric analyses of CLPE and MPC-CLPE liner surfaces. (B) Confocal scanning laser microscopic analysis of the contact areas. Scale bar, 200 μm.

gradually increased at 60 and 70 million cycles (Figs. 5B and 6A). However, comparison with particles obtained after 20 million cycles of untreated CLPE liners showed that grafting decreased the total number

(1,107,000 vs. 346,500/million cycles) and volume (24.6 vs. $0.43 \times 10^{-6} \text{ mm}^3/\text{million cycles}$) of particles by 68.7% and 98.2%, respectively. These results raise the possibility of the initiation of wear, so we are continuing this

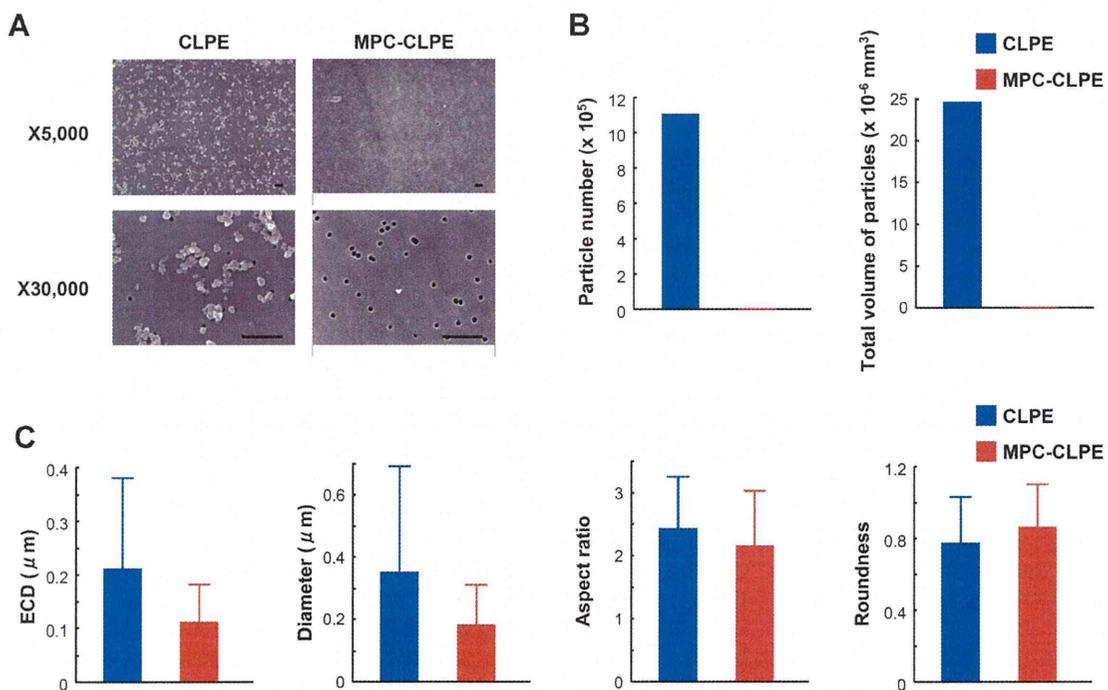


Figure 4. Analyses of wear particles. (A) SEM images of wear particles from the CLPE and MPC-CLPE liners at an interval of 20 (19.5–20.0) million cycles. Low (top) and high (bottom) magnifications. Scale bar, 1.0 μm. (B) Total number and volume of particles per million cycles. (C) Size and shape descriptors of each particle. Data are expressed as mean ± std. dev.

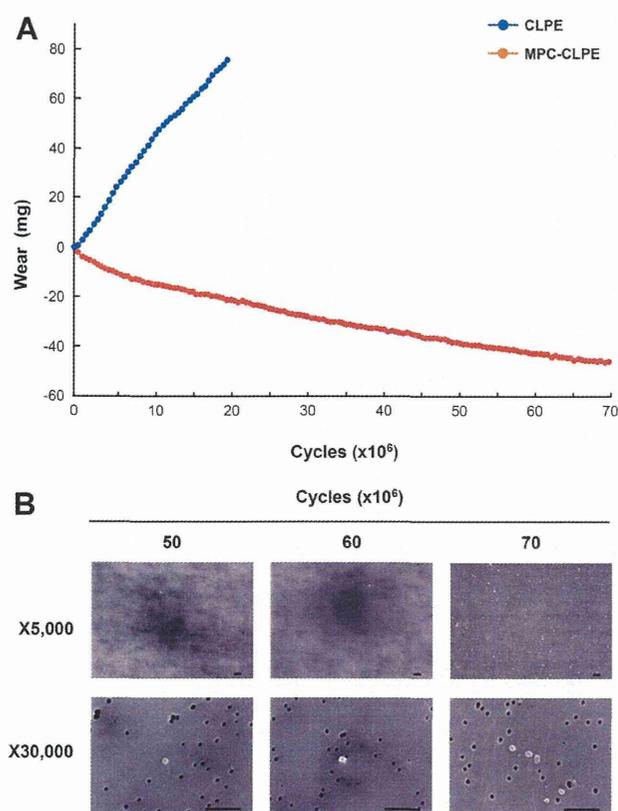


Figure 5. Wear amounts in a PMPC-grafted CLPE liner and SEM images of wear particles isolated from lubricants. (A) Time course of wear amount in a PMPC-grafted CLPE liner during 70 million cycles. (B) SEM images of wear particles from a PMPC-grafted CLPE liner. Low (top) and high (bottom) magnifications of the SEM images. Scale bar, 1.0 μm .

simulator test. There were no differences in the particle size and shape descriptors (Fig. 6B).

DISCUSSION

Our previous study showed that grafting of PMPC dramatically decreased the production of wear particles during 10 million cycles in the hip joint simulator.¹⁷ However, evaluation of the long-term effects of PMPC grafting on wear resistance is needed, especially since young, active patients are at higher risk of revision surgery.^{25,26} In fact, it was estimated that demand for primary THA among patients <65 years old would exceed 50% of all THA patients by 2011.²⁵ Therefore, we investigated the wear resistance of the PMPC-grafted CLPE liner during 20 million cycles. We also continued the test of one PMPC-grafted CLPE liner to 70 million cycles.

We previously established the advantages of a photoinduced graft polymerization technique: strong C–C covalent bonding between the graft polymer and CLPE surfaces, which assures long-term stability of the graft chains,¹⁰ and grafting only on the surface, with no effect on the bulk properties of the liner.^{16,27} Clinically, this lack of effect on bulk properties pro-

vides a clinical advantage, because the CLPE liner also acts as a structural material in the hip joint system. Generally, increased cross-linking degrades PE mechanical properties, producing a trade-off between wear resistance and mechanical properties.^{4,28} When the PMPC graft layer is removed from the liner surface, the CLPE substrate is exposed.⁸ Hence, in our previous tests, the wear rate of MPC-CLPE increased to about the same as that of untreated CLPE.^{8,17,21} Using this technique, we produced a new MPC-CLPE liner (Aquala[®] liner; Kyocera Medical Corp.), which was approved by the Japanese government for clinical use in artificial hip joints in April, 2011.²⁹

To prevent periprosthetic osteolysis, the bone-resorptive response to generated wear particles must be reduced. The response depends not only on the total number of wear particles but also on the proportion of particles within the most biologically active size range.^{3,5,30} In this study, we showed that the CLPE liners released a large number of submicron and nanometer-sized particles, as previously reported; these particles induce a greater inflammatory response than do larger particles.^{3,5} Because increased biological responses to these small particles might partially offset the decrease in the total number of particles, it is necessary to further reduce wear. Although we found no significant differences in particle size and shape, PMPC grafting dramatically decreased the total number, area, and volume of the particles by 99%, suggesting that PMPC grafting might reduce osteolysis by reducing bone-resorptive responses. Our previous study revealed that PMPC particles were rarely phagocytosed by macrophages and did not induce the production of bone-resorptive cytokines. In addition, conditioned medium from macrophages exposed to PMPC nanoparticles did not induce osteoclast formation from bone marrow cells.

MPC-CLPE liners showed weight gain and a significantly lower wear rate during 20 million cycles than did CLPE liners. Furthermore, an MPC-CLPE liner showed continuous weight gain during 70 million cycles, confirming that the PMPC layer was maintained even after 70 million cycles. The increased wear resistance is likely due to the hydrated lubricating layer formed by PMPC grafting. Given that MPC, a biocompatible synthetic phospholipid, is highly hydrophilic, a nanometer-scale layer of PMPC with cartilage-mimicking structures on a CLPE liner surface may provide hydrophilicity and lubricity identical to those of the physiological joint surface. We previously showed that PMPC grafting increased wettability and decreased friction at the joint surface by 80–90%.^{9,17,21}

Our study has several limitations. First, in vitro findings do not always translate to clinical success.³¹ We have conducted multicenter clinical trials of PMPC-grafted CLPE acetabular liners in Japan since 2007,²⁹ and observed neither osteolysis nor any revision surgery after follow-up for a minimum of 5 years and a maximum of 7 years. We plan to continue this

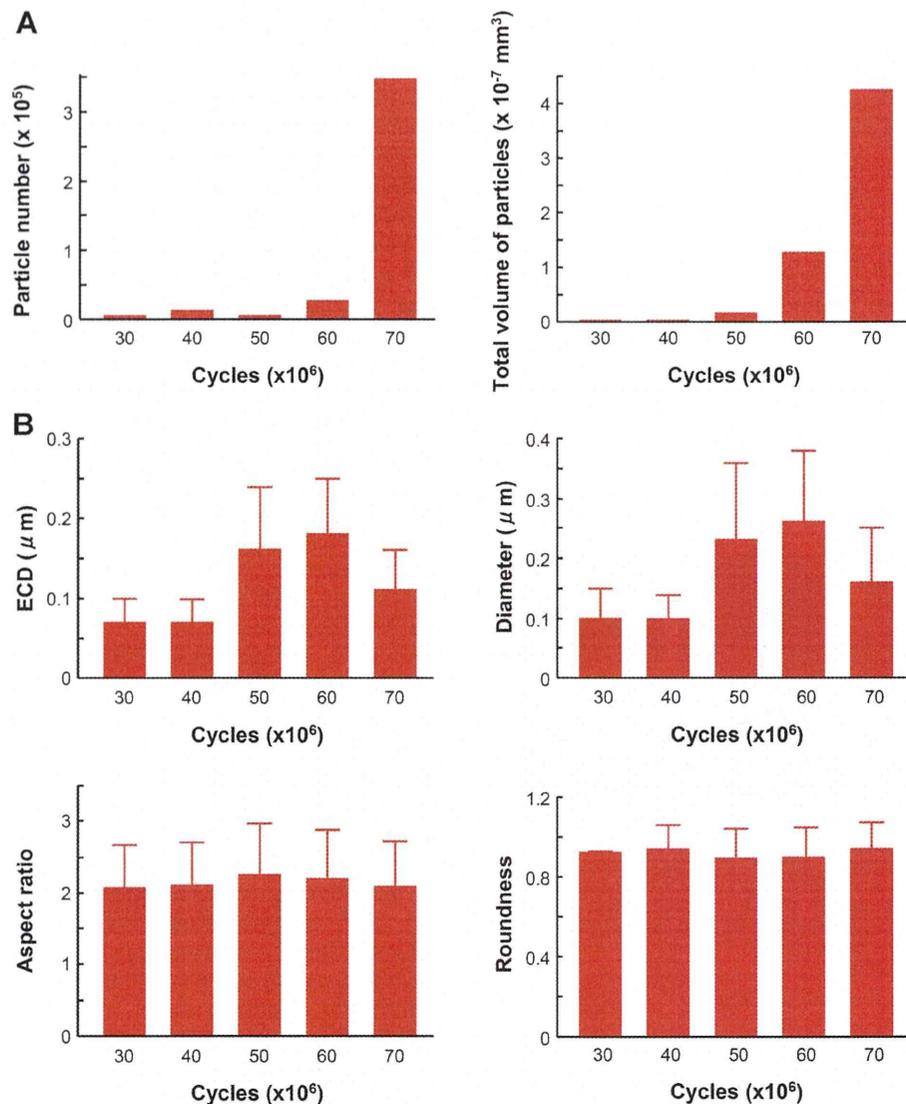


Figure 6. Analyses of wear particles. (A) Total number and volume of wear particles per million cycles. (B) Size and shape descriptors of each particle. Data are expressed as mean \pm std. dev.

trial (UMIN000003681). Moreover, to the best of our knowledge, no reports of complications from other medical devices using MPC polymer, such as stents and artificial hearts, exist.

Second, we used only CoCr alloy balls with a 26-mm diameter. Although osteolysis and subsequent aseptic loosening is among the most common reasons for late revision surgery, dislocation is the biggest short-term problem. A large head allows for an increased head/neck ratio, which is directly related to the range of motion prior to impingement of the trunnion on the liner, and increases the jump distance.²⁸ Hence, larger heads are frequently used because they are thought to improve stability. We believe that our limitation is partially offset by the long duration of testing. We are now running the hip simulator test with larger heads and thinner liners.

Third, although hip simulators are widely used to model wear on bearing surfaces, the system does not more severe conditions. In recent years, more severe conditions including jogging, stair climbing, head-cup microseparation, third-body abrasion, and neck-socket impingement, have been modeled.³² Because our study was performed with a combination of nanometer-scale PMPC-grafted CLPE liners and highly polished commercial heads, we do not know how well the PMPC-grafted CLPE liner will resist abrasion by a head that has been damaged by third-body abrasion. We are now running the test with several types of roughened heads that represent the surface roughness of heads retrieved during revision surgery.

Fourth, the CLPE liners used in our study were not remelted. Remelting and annealing have advantages and disadvantages, and the preferred method varies

among producers of orthopedic implants.⁴ Remelting results in a material with no detectable free radicals but at the expense of reduced crystallinity and mechanical properties.³³ Annealing preserves crystallinity and mechanical properties.³⁴ Although we demonstrated that long-term shelf aging does not affect the PMPC grafting, we do not know the effects of longer-term oxidation on the PMPC layer and CLPE substrate. Therefore, we are planning hip simulator testing with accelerated-aged PMPC-grafted CLPE liners.

In conclusion, we believe that PMPC grafting will significantly improve artificial hip joints by preventing periprosthetic osteolysis. Considering the need for artificial hip joints with increased longevity, we believe that this nanotechnology will improve the quality of care for patients undergoing joint replacement and thus substantially benefit public health.

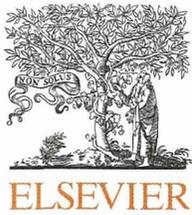
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Research Paper

Grafting of poly(2-methacryloyloxyethyl phosphorylcholine) on polyethylene liner in artificial hip joints reduces production of wear particles



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ABSTRACT

Despite improvements in the techniques, materials, and fixation of total hip arthroplasty, periprosthetic osteolysis, a complication that arises from this clinical procedure and causes aseptic loosening, is considered to be a major clinical problem associated with total hip arthroplasty. With the objective of reducing the production of wear particles and eliminating periprosthetic osteolysis, we prepared a novel hip polyethylene (PE) liner whose surface graft was made of a biocompatible phospholipid polymer—poly(2-methacryloyloxyethyl phosphorylcholine) (MPC). This study investigated the wear resistance of the poly(MPC)-grafted cross-linked PE (CLPE; MPC-CLPE) liner during 15×10^6 cycles of loading in a hip joint simulator. The gravimetric analysis showed that the wear of the acetabular liner was dramatically suppressed in the MPC-CLPE liner, as compared to that in the non-treated CLPE liner. Analyses of the MPC-CLPE liner surface revealed that it suffered from no or very little wear even after the simulator test, whereas the CLPE liners suffered from substantial wears. The scanning electron microscope (SEM) analysis of the wear particles isolated from the lubricants showed that poly(MPC) grafting dramatically decreased the total number, area, and volume of the wear particles. However, there was no significant difference in the particle size distributions, and, in particular, from the SEM image, it was observed that particles with diameters less than $0.50 \mu\text{m}$ were present in the range of the highest frequency. In addition, there were no significant differences in the particle size descriptors and particle shape descriptors.

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The results obtained in this study show that poly(MPC) grafting markedly reduces the production of wear particles from CLPE liners, without affecting the size of the particles. These results suggest that poly(MPC) grafting is a promising technique for increasing the longevity of artificial hip joints.

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1. Introduction

Sir John Charnley introduced the use of polyethylene (PE) components in total hip arthroplasty (THA) in the 1960s, and since then, these components have been extensively used for 50 years (Charnley, 1961). However, aseptic loosening resulting from periprosthetic osteolysis—which is a clinical complication arising from THA—is the prevalent cause of revision surgery (Bozic et al., 2009). Previous studies have revealed that PE particles generated from liners play a major etiological role in periprosthetic osteolysis. Macrophage phagocytosis of the PE particles is followed by the secretion of prostaglandin E2 (PGE2) and cytokines, which induce the receptor activator of the NF- κ B ligand (RANKL) expression, consequently resulting in osteoclastogenesis and bone resorption (Harris, 2004; Jacobs et al., 2001). Further, periprosthetic osteolysis is closely related to the rate of PE wear and the characteristics of the wear particles (Catelas and Jacobs, 2010). Hence, various attempts have been made to improve the wear resistance of PE liners, such as enhancing the cross-linking of PE (CLPE) (Callaghan et al., 2008).

In the previous studies, we introduced a nanometer-scaled poly(2-methacryloyloxyethyl phosphorylcholine (MPC)) grafting layer on the surface of CLPE liners. We found that such type of grafting dramatically decreased the wear of the liner surface (Moro et al., 2009, 2006). In the present study, we investigated the effect of poly(MPC) grafting on the production of wear particles, using a hip wear simulator up to 15×10^6 cycles.

2. Materials and methods

2.1. Poly(MPC) grafting

Nanometer-scaled grafting (100–150 nm in thickness) of the poly (MPC) onto the PE liner surface was carried out by a photo-induced polymerization technique. The CLPE liners (K-MAX[®] CLQC; KYOCERA Medical Corp., Osaka, Japan) were immersed in an acetone solution containing 10 mg/mL of benzophenone for 30 s and then dried at room temperature to remove the acetone. Then, MPC (NOF Corp., Tokyo, Japan) (Ishihara et al., 1990) was dissolved in degassed pure water to obtain a 0.50 mol/L MPC aqueous solution, and the benzophenone-coated CLPE liners were immersed in this solution. Photoinduced graft polymerization was carried out on the CLPE liner surface using ultraviolet irradiation (UVL-400HA ultra-high-pressure mercury lamp; Riko-Kagaku Sangyo Co., Ltd., Funabashi, Japan) with an intensity of 5.0 mW/cm² at 60 °C for 90 min; subsequently, a filter (Model D-35; Toshiba Corp., Tokyo, Japan) was used to restrict the passage of ultraviolet light to wavelengths of 350 ± 50 nm. After the poly (MPC)-grafted CLPE (MPC-CLPE) liners were polymerized, they were washed with pure water and ethanol and dried at room

temperature. These specimens were then sterilized by 25-kGy gamma rays under N₂ gas (Kyomoto et al., 2008).

2.2. Hip joint simulator

A 12-station hip simulator (MTS Systems Corp., Eden Prairie, MN) with CLPE and MPC-CLPE liners, each with inner and outer diameters of 26 and 52 mm, respectively, was used for the hip simulator wear test performed according to the ISO Standard 14242-3. A Co–Cr alloy femoral head with a diameter of 26 mm (K-MAX[®] HH-02; KYOCERA Medical Corp.) was used as the femoral component. A biaxial rocking motion was applied to the head/cup interface via an offset bearing assembly with an inclined angle of +23°. Both the loading and motion were synchronized at 1 Hz. According to the double-peaked Paul-type physiologic hip load, the applied peak loads were 1793 and 2744 N (Paul, 1967). Bovine calf serum (25 vol%) diluted in distilled water was used as a lubricant. Sodium azide (10 mg/L) and EDTA (20 mM) were added to prevent microbial contamination and to minimize the formation of calcium phosphate on the implant surface.

The simulator was run up to 15×10^6 cycles. The liners were cleaned and weighed on a microbalance (Sartorius Genius ME215S, Sartorius AG, Goettingen, Germany) at intervals of 0.5×10^6 cycles. The lubricant was collected and stored at –20 °C for further analysis. Wear was determined from the weight loss of each liner and corrected by cyclically loaded soak controls according to the ISO Standard 14242-2. The wear rates were determined by linear regression.

After complete loading, morphological changes in the liner surface were measured using a three-dimensional (3D) coordinate measuring machine (BHN-305, Mitsutoyo Corp., Kawasaki, Japan) and reconstructed using 3D modeling software (ImageWare, Siemens PLM Software Inc., TX, USA). The liner surface was analyzed using a confocal scanning laser microscope (OLS1200, Olympus, Tokyo, Japan), as previously reported.

The wear particles were isolated from the bovine serum solution. For isolating the wear particles from the lubricant, the lubricant was incubated with 5.0 mol/L of NaOH solution for 3 h at 65 °C after it was tested, in order to digest adhesive proteins that were degraded and precipitated. To avoid artifacts, contaminating proteins were removed by extraction with sugar solution (1.20 g/cm³ and 1.05 g/cm³) and isopropyl alcohol solutions (0.98 and 0.90 g/cm³). After the lubricant was centrifuged at 25,500 rpm for 3 h at 5 °C, the particles were collected, subjected to sequential filtrations (minimum pore size of 0.1 μ m) (Fisher et al., 2004; Tipper et al., 2006), and subsequently dried. The filter was then sputter coated with gold palladium and digitally imaged on a field emission scanning electron microscope (JSM-6330F, JEOL Datum Co., Ltd, Tokyo, Japan). An image-processing program (Scion image, Scion Corp., Frederick, MD) based on the

NIH image software was used to measure the total number, area, and volume of the wear particles per 10^6 cycles (Campbell et al., 1996; Dean et al., 1999). Two size descriptors, namely, the equivalent circle diameter (ECD) and the diameter (D), and two shape descriptors, namely, the aspect ratio (AR) and roundness (R), were used to define each wear particle, according to ASTM F1877-98. Each parameter is defined as follows. ECD is defined as the diameter of a circle with an area that is equivalent to that of one wear particle. Diameter is defined using the maximum dimensions determined by the SEM analysis. Aspect ratio is defined as the ratio of the major diameter to the minor diameter. It should be noted that the major diameter is the longest straight line that can be drawn between any two points on the outline. On the other hand,

the minor diameter is the longest line that is perpendicular to the major diameter. Roundness is a measure of how closely a wear particle resembles a circle; its values range from 0 to 1, with a perfect circle having a roundness value of 1.

2.3. Statistical analysis

The significance of differences was determined by the student's t-test. All statistical analyses were performed using add-in software (Statcel 2; OMS publishing Inc, Tokorozawa, Japan) on a computerized worksheet (Microsoft Excel[®] 2003; Microsoft Corp, Redmond, WA).

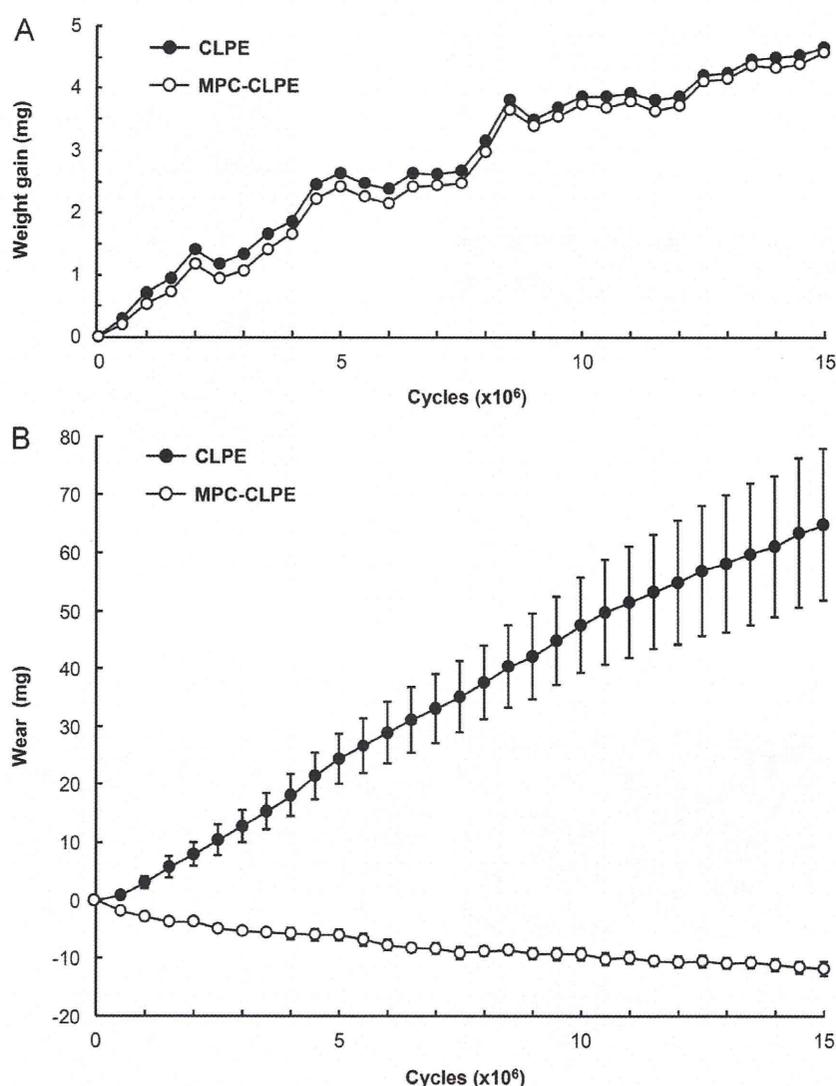


Fig. 1 - Wear amounts of cross-linked PE liners with or without MPC grafting in the THA simulator. (A) Load-soak controls. Fluid absorption of the liners that were axially loaded cyclically to the acetabular liners with the same pressure as the THA simulator, but without rotational motion. Data are expressed as means (symbols) for 2 inserts/group. (B) Time course of wear amount in the THA simulator during 15×10^6 cycles of rotational motion and axial loading against Co-Cr alloy femoral heads. The wear amount was estimated from the weight loss of the inserts after correction by the average weight gain in the respective load-soak controls (weight loss in the THA simulator+average of weight gain in the load-soak control). Data are expressed as means (symbols) \pm standard deviation (SD) for 4 liners/group.

3. Results

Two types of load-soak control liners, which were only loaded axially to the femoral heads and without any rotational motion in the simulator, showed comparable weight gains during the 15×10^6 cycles, irrespective of whether poly(MPC) grafting (Fig. 1A) was carried out; this observation confirmed that weight gain was caused by the absorption of the fluid by the liner material, and not by the fluid that was retained in the surface poly(MPC) layer (Kyomoto et al., 2011; Moro et al., 2006, 2009). We then evaluated gravimetric wear by assessing the weight loss of the liners after correction by the average weight gain in the respective load-soak controls. The gravimetric analysis performed in the hip simulator study showed that the CLPE liners suffered from a total weight loss of 64.8 ± 11.7 mg (mean \pm standard deviation) after 15×10^6 cycles of loading (Fig. 1B). In contrast, it was found that the MPC-CLPE liners continued to gain weight, showing a total weight gain of 13.1 ± 1.2 mg. This weight gain might be at least partially attributed to greater fluid (e.g., water, proteins, and lipids) absorption in the tested liners than in the load-

soak controls, suggesting the underestimation of the load-soak control, as reported previously (Dumbleton et al., 2006; Muratoglu et al., 2001; Oral et al., 2006; Shen et al., 2011). When the wear rate was counted at an interval of every 10^6 cycles, poly(MPC) grafting was shown to maintain similar wear resistance in 0-1 ($p=0.0016$), 4-5 ($p=0.0019$), 9-10 ($p=0.0022$), 14-15 ($p=0.0075$), and the total ($p=0.002$) intervals (Table 1).

3D coordinate measurements of the MPC-CLPE liner surface revealed no or very little detectable volumetric wear, while the cross-linked PE liners suffered from substantial wears (Fig. 2A). The confocal scanning laser microscopic analysis of the liner surface showed that the original machine marks that are clearly visible before the loading still remained on the MPC-CLPE liner surface, although they were completely obliterated on the cross-linked PE liner.

Table 1 – Wear rate estimated by the corrected weight loss of CLPE and MPC-CLPE liners.

Test period (10^6 cycles)	Wear rate (mg/ 10^6 cycles)		p-value
	CLPE	MPC-CLPE	
0-1	2.34 ± 0.99	-3.43 ± 0.42	0.0016
4-5	5.47 ± 1.09	-1.05 ± 0.06	0.0019
9-10	4.85 ± 0.91	-0.47 ± 0.08	0.0022
14-15	3.60 ± 1.22	-0.73 ± 0.23	0.0075
Total	4.01 ± 0.87	-1.09 ± 0.08	0.0020

Data are expressed as mean \pm standard deviation (SD).

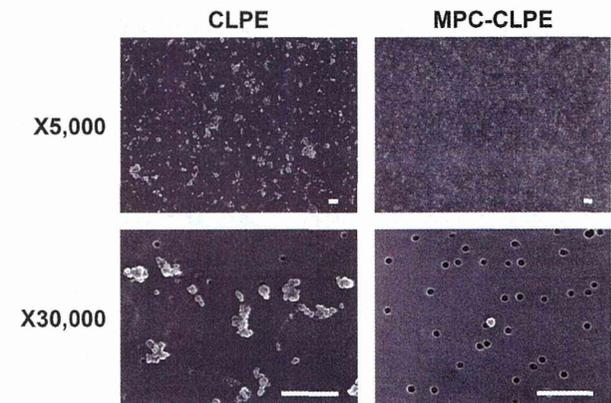


Fig. 3 – Scanning electron microscopic images of the wear particles from CLPE and MPC-CLPE liners. Low (top) and high (bottom) magnifications of the SEM images. Scale bars: 1.0 μ m.

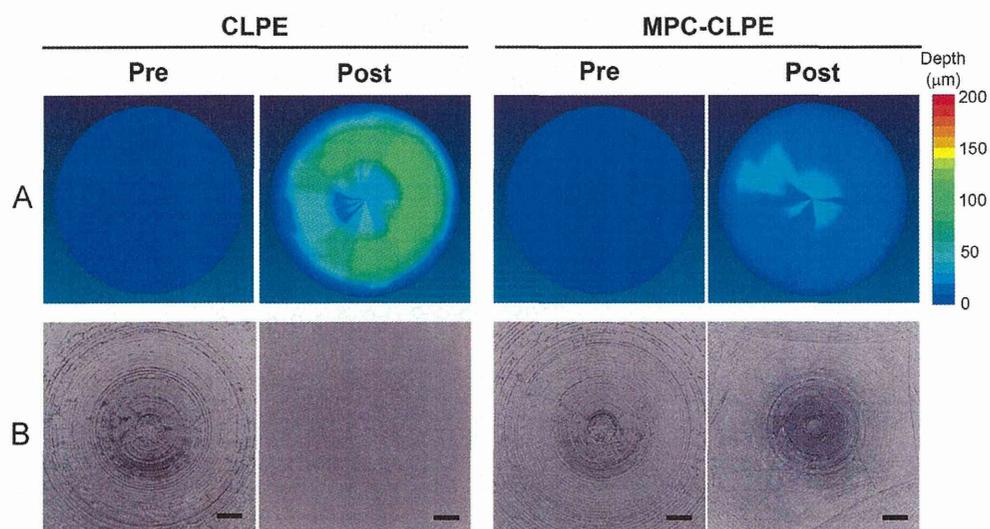


Fig. 2 – Optical findings of the surfaces of the two liners in the THA simulator. (A) Three-dimensional morphometric analyses of surfaces of the CLPE and MPC-CLPE liners before (pre) and after (post) 15×10^6 cycles. (B) Confocal scanning laser microscopic analysis of the contact areas in the two liner surfaces before (pre) and after (post) 15×10^6 cycles. Scale bars: 200 μ m.

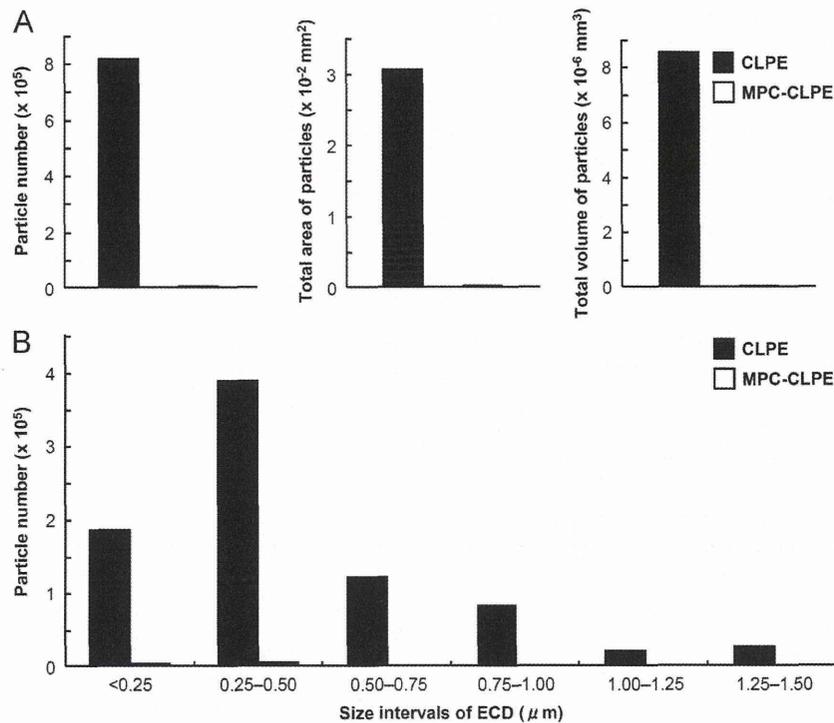


Fig. 4 – Analyses of wear particles isolated from lubricants in the hip simulator. (A) The graphs show the total number, area, and volume of the wear particles per 10⁶ cycles. (B) Number of particles per 10⁶ cycles in each size range of the equivalent circle diameter from CLPE and MPC-CLPE liners.

Table 2 – Assessments of the particle from CLPE and MPC-CLPE liners using size and shape descriptors.

Particle characterization	CLPE	MPC-CLPE	p-value
ECD (μm)	0.18±0.13	0.13±0.06	0.0000
Diameter (μm)	0.28±0.24	0.19±0.11	0.0001
Aspect ratio	2.31±0.79	2.10±0.51	0.0211
Roundness	0.83±0.22	0.92±0.13	0.0000

Two size descriptors, i.e., equivalent circle diameter (ECD) and diameter (D), and two shape descriptors, i.e., aspect ratio (AR) and roundness (R), were used to define each particle. Data are expressed as mean±standard deviation (SD).

The SEM analysis of the wear particles isolated from the lubricants indicated that poly(MPC) grafting dramatically decreased the total number, area, and volume of the wear particles by 99.3%, 99.9% and 99.9%, respectively (Fig. 3, Fig. 4A). However, there was no significant difference in the particle size distributions expressed by the equivalent circle diameter of each liner, and, in particular, from the SEM image, it was observed that particles with diameters less than 0.50 μm were present in the range of the highest frequency (Fig. 4C). In addition, there were no significant differences in the particle size descriptors, equivalent circle diameter ($p < 0.0001$), and diameter ($p = 0.0001$), as well as in the particle shape descriptors, aspect ratio ($p = 0.0211$), and roundness ($p < 0.0001$) (Table 2).

4. Discussion

An MPC molecule is one of the synthesized phospholipids and mimicks the surface of cellmembranes (Ishihara et al., 1990). Thus, poly(MPC) grafting onto medical devices makes their surface hydrophilic and biocompatible. Further, a thin film of water is formed under physiological conditions (Kitano et al., 2003). At the time of writing, the MPC polymers are applied to the surface of intravascular stents (Kuiper and Nordrehaug, 2000; Palmer et al., 2004), soft contact lenses (Selan et al., 2009), and artificial lungs and hearts (Kihara et al., 2003; Snyder et al., 2007) under the authorization of the U. S. Food and Drug Administration (FDA).

Because the PE liners are subjected to multidirectional heavy loads, we used a photoinduced radical graft polymerization technique for grafting. This technique produces a strong C–C covalent bond between a carbon atom of PE and the end-group of a poly(MPC) main chain. The advantages of this technique are that it not only results in the production of a uniform poly(MPC) layer (100–150 nm in thickness) but also causes a negligible effect on the physical and mechanical properties of the CLPE substrate (Ishihara et al., 2000; Kyomoto et al., 2007). Using this technique, we produced a new MPC-CLPE acetabular liner (Aquala[®] liner; KYOCERA Medical Corp.) and the Japanese government (Ministry of Health, Labor, and Welfare) approved its clinical use in artificial hip joints in April 2011.

In addition to wear resistance, the durability of the nanometer-scaled poly(MPC) layer is also of major concern.