two kinds of PVA hydrogels prepared by repeated freeze-thawing method and cast-drying method were examined in reciprocating tests and biphasic FE analyses.

Articular cartilage showed initial low friction and gradual increase in saline lubrication where biphasic fluid load support mechanism subsides with rubbing as indicated by biphasic FE analysis. However, the addition of a simulated synovial fluid enabled the superior lubrication by appropriate adsorbed film formation in boundary lubrication mode.

In artificial cartilage materials in saline, cast-drying PVA with low permeability clearly showed significantly lower friction than freeze-thawing PVA with high permeability. For freeze-thawing PVA hydrogel in which biphasic lubrication mechanism diminished with rubbing, the supply of appropriate synovia constituents improved friction and wear properties in boundary lubrication mode.

It was shown that the synergistic combination of biphasic lubrication and boundary lubrication becomes effective to sustain superior lubricity in articular cartilage and PVA hydrogels even at slow movement under continuous loading.

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Appendix

Notation

C	constant
$f(t)$	compressive stress during stress relaxation
G	shear modulus of rigidity
k	permeability
K	bulk modulus of elasticity
t	time
t_{rel}	relaxation time
W	shorter width of specimen
ε_{z0}	compressive strain
μ_{solid}	friction coefficient for solid-to-solid contact

Long-Term Hip Simulator Testing of the Artificial Hip Joint Bearing Surface Grafted with Biocompatible Phospholipid Polymer

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ABSTRACT: To prevent periprosthetic osteolysis and subsequent aseptic loosening of artificial hip joints, we recently developed a novel acetabular highly cross-linked polyethylene (CLPE) liner with graft polymerization of 2-methacryloyloxyethyl phosphorylcholine (MPC) on its surface. We investigated the wear resistance of the poly(MPC) (PMPC)-grafted CLPE liner during 20 million cycles in a hip joint simulator. We extended the simulator test of one liner to 70 million cycles to investigate the long-term durability of the grafting. Gravimetric, surface, and wear particle analyses revealed that PMPC grafting onto the CLPE liner surface markedly decreased the production of wear particles and showed that the effect of PMPC grafting was maintained through 70 million cycles. We believe that PMPC grafting can significantly improve the wear resistance of artificial hip joints. © 2013 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res

Keywords: artificial hip joint; total hip arthroplasty; periprosthetic osteolysis; aseptic loosening

Total hip arthroplasty (THA) is one of the most successful joint surgeries,[1] but periprosthetic osteolysis and subsequent aseptic loosening remains a serious complication often requiring revision surgery.[2] The pathogenesis of periprosthetic osteolysis and aseptic loosening is linked to the host inflammatory response initiated by the foreign body reaction of macrophages to wear particles, which arise mainly from the interface between the acetabular polyethylene (PE) liner and the femoral head.[3] Hence, two approaches exist to preventing osteolysis: reduce the amount of PE wear particles and suppress subsequent bone-resorptive responses. Of materials used to achieve the former, highly cross-linked PE (CLPE) has achieved the greatest reduction in wear rate compared with conventional PE, and has been widely used since 1998.[4] Clinical studies of CLPE liners consistently report lower head penetration and an 87% lower risk of osteolysis.[4] However, the osteolysis problem has not been eliminated. CLPE liners release a large number of submicron and nanometer-sized particles that induce a greater inflammatory response in vitro than do larger particles.[5] Hence, new technologies that decrease not only the production of wear particles but also their resorptive response are needed.

In natural synovial joints under physiological conditions, fluid-film lubrication by the intermediate hydrated layer is essential for smooth motion.[6] A nanometer-scale phospholipid layer that covers the joint cartilage surface provides hydrophilicity and works as an effective boundary lubricant.[7] Hence, we hypothesized that grafting a biocompatible phospholipid-like layer on the surface of the PE liner would provide ideal hydrophilicity and lubricity. We recently developed a novel acetabular CLPE liner with graft polymerization of 2-methacryloyloxyethyl phosphorylcholine (MPC) on the surface (Fig. 1).[8–10] MPC is a methacrylate monomer with a phospholipid polar group side chain that mimics the neutral phospholipids of biomembranes.[11] The MPC polymer surface suppresses protein adsorption[11,12] and thus exhibits unique properties such as cytocompatibility without inducing a foreign body reaction from endogenous cells,[10] anti-thrombogenicity,[13] high lubricity, and low friction.[8–10]

The poly(MPC) (PMPC)-grafted CLPE liner is a new medical implant prepared with MPC polymer, which has previously been used on the surfaces of implants such as intravascular stents,[14] soft contact lenses,[15] and artificial lungs, under authorization from the FDA. Such implants were introduced in 1997, and no adverse reactions to MPC polymer have been reported. Therefore, the efficacy and safety of MPC polymer as a biomaterial are well established.[14] The major difference between the PMPC-grafted CLPE liner and other devices is the method of modification of the MPC polymer surface. To create the PMPC-grafted CLPE liners, a method of photoinduced graft polymerization was developed to produce covalent bonding between the PMPC and CLPE; this bonding should better withstand weight bearing.[8–10] Previously, we found that PMPC grafting decreased friction torque by 80–90% without affecting the physical or mechanical properties of the CLPE substrate.[16] In a hip joint simulator test, PMPC grafting dramatically decreased the production of wear particles over 10 million cycles.[17] The PMPC-grafted particles were biologically inert and did not cause a bone-resorptive response,[10]

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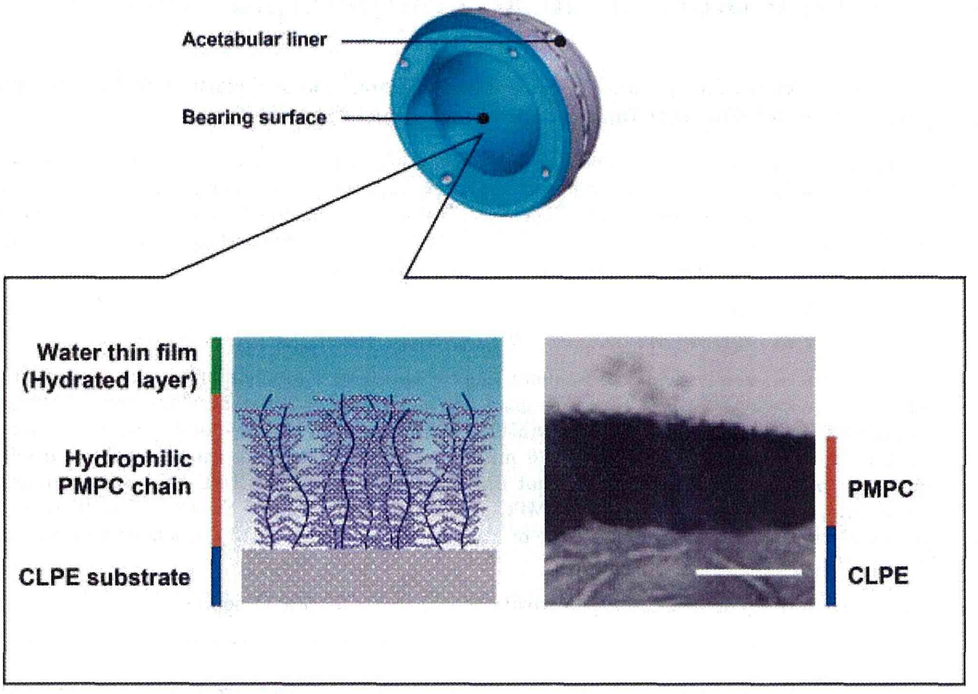

Figure 1. Schema of a THA with the cartilage-mimicking structure of the PMPC-grafted CLPE liner. PMPC was covalently bound to the liner using photoinduced graft polymerization. A transmission electron microscope image of the surface is shown on the right. Orange and blue lines indicate the PMPC layer and the liner surface, respectively. Scale bar, 100 nm.

indicating that this technology both reduces the production of wear particles and decreases the biological reactivity of the particles produced. We confirmed that the improvements due to PMPC grafting surpassed those attributable to liner cross-linking alone or to changes in the femoral head material.[9] We further confirmed the stability of the PMPC layer on the surface after sterilization by gamma irradiation.[17–19]

The need for THA longevity is increasing because of increased life expectancy and because of joint problems in young, active patients. Therefore, we investigated the wear resistance of the PMPC-grafted CLPE liner during 20 million cycles of loading in a hip simulator. One PMPC-grafted CLPE liner was subjected to 70 million cycles of loading to assess the long-term durability of the PMPC grafting.

MATERIALS AND METHODS

Hip Joint Simulator

CLPE liners (K-MAX® CLQC, Kyocera Medical Corp., Osaka, Japan) were manufactured from compression-molded PE sheet stock (GUR 1020 resin), which was treated with 50 kGy of gamma irradiation in nitrogen gas for cross-linking and annealed at 120°C for 7.5 h in nitrogen gas. For PMPC grafting (100–150 nm in thickness), the CLPE liners were placed in the MPC solution (0.5 mol/L), and surface polymerization was photoinduced using an ultra-high pressure mercury lamp (UVL-400HA, Riko-Kagaku Sangyo Co., Ltd., Chiba, Japan).[10,19] All liners were sterilized with 25 kGy of gamma irradiation in nitrogen gas. The PMPC grafting was confirmed by contact angle measurements.[10,17] A 12-station hip simulator (MTS Systems Corp., Eden Prairie, MN) was used under ISO 14242-3 conditions to compare CLPE ($N=3$) with MPC-CLPE ($N=3$) acetabular liners against a 26-mm CoCr alloy femoral head (K-MAX® HH-02, Kyocera Medical Corp.). 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. We used a physiological loading curve (Paul-type) with double peaks at 1,793 and 2,744 N loads with a multidirectional (biaxial and orbital) motion at 1 Hz.[20] Liners were removed at intervals of 500,000 cycles and weighed on a microbalance (Sartorius Genius ME215S, Sartorius AG, Goettingen, Germany). At the same time, the lubricant was changed, collected, and stored at −20°C for wear particle analysis. Load–soak controls ($N=2$) were cyclically axial-loaded against femoral heads without rotational motion to compensate for the fluid absorption by the specimens (ISO standard 14242-2). Weight loss in the tested liners was corrected by subtracting the weight gain of the load–soak controls.

Wear rates were calculated as the change in the corrected weight between 0 and 1 million cycles (initial), 19 and 20 million cycles (steady), and 0 and 20 million cycles (total). After 20 million cycles, the volumetric wear was measured using a 3D coordinate measurement machine (BHN-305; Mitutoyo Corp., Kawasaki, Japan). The thickness of the bearing hemisphere was measured at the head center and at 0.4 mm intervals anteroposteriorly and 3.6° intervals rotationally from that point; the number of measured points was 3,600. The volumetric wear was calculated by comparing the measurements of the indicated coordinates of the liner before and after the test. The 3D morphometric images were constructed using 3D modeling software (Imageware; Siemens PLM Software, Inc., Plano, TX). After 20 million cycles, morphological changes in the liner surface were also analyzed using a confocal scanning laser microscope (OLS1200, Olympus, Tokyo, Japan). Wear particles isolated from the lubricant were analyzed according to the ASTM F1877-05 standard.[9,17,21,22] An image-processing program (Scion Image, Scion Corp., Frederick, MD) was used to measure the total number, area, and volume of wear particles/million cycles.[21,22] Two size descriptors, the equivalent circle diameter (ECD) and the diameter (D), and 2 shape descriptors, the aspect ratio (AR) and roundness (R), were used to define each particle in accordance with ASTM F1877-98.

Longevity of PMPC Grafting

One PMPC-grafted CLPE liner was subjected to 70 million cycles. The load–soak control test was not performed after 20 million cycles because loading of 70 million cycles and periodic weighing of liners takes 5–6 years. The weight change was again evaluated every 500,000 cycles. Wear particle analysis was also performed. Analyses of joint surfaces were not performed because this simulator test is ongoing, now over 70 million cycles.

Statistical Analysis

The significance of differences between wear rates and between the size and shape descriptors of particles (20 million cycles) was determined using Student's *t*-test. The mean values of the particle characterizations of the interval groups (30, 40, 50, 60, and 70 million cycles) were compared by one-factor ANOVA, and the significance of differences was determined by post hoc testing using Bonferroni's method.

RESULTS

Effects of PMPC Grafting on Liner Wear

The load–soak control liners showed comparable weight gains, irrespective of the presence of PMPC grafting (Fig. 2A), confirming that weight gain was attributable to PE fluid absorption and not to that retained on the PMPC surface layer.[8,9,17] The wear of the CLPE liner increased in a cycle-dependent manner, with a final total weight loss of 80.3 ± 18.7 mg (mean $\pm$ std. dev.) after 20 million cycles (Fig. 2B). In contrast, MPC-CLPE liners continued to gain weight even after correction for water absorption, showing a total weight gain of 16.1 ± 0.9 mg (Fig. 2B). This weight gain might be due in part to absorption of fluid by the liners during soaking, suggesting underestimation of the load–soak control.[23,24] The wear rates of the CLPE liner at the initial, steady, and total intervals were 2.72 ± 0.85, 3.12 ± 1.03, and 3.77 ± 0.94 mg/million cycles, respectively. In contrast, those of the MPC-CLPE liners were -3.70 ± 0.22, -0.91 ± 0.46, and -1.05 ± 0.04 mg/million cycles, respectively. The PMPC grafting maintained similar wear resistance at the initial ($p = 0.0005$), steady ($p = 0.0072$), and final ($p = 0.0019$) intervals.

The MPC-CLPE liner surface revealed no or little deformation, whereas substantial deformation was detected in the CLPE liners (Fig. 3A). The original machine marks, clearly visible before loading, were still detectable on the MPC-CLPE liner surface,

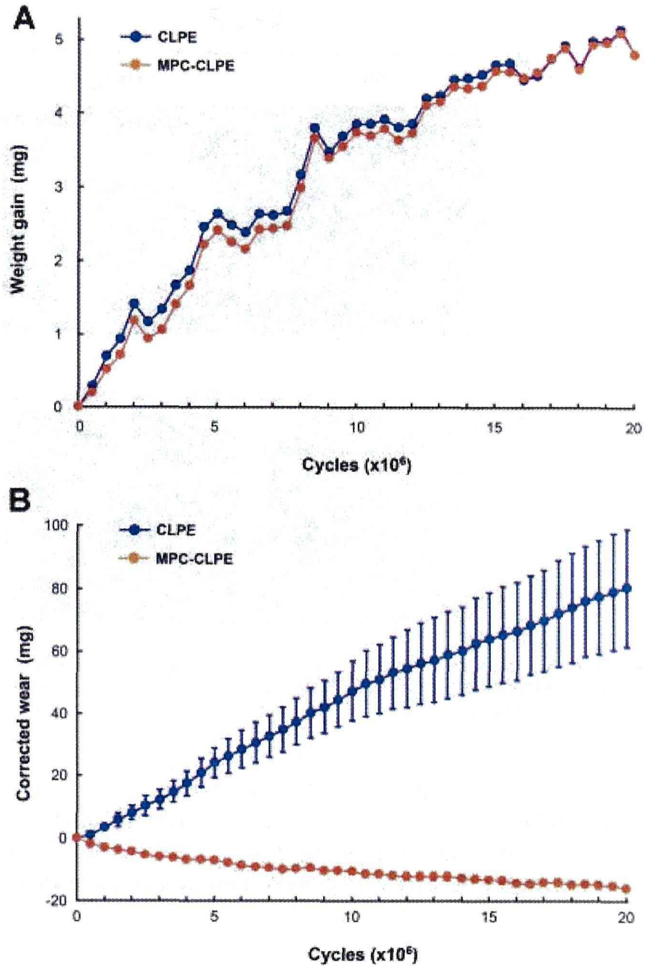

Figure 2. Wear amounts of CLPE liners with or without PMPC grafting. (A) Weight changes in the load–soak controls due to fluid absorption during axial cyclic with the same load as that of the hip simulator, but without rotational motion, according to the ISO 14242-2. Data are expressed as means (symbols) for 2 inserts/group. (B) Time course of corrected wear amount of CLPE liners with or without PMPC grafting during 20 million cycles of loading. Data are expressed as means (symbols) $\pm$ std. dev. for 3 liners/group.

whereas they had been obliterated from the CLPE liner surface (Fig. 3B). PMPC grafting dramatically decreased the total number (1,107,000 vs. 1,500/million cycles) and volume (24.6 vs. 0.003×10^{-6} mm^3/million cycles) of wear particles by 99.9% (Fig. 4A and B). However, there were no significant differences in the particle size descriptors ECD ($p = 0.06$) and D ($p = 0.10$) or in the particle shape descriptors AR ($p = 0.32$) and R ($p = 0.29$) (Fig. 4C).

Long-Term Durability of PMPC Grafting

The MPC-CLPE liner continued to gain weight through 70 million cycles (Fig. 5A). PMPC grafting maintained similar wear resistance at intervals of 30 (−6.51 mg/million cycles), 40 (−5.20 mg/million cycles), 50 (−5.38 mg/million cycles), 60 (−4.23 mg/million cycles), and 70 (−3.49 mg/million cycles) million cycles. The total number, area, and volume of particles

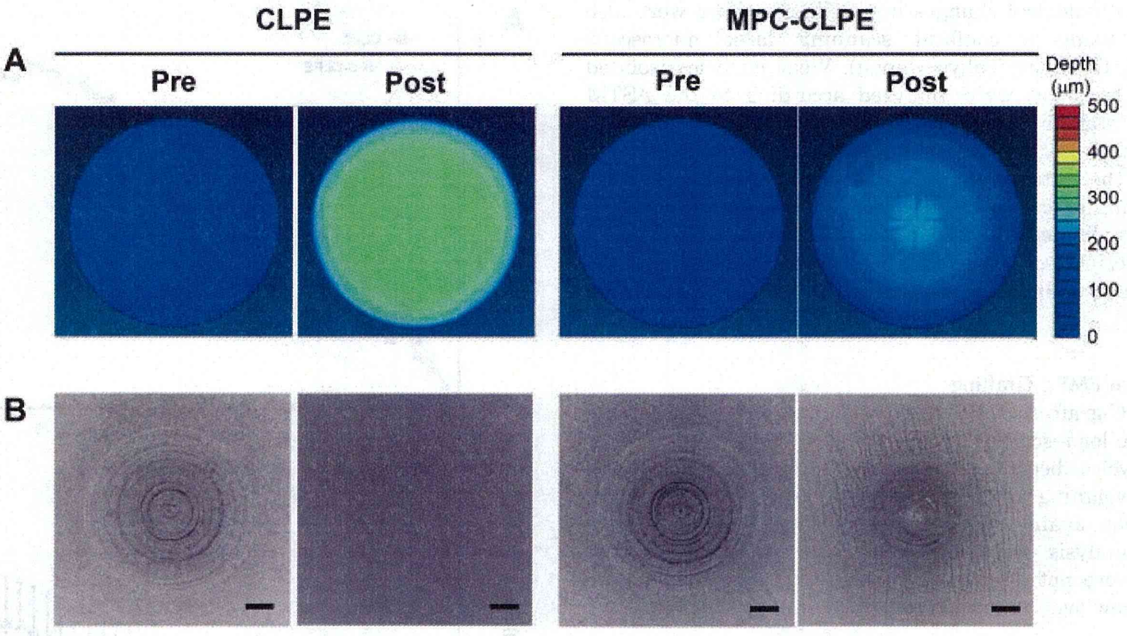

Figure 3. Surface characteristics with or without PMPC graft layer before (pre) and after (post) 20 million cycles. (A) 3D morphometric analyses of CLPE and MPC-CLPE liner surfaces. (B) Confocal scanning laser microscopic analysis of the contact areas. Scale bar, 200 μm.

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. $0.43 \times 10^{-6}\,mm^3$/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

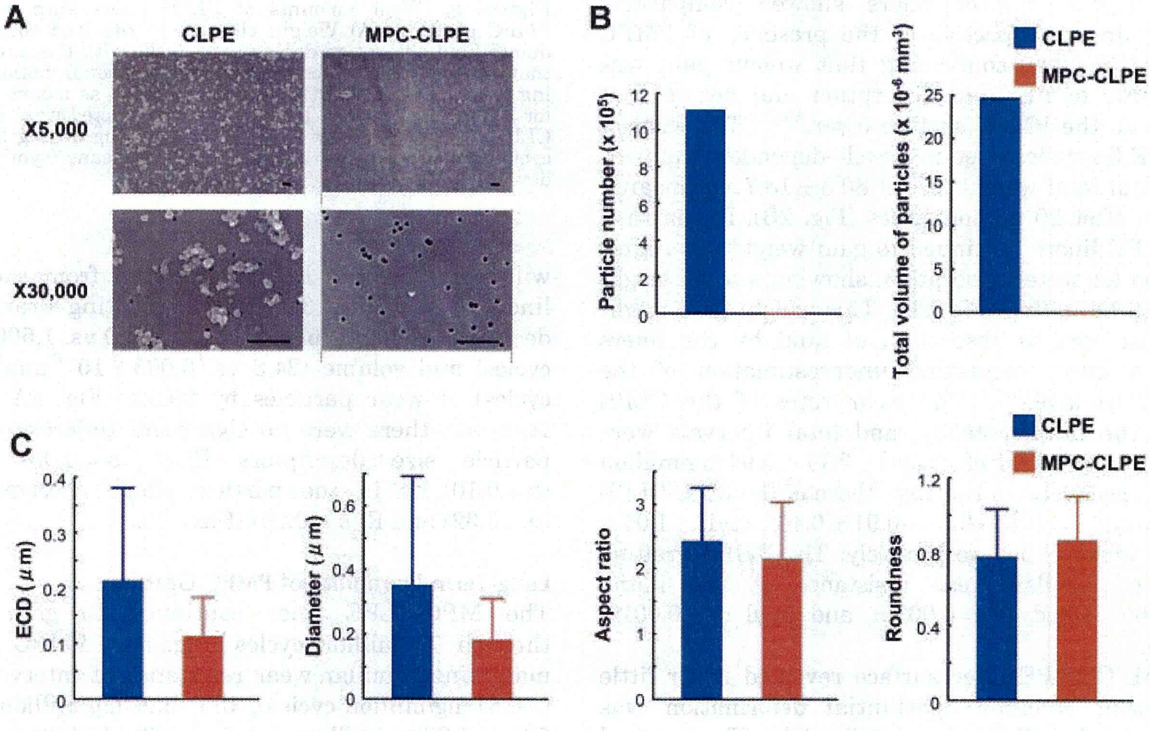

Figure 4. Analyses of wear particles. (A) SEM images of wear particles from the CLPE and MPC-CLPE liners at an interval of 20 (19.5–20.0) million cycles. Low (top) and high (bottom) magnifications. Scale bar, 1.0 μm. (B) Total number and volume of particles per million cycles. (C) Size and shape descriptors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

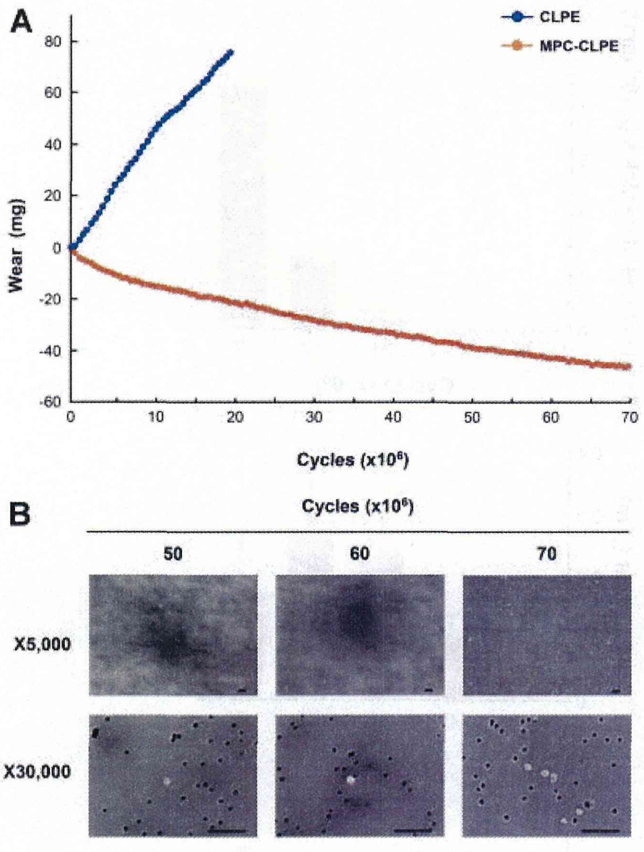

Figure 5. Wear amounts in a PMPC-grafted CLPE liner and SEM images of wear particles isolated from lubricants. (A) Time course of wear amount in a PMPC-grafted CLPE liner during 70 million cycles. (B) SEM images of wear particles from a PMPC-grafted CLPE liner. Low (top) and high (bottom) magnifications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

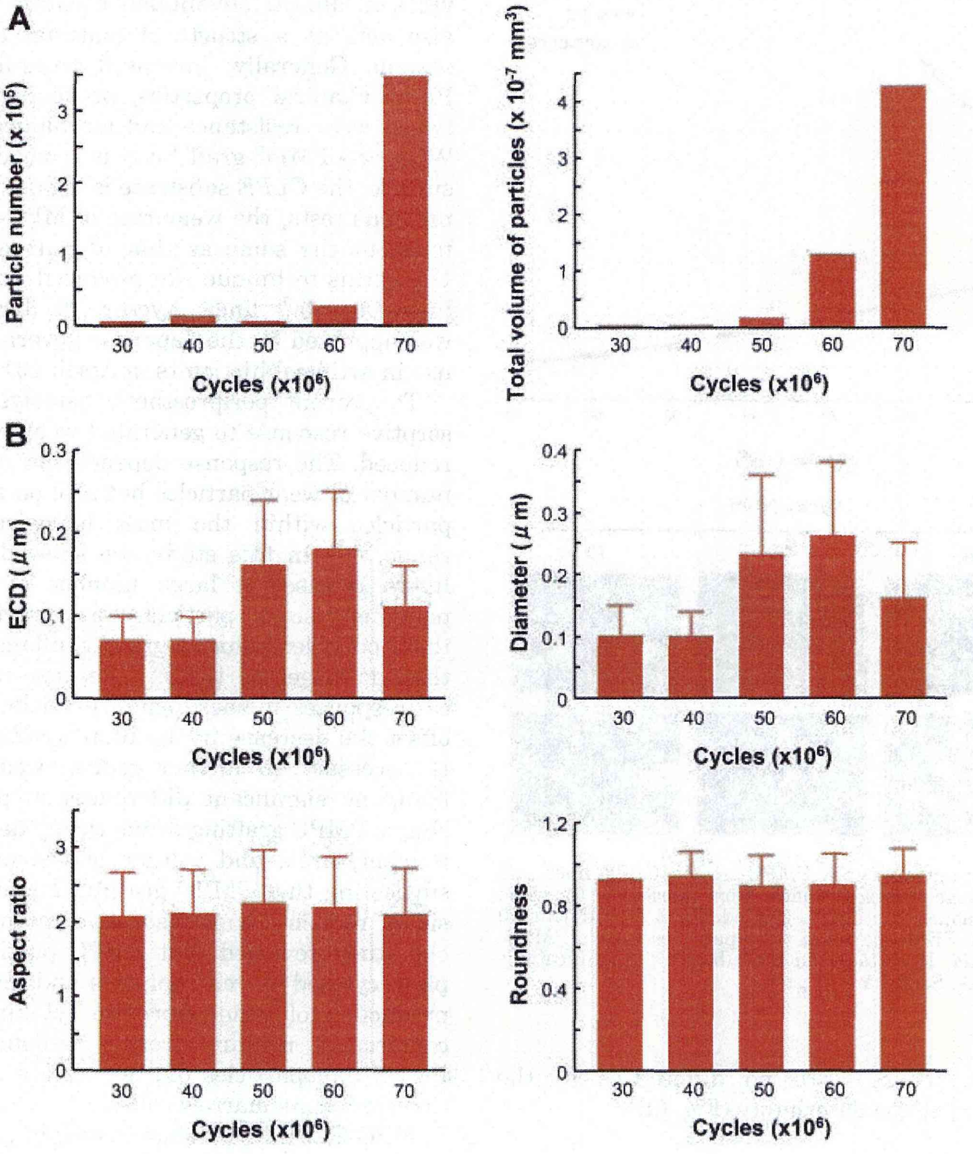

Figure 6. Analyses of wear particles. (A) Total number and volume of wear particles per million cycles. (B) Size and shape descriptors of each particle. Data are expressed as mean ± std. dev.

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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