

osteolysis has emerged as a serious issue [7, 41]. Osteolysis is triggered by host inflammatory responses to PE wear particles originating from the interface [6, 14, 35], which induces their phagocytosis by macrophages and the ensuing secretion of bone-resorptive cytokines [3]. Hence, different combinations of bearing surfaces (ie, ceramic-on-PE, metal-on-metal, etc) and improvements in bearing materials (ie, crosslinked PE [CLPE]) have been introduced with the aim of reducing the number of PE wear particles and extending the longevity of the artificial hip [21, 22, 29, 33, 36].

Surface modification is important for the improvement of bearing materials. Recently, we developed an artificial hip based on a new concept by using poly(2-methacryloxyethyl phosphorylcholine (PMPC) grafted onto the surface of CLPE (PMPC-grafted CLPE) [23–27, 30–32]. This implant was designed to suppress wear and thus suppress bone resorption [23–27, 30–32]. 2-Methacryloyloxyethyl phosphorylcholine (MPC), a methacrylate monomer, is a novel biomaterial that mimics the neutral phospholipids of cell membranes [11]. MPC polymers are one of the most common biocompatible and hydrophilic polymers studied thus far and have potential applications in a variety of fields, including biology, biomedical science, and surface chemistry [9, 10, 18, 19, 37, 39, 40, 43]. Surface modifications of MPC polymers for other medical devices have suppressed biologic reactions when they were put in contact with living organisms [9, 18, 43] and are now clinically used on the surfaces of intravascular stents [19, 37], soft contact lenses [39], and artificial lungs and hearts [15, 40] under the authorization of the US Food and Drug Administration.

The grafting of polymeric molecules onto the substrate through covalent bonding is well known as a method for modifying the polymer surface [45]. Grafting polymerization is mostly performed using either of the following methods: (1) surface-initiated graft polymerization, termed the “grafting from” method, in which monomers are polymerized from initiators or comonomers [9]; and (2) adsorption of the polymer to the substrate, termed the “grafting to” method (ie, dipping, crosslinking, and ready-made polymers reacting with the substrate [13, 44]). The former method has an advantage over the latter method in that it synthesizes a high-density polymer brush. The nanometer-scale surface modification we have introduced uses a photoinduced radical polymerization technique similar to that used in the “grafting from” method. However, in this technique, controlling the density of the grafted PMPC is difficult due to the reaction rate of radical polymerization being extremely high.

We asked whether (1) the photoirradiation time would affect the surface density of the PMPC graft chains, (2) the

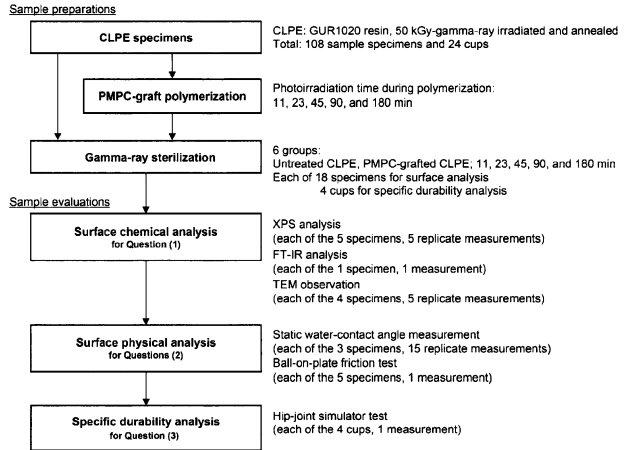
photoirradiation time would affect hydration and friction kinetics of the polymer chain, and (3) the PMPC-grafted surface characteristics would assure the durability of artificial hips.

Materials and Methods

For each of the PMPC-grafted CLPE surfaces with various photoirradiation times (six groups: 0 [untreated CLPE], 11, 23, 45, 90, and 180 minutes), 18 sample pieces (total of 108 samples) were prepared for surface analyses, and four cups (total of 24 samples) were prepared for specific durability analysis (Fig. 1). First, the surface characteristics of the PMPC layers with various photoirradiation times were verified using an xray photoelectron spectroscopy (XPS) analysis, a Fourier-transform infrared (FT-IR) spectroscopic analysis, and a transmission electron microscope (TEM) to determine the effect of photoirradiation times on the surface chemical characteristics. The dependent variable in the second research questions was the hydration kinetics and stability and mobility of the polymer chain; the hydrophilicity and the lubricity of the PMPC-graft CLPE with various photoirradiation times were evaluated using the contact angle of a water drop and a ball-on-plate friction test. Finally, the durability of the PMPC-grafted CLPE on the artificial hips (K-MAX AQUALA[®] CLQC; Japan Medical Materials Corp, Osaka, Japan) was examined using a hip simulator under the conditions recommended by the International Organization for Standardization (ISO) and was compared among various photoirradiation times.

Compression-molded UHMWPE (GUR1020 resin; Quadrant PHS Deutschland GmbH, Vreden, Germany) sheet stock was irradiated with a gamma ray of 50 kGy in N₂ gas and annealed at 120°C for 7.5 hours in N₂ gas to attain crosslinking. CLPE specimens (108 sample specimens and 24 cups) were machined from this sheet stock after cooling. The CLPE specimens were immersed in an acetone solution containing 10 mg benzophenone per milliliter for 30 seconds and then dried at room temperature to remove the acetone. MPC (NOF Corp, Tokyo, Japan) [8] was dissolved in degassed pure water to obtain an 0.50-mol/L MPC aqueous solution, and the benzophenone-coated CLPE specimens were immersed in this solution. Photoinduced graft polymerization on the CLPE surface was performed using ultraviolet irradiation (UVL-400HA ultra-high-pressure mercury lamp; Riko-Kagaku Sangyo Co, Ltd, Funabashi, Japan) with an intensity of 5 mW/cm² at 60°C for 11 to 180 minutes; 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 polymerization, the PMPC-grafted CLPE specimens were

Fig. 1 An overview of the study design is shown.



removed, washed with pure water and ethanol, and dried at room temperature. These specimens were then sterilized by 25-kGy gamma ray under N_2 gas [27].

The surface elemental contents of obtained PMPC-grafted CLPE were analyzed using XPS. The XPS spectra were obtained using an XPS spectrophotometer (AXIS-HSi165; Kratos/Shimadzu Co, Kyoto, Japan) equipped with an Mg-K α radiation source by applying a voltage of 15 kV at the anode. The takeoff angle of the photoelectrons was maintained at 90°. Each measurement was scanned five times, and five replicate measurements were performed on each sample. The average values were taken as the surface elemental contents.

We examined the molecular characteristics (ie, functional groups) of one PMPC-grafted CLPE surface using attenuated total reflection (ATR) by FT-IR spectroscopy. FT-IR/ATR spectra were obtained in 100 scans over a range of 800 to 2000 cm^{-1} by using an FT-IR analyzer (Perkin-Elmer FT-IR 1650; Perkin-Elmer Corp, Waltham, MA) at a resolution of 4.0 cm^{-1} . The relative amount of PMPC units grafted onto the CLPE surface was evaluated by quantifying of the phosphate (P-O) groups contained within the structure of an MPC unit. The relative amount of phosphate groups was defined as the P-O group index and was calculated as follows [24]:

$$\begin{aligned}
 & \text{P-O group index} \\
 &= (1080 \text{ cm}^{-1} \text{ peak intensity}) / (1460 \text{ cm}^{-1} \text{ peak intensity}) \\
 & \quad (1)
 \end{aligned}$$

A cross-section of the PMPC layer on the PMPC-grafted CLPE surface was observed using a TEM (JEM-1010; JEOL, Ltd, Tokyo, Japan). In the case of each photoradiation time, four specimens were first embedded in epoxy resin, stained with ruthenium oxide vapor at room temperature, and then sliced into ultrathin films (approximately 100 nm thick) by using a Leica Ultra Cut UC microtome (Leica Microsystems, Ltd, Wetzlar, Germany). The thickness of the PMPC layer was determined by averaging 20 points on the cross-sectional TEM image.

The static water-contact angles of PMPC-grafted CLPE were measured with an optical bench-type contact angle goniometer (Model DM300; Kyowa Interface Science Co, Ltd, Saitama, Japan) using the sessile drop method according to ISO Standard 15989. Subsequently, 15 replicate measurements were performed on each of three samples, and the average values were taken as the contact angles.

The friction test was performed using a ball-on-plate machine (Tribostation 32; Shinto Scientific Co, Ltd, Tokyo, Japan) according to ASTM Standard F732. Each of the six PMPC-grafted CLPE surfaces with various photoradiation times were used to prepare five sample pieces (a total of 30 samples). A Co-Cr-Mo alloy ball with a diameter of 9 mm was prepared. The surface roughness (R_a) of the ball was < 0.01 μm , which was comparable to that of femoral head products. The friction tests were performed at 37°C with a load of 0.98 N (the contact pressure calculated roughly with the Hertzian theory is approximately 31 MPa), sliding distance of 25 mm, and

frequency of 1 Hz for a maximum of 100 cycles. A mixture of 25 vol% bovine serum, 20 mmol/L ethylene diamine tetraacetic acid, and 0.1 mass% sodium azide was used as the lubricant. The mean dynamic coefficients of friction were determined by averaging five data points from the 100 (96–100) cycle measurements.

A 12-station hip simulator (MTS Systems Corp, Eden Prairie, MN) with CLPE and PMPC-grafted CLPE (K-MAX[®] CLQC and K-MAX AQUALA[®] CLQC; Japan Medical Materials Corp) cups, each with inner and outer diameters of 26 and 52 mm, respectively, was used for the hip simulator wear test according to ISO Standard 14242-3. For each photoirradiation time, four sample pieces were prepared. A Co-Cr-Mo alloy ball with a diameter of 26 mm (K-MAX[®] HH-02; Japan Medical Materials Corp) was used as the femoral component. A mixture of 25 vol% bovine serum was used as the lubricant, which was replaced every 0.5×10^6 cycles. Gait cycles, which simulated a physiologic loading curve (Paul-type) with double peaks at 1793- and 2744-N loads with a multidirectional (biaxial and orbital) motion of 1-Hz frequency, were applied. Gravimetric wear was determined by weighing the cups at intervals of 0.5×10^6 cycles. Load-soak controls ($n = 2$) were used to compensate for the fluid absorption by the specimens according to ISO Standard 14242-2. Testing was continued until a total of 5.0×10^6 cycles was completed. When the gravimetric method was used, the weight loss of the tested cups was corrected by subtracting the weight gain in the load-soak controls; however, this correction could not be achieved perfectly because only the tested cups were continuously subjected to the motion and the load. In addition, after 5.0×10^6 cycles of the hip simulator test, volumetric wear of the cups was measured using a three-dimensional coordinate measurement machine (BHN-305; Mitsutoyo Corp, Kawasaki, Japan) and reconstructed using three-dimensional modeling software (Imageware; Siemens PLM Software Inc, Plano, TX).

Wear particles were observed by field emission scanning electron microscope (FE-SEM) analysis. The wear particles were isolated from the bovine serum solution, which was used as a lubricant in the hip simulator wear test. For isolating the wear particles, the lubricant was incubated with a 5-mol/L sodium hydroxide solution for 3 hours at 65°C to digest adhesive proteins that were degraded and precipitated. To avoid artifacts, the contaminating proteins were removed by extraction with solutions having several densities: sugar solution, 1.05 g per cm³; and isopropyl alcohol solution, 0.98 and 0.90 g per cm³. This was followed by centrifugation at 4000 rpm for 3 hours at 5°C. The collected solution was sequentially filtered through a 0.1- μ m membrane filter, and the membrane was observed directly by FE-SEM (JSM-6330F; JEOL DATUM Ltd,

Tokyo, Japan) at an acceleration voltage of 20 kV after gold deposition.

The mean values of the groups (untreated CLPE [photoirradiation time = 0 minute] and PMPC-grafted CLPE [photoirradiation times = 11, 23, 45, 90, and 180 minutes]) were compared by one-factor ANOVA. The significance of differences in the P concentration (XPS analysis), the PMPC-graft layer thickness (TEM observation), static water-contact angle (static water-contact angle measurement), dynamic friction coefficient (ball-on-plate friction test), and gravimetric wear (hip simulator test) was determined by post hoc testing using Bonferroni's method. 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).

Results

The photoirradiation time affected the surface density of the PMPC graft chains. In the XPS spectra, clear peaks were observed only for PMPC-grafted CLPE; these peaks are characteristic of the phosphorylcholine in the MPC units (Fig. 2A–B). In the FT-IR/ATR spectra, the peaks ascribed to the ketone (C=O) and phosphate (P–O) groups in the MPC unit were observed only for PMPC-grafted CLPE. This implies the PMPC is successfully grafted. The P concentration increased ($p < 0.001$) with photoirradiation time; the measured content of P in PMPC-grafted CLPE with a 90-minute photoirradiation time was 5.2 (Fig. 2C). This value was almost equivalent to the theoretical value ($P = 5.3$) of PMPC calculated from the chemical structure. In addition, the P–O group index also increased with the irradiation time (Fig. 2D). With photoirradiation times longer than 45 minutes, a uniform PMPC layer was clearly observed on the CLPE surface (Fig. 3A); the PMPC graft layer thicknesses became almost constant at 100 nm (Fig. 3B).

The photoirradiation time affected hydration and friction kinetics of the PMPC graft chains. The static water-contact angle of untreated CLPE was 90° and decreased ($p < 0.001$) with an increase in the photoirradiation time (Fig. 4A). The coefficients of friction decreased with an increase in photoirradiation time and were lowest at 90 minutes; however, they increased ($p < 0.001$) at a photoirradiation time of 180 minutes (Fig. 4B). The PMPC-grafted CLPE exhibited approximately 80% reduction in its dynamic friction coefficients when compared with untreated CLPE.

In the hip simulation test, the PMPC-grafted surface characteristics affected the durability of artificial hips. PMPC-grafted CLPE cups were associated with less

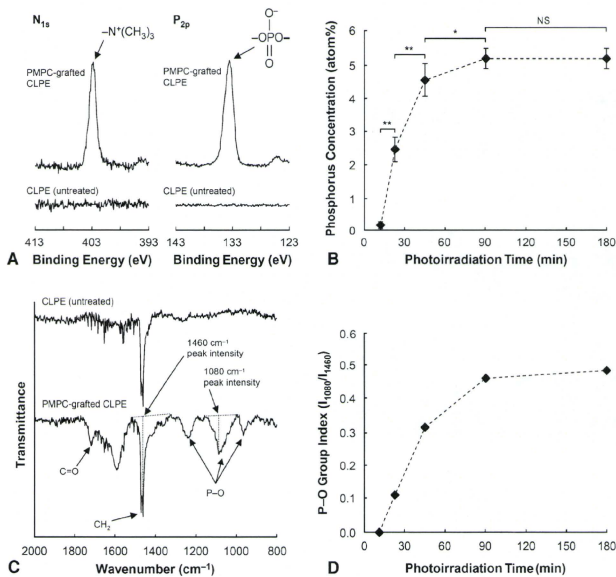


Fig. 2 A–D XPS and FT-IR/ATR analyses of PMPC-grafted cross-linked CLPE are shown. (A) In XPS spectra of untreated CLPE and PMPC-grafted CLPE surfaces, the peaks in the nitrogen (N_{1s}) and phosphorus (P_{2p}) atom regions at 403 and 135 eV, respectively, are specific to MPC. (B) The surface elemental concentration ($n = 5$) of PMPC-grafted CLPE is shown as a function of photoirradiation time. Data are expressed as means \pm SDs. * $p < 0.05$; ** $p < 0.01$; NS = no statistical difference. (C) In FT-IR/ATR spectra of the surfaces, absorptions representing the phosphate group (P–O) at 1240, 1080,

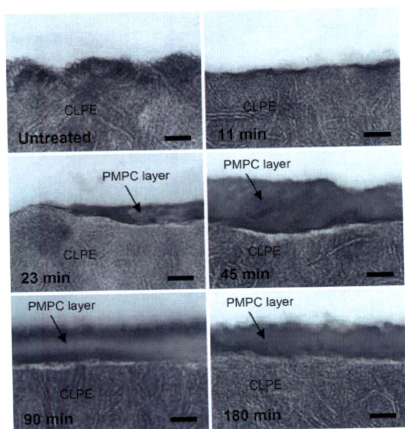
and 970 cm^{-1} and ketone group (C=O) at 1720 cm^{-1} are also specific to MPC, whereas the methylene group (CH_2) at 1460 cm^{-1} is common to the untreated CLPE and PMPC-grafted CLPE surfaces. (D) The P–O group index ($n = 1$) of PMPC-grafted CLPE surfaces is shown as a function of photoirradiation time. (A) XPS and (C) FT-IR/ATR spectra imply the PMPC is successfully grafted. (B) N and P concentrations and (D) P–O group index, i.e., the density of the PMPC layer on the CLPE surface, increase with an increase in the photoirradiation time.

($p < 0.001$) gravimetric wear than untreated CLPE cups (Fig. 5). The gravimetric wear of PMPC-grafted CLPE cups subjected to a 23-minute photoirradiation time started to increase after 2.5×10^6 cycles. PMPC-grafted CLPE cups showed an increase (eg, 90-minute photoirradiation time, $p < 0.001$) in weight. This was partially attributable to greater fluid absorption in the tested cups than in load-soak controls. Three-dimensional coordinate measurements with PMPC-grafted CLPE cups revealed little or no detectable volumetric wear, whereas substantial volumetric wear was detected in untreated CLPE (Fig. 6A). The wear particles of untreated CLPE and PMPC-grafted CLPE cups during 4.5 to 5.0×10^6 cycles of the hip simulation test, as characterized by FE-SEM, were predominantly submicrometer-sized granules (Fig. 6B). Substantially fewer wear particles were found for PMPC-grafted CLPE cups

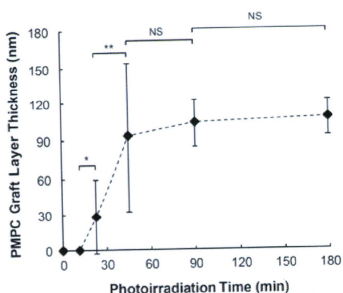
with photoirradiation times of 45, 90, and 180 minutes than for untreated CLPE cups and for PMPC-grafted CLPE cups with a 23-minute photoirradiation time.

Discussion

In natural synovial joints under physiologic conditions, fluid film lubrication by the hydrated intermediate layer is essential for the smooth motion of joints [2, 8], and a nanometer-scale phospholipid layer that covers the joint cartilage surface provides hydrophilicity and works as an effective boundary lubricant [16]. Hence, grafting a phospholipidlike layer onto the surface may realize ideal hydrophilicity and lubricity resembling those of the physiologic joint surface. We asked whether (1) the



A



B

Fig. 3A–B A cross-sectional analysis of PMPC-grafted CLPE is shown. (A) Cross-sectional TEM images of PMPC-grafted CLPE were obtained with various photoirradiation times. Scale bar = 100 nm. (B) The PMPC graft layer thickness ($n = 20$) was determined by TEM observation. Data are expressed as means \pm SDs. * $p < 0.05$; ** $p < 0.01$; NS = no statistical difference. When the photoirradiation time was more than 45 minutes, a 100-nm-thick PMPC layer was clearly observed on the CLPE substrate. The PMPC-covered region was consistent with the uncovered regions after an irradiation time of 23 minutes, although the thickness of the covered region on the PMPC layer remained the same. These results supported the information related to the density of the PMPC layer (Fig. 2).

photoirradiation time would affect the surface density of the PMPC graft chains, (2) the photoirradiation time would affect hydration and friction kinetics of the polymer chain, and (3) the PMPC-grafted surface characteristics would assure the durability of artificial hips.

Our study is subject to a number of limitations. First, we used a confined period for the hip simulator test. Although the 5.0×10^6 cycles in the hip simulator are comparable to 3 to 5 years of physical walking, this may not be sufficiently long for young active patients. We are now running the hip simulator longer and thus far have confirmed almost no wear on the PMPC-grafted CLPE cups after 1×10^7 cycles [32]. Second, we did not entirely capture the range of loading and motion conditions of the in vivo environment in terms of the variety of positions, the magnitude of loading, or the daily routine, although we believe this, according to ISO Standard 14242-3, can provide some indication of the wear performances. Third, the procedure for the isolation of wear particles in this study does not entirely capture the contribution of wear particles with a diameter of less than $0.1 \mu\text{m}$ as previously reported [5, 42]. Cellular response to particles is believed to be dependent on factors such as particle number, size, shape, surface area, and material chemistry. If nanometer-scale particles are generated in vivo, it will be important to determine their biologic activity in relation to that of micrometer-scale particles.

Chen et al. [1] and Kobayashi et al. [17] reported the water molecules adsorbed on the surface of the highly hydrophilic PMPC brushes act as lubricants and reduce the interaction between the brushes and the countersurface. Therefore, the artificial hip bearing with the PMPC-grafted surface exhibited considerably higher lubricity than that without PMPC. The substantial reduction in the coefficient of friction of the PMPC-grafted surface resulted in a substantial improvement in wear resistance (Fig. 4B). We assume the bearing surface of the artificial hip combined with PMPC exhibited the fluid film lubrication of the hydrated intermediate layer (ie, hydration lubrication [12]) and suggest this novel artificial hip mimics the cartilage in natural joints.

To obtain a PMPC layer with high density, the photoirradiation time must be controlled [9]. The density of PMPC chains on the surface of the CLPE gradually increased with increasing photoirradiation time as previously reported [9], and the entire surface of the CLPE was coated using photoirradiation times longer than 45 minutes. In PMPC-grafted CLPE cups with a high surface density of PMPC graft chains, the PMPC graft chains are assumed to stand up and exhibit a brushlike structure [1, 4, 28]. The P–O group index changed remarkably within the range of 0.3 to 0.5, even if the water wettability and thickness of the PMPC layer in PMPC-grafted CLPE were constant (15° and 100 nm, respectively); this implies the density of PMPC chains on the CLPE surface was different. These results indicate the density of the grafted PMPC can be controlled by polymerization time, because the number of polymer chains produced in a radical polymerization

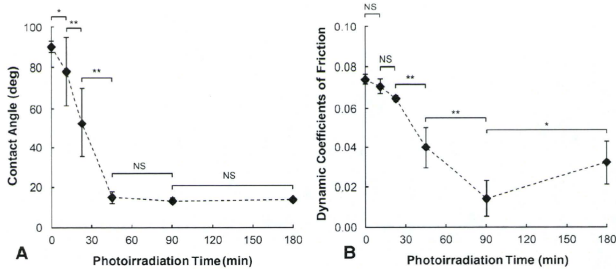


Fig. 4A–B Surface functional analysis of PMPC-grafted CLPE is shown. **(A)** The static water-contact angle ($n = 15$) of PMPC-grafted CLPE is shown as a function of photoirradiation time. Data are expressed as means \pm SDs. As the PMPC grafting proceeded, the CLPE surface became drastically wettable; the surface changed from

hydrophobic to hydrophilic. **(B)** Dynamic coefficients of friction ($n = 5$) for PMPC-grafted CLPE are shown as a function of photoirradiation time. Data are expressed as means \pm SDs. * $p < 0.05$; ** $p < 0.01$; NS = no statistical difference. The dynamic coefficient of friction tended to decrease with an increase in the contact angle.

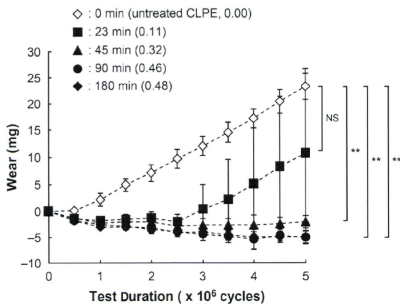


Fig. 5 Gravimetric wear ($n = 4$) of PMPC-grafted CLPE cups with various photoirradiation times was measured during the hip simulator wear test. The P–O group indices are shown in parentheses. Data are expressed as means \pm SDs. ** $p < 0.01$; NS = no statistical difference.

reaction is generally correlated with the photoirradiation time [5, 42].

After 5.0×10^6 cycles of the hip simulator test, we confirmed PMPC-grafted CLPE cups with a P–O group index of 0.32 to 0.48 exhibited a relatively low steady wear rate (-0.02 to 0.32 mg/ 10^6 cycles). This indicates PMPC-grafted CLPE cups with a P–O group index of greater than 0.32 show a greater than 90% reduction in steady wear rate compared with untreated CLPE and with PMPC-grafted CLPE cups having a low P–O group index (0.11) and a low density of PMPC graft chains. The steady wear rates of the PMPC-grafted CLPE cups with

23-minute photoirradiation time and of untreated CLPE are almost the same. This result indicates, when the PMPC graft layer is removed from the surface, only the surface of the CLPE substrate is exposed. The advantage of photoinduced graft polymerization comes from the fact that the grafted PMPC gave high lubricity only on the surface and had no effect on the bulk properties of the CLPE substrate [23]. The PMPC-grafted CLPE did not lose weight; instead, it gained weight even after the correction by water absorption in the load-soak control, suggesting an underestimation of the load-soak control as previously reported [33, 34]. The cups showed comparable weight gains during 5.0×10^6 cycles irrespective of the presence or absence of the PMPC graft layer, confirming the weight gain was the result of the water absorbed by the cup material (ie, the CLPE substrate) and not the result of that retained in the surface PMPC graft layer. PMPC-grafted CLPE cups decreased the amount of wear particles isolated from the lubricants. Because wear particles from PMPC-grafted CLPE surfaces were hardly observed because of their extremely small amounts, they could not be classified according to size as previously reported [30, 32] (Fig. 6B). Moro et al. [31] showed polymer particles (the size of most of the particles was approximately $0.5 \mu\text{m}$) covered with PMPC are biologically inert with respect to phagocytosis by macrophages and subsequent bone resorptive actions. The majority size of the wear particles from untreated CLPE surfaces was 0.1 to $1.0 \mu\text{m}$ as previously reported [38, 42]. In addition to enhancing the wear resistance of the cups, reducing bone-resorptive responses to generated wear particles is important for preventing periprosthetic osteolysis. Such responses are dependent not only on the total amount of

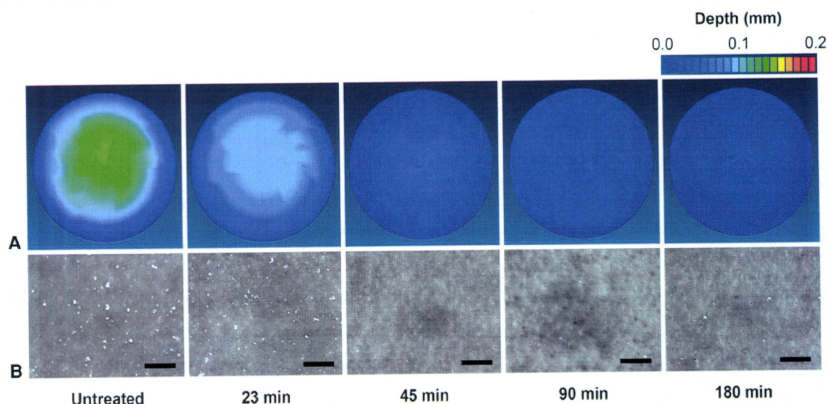


Fig. 6A–B Analysis of PMPC-grafted CLPE after the hip simulator wear test is shown. **(A)** Three-dimensional coordinate measurements of PMPC-grafted CLPE cups were obtained with various photoirradiation times. Volumetric wear images supported the gravimetric

wear results (Fig. 5). **(B)** SEM images of wear particles isolated from lubricants of the hip simulator wear test are shown. Scale bar = 5 μ m. In all cases, the morphologies of the wear particles exhibited no remarkable difference.

wear particles but also on the proportion of particles within the most biologically active size range [5]. The CLPE cups release a high number of submicrometer- and nanometer-sized particles, which are known to induce a greater inflammatory response than larger particles [38]. Hence, although CLPE indeed causes a reduction in the total amount of particles, detailed clinical evidence with long-term followup regarding the longevity of artificial joints with CLPE will be required. Recently, multicenter trials of THA with PMPC-grafted CLPE acetabular cups have been started to evaluate clinical efficiency. Thus, clinical validity of the *in vitro* findings reported here is anticipated in the future.

In conclusion, PMPC-grafted CLPE with a high P–O group index (cups with a high density of PMPC graft chains) exhibited a greater than 90% reduction in steady wear rate when compared with untreated CLPE and PMPC-grafted CLPE with a low P–O group index. Thus, PMPC grafting at a high density appears essential for maintaining the high wear resistance of PMPC-grafted CLPE acetabular cups in THA over long periods of time. To obtain a PMPC layer with high density, the photoirradiation time must be greater than 45 minutes (approximately 90 minutes). The data suggest the cartilage-mimicking, high-density brushlike structure of PMPC-grafted CLPE could confer high durability to acetabular cup bearings in THA by varying the characteristics of the nanometer-scale PMPC layer formed on the

CLPE surface through photoinduced radical graft polymerization using various photoirradiation times.

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