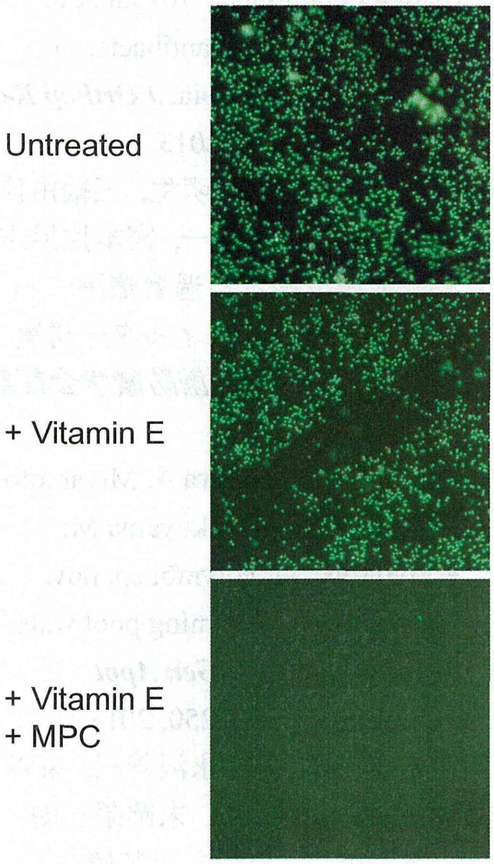

図4. CLPE表面における黄色ブドウ球菌NBRC12732株の付着（対物40倍）

② 付着生菌数

MPC 未処理表面では 1.2×10^7 CFU前後であったのに対し、MPC 処理を施すことによって 3.1×10^5 CFU と大きく低下しており、蛍光顕微鏡観察の結果とよく一致していた（図 5 上）。一方、浮遊菌数は、MPC 処理の有無にかかわらず 1~2×10^8 CFU で、差は認められなかった（図 5 下）。ビタミン E 未添加（MPC 未処理）の CLPE 表面に付着した菌数は、ビタミン E 添加（MPC未処理）CLPE表面と同程度で、ビタミン E 添加は黄色ブドウ球菌 NBRC12732 株の付着を抑制も促進もしなかった。

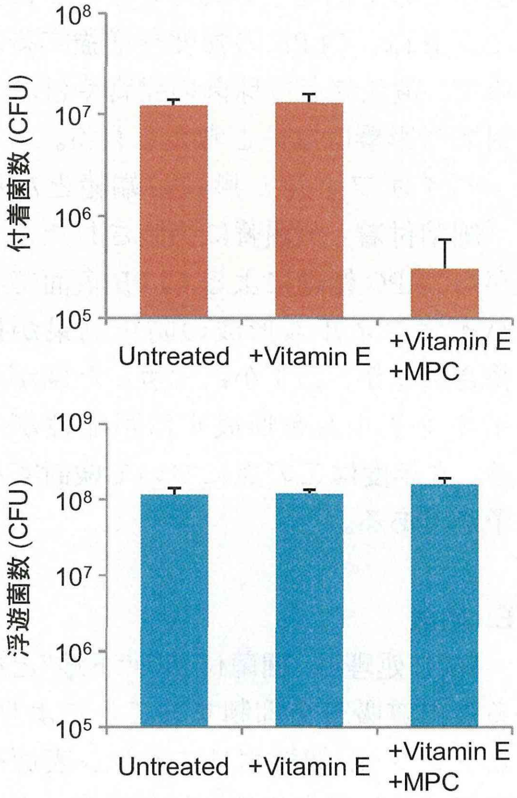

図5. CLPE表面に付着した黄色ブドウ球菌NBRC12732株の生菌数（上）および未付着浮遊菌の生菌数（下）

D. 考察

2 株の黄色ブドウ球菌どちらの場合でも、MPC 処理によって CLPE 表面への菌の付着が劇的に抑制されることがわかった。MPC 処理が CLPE 表面に高親水性と双極性電荷を賦与することで蛋白質の吸着を抑制し、黄色ブドウ球菌の定着が阻止されたものと推測される。

一方、MPC 処理の有無で浮遊菌数に差が認められないことから、MPC 処理による試験片表面の付着菌の減少は菌の殺滅によるものではなく、表

面への菌の付着が阻害されたことによるものであるといえる。また、ビタミンEは、CLPEの強度を増強するのみで、黄色ブドウ球菌の発育や付着に対する影響はないと考えられる。

バイオフィルム形成の端緒となる「細菌付着」が顕著に抑制されたことから、MPC処理によるCLPE表面でのバイオフィルム形成の防止効果が期待されるが、わずかに付着した菌がバイオフィルムを形成する可能性がある。次年度はこの点について検討する予定である。

E. 結論

MPC処理は、細菌付着の“下地”となる蛋白質吸着を抑制することにより、ビタミンE架橋ポリエチレン表面への細菌の付着を劇的に抑制する。人工股関節のライナー表面にMPC処理を施すことで、効果的に抗感染性を賦与することが期待できる。

F. 健康危険情報

なし。

G. 研究発表

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H. 知的財産権の出願・登録状況

特になし。

研究成果の刊行に関する一覧表レイアウト

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kyomoto M, Moro T, Takatori Y, Tanaka S, Ishihara K	Wear and fatigue of phospholipid-polymer-grafted and vitamin-E-blended crosslinked polyethylene: A pilot study	***Clin Orthop Rel Res***			in contribution
Kyomoto M, Moro T, Yamane S, Watanabe K, Hashimoto M, Takatori Y, Tanaka S, Ishihara K	Poly(2-methacryloyloxyethyl phosphorylcholine) grafting and vitamin E blending for high wear resistance and oxidative stability of orthopedic bearings.	***Biomaterials***			in press
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Wear and fatigue of phospholipid-polymer-grafted and vitamin-E-blended cross-linked polyethylene: A pilot study

Running title: Wear and fatigue PMPC-grafted HD-CLPE(VE)

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Abstract

Background The ultimate goal in manipulating the surface and substrate of a cross-linked polyethylene (CLPE) liner is to obtain not only high-wear resistance but also high oxidative stability and high mechanical properties for life-long orthopedic bearings. A grafted poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC) layer on a vitamin E-blended cross-linked PE (HD-CLPE(VE)) surface may provide hydrophilicity, lubricity, and oxidative stability.

Questions/purposes We asked three questions: (1) Will the modifications (PMPC grafting and vitamin E blending) affect the lubrication characteristics of the CLPE surface? (2) Will the modifications affect wear resistance? (3) Will the modifications affect fatigue resistance? To search for the answers, we investigated the effects of surface and substrate modifications (PMPC grafting and vitamin E blending) on the wear and fatigue fracture of thin CLPE samples by conducting a multidirectional wear test and an impact-to-wear test.

Methods For each of the untreated and PMPC-grafted CLPE and PMPC-grafted HD-CLPE(VE) surfaces (4 groups), 27 sample pieces were evaluated in surface analyses, and 6 disks were evaluated in multidirectional wear and impact-to-wear tests using a pin-on-disk (POD) testing machine.

Results The water wettability and lubricity of the PMPC-grafted surfaces were greater than that of the untreated surface, regardless of vitamin E additives. It was observed that the PMPC grafting significantly contributed to reduced gravimetric wear in the POD wear test.

Conclusions PMPC grafting affected the surface hydrophilicity and lubricity, and it reduced the gravimetric wear in terms of multidirectional sliding. It did not result in significant differences in terms of the impact-to-unidirectional-sliding regardless of vitamin E blending.

Clinical Relevance Our in vitro findings anticipate some improvements of the wear performances of cross-linked polyethylene acetabular liners in total hip arthroplasty.

Introduction

Wear and oxidation degradation are two important indicators of the clinical performance of acetabular liners. Polyethylene (PE) wear particles from the acetabular liner may be responsible for osteolysis, which may lead to aseptic loosening [7]. Many different strategies or techniques have been introduced in order to reduce the number of PE wear particles and extend the longevity of the artificial hip joint [3, 11, 17, 20, 23, 28].

To reduce wear and thus suppress bone resorption, we have recently developed a new articular-cartilage-inspired technology for surface modification with synthetic phospholipid polymer poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC) grafting for life-long acetabular liners in artificial hip joints [12-16, 18, 19, 23, 24, 29]. Modification of the bearing surfaces of an artificial joint with a hydrophilic layer should increase lubrication to levels provided by articular cartilage under physiological conditions. MPC polymers are one of the most common biocompatible and hydrophilic polymers that have been clinically applied [9, 29]. A nanometer-scale layer of PMPC was formed on a cross-linked PE (CLPE) surface to better reproduce the ideal hydrophilicity and lubricity of the physiological joint surface.

However, wear is only one of several important indicators of the clinical performance of acetabular liners. Oxidation degradation of the first generation of CLPE with gamma-ray sterilization has been considered a potential limiting factor for the longevity of artificial hip joints [5, 22]. During gamma-ray irradiation, free radicals formed in the PE molecular structure cause embrittlement through a cascading oxidation reaction [5]. Hence, the incorporation of the antioxidant vitamin E (α-tocopherol) has been proposed recently to prevent oxidation [3, 28]. Vitamin E is a free-radical scavenger and has been well-established as a biological antioxidant.

Moreover, dislocation has recently been determined as the leading cause of revision arthroplasty [22]. In artificial hip joints, dislocation is almost always caused by the impingement of the femoral stem neck on the acetabular liner. The impaction between the femoral stem neck and the acetabular cup can be potentially avoided by using a large-diameter femoral head to treat the condition [27]. However, a large-diameter femoral head must be used in conjunction with a thin PE liner owing to the limited volume along the acetabulum, and the thin PE liner poses considerable risks in terms of wear and fatigue fracture when subjected to severe physiological conditions.

In search of a solution, we investigated the effects of surface and substrate modifications (PMPC grafting and vitamin E blending) on the wear and fatigue fracture of thin CLPE samples by conducting a multidirectional wear test and an impact-to-wear test in this pilot study. Such investigations are of great importance in the design of life-long artificial hip joints and for obtaining a better understanding of limitations resulting from the use of this material. During our studies, we sought answers to three questions: (1) Will the modifications (i.e., PMPC grafting and vitamin E blending) affect the lubrication characteristics of CLPE surface? (2) Will the modifications affect wear resistance? (3) Will the modifications affect impact fatigue resistance?

Materials and Methods

For each of the untreated and PMPC-grafted CLPE with and without vitamin E-blended surfaces (4 groups), 27 sample pieces were prepared for surface-lubrication analyses and 12 disks were prepared for specific durability analyses (Fig. 1). First, the dependent variables were the hydration kinetics and stability of the grafted PMPC layer; the hydrophilicity and the lubricity of the PMPC layers on the substrates with and without vitamin E were evaluated using the contact angle of a water drop and a ball-on-plate friction test. The dependent variable in the question (2) of the research, i.e., the wear resistance of the PMPC-grafted substrates with and without vitamin E, was examined using a pin-on-disk (POD) testing machine under the multidirectional-sliding condition. Finally, the fatigue resistance of the PMPC-grafted substrates with and without vitamin E was examined using a POD testing machine under the impact-to-unidirectional-sliding condition.

A compression-molded bar stock of 0.1 mass% vitamin E-blended PE (PE(VE); GUR1020E resin, Orthoplastics Ltd, Lancashire, UK) was irradiated with a high dose (HD; 100 kGy) of gamma-rays in a N_2 gas atmosphere and annealed at 120 °C for 12 h in N_2 gas in order to facilitate cross-linking. Hereafter, this PE material is referred to as HD-CLPE(VE). As the control, a compression-molded bar stock of PE without any additives (GUR1020 resin, Orthoplastics Ltd., Lancashire, UK) was irradiated with a 50-kGy dose of gamma-rays in a N_2 gas atmosphere. It was then annealed at 120 °C for 7.5 h in N_2 gas to facilitate cross-linking. Hereafter, this polyethylene material is referred to as CLPE. Samples of CLPE and HD-CLPE(VE) were machined from the bar stocks and then washed. Surface cleanliness without fouling that involved an antioxidant (radical scavenger) was critical for the polymerization. In particular, the vitamin E surface was fully washed with an aqueous polysorbate-surfactant solution and ethanol from the surface. PMPC grafting of the surfaces of the CLPE and HD-CLPE(VE) was performed using a photoinduced polymerization technique as previously reported [12-16, 18, 19, 23, 24]. Photoinduced graft polymerization was carried out on the CLPE and HD-CLPE(VE) surfaces using UV irradiation with an intensity of 5 mW/cm^2 at 60°C for 90 min and an aqueous 0.5 M MPC (NOF Corp., Tokyo, Japan) solution. The resulting samples were then sterilized by 25-kGy gamma ray under a N_2 gas atmosphere.

The static contact angles of water on PMPC-grafted CLPE and PMPC-grafted HD-CLPE(VE) were measured with an optical bench-type contact angle goniometer (Model DM300; Kyowa Interface Science Co., Ltd., Saitama, Japan) using the sessile-drop (1 μL) method according to ISO 15989. Subsequently, 15 measurements were repeated on each of the three samples, and the mean values ± the standard deviation were calculated.

The friction test was performed using a ball-on-plate machine (Tribostation 32; Shinto Scientific Co., Ltd., Tokyo, Japan). Six samples of PMPC-grafted CLPE and PMPC-grafted HD-CLPE(VE) were evaluated. A cobalt–chromium–molybdenum (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 is comparable to that of femoral head products. The friction tests were performed at 37°C with a load of 0.49–9.8 N (the contact pressure roughly calculated using the Hertzian theory is approximately 22–62 MPa), sliding distance of 25 mm, frequency of 1 Hz for a maximum of 100 cycles, and pure water as the lubricant. The mean coefficients of dynamic friction were determined by averaging five data points from the 96–100 cycle measurements.

Multidirectional wear and impact-to-wear tests were conducted using a POD testing machine (Ortho POD; AMTI, Watertown, MA, USA). PMPC-grafted CLPE and PMPC-grafted HD-CLPE(VE) disks were used for the wear tests and control soak tests to correct the water-absorption increments ($n = 3$). The disks were attached to the POD testing machine with a titanium–aluminum–vanadium alloy (Ti–6Al–4V) fixation component that had an 8-mm-diameter hole to simulate an acetabular shell with a screw hole (Fig. 2). The Co–Cr–Mo alloy pins had a 30-mm surface-curvature radius and surface roughness of $R_a < 0.01$. A mixture of 27 vol% fetal bovine serum (Biowest, Nuaillé, France), 20 mM ethylene diamine-*N, N, N', N'*-tetraacetic acid (EDTA), and 0.1 mass% sodium azide was used at 37 °C as the lubricant. The multidirectional wear test was conducted on a rectangular sliding surface. The test conditions were specified to be a static load of 213 N, sliding distance of 30 mm, and frequency of 1 Hz for a maximum of 1.0×10^6 cycles. Impact-to-wear testing was performed on a unidirectional sliding surface with a maximum impact load of 150 N, sliding distance of 10 mm, and frequency of 1 Hz for a maximum of 2.0×10^6 cycles. These sliding conditions were implemented according to ASTM F732. Gravimetric wear was determined by weighing the disks. Soak controls were used to compensate for fluid absorption by the specimens. Because the gravimetric method was used, the weight loss of each of the tested disks was corrected by subtracting the weight gain resulting from the soak control. However, this correction was not considered to be perfect because only the tested disks were continuously moved and subjected to the load. After the multidirectional wear and impact-to-wear tests, the volumetric wear of the disks was evaluated using a noncontact optical three-dimensional profiler (Talysurf CCI Lite, Taylor Hobson Ltd., Leicester, UK).

The mean values of the three comparative groups (untreated CLPE vs. PMPC-grafted CLPE, untreated HD-CLPE(VE) vs. PMPC-grafted HD-CLPE(VE), and PMPC-grafted CLPE vs. PMPC-grafted HD-CLPE(VE)) were evaluated using a Student's *t*-test (statistical significance, $p < 0.05$). All the statistical analyses were performed using an add-on (Statcel 2, OMS Publishing Inc., Tokorozawa, Japan) to Microsoft Excel® 2003 (Microsoft Corp., Redmond, WA, USA).

Results

The PMPC grafting affected the hydration- and friction-kinetics of the surfaces, regardless of vitamin E blending. The static water contact angles on the PMPC-grafted CLPE and PMPC-grafted HD-CLPE(VE) surfaces, as well as the dynamic coefficients of friction between water and the surfaces changed as a result of the modification (Fig. 3). The static water contact angles on both untreated CLPE and HD-CLPE(VE) were 90°, and they decreased markedly to 23° ($p = 1.87 \times 10^{-31}$) and 26° ($p = 7.06 \times 10^{-27}$), respectively, after PMPC grafting (Fig. 3A). The dynamic coefficients of friction of PMPC-grafted CLPE and PMPC-grafted HD-CLPE(VE) decreased markedly, with the surfaces exhibiting an approximately 85–90% reduction ($p = 3.00 \times 10^{-8}$ and 3.19×10^{-8}, respectively) in the coefficient compared with the untreated CLPE and untreated HD-CLPE(VE) surfaces under a 9.8 N loadings (Fig. 3B). Interestingly, the dynamic coefficients of friction of the both PMPC-grafted CLPE and PMPC-grafted HD-CLPE(VE) decreased gradually with an increasing of loadings.

In the multidirectional wear test, the PMPC-grafted surface characteristics affected the wear resistance regardless of vitamin E blending. In the absence of the PMPC grafting, fluid (e.g., water, proteins, and lipids) absorption in the CLPE soak control disks, determined by the weight gain, increased in a cycle-dependent manner (Fig. 4A). In contrast, the fluid absorption in the both untreated and PMPC-grafted HD-CLPE(VE) soak control disks was constant for all test durations. During the wear test, the PMPC grafting drastically decreased the gravimetric wear not only in the CLPE disks ($p = 3.73 \times 10^{-3}$), but a similar reduction was also observed in the HD-CLPE(VE) disks ($p = 3.83 \times 10^{-2}$) (Fig. 4B). Three-dimensional profile measurements of sliding surfaces on all disks revealed substantial volumetric wear (Fig. 5A). Penetration and circle scratches that were caused by the edge of the hole were clearly observed on the backside surface of all disks. The type of material had no discernible effect on the backside penetration.

In the impact-to-wear wear, the PMPC-grafted surface characteristics did not affect the impact fatigue resistance regardless of vitamin E blending. During the impact-to-wear test, all groups showed an increase in weight. This is partially attributable to greater fluid absorption in the tested disks than in soak controls (Fig. 6). The volumetric wear or penetration of sliding or backside surfaces did not differ significantly between all groups examined in this study (Fig. 7). Even after impact loads of 2.0×10^6 cycles, we observed neither mechanical fracture nor delamination in the sliding or backside surfaces of all groups. The type of material had no discernible effect on the impact fatigue resistance.

Discussion

The fluid-film lubrication provided by the hydrated layer is essential in natural synovial joints, and a phospholipid layer that covers the joint cartilage surface provides hydrophilicity and works as an effective boundary lubricant [6, 10]. Therefore, grafting a phospholipid-like layer onto the surface may realize ideal hydrophilicity and lubricity resembling those of the physiological joint surface. At the beginning of the studies, we asked three questions: (1) Will the modifications (i.e., PMPC grafting and vitamin E blending) affect the lubrication characteristics of CLPE surface? (2) Will the modifications affect wear resistance? (3) Will the modifications affect impact fatigue resistance? So far, the experimental results provided preliminary evidence that PMPC grafting affected the surface hydrophilicity, lubricity, and wear resistance of the liner regardless of vitamin E blending. In contrast, PMPC grafting or vitamin E blending did not affect impact fatigue resistance but the resulting modification was non-recessive compared to untreated CLPE without additives. This suggests the approach may be promising for improving the longevity of total hip arthroplasty (THA) by employing PMPC grafting or even vitamin E-blended CLPE.

Our study has been subject to a number of limitations. First, we used a confined period for the multidirectional wear and impact-to-wear tests with the POD testing machine for the preliminary examination. This may not have provided a sufficient range of loading and motion conditions for physical walking or during daily routines, although we believe the multidirectional wear and impact-to-wear tests provided some indication of the wear and impact fatigue performances [2]. In current tests, we are now running the hip-simulator for longer periods using the PMPC-grafted CLPE and PMPC-grafted HD-CLPE(VE) liners, and thus far have confirmed almost no wear on the PMPC-grafted liners after 1 × 10^7 cycles [21]. Second, the material properties of PMPC-grafted CLPE and PMPC-grafted HD-CLPE(VE) we report here are only valid for these specific levels of wear and fatigue resistances. Although wear and fatigue resistances are one of the most common characteristics of acetabular liners in artificial hip joints, oxidation stability is regarded as a potential limiting factor for the longevity of the joints (the clinical impact of this oxidation degradation still requires clarification [22]). Therefore, the incorporation of the antioxidant vitamin E has been proposed recently to avoid oxidation of the liner because vitamin E is a free-radical scavenger and a well-established biological antioxidant [3].

The water wettabilities of the PMPC-grafted CLPE and PMPC-grafted HD-CLPE(VE) surfaces were imparted by the presence of a PMPC graft layer resulting from the polymerization of the highly hydrophilic MPC monomer. The PMPC hydrated layer clearly affected the friction response; the dynamic coefficients of friction of the PMPC-grafted CLPE and PMPC-grafted HD-CLPE(VE) surfaces were significantly lower than those of the untreated CLPE surface. This is attributed to the significant increase in hydrophilicity that was evident from the reduction in the static water contact angles of the PMPC-grafted surfaces [14]. Additionally, the improvement in the dynamic coefficients of friction of both PMPC-grafted surfaces with increases in loading has revealed very interesting observations—the PMPC grafted layer did not follow Amonton's law ($F = \mu N$). As the elastic CLPE and HD-CLPE(VE) substrates were slightly deformed by the loads, the low friction coefficient may have been necessary to amass a larger volume of water in the thin film over the larger contact area of the concave surface [16]. We also think that these results imply that the lubrication of the PMPC-grafted surfaces was dominated by the hydration lubrication mechanism [8].

In the multidirectional wear, the PMPC-grafted surfaces exhibited high wear resistance regardless of vitamin E blending. We believe that hydration lubrication of the PMPC-grafted surface was provided by the hydrated layer, and it was essential for high wear resistance. Moreover, the PMPC-grafted HD-CLPE(VE) exhibited a higher wear resistance compared to the PMPC-grafted CLPE despite similar surface hydrophilicity and lubricity. Okubo et al. suggested that a load-dependent frictional improvement of vitamin E-blended PE would be limited in the initial friction only [25]. Hence, we hypothesize that the higher wear resistance of the PMPC-grafted HD-CLPE(VE) was caused by the more effective cross-linking with a gamma-ray irradiation of 100-kGy dose [26]. Backside damages, such as volumetric penetration and circular scratching, were observed clearly on the disk surface owing to the multidirectional wear and impact-to-wear tests. Using a finite elemental analysis, Chang et al. reported that the internal stress and plastic flow of PE increases with decreasing PE thickness [4]. It was thought that high internal stress occurred in thin PE disks and that plastic flow was caused by the backside surface rubbing against the edge of the hole in the fixation component. Therefore, backside damage was affected mainly by the degree of thickness. Based on these results, we believe that the risks posed by wear as well as fracturing are increased by using a thin acetabular liner.

Cyclic impact loadings under physical walking, such as heel-strike and toe-off, are severe motion conditions for acetabular liners and are more important factors for young active patients. Unfortunately, the PMPC hydrated layer was not effective despite vitamin E blending, and it could not support the cyclic impact loadings owing to a lack of thickness (approximately 100 nm) of the grafted PMPC layer. As a result, the cyclic impact loadings was supported by the CLPE or HD-CLPE(VE) substrate. The retention of the bulk properties of the substrates is important because the CLPE or HD-CLPE(VE) used as acetabular liners act not only as surface-functional materials, but also as structural materials in vivo. The advantage of PMPC grafting was that the grafted PMPC layer produces high lubricity while only affecting the surface, and it has no effect on the properties of the substrate [12, 21]. Recently, a review of voluntary reports of fractured CLPE liners showed that liners thinner than 7 mm at the weight bearing or liners that are 4.8-mm-thick at the rim should be used with caution [1]. Our group focused on the effect of thin PE disks on wear and impact fatigue. In this study, we observed neither mechanical fracture nor delamination in the sliding or backside surfaces of all groups. Therefore, we believe that the CLPE and HD-CLPE(VE) substrates have sufficiently strong mechanical properties and cyclic impact-fatigue resistances.