Biomaterials 112 (2017) 122–132

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

# A hydrated phospholipid polymer-grafted layer prevents lipid-related oxidative degradation of cross-linked polyethylene

Masayuki Kyomoto [a, b, c], Toru Moro [b, d], Shihori Yamane [a, b, c], Yoshio Takatori [b, d], Sakae Tanaka [d], Kazuhiko Ishihara [a, *]

[a] Department of Materials Engineering, School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan
[b] Division of Science for Joint Reconstruction, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[c] Research Department, KYOCERA Medical Corporation, 3-3-31 Miyahara, Yodogawa-ku, Osaka 532-0003, Japan
[d] Sensory & Motor System Medicine, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

ARTICLE INFO

*Article history:*
Received 20 September 2016
Received in revised form
4 October 2016
Accepted 11 October 2016
Available online 11 October 2016

*Keywords:*
Joint replacement
Polyethylene
Phosphorylcholine
Oxidation
Lipids

ABSTRACT

The surface and substrate of a cross-linked polyethylene (CLPE) liner are designed to achieve resistance against oxidative degradation in the construction of hip joint replacements. In this study, we aimed to evaluate the oxidative degradation caused by lipid absorption of a highly hydrophilic nanometer-scaled thickness layer prepared by grafting a poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC) layer and a high-dose gamma-ray irradiated CLPE with vitamin E blending (HD-CLPE[VE]). The HD-CLPE(VE) and PMPC-grafted HD-CLPE(VE) exhibited extremely high oxidation resistance regardless of lipid absorption, even though residual-free radical levels were detectable. The water wettability of the PMPC-grafted CLPE and PMPC-grafted HD-CLPE(VE) surfaces was considerably greater than that of untreated surfaces. The hydrated PMPC-grafted layer also exhibited extremely low solubility for squalene. Lipids such as squalene and cholesterol esters diminished the oxidation resistance of CLPE despite the vitamin E improvement. Notably, the PMPC-grafted surface was resistant to lipid absorption and diffusion as well as subsequent lipid-related oxidative degradation, likely because of the presence of the hydrated PMPC-grafted layer. Together, these results provide preliminary evidence that the resistance against lipid absorption and diffusion of a hydrated PMPC-grafted layer might positively affect the extent of resistance to the *in vivo* oxidation of orthopedic implants.



## 1. Introduction

The number of primary total hip arthroplasty (THA) procedures performed each year has increased significantly owing to the aging global population [1]. Most patients experience dramatic pain relief, increased activity in daily life, and restored quality of life after THA. However, the number of revision surgeries has also increased annually, despite advances in surgical techniques and implant designs [2]. One of the major complications of THA, *e.g.*, aseptic loosening limits the duration and clinical outcomes following surgery [3]. Recently, we have developed an articular cartilage-inspired technology that allows surface modification of the acetabular liners used in artificial hip joints by grafting water-soluble poly(2-methacryloyloxyethyl phosphorylcholine [MPC]) (PMPC) on cross-linked polyethylene (CLPE) for the prevention of aseptic loosening [4–6]. Modifying the CLPE surfaces of an artificial joint with a hydrophilic layer has been reported to increase lubrication to a degree similar to that obtained for articular cartilage under physiological conditions. Our previous study on the function and efficacy of PMPC revealed that such grafting greatly improves the wear resistance of the modified CLPE [4]. However, wear resistance is only one of several important indicators of the clinical performance of acetabular liners; oxidation resistance is also an important measure. Oxidation is a free radical-initiated chemical reaction and is expected to result in molecular chain scission [7]. The sequential decrease in the molecular weight and cross-link density or an increase in crystallinity would be expected following oxidative degradation of the CLPE; such changes of the chemical and physical structures have been shown to compromise their mechanical properties and might ultimately lead to implant failures such as rim fracture or delamination [8–10]. Therefore, the

* Corresponding author. Department of Materials Engineering, School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan.
*E-mail address:* ishihara@mpc.t.u-tokyo.ac.jp (K. Ishihara).

http://dx.doi.org/10.1016/j.biomaterials.2016.10.021
0142-9612/

free radicals generated during high-energy (*e.g.*, gamma-ray) irradiation might limit the longevity of artificial hip joints. The initial approach attempted for preventing oxidative degradation was a reduction of the residual free radicals by thermal treatment (*i.e.*, annealing or melting). However, several retrieval studies have recently reported that the *in vivo* oxidation of the CLPE liner occurs despite either thermal treatment [8,11]. Therefore, two potential triggers are considered to have played a role in inducing the changes *in vivo* that led to the oxidation of the CLPE. One trigger is the residual free radicals in the CLPE substrate, and the other is the absorbed lipids from the synovial fluid that can initiate and accelerate an oxidation cascade. Costa et al. reported that several lipids (*e.g.*, cholesterol esters and squalene) from the synovial fluid *in vivo* had been absorbed into the polyethylene (PE) substrate in the previous retrieval study [12]. Furthermore, Oral et al. suggested that the oxidative degradation caused by the lipid absorption of PE or CLPE served as an additional oxidation cascade [13]. Although the clinical impact of this oxidative degradation of CLPE is unclear, *in vivo* oxidative degradation is generally regarded as being undesirable.

Dislocation is the other major complication associated with THA [3]. A thin acetabular liner placed against a large femoral head not only allows for an increased head/neck ratio, which is directly related to the range of motion prior to the impingement of the trunnion on the liner [14], but also increases the resultant jumping distance [15]. Hence, the use of implants with such dimensions is becoming more common in the effort to improve the stability of the bearing surface [16]. On the other hand, mechanical fracture attributed to scission of the PE chains owing to oxidative degradation in the thin acetabular liners mediated by the possible impingements must therefore be monitored. Several previous studies have reported that the observed mechanical fracture was caused by the neck impingements in CLPE liners that had been thermally treated via both annealing and melting [8,11,17]. Sakoda et al. further reported the negative impacts of lipid-related oxidative degradation on the mechanical properties of PE and CLPE [18]. Therefore, we considered that for the CLPE to maintain a high level of mechanical properties during long-term clinical use as the structural material for thin acetabular liners; an additional or alternative process would be necessary for the prevention of lipid absorption and diffusion in addition to the stabilization of the residual free radicals with an antioxidant.

The combined effects of substrate and surface defenses are responsible for preventing lipid absorption and diffusion from the synovial fluids around the implant site. It is becoming increasingly obvious, however, that the biomaterial itself also plays a key role in preventing oxidative degradation. The first approach to producing biomaterials with enhanced resistance against radical-initiated oxidation was the incorporation of an antioxidant such as vitamin E ($\alpha$-tocopherol) into the substrate to scavenge any residual free radicals [19]. Alternatively, the surface modification of the implant itself might minimize lipid absorption. However, despite the known negative impact of the absorption from the implant surface, this latter approach has not yet been a focus of current research. As mentioned above, we have recently developed surface modified PMPC-grafted CLPE for use as an acetabular liner of life-long duration in an artificial hip replacement. MPC polymers have great potential for applications in the fields of biomedical science and bioengineering because they possess beneficial properties such as excellent anti-biofouling ability [20–22]. Thus, PMPC grafting is expected to be a useful surface modification on the CLPE, with a potential secondary benefit of resisting lipid absorption from the surface of the implant.

In this study, we aimed to evaluate the resistance to lipid-related oxidative degradation afforded by the use of a highly hydrophilic nanometer-scale surface prepared by grafting a PMPC layer and an anti-oxidant additive CLPE substrate generated by vitamin E blending. Our ultimate goal in manipulating the surface and substrate of the CLPE liner was not just to obtain high wear resistance [19,23], but also to promote high anti-oxidation properties for life-long orthopedic bearings. Such investigations are of considerable importance in the design of life-long polymeric biomaterials and improving our understanding of the mechanisms mediating the interaction between the physiological synovial fluid including lipids and the implant surface or substrate. Thus, we attempted to address whether the PMPC-grafted layer and the vitamin E-blended substrate could affect the oxidative degradation caused by lipid absorption.

## 2. Materials and methods

### 2.1. Chemicals and surface modification by PMPC grafting

Benzophenone (BP) and acetone were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Industrially synthesized MPC (purity $\geq$ 98.0%) was purchased from NOF Corp. (Tokyo, Japan) [21,24]. 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 an atmosphere containing $N_2$ gas, and annealed at 120 °C for 7.5 h in $N_2$ gas to facilitate cross-linking; this product is hereafter referred to as CLPE. A compression-molded bar stock of 0.1 mass% vitamin E-blended PE (GUR1020E resin; Orthoplastics Ltd.) was irradiated with a high dose (HD; 100 kGy) of gamma-rays in an atmosphere containing $N_2$ gas and annealed at 120 °C for 12 h in $N_2$ gas in order to facilitate cross-linking; this product is hereafter referred to as HD-CLPE(VE). Samples of CLPE and HD-CLPE(VE) were then machined from the bar stocks after cooling, washed with aqueous polysorbate-surfactant solutions and/or ethanol, and dried at room temperature for 1 h in a vacuum.

The CLPE and HD-CLPE(VE) samples were immersed for 30 s in acetone containing 10 mg/mL BP, and then dried in the dark at room temperature to remove the acetone. MPC was dissolved in degassed pure water to a concentration of 0.5 M [25]. The BP-coated CLPE and HD-CLPE(VE) samples were then immersed in the MPC aqueous solution. Photoinduced-radical graft polymerization was carried out on the CLPE and HD-CLPE(VE) surfaces using ultraviolet (UV) irradiation (UVL-400HA ultra-high pressure mercury lamp; Riko-Kagaku Sangyo Co., Ltd., Funabashi, Japan) with an intensity of 5 mW/cm$^2$ at 60 °C for 90 min [25–27]; a filter (model D-35; Toshiba Corp., Tokyo, Japan) was used to permit the sole passage of UV light with a wavelength of 350 $\pm$ 50 nm. After polymerization, the PMPC-grafted CLPE and HD-CLPE(VE) samples were removed, washed with pure water and ethanol, and dried at room temperature for 1 h in a vacuum. The obtained samples of the 4 groups, *i.e.*, CLPE, PMPC-grafted CLPE, HD-CLPE(VE), and PMPC-grafted HD-CLPE(VE), were sterilized with a 25-kGy dose of gamma-ray irradiation under $N_2$ gas [28].

### 2.2. Cross-link density measurement

The cross-link density of the CLPE, PMPC-grafted CLPE, HD-CLPE(VE), and PMPC-grafted HD-CLPE(VE) samples was evaluated according to previously reported methods [27]. Specimens from each sample (approximately 0.5 g) were weighed, allowed to swell for 72 h in *p*-xylene containing 0.5 mass% 2-*t*-butyl-4-methylphenol at 130 °C, and then reweighed. The samples were then immersed in acetone, dried at 60 °C under vacuum, and weighed again. The swelling ratio was determined from the weight gain and densities of the polyethylene and xylene, and the cross-