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SYMPOSIUM: ADVANCES IN UHMWPE BIOMATERIALS

Natural Polyphenols Enhance Stability of Crosslinked UHMWPE for Joint Implants

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Abstract

Background Radiation-crosslinked UHMWPE has been used for joint implants since the 1990s. Postirradiation remelting enhances oxidative stability, but with some loss in strength and toughness. Vitamin E-stabilized crosslinked UHMWPE has shown improved strength and stability as compared with irradiated and remelted UHMWPE. With more active phenolic hydroxyl groups, natural polyphenols are widely used in the food and pharmaceutical industries as potent stabilizers and could be useful for oxidative stability in crosslinked UHMWPE.

Questions/purposes We asked whether UHMWPE blended with polyphenols would (1) show higher oxidation resistance after radiation crosslinking; (2) preserve the mechanical properties of UHMWPE after accelerated aging; and (3) alter the wear resistance of radiation-crosslinked UHMWPE.

Methods The polyphenols, gallic acid and dodecyl gallate, were blended with medical-grade UHMWPE followed by consolidation and electron beam irradiation at 100 kGy. Radiation-crosslinked virgin and vitamin E-blended UHMWPEs were used as reference materials. The UHMWPEs were aged at 120 °C in air with oxidation levels analyzed by infrared spectroscopy. Tensile ($n = 5$ per group) and impact ($n = 3$ per group) properties before and after aging as per ASTM F2003 were evaluated. The wear rates were examined by pin-on-disc testing ($n = 3$ per group). The data were reported as mean ± SDs. Statistical analysis was performed by using Student's t-test for a two-tailed distribution with unequal variance for tensile and impact data obtained with $n \geq 3$. A significant difference is defined with $p < 0.05$.

Results The oxidation induction time of 100 kGy UHMWPE was prolonged to 144 hours with 0.05 wt% dodecyl gallate and 192 hours with 0.05 wt% gallic acid compared with 48 hours for 0.05 wt% vitamin E-blended UHMWPE. Accelerated aging of these polyphenol-blended UHMWPEs resulted in ultimate tensile strength of 50.4 ± 1.4 MPa and impact strength of 53 ± 5 kJ/m^2 for 100 kGy-irradiated UHMWPE with 0.05 wt% dodecyl gallate, for example, in comparison to 51.2 ± 0.7 MPa ($p = 0.75$) and 58 ± 5 kJ/m^2 ($p = 0.29$) before aging. The pin-on-disc wear rates of 100 kGy-irradiated UHMWPE with 0.05 wt% dodecyl gallate and 0.05 wt% gallic acid

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were 2.29 ± 0.31 and 1.65 ± 0.32 mg/million cycles, comparable to 1.68 ± 0.25 and 2.05 ± 0.22 mg/million cycles for 100 kGy-irradiated virgin and 0.05 wt% vitamin E-blended UHMWPE.

Conclusions Based on the sample numbers tested in this study, polyphenols appear to effectively enhance the oxidation stability without altering the mechanical properties or pin-on-disc wear rate of radiation-crosslinked UHMWPE.

Clinical Relevance Crosslinked UHMWPE with natural polyphenols with improved oxidative stability and low wear may find clinical application in joint implants.

Introduction

Currently, more than 600,000 total joint arthroplasties are performed each year in the United States. This number is estimated to exceed 4 million per year by 2030 [20]. More than 70% of total joint implants consist of a metal or ceramic component articulating against a UHMWPE component [21, 26]. The long-term oxidation of historical UHMWPE components sterilized in the presence of oxygen is a cause of fracture[4] and wear [46] that can lead to osteolysis, aseptic loosening, and instability, which are common reasons for revision total joint arthroplasty [26, 39]. Radiation-crosslinked UHMWPE has been used clinically for joint implants since the 1990s [21]. The highly crosslinked materials lead to 70% to 90% reduction in wear rates according to 10-year followup studies [25]. Postirradiation thermal treatments [8, 24, 30], ie, annealing below the peak melting point and remelting above the melting point, have been used to reduce the levels of radicals generated during ionizing irradiation that otherwise would induce oxidation and embrittlement. Despite the clinical success of these materials for more than one decade, the decreased mechanical strength and fatigue resistance remain as concerns and may account for reports of early rim fractures of implants [14, 15]. Moreover, in vivo oxidation of implants and in vitro oxidation of explants have recently been reported [6, 7, 28], even for remelted crosslinked UHMWPEs that show excellent oxidative stability during laboratory tests. In vivo challenges, including cyclic loading and synovial fluid lipid adsorption, have been suggested as possible mechanisms for in vivo or ex vivo oxidation of remelted UHMWPE implants [32, 34].

Stabilization of irradiated UHMWPE with antioxidants has been studied extensively in vitro and has demonstrated a promising alternative strategy to prevent UHMWPE oxidation [13, 16, 17, 45]. Vitamin E, or more specifically α-tocopherol, has been introduced into clinical use and to date appears to be a successful antioxidant used to stabilize radiation-crosslinked UHMWPE. The stabilization mechanism involves the abstraction of a hydrogen radical from the phenolic hydroxyl group by a macroradical by irradiation [1, 5]. No postirradiation thermal treatments are necessary in the presence of vitamin E; the crystal structures and thus the tensile strength and impact toughness are improved in comparison to the first-generation highly crosslinked and remelted UHMWPEs [38], which may be beneficial for joint implants. Moreover, vitamin E in trace amounts [22] has been demonstrated to be effective in preventing lipid-related oxidation according to laboratory studies [12].

Natural polyphenols as free radical scavengers have been widely used in food and pharmaceutics as potent antioxidants [3, 11]. In contrast to vitamin E, natural polyphenols containing multiple phenolic hydroxyl groups may offer higher antioxidation capability. Consequently, we asked whether UHMWPE blended with two natural polyphenols would (1) show higher oxidation resistance after radiation crosslinking; (2) preserve the mechanical properties of UHMWPE after accelerated aging; and (3) alter the wear resistance of radiation-crosslinked UHMWPE.

Materials and Methods

UHMWPE Materials

We investigated radiation-crosslinked UHMWPE with two natural polyphenols, gallic acid and dodecyl gallate, containing three phenolic hydroxyl groups each with radiation-crosslinked virgin and vitamin E-blended UHMWPE as controls. Medical-grade UHMWPE (GUR® 1050; Ticona, Hoechst, Germany) was used for all UHMWPE materials tested. The polyphenol-blended UHMWPE materials were prepared as follows. First, gallic acid and dodecyl gallate were dissolved in acetone and the solutions were blended with UHMWPE powder with 1 wt% polyphenol with homogeneous polyphenol distribution. The blended powders were dried at 60 °C in a vacuum oven for 1 week and diluted with virgin UHMWPE powders to achieve final concentrations of 0.05 and 0.1 wt%, because these values have been documented in the literature [5, 17] and are of clinical relevance.

Consolidation was performed through slab compression. To avoid UHMWPE oxidation during the consolidation process, the blended powders were preheated in a stainless steel mold at 200 °C in a vacuum oven until the polyphenol-blended UHMWPE powders completely melted followed by consolidation at 190 °C and 10 MPa for 30 minutes by using a hydraulic press. After cooling down to room temperature, polyphenol-blended UHMWPE blocks with 10 cm diameter and approximately 1.5 cm height were obtained. The consolidated blocks were

vacuum-packaged and irradiated with a 10-MeV electron beam (Huaneng Electron Accelerator Co, Shaoxing, China) at 25 kGy per pass at room temperature to a total dose of 100 kGy. The temperature of the samples after each irradiation run was no higher than 50 °C. Radiation-crosslinked virgin and vitamin E-blended blocks were prepared in our laboratory following the procedure described previously without using polyphenols and used as reference.

Oxidation Level

Two accelerated aging protocols were used, one to determine oxidation level and the other to determine the mechanical properties of the UHMWPE. In the first method, thin slices of UHMWPE (one slice for each material) were aged at 120 °C to distinguish the antioxidation potency in a relatively short time scale, as reported in the literature [16]. Thin slices of the UHMWPE were microtomed to a thickness of 100 μm and subjected to accelerated aging in a ventilated oven at 120 °C until the samples became too brittle to handle. This aging was replicated for three times for all the slices to verify the reproducibility of the results. The oxidation levels of UHMWPEs were tracked and examined through Fourier transform infrared (FTIR) spectroscopic analysis. FTIR spectra of the oxidized samples after hexane extraction were collected in transmission mode from 4000 to 400 cm^{-1} with 4 cm^{-1} resolution and 32 scans each using a Cary 640 spectrometer (Agilent Technologies Australia, Mulgrave, Australia). The absorbance at 1718 cm^{-1} (carbonyl groups) was used to evaluate the oxidation level of UHMWPE. The absorbance at 2018 cm^{-1} (CH_2 twisting), which has been shown to remain relatively unaffected by the changes in the polymer structure induced by thermal, high-energy radiation or mechanical treatments, was used as the internal reference for the normalization of all spectra to an absorbance of 0.05 for a slice thickness of approximately 100 μm [16, 40]. The base of this peak was zeroed at 2000 cm^{-1}. The FTIR spectra of aged samples were subtracted from those of unaged counterparts to reveal variations between the unaged and aged conditions. We determined oxidation induction time for the UHMWPEs, which was defined as the time taken for the materials to reach an oxidation level of 0.15. For this purpose, the oxidation level was defined as the ratio of band area at 1680 to 1820 cm^{-1} (carbonyl stretching) over that at 1370 to 1390 cm^{-1} (polyethylene skeleton).

Tensile and Impact Tests

In the second accelerated aging protocol, UHMWPE blocks were aged at 70 °C in 5 atm O_2 for 2 weeks as per ASTM F2003 [41]. The effect of this aging process on the mechanical properties of the UHMWPE was investigated by tensile and impact tests before and after aging for 100-kGy-irradiated UHMWPE ($n = 5$ per group). The irradiation dose of 100 kGy is close to that applied for some of the manufactured first-generation highly crosslinked UHMWPEs, which have been in clinical use and have shown a 70% to 90% reduction in annual implant wear [25].

For uniaxial tensile tests, dumbbell-like Type V tensile samples (with 63.5 mm length, 3.18 mm width, and 7.62 mm gauge length; $n = 5$ per group) were stamped from 3.2-mm-thick UHMWPE blocks according to ASTM D638 [44]. The samples were tested on an Instron 5567 frame (Instron Inc, Norwood, MA, USA) at a crosshead speed of 10 mm/minute. The load and crosshead displacement were recorded and used to calculate the ultimate tensile strength and elongation at break.

For Izod impact tests, UHMWPE bars 63.5 mm long, 12.7 mm wide, and 6.35 mm thick ($n = 3$ per group) were machined and double-notched with a sharp blade to a depth of 4.57 ± 0.08 mm according to ASTM F648 [42]. Izod impact tests were conducted by using a XJ-50Z tester (Chengde Dahua Inc, Chengde, China). The absorbed energy of the hammer (in kilojoules per square meter) was recorded as the impact strength.

Wear Tests

We also examined the effect of polyphenol chemistry and concentration on the wear rate of irradiated UHMWPE with 100 kGy. The 100-kGy irradiated and remelted virgin UHMWPE was used a control. For this purpose, pin-on-disc (POD) tests were conducted, as recommended by ASTM G99-05 [43].

UHMWPE pins of 9 mm diameter and 13 mm length ($n = 3$ per group) were machined out of the blocks and bidirectionally tested at 2 Hz against implant-grade polished CoCrMo alloy discs ($R_a < 0.05$) by using a custom-built machine with bovine serum lubrication at a constant load of 1865 N. The bovine serum was exchanged and the pins were weighed every day to up to 2 million cycles. The weight loss was analyzed with a linear regression method to determine the mean wear rate of the UHMWPE materials.

Statistical Analysis

In this study, small sample numbers ($n = 3$ or 5 per group) were used. We conducted statistical analysis to examine the significance of the difference between groups out of the

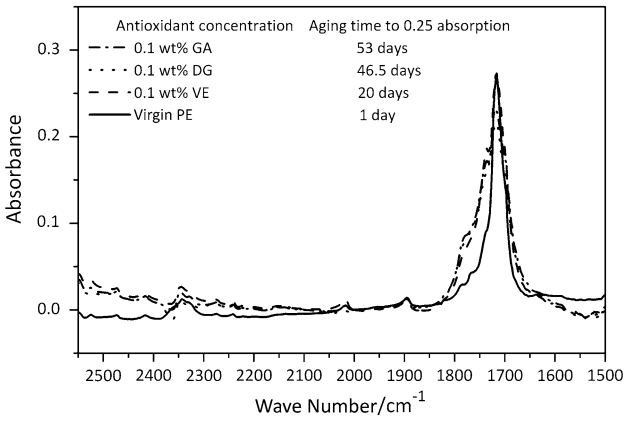

Fig. 1 FTIR spectral subtractions of UHMWPE slices with different antioxidants are summarized after aging in air at 120 °C for different times until reaching a band intensity of 0.25 at 1718 cm^{-1}. VE = vitamin E; DG = dodecyl gallate; GA = gallic acid.

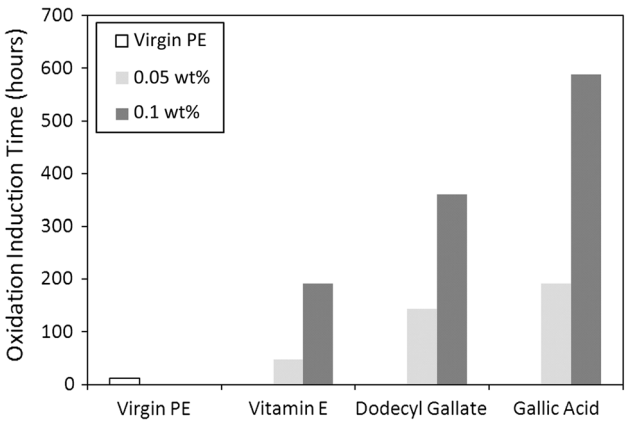

Fig. 2 Graph shows the oxidative induction time (when the absorbance at 1718 cm^{-1} increased to 0.15) of 100-kGy-irradiated UHMWPE aged in air at 120 °C. VE = vitamin E; DG = dodecyl gallate; GA = gallic acid.

limited numbers available. The groups in comparison were tested by using a Student's t-test method for a two-tailed distribution with unequal variance. The threshold for a significant difference is defined at $p < 0.05$. The exact p values are shown unless they are < 0.001.

Results

We compared the aging times needed for the UHMWPEs at 120 °C to reach a band absorbance of 0.25 at 1718 cm^{-1}. It took 53 days for the 100-kGy-irradiated 0.1 wt% gallic acid-blended UHMWPE compared with 46.5 days for 100-kGy-irradiated 0.1 wt% dodecyl gallate-blended UHMWPE, 20 days for 100-kGy-irradiated 0.1 wt% vitamin E-blended UHMWPE, and 1 day for irradiated virgin UHMWPE (Fig. 1). The oxidation induction times of 100-kGy-irradiated 0.05 wt% dodecyl gallate-blended and gallic acid-blended

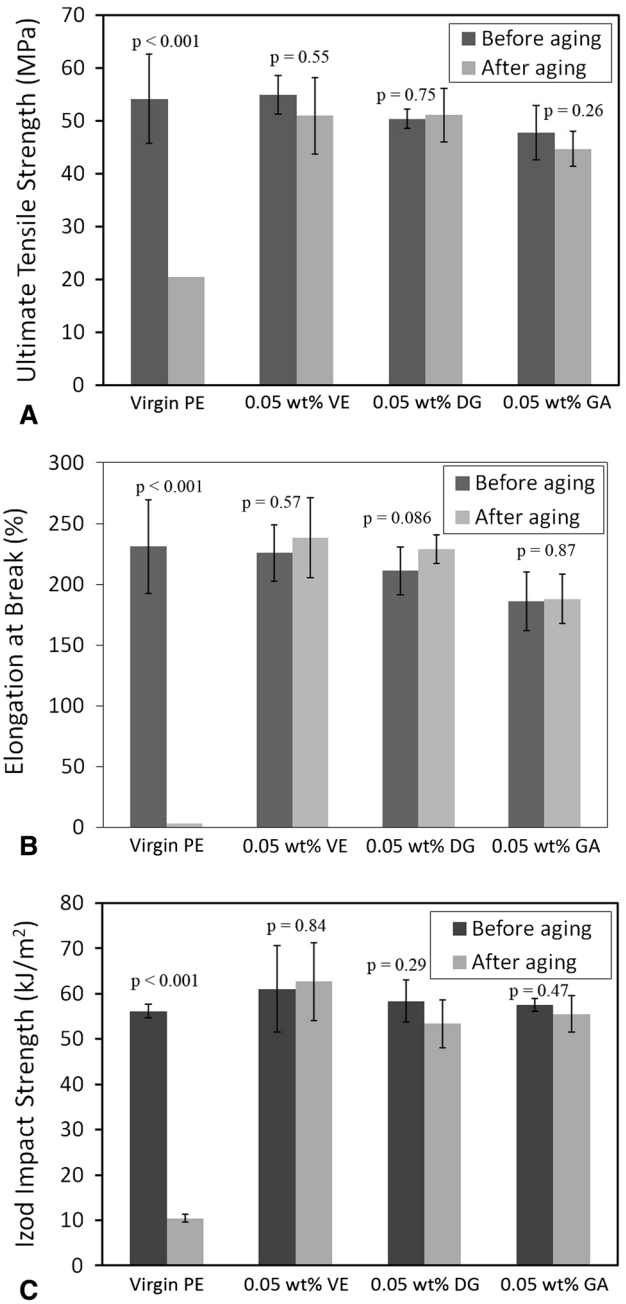

Fig. 3A–C Graphs show the mechanical properties, (**A**) ultimate tensile strength, (**B**) elongation at break (n = 5 per group), and (**C**) double-notched Izod impact strength (n = 3 per group) of the 100-kGy-irradiated UHMWPE groups with 0.05 wt% antioxidants before and after accelerated aging according to ASTM F2003. VE = vitamin E; DG = dodecyl gallate; GA = gallic acid.

UHMWPEs were 144 and 192 hours, respectively, which were longer than the 48 hours for 0.05 wt% 100-kGy-irradiated vitamin E-blended UHMWPE (Fig. 2). With 0.1 wt% antioxidants, the oxidative induction time was further increased to 360, 588, and 192 hours for dodecyl gallate, gallic acid, and vitamin E, respectively. All these values were much longer than for virgin UHMWPE (approximately 12 hours).

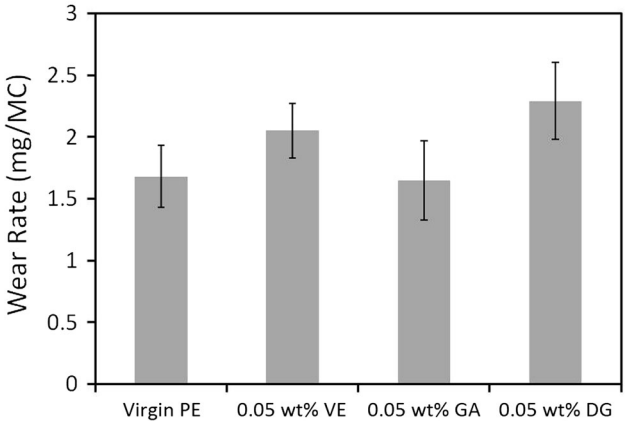

Fig. 4 Graph shows the wear rates of 100-kGy irradiated UHMWPE materials with 0.05 wt% antioxidants (n = 3 per group). VE = vitamin E; DG = dodecyl gallate; GA = gallic acid; MC = million cycles.

The mechanical properties of the 100-kGy-irradiated UHMWPE with antioxidants were preserved after accelerated aging according to ASTM F2003 (Fig. 3). For 100-kGy-irradiated virgin UHMWPE, aging at 70 °C in 5 atm O_2 for 2 weeks decreased its tensile strength, elongation, and Izod impact strength from 55.5 ± 7.9 MPa, 231% ± 38%, and 56 ± 2 kJ/m^2 before aging to less than 20 MPa, 2% (n = 1, only one specimen survived), and 10 ± 1 kJ/m^2 after aging ($p < 0.001$), respectively. In contrast, with the numbers available, the ultimate tensile strength values before and after aging are 50.3 ± 1.8 MPa and 51.0 ± 5.1 MPa with 0.05 wt% dodecyl gallate (DG, $p = 0.75$), 47.8 ± 5.1 MPa and 44.7 ± 3.3 MPa with 0.05 wt% gallic acid (GA, $p = 0.26$), and 54.9 ± 3.6 MPa and 50.9 ± 7.2 MPa with 0.05 wt% vitamin E (VE, $p = 0.36$). The elongation at break values before and after aging are 211 ± 19.6% and 229 ± 11.8% with 0.05 wt% DG ($p = 0.086$), 186 ± 24.2% and 188 ± 20.3% with 0.05 wt% GA ($p = 0.87$), and 226 ± 23.4% and 238 ± 32.9% with 0.05 wt% VE ($p = 0.57$). The Izod impact strength values before and after aging are 58.3 ± 4.6 MPa and 53.4 ± 5.3 MPa with 0.05 wt% DG ($p = 0.29$), 57.4 ± 1.4 MPa and 55.5 ± 4.0 MPa with 0.05 wt% GA ($p = 0.47$), and 61.1 ± 9.5 MPa and 62.6 ± 8.6 MPa with 0.05 wt% VE ($p = 0.84$). On the other hand, these values are not different from those for virgin UHMWPE before aging with the numbers available.

The 100-kGy-irradiated polyphenol-blended UHMWPE showed low wear rates with POD tests (Fig. 4). With the numbers available, the wear rate of 100-kGy-irradiated 0.05 wt% gallic acid-blended UHMWPE (1.65 ± 0.32 mg/million cycles) was comparable to that of 100-kGy-irradiated and remelted virgin UHMWPE (1.68 ± 0.25 mg/million cycles) and 100-kGy-irradiated 0.05 wt% vitamin E-blended UHMWPE (2.05 ± 0.22 mg/million cycles). Note that the wear rate of unirradiated virgin UHMWPE was 12.38 ± 2.28 mg/million cycles as tested in our laboratory.

Discussion

Midterm clinical followup studies on highly crosslinked UHMWPE components have found 70% to 90% reduction in wear rates [25]. The decreased mechanical strength and fatigue resistance remain as concerns [14, 15]. Alternatively, stabilization of irradiated UHMWPE with vitamin E has improved strength and toughness [35–38]. Natural polyphenols have been used in food and pharmaceutics as potent antioxidants [3, 11]. Herein, the use of gallic acid and dodecyl gallate appeared to effectively improve the oxidative stability of radiation-crosslinked UHMWPE. The tensile and impact properties of these polyphenol-stabilized irradiated UHMWPE were preserved after accelerated aging. Moreover, these stabilized materials qualitatively showed low wear rates comparable to those of highly crosslinked and remelted UHMWPE and vitamin E-stabilized crosslinked UHMWPE.

We acknowledge that there are limitations to our study. First, we accelerated the oxidative reactions in irradiated UHMWPE through a procedure that involves temperatures much higher than human body temperature and is incapable of mimicking the in vivo environment of an UHMWPE implant in the human body. Thus, we did not attempt to predict the in vivo performance of polyphenol-blended UHMWPE. Rather, we sought to compare the antioxidation capability of polyphenols with vitamin E by oxidizing the antioxidant-containing UHMWPEs under the same accelerated aging conditions. Second, the outcome of oxidative induction time was conducted through single-sample groups. Replicate experiments (data not shown) presented results with strong consistence with those reported in Fig. 2. Third, the tensile and impact results are based on tests with small sample size. According to the mean and SD values as well as p values, these data showed narrow distribution with the numbers available, which could be regarded as representative, although larger sample sizes may provide stronger confidence.

Oxidation of UHMWPE articular implants initiated by radicals generated by irradiation could reduce the mechanical properties by 20% to 90%, depending on the oxidation level [9, 23], which was also demonstrated by our data obtained for the unstabilized UHMWPE. The use of antioxidants to stabilize the radicals in irradiated UHMWPE has been successful in both experimental studies and clinical applications. Vitamin E is a potent antioxidant to stabilize the radicals and improves the oxidative stability of radiation-crosslinked UHMWPE [2, 22,

27]. In our study, the time to reach a specific oxidation level was qualitatively much longer for polyphenol-blended UHMWPE than virgin UHMWPE (Fig. 1), suggesting the polyphenols were effective in stabilizing the macroradicals to delay the postirradiation oxidation of UHMWPE as vitamin E does [36]. Moreover, the oxidative induction times of gallic acid-blended and dodecyl gallate-blended UHMWPEs were qualitatively longer than those of vitamin E-blended UHMWPE at antioxidant concentrations of 0.05 and 0.1 wt% (Fig. 2), suggesting a higher antioxidation potency of polyphenols than vitamin E.

The tensile and impact properties were retained for the polyphenol-stabilized irradiated UHMWPE after accelerated aging according to ASTM F2003. In comparison to the dramatic drop in the strength and toughness of irradiated virgin UHMWPE after aging, the ultimate tensile strength, elongation at break, and impact strength values of irradiated polyphenol-blended UHMWPE showed no differences after accelerated aging versus before aging (Fig. 3). Moreover, the presence of 0.05 wt% polyphenols did not adversely affect the strength and toughness of UHMWPE. These mechanical properties may be improved in comparison to the first-generation highly crosslinked and remelted UHMWPEs and hopefully would not decrease as a result of the loss of oxidative stability.

The wear rate of crosslinked UHMWPE is also an important parameter influencing joint implant survivorship. Previous studies have demonstrated that radiation crosslinking significantly reduces UHMWPE wear [18, 29, 31, 33]. Moreover, clinical studies of highly crosslinked UHMWPE joint arthroplasty have confirmed these findings with approximately 30% to 80% reduction in wear compared with noncrosslinked conventional UHMWPE at 3 to 5 years [10, 19]. In our study, the use of gallic acid and dodecyl gallate with 0.05 wt% and 0.1 wt% concentrations did not reduce the crosslink density of the materials [13]. With the introduction of 0.05 wt% dodecyl gallate and gallic acid, the wear resistance of UHMWPE materials was not altered and comparable to that of 0.05 wt% vitamin E-blended UHMWPE receiving the same radiation dose (Fig. 4). Moreover, high-dose irradiation did not detrimentally decrease the stability of gallic acid and dodecyl gallate, which, with the numbers available, exhibit an improved oxidative stability compared with vitamin E at the same concentration and irradiation dose (Fig. 2).

This study suggests that polyphenol-blended UHMWPEs exhibit improvements in oxidation resistance, as measured by oxidation induction time, in comparison with vitamin E-blended materials while preserving mechanical properties after accelerated aging based on the sample numbers available. The addition of polyphenols to UHMWPE did not alter the low POD wear rates after irradiation. Such strong antioxidation potency of radiation-crosslinked UHMWPE containing natural polyphenols, together with low wear, may find potential clinical applications for orthopaedic implants. Further research is needed to evaluate the oxidative stability of polyphenol-blended UHMWPE in the presence of synovial fluid lipids, which may offer useful clues to the possible performance of these materials in vivo.

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