Vitamin E-stabilized UHMWPE for Total Joint Implants: A Review

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Running title: Vitamin E-stabilized UHMWPE for Arthroplasty

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Abstract

Background Osteolysis due to wear of UHMWPE limits the longevity of joint replacement. Oxidative degradation of UHMWPE gamma sterilized in air increases its wear while decreasing mechanical strength. Vitamin E (α-tocopherol) stabilization of UHMWPE was proposed to improve oxidation resistance while maintaining wear resistance and fatigue strength. The goal of this review was to summarize pre-clinical research on the development and testing of vitamin E-stabilized UHMWPEs for total joint implants.

Questions/purposes We raised three questions: (1) What is the rationale behind protecting irradiated UHMWPE against oxidation by vitamin E? (2) What are the effects of vitamin E on the microstructure, tribologic, and mechanical properties of irradiated UHMWPE? And (3) is vitamin E expected to affect the periprosthetic tissue?

Methods We performed searches in PubMed, Scopus, and Science Citation Index to review the development of vitamin E-stabilized UHMWPEs and their feasibility as clinical implants.

Results The rationale for using vitamin E in UHMWPE was two-fold: improving oxidation resistance of irradiated UHMWPEs, and the fatigue strength of irradiated UHMWPEs with an alternative to post-irradiation melting. Vitamin E-stabilized UHMWPE showed oxidation resistance superior to that of irradiated UHMWPEs with detectable residual free radicals. It showed equivalent wear and improved mechanical strength compared to irradiated and melted UHMWPE. The biocompatibility was confirmed by simulating elution, if any, of the antioxidant from implants.

Conclusions Vitamin E-stabilized UHMWPE offers a joint arthroplasty technology with good

mechanical, wear, and oxidation properties.

Clinical Relevance Vitamin E-stabilized, irradiated UHMWPEs were recently introduced clinically. The rationale behind using vitamin E and in vitro tests comparing its performance to older materials is of great interest.

Introduction

Reducing osteolysis has been the driving force behind the development of a new generation of UHMWPEs. The occurrence of osteolysis in cementless hip implants has led to its realization as a clinical problem associated mainly with UHMWPE implant wear particles [35].

Sterilization of UHMWPE with gamma radiation in air was common practice until the late 1990s, but it was proven to induce severe oxidation of the polymer. Oxidation and subsequent embrittlement of UHMWPE decrease the abrasive wear resistance and increase the wear debris associated with the polymer [9, 27, 28, 49]. Radiation crosslinking of UHMWPE reduces wear *in vitro* [48, 50, 51, 53] and *in vivo* [29, 47]; but also induces free radicals, which can cause oxidation. Postirradiation melting renders crosslinked UHMWPE oxidation resistant by allowing these residual free radicals trapped in the crystalline regions [8, 40] to recombine. However, the postirradiation melting step reduces the fatigue strength of irradiated UHMWPE [34], which is already decreased by crosslinking [58], due to a decrease in crystallinity that accompanies postirradiation melting.

To develop an oxidation-resistant UHMWPE and improve the fatigue properties of crosslinked UHMWPE by avoiding postirradiation melting, an alternative method is the stabilization of the radiation-induced free radicals by using the antioxidant vitamin E. The major physiologic role of vitamin E [64] is to react with free radicals in cell membranes and protect polyunsaturated fatty acids from degradation due to oxidation [14, 41, 76, 78, 80]. Oxidation reactions in polyethylene, which contains very long, mostly saturated aliphatic chains, are believed to follow a mechanism similar to that in lipids [1, 27].

There are two methods of incorporating vitamin E into UHMWPE (Fig. 1). One is to blend

vitamin E with UHMWPE powder before consolidation. Once consolidated, the blend can be crosslinked with the use of ionizing radiation. The presence of vitamin E in UHMWPE during irradiation protects the polymer from oxidation but reduces the efficiency of crosslinking [56, 57, 65] while the vitamin E itself is reacted; therefore, the vitamin E concentration and the subsequent radiation dose must be optimized to obtain a simultaneously wear- and oxidation-resistant UHMWPE. The alternative method is the diffusion of vitamin E into UHMWPE after radiation crosslinking [62, 63]. The crosslinking efficiency of UHMWPE is not adversely affected in this method since vitamin E is not present during irradiation. Therefore, the amount of vitamin E that can be incorporated into the material is not limited by concerns for crosslink density. On the other hand, the polymer remains unprotected against oxidation during irradiation and following storage, until vitamin E is incorporated. Furthermore, a homogenization step is required after incorporation to obtain adequate antioxidant concentration throughout the implants.

We reviewed the vitamin E-stabilized UHMWPE development with the following questions in mind: (1) What is the rationale behind protecting irradiated UHMWPE against oxidation by vitamin E? (2) What are the effects of vitamin E on the microstructure, tribologic, and mechanical properties of irradiated UHMWPE? And (3) is vitamin E expected to affect the periprosthetic tissue negatively?

Search Strategy and Criteria

We performed parallel searches of PubMed, Science Citation Indices, and Scopus, the latter ones including also more specialized, not strictly biomedical, literature (ie, on polymer chemistry). A search of PubMed for “UHMWPE AND vitamin E” returned 29 papers; the same search in

Scopus yielded 32 results and in Science Citation Indices 73 results. These three searches resulted in 73 unique articles. We excluded 34 articles focused on antioxidants other than vitamin E and forms of polyethylene not clinically relevant at this time (eg, high-pressure crystallized UHMWPE or polyethylene nanocomposites). A total of 39 references were included from this search.

To cover the function of vitamin E in biologic systems, we performed a search for "vitamin E AND function AND humans" and restricted our search to reviews. The search returned 132 results of which we included 6. Our exclusion criteria were transport mechanisms, animal-centered articles, discussion on tocotrienols specifically, and overlap from authors from the same group.

To compare vitamin E-stabilized materials to previously available irradiated and melted UHMWPE materials without free radicals, a search for "UHMWPE AND crosslinking effects", "UHMWPE AND irradiation AND melting", "UHMWPE and oxidation and crosslinked" and "UHMWPE AND free radicals AND trapped" were performed, returning a total of 183 results. We analyzed all abstracts and included 29 articles on the irradiation effects on crosslinking and postirradiation oxidation. We excluded 154 articles overlapping with other searches, repeat publications from same group, and those on oxidation effects during irradiation. Additionally, we added 4 book chapters, 3 patents and 1 thesis we thought relevant to the topic or contained otherwise unpublished results. Also, there was 1 FDA report, 1 ASTM standard and 1 manuscript accepted for publication included.

Thus, we read 143 full articles, 10 book chapters and 25 patents and included 85 references. We describe concepts, methods, results and statistical analyses from these references where

appropriate.

The Rationale in using the Antioxidant Vitamin E

The rationale for using vitamin E was two-fold: improving oxidation resistance of irradiated UHMWPEs and improving the fatigue strength of irradiated UHMWPEs using an alternative to post-irradiation melting [10, 12, 44, 47, 60, 67, 89].

Tocopherol compounds were proposed as stabilizers for polyolefins in the 1980s [31] but did not include orthopaedic implants. In 1994, Hoechst researchers (now Ticona, Kelsterbach, Germany) described consolidated forms of UHMWPE with antioxidants for orthopaedic implants [7]. To stabilize UHMWPE, Brach del Prever et al. [13] also described vitamin E-blended UHMWPE for orthopaedics. In 1998, a gamma-sterilized UHMWPE blended with 0.1% wt% α-tocopherol was developed by Sulzer (Winterthur, Switzerland) in collaboration with Lederer et al. [65, 82–85]. For reasons unknown to the authors, this UHMWPE (VITASUL®) was never released. In Japan, the research of Tomita et al. resulted in a vitamin E-blended UHMWPE for total knee implants [71–73, 75, 77] (Nakashima Medical Ltd, Okayama, Japan) which have been in clinical use in Japan since 2006 [71]. In 2007, ASTM published a standard specification for medical-grade UHMWPE blended with vitamin E [3] followed, in 2009, by commercialization by Ticona of the first vitamin E-containing UHMWPE resins for use in orthopaedics. Also in 2007, the first vitamin E-diffused, irradiated UHMWPE hip implant was clinically introduced in the US (Biomet, Warsaw, IN), followed by knees in 2008.

Under accelerated aging at elevated temperatures and/or in the presence of pure oxygen, vitamin E-stabilized, irradiated UHMWPE was oxidatively more stable than gamma-sterilized or high-dose irradiated UHMWPE [11, 55, 60, 62, 84]. Thus, in vitro studies corroborated the hypothesis

that vitamin E would increase the oxidative stability of irradiated UHMWPEs.

Effects of Vitamin E on Microstructure, Tribologic, and Mechanical Properties of Irradiated UHMWPE

The mechanical and fatigue strength of vitamin E-stabilized, crosslinked UHMWPEs were improved compared to irradiated and melted UHMWPE (Table 1) [33, 62]. The strength of vitamin E-stabilized UHMWPE remained unchanged when accelerated aged, while that of gamma-sterilized UHMWPE deteriorated considerably [55, 59]. Vitamin E alone had no effect on the mechanical properties of UHMWPE [75].

For virgin and vitamin E-doped UHMWPE with an initial radiation dose of 85 to 100 kGy and a terminal gamma sterilization [55, 62] the wear reduction in irradiated/vitamin E-diffused UHMWPE compared to conventional UHMWPE was comparable to that observed previously with irradiated and melted UHMWPE compared to conventional UHMWPE [50, 52]. A study comparing the wear of vitamin E-blended (0.3 wt%), unirradiated UHMWPE versus conventional UHMWPE in a knee simulator showed lower wear volume and different debris for the former [75], suggesting vitamin E alone may improve the wear/delamination resistance [77].

Effects of Vitamin E on Periprosthetic Tissue

Wolf et al. [83] have determined there were no cytotoxic or genotoxic effects of vitamin E from vitamin E-blended and gamma-sterilized UHMWPE containing 0.8 wt% vitamin E *in vitro*. To investigate the local toxicity of vitamin E, an emulsion (10 mg vitamin E) was injected into knees in a rabbit model. At 2 and 12 weeks, the synovial tissue had a normal appearance and there were no signs of inflammation or sterile puss [39].

Discussion

One approach of vitamin E stabilization of UHMWPE focuses on reducing the oxidation of gamma-sterilized UHMWPE, while the alternative introduces vitamin E into highly crosslinked UHMWPE, to improve its mechanical properties compared to clinically available irradiated and melted UHMWPE. The first hypothesis was that vitamin E stabilization will protect irradiated UHMWPE from oxidative degradation. The second issue was the effect of vitamin E on the device performance of UHMWPE. Finally, we looked at the effect of vitamin E on periprosthetic tissue.

Our review is subject to a number of limitations. First, there are no published clinical studies on vitamin E-stabilized UHMWPE and we are limited by in vitro results. Second, our review is intended to be directed to a broad audience; we generally omitted discussions on polymer chemistry. Third, this compilation is related only to the use of vitamin E as a stabilizer of UHMWPE for biomedical implants. Fourth, we could not include recent developments in this rapidly evolving field, which are not yet fully published.

The main purpose of using vitamin E in UHMWPE is to prevent oxidative degradation. Due to radiolytic bond scission, free radicals are produced in irradiated UHMWPE [15, 18, 20, 30, 38], which react with oxygen and trigger the oxidation cascade [2, 16, 17, 20, 22, 25-27, 54, 69] (Fig. 2A, Reactions 1-4). Oxidation is accompanied by chain scissioning, deteriorating its mechanical properties [19, 24, 43]. The stabilization mechanism of α-tocopherol (vitamin E) in UHMWPE was studied [11, 20, 23, 85]. It is believed that α-tocopherol can stabilize peroxy radicals formed by oxidation and can also directly react with alkyl macroradicals (Fig. 2A, Reactions 5 and 6) [11, 23]. The formed tocopheryl product (Fig. 2B) can in turn interact with another alkyl

157 macroradical, furthering the stabilizing effect [11]. The oxidation cascade in irradiated
158 polyethylene is therefore hindered, even in the presence of a small amount of vitamin E (0.05%
159 wt%) [42, 44].

160 When radiation crosslinking UHMWPE **blended** with vitamin E, there is a decrease in
161 crosslinking efficiency. Since 50- to 100-kGy of radiation is required for wear resistance of
162 virgin UHMWPE, low concentrations of vitamin E would be recommended to minimize the
163 adverse effect on crosslinking. But, a sufficient amount of antioxidant is necessary for effective
164 stabilization. Concentrations in the range of 0.05% to 0.1% wt%, along with a small/moderate
165 increase in the radiation dose commonly used for crosslinking of unstabilized material [43, 56]
166 can represent an optimum balance between stabilization and crosslinking efficiency. The main
167 goal of **diffusing** vitamin E into radiation-crosslinked UHMWPE was to obtain enough vitamin
168 E throughout implants to protect against long-term oxidation. A two-step diffusion process at
169 elevated temperatures below the melting point was developed involving doping of UHMWPE
170 with vitamin E with subsequent homogenization [63]. Vitamin E improved the oxidative
171 resistance of irradiated UHMWPE *in vitro* using either method although there are differences in
172 concentration and radiation exposure.

173 The fatigue strength increases with crystallinity and decreases with crosslinking [5, 34, 45, 79,
174 81]. While conventional UHMWPE has high crystallinity and fatigue strength in its unaged
175 form, its fatigue resistance is severely deteriorated due to oxidation [58, 66]. Irradiated and
176 melted UHMWPEs have low fatigue strength, caused by crosslinking and the loss of crystallinity
177 during melting [4, 46, 53, 62]. The fatigue strength loss due to postirradiation melting has been
178 recovered by vitamin E stabilization due to the maintenance of crystallinity. The fatigue strength
179 of a vitamin E-blended UHMWPE with an equivalent crosslink density to 100-kGy irradiated

and melted virgin UHMWPE is improved approximately 30% [33, 58, 62]. Tensile mechanical and fatigue testing after accelerated aging of vitamin E-stabilized UHMWPE corroborated the lack of oxidative degradation of these properties [59].

It appears that crosslink density was the major factor affecting the wear resistance of UHMWPE and vitamin E incorporation did not detrimentally affect the wear resistance of crosslinked UHMWPE. Wear debris of conventional UHMWPE has been associated with osteolysis and implant loosening [6, 36, 74]. Currently, there is no consensus on the differences in the biologic activity of the wear debris from crosslinked UHMWPE compared to conventional UHMWPE. While the average particle size from highly crosslinked UHMWPEs appears smaller than that of conventional UHMWPE, the number of particles is also lower. The oxidative state of wear particles may also play a role in inciting an inflammatory response [10, 37, 67, 68]. Conventional UHMWPE has been associated with high oxidation not observed in irradiated and melted UHMWPE [12, 21]. The effect of vitamin E on the immunogenicity of UHMWPE wear particles is not yet fully investigated; however, it is widely accepted the oxidation level of the particles will be less than the particles from conventional UHMWPE.

One concern is the elution of vitamin E *in vivo* and its local/systemic effects. Vitamin E is abundant naturally [70] but the vitamin E commonly used for the stabilization of UHMWPE is produced synthetically (97% pure α-tocopherol). Both are safe for human consumption in prepared food [32] but their intra-articular effects are not known. Simulated manufacturing conditions showed no detectable elution from vitamin E-diffused UHMWPE [20, 59]. But, there was measurable elution in water at 40° C. The concentration profile became uniform at ~0.7 wt% at 3 years, suggesting saturation at this concentration at 40° C. These components did not show

any detectable oxidation at 3 years. Also, similar samples extracted harshly to remove all detectable vitamin E [61] were exposed to accelerated aging and did not oxidize. This suggested that under clinically relevant conditions, the complete removal of vitamin E was unlikely and the components would be protected even under adverse conditions. Small animal studies [39] have also suggested the elution of vitamin E from the components, even under adverse conditions, is unlikely to cause substantial periprosthetic effects *in vivo*.

In conclusion, vitamin E-stabilized UHMWPEs are good alternative bearing surfaces. Vitamin E protected UHMWPE from oxidative degradation *in vitro* resulting in improved mechanical and wear properties. In vitro and animal studies did not register adverse biologic responses to vitamin E-stabilized UHMWPE. The clinical performance of these materials will best be determined by long-term prospective randomized clinical studies.

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References

1. Al-Malaika S. Autoxidation. In: Scott G, ed. *Atmospheric Oxidation and Antioxidants.* Amsterdam, The Netherlands: Elsevier Science Publishers BV; 1993:I:45-82.
2. Assink R, Celina M, Dunbar T, Alam T, Clough R, Gillen K. Analysis of hydroperoxides in solid polyethylene by MAS 13C NMR and EPR. *Macromolecules*. 2000;33:4023-4029.
3. ASTM International. ASTM F 2695-07. *Standard Specification for Ultra-high Molecular Weight Polyethylene Powder Blended With alpha-Tocopherol (Vitamin E) and Fabricated Forms for Surgical Implant Applications.* West Conshohocken, PA: ASTM International; 2007.
4. Baker DA, Bellare A, Pruitt L. The effect of degree of crosslinking on the fatigue crack initiation and propagation resistance of orthopedic-grade polyethylene. *J Biomed Mater Res A*. 2003;66:146-154.
5. Baker DA, Hastings RS, Pruitt L. Study of fatigue resistance of chemical and radiation crosslinked medical grade UHMWPE. *J Biomed Mater Res.* 1999;46:573-581
6. Bauer T, Schils J. The pathology of total joint arthroplasty-II: mechanisms of implant failure. *Skeletal Radiol*. 1999;28:483-497.
7. Berzen J, Luketic D. Stabilised polyethylene moulding materials, for implants containing polyethylene with molecular wt. 10^5–10^7, antioxidant, and tocopherol, α- tocopherol or Vitamin E, as stabiliser. European Patent 613,923. 1994.
8. Bhateja S, Duerst R, Aus E, Andrews E. Free radicals trapped in polyethylene crystals. *J Macromol Sci Phys B.* 1995;34:263-272.
9. Blunn G, Brach del Preva EM, Costa L, Fisher J, Freeman MA. Ultra high molecular-weight polyethylene (UHMWPE) in total knee replacement: fabrication, sterilisation and wear. *J*

Bone Joint Surg Br. 2002;84:946-949.

10. Bosetti M, Zanardi L, Bracco P, Costa L, Cannas M. In vitro evaluation of the inflammatory activity of UHMWPE. *Biomaterials.* 2003;24:1419-1426.
11. Bracco P, Brunella V, Zanetti M, Luda MP, Costa L. Stabilisation of UHMWPE with vitamin E. *Polym Degrad Stab.* 2007;92:2155-2162
12. Brach del Prever EM, Bistolfi A, Costa L, Bracco P, Linari A, Botto Micca F, Crova M, Gallinaro P. The biological reaction to polyethylene wear debris can be related with oxidation of the UHMWPE cups. *Chir Organi Mov.* 2003;88:291-303.
13. Brach del Prever EM, Camino G, Costa L, Crova M, Dallera A, Gallinaro P. Impianto protesico contenente un componente di materiale plastico. Italian Patent 1271590. 1994.
14. Brigelius-Flohe R, Traber MG. Vitamin E: function and metabolism. *FASEB J.* 1999;13:1145-1155.
15. Brunella V, Bracco P, Carpentieri I, Paganini MC, Zanetti M, Costa L. Lifetime of alkyl macroradicals in irradiated UHMWPE. *Polym Degrad Stab*. 2007;92:1498-1503.
16. Carlsson D, Chmela S, Lacoste J. On the structures and yields of the first peroxyl radicals in γ-irradiated polyolefins. *Macromolecules*. 1990;23:4934-4938.
17. Carlsson D, Dobbin C, Wiles D. Direct observations of macroperoxyl radical propagation and termination by electron spin resonance and infrared spectroscopies. *Macromolecules.* 1985;18:2092-2094.
18. Charlesby A, Libby D, Ormerod M. Radiation damage in polyethylene as studied by electron spin resonance. *Proc R Soc (London) A.* 1961;262:207.
19. Collier J, Sutula L, Currier B, John H, Wooding R, Williams I, Farber K, Mayor M. Overview of polyethylene as a bearing material: comparison of sterilization methods. *Clin*

Orthop Relat Res. 1996;333:76-86.

20. Costa L, Bracco P. Mechanisms of crosslinking, oxidative degradation and stabilization of UHMWPE. In: Kurtz SM, ed. The *UHMWPE Biomaterials Handbook*. Burlington, MA: Elsevier Academic Press; 2009:309-323.
21. Costa L, Bracco P, Brach Del Prever EM. Physicochemical and mechanical properties of UHMWPE: 45 years' experience. *Interact Surg*. 2007;2:169-173.
22. Costa L, Carpentieri I, Bracco P. Post electron-beam irradiation oxidation of orthopaedic UHMWPE. *Polym Degrad Stab*. 2008;93:1695-1703.
23. Costa L, Carpentieri I, Bracco P. Post electron-beam irradiation oxidation of orthopaedic UHMWPE stabilized with vitamin E. *Polym Degrad Stab*. 2009;94:1542-1547.
24. Costa L, Jacobson K, Bracco P, Brach del Prever EM. Oxidation of orthopaedic UHMWPE. *Biomaterials.* 2002;23:1613-1624.
25. Costa L, Luda MP, Trossarelli L. Ultra-high molecular weight polyethylene: I. Mechano-oxidative degradation. *Polym Degrad Stab*. 1997;55:329-338.
26. Costa L, Luda MP, Trossarelli L. Ultra-high molecular weight polyethylene: II. Thermal- and photo-oxidation. *Polym Degrad Stab*. 1997;58:41-54.
27. Costa L, Luda MP, Trossarelli L, Brach del Prever EM, Crova M, Gallinaro P. Oxidation in orthopaedic UHMWPE sterilized by gamma radiation and ethylene oxide. *Biomaterials.* 1998;19:659-668.
28. Costa L, Luda MP, Trossarelli L, Brach Del Prever EM, Crova M, Gallinaro P. In vivo UHMWPE biodegradation of retrieved prosthesis. *Biomaterials.* 1998;19:1371-1385.
29. Digas G, Karrholm J, Thanner J, Herberts P. 5-year experience of highly crosslinked polyethylene in cemented and uncemented sockets: two randomized studies using

radiostereometric analysis. *Acta Orthop*. 2007;78:746-754.

30. Dole M. Free radicals in irradiated polyethylene. In: Dole M, ed. *The Radiation Chemistry of Macromolecules.* New York, NY: Academic Press. 1972:335-348.
31. Dolezel B, Adamirova L. Method of hygienically safe stabilization of polyolefines against thermoxidative and photooxidative degradation. Czechoslovakian Socialist Republic Patent 221,403. 1982.
32. Food and Drug Administration Department of Health and Human Services. Code of Federal Regulations 184.1890: Direct Food Substances Affirmed as Generally Recognized as Safe–[alpha]-tocopherols. Title 21, Volume 3. Revised April 1, 2004.
33. Furmanski J. *Mechanistic and Clinical Aspects of Fatigue of Ultrahigh Molecular Weight Polyethylene* [dissertation]. Berkeley, CA: University of California, Berkeley; 2008.
34. Gencur SJ, Rimnac CM, Kurtz SM. Fatigue crack propagation resistance of virgin and highly crosslinked thermally treated UHMWPE. *Biomaterials.* 2006;27:1550-1557.
35. Harris W. The problem is osteolysis. *Clin Orthop Relat Res.* 1995;311:46-53.
36. Ingham E, Fisher J. Biological reactions to wear debris in total joint replacement. *Proc Inst Mech Eng H*. 2000;214:21-37.
37. Ingram JH, Stone M, Fisher J, Ingham E. The influence of molecular weight, crosslinking and counterface roughness on TNF-alpha production by macrophages In response to UHMWPE particles. *Biomaterials.* 2004;25:3511-3522.
38. Jahan MS, King MC, Haggard WO, Sevo KL, Parr JE. A study of long-lived free radicals in gamma-irradiated medical grade polyethylene. *Radiat Phys Chem.* 2001;62:141-144.
39. Jarrett B, Cofske J, Rosenberg A, Oral E, Muratoglu O, Malchau H. In vivo biological response to vitamin E and vitamin E-doped polyethylene. *J Bone Joint Surg Am*. In press.

40. Keller A, Ungar G. Radiation effects and crystallinity in polyethylene. *J Phys Chem*. 1983;22:155-181.

41. Kiyose C, Ueda T. Distribution and metabolism of tocopherols and tocotrienols in vivo. *J Clin Biochem Nutr.* 2004.35:47-52.

42. Kurtz SM, Dumbleton J, Siskey RS, Wang A, Manley M. Trace concentrations of vitamin E protect radiation crosslinked UHMWPE from oxidative degradation. *J Biomed Mater Res A*. 2009;90:549-563.

43. Kurtz SM, Hozack W, Marcolongo M, Turner J, Rimnac C, Edidin A. Degradation of mechanical properties of UHMWPE acetabular liners following long-term implantation. *J Arthroplasty*. 2003;18(7 Suppl 1):68-78.

44. Lerf R, Zurbrugg D, Delfosse D. Use of vitamin E to protect cross-linked UHMWPE from oxidation. *Biomaterials.* 2010;31:3643-3648.

45. Luisetto Y, Wesslen B, Maurer F, Lidgren L. The effect of irradiation, annealing temperature and artificial aging on oxidation, mechanical properties and fracture mechanisms of UHMWPE. *J Biomed Mater Res A.* 2003;67:908-917.

46. Lyons B. Radiolytic unsaturation decay in polyethylene. Part II: The effect of irradiation temperature, thermal history and orientation. *Radiat Phys Chem.* 2004;69:503-510.

47. Martell JM, Verner JJ, Incavo SJ. Clinical performance of a highly cross-linked polyethylene at two years in total hip arthroplasty: a randomized prospective trial. *J Arthroplasty* 2003;18(7 Suppl 1):55-59.

48. McKellop H, Shen FW, Lu B, Campbell P, Salovey R. Development of an extremely wear resistant ultra-high molecular weight polyethylene for total hip replacements. *J Orthop Res.* 1999;17:157-167.

49. McKellop H, Shen FW, Lu B, Campbell P, Salovey R. Effect of sterilization method and other modifications on the wear resistance of acetabular cups made of ultra-high molecular weight polyethylene: a hip-simulator study. *J Bone Joint Surg Am*. 2000;82:1708-1725.

50. Muratoglu OK, Bragdon CR, O'Connor DO, Jasty M, Harris WH. 1999 HAP Paul Award. A novel method of crosslinking UHMWPE to improve wear, reduce oxidation and retain mechanical properties. *J Arthroplasty.* 2001;16:149-160.

51. Muratoglu OK, Bragdon CR, O'Connor DO, Jasty M, Harris WH, Gul R, McGarry F. Unified wear model for highly crosslinked ultra-high molecular weight polyethylenes (UHMWPE). *Biomaterials.* 1999;20:1463-1470.

52. Muratoglu OK, Bragdon CR, O'Connor DO, Perinchief RS, Estok DM, Jasty M, Harris WH. Larger diameter femoral heads used in conjunction with a highly cross-linked ultra-high molecular weight polyethylene: a new concept. *J Arthroplasty*. 2001;16(8 Suppl):24-30.

53. Muratoglu OK, Merrill EW, Bragdon CR, O'Connor D, Hoeffel D, Burroughs B, Jasty M, Harris WH. Effect of radiation, heat, and aging on in vitro wear resistance of polyethylene. *Clin Orthop Relat Res*. 2003;417:253-262.

54. Ohnishi S, Sugimoto S, Nitta I. Electron spin resonance study of radiation oxidation of polymers. IIIA. Results for polyethylene and some general remarks. *J Polym Sci A Poly Chem.* 1963;1:605-623.

55. Oral E, Christensen S, Malhi A, Wannomae K, Muratoglu O. Wear resistance and mechanical properties of highly crosslinked UHMWPE doped with vitamin E. *J Arthroplasty.* 2006;21:580-591.

56. Oral E, Godleski Beckos C, Malhi A, Muratoglu O. The effects of high dose irradiation on the cross-linking of vitamin E-blended UHMWPE. *Biomaterials.* 2008;29:3557-3560.

57. Oral E, Greenbaum ES, Malhi AS, Harris WH, Muratoglu OK. Characterization of irradiated blends of alpha-tocopherol and UHMWPE. *Biomaterials.* 2005;26:6657-6663.

58. Oral E, Malhi A, Muratoglu O. Mechanisms of decrease in fatigue crack propagation resistance in irradiated and melted UHMWPE. *Biomaterials.* 2006;27:917-925.

59. Oral E, Malhi A, Wannomae K, Muratoglu O. 2006 HAP Paul Award. Highly cross-linked UHMWPE with improved fatigue resistance for total joint arthroplasty. *J Arthroplasty.* 2008;23:1037-1044.

60. Oral E, Rowell SL, Muratoglu OK. The effect of α-tocopherol on the oxidation and free radical decay in irradiated UHMWPE. *Biomaterials.* 2006;27:5580-5587.

61. Oral E, Wannomae K, Rowell S, Muratoglu O. Migration stability of alpha-tocopherol in irradiated UHMWPE. *Biomaterials*. 2006;27:2434-2439.

62. Oral E, Wannomae KK, Hawkins NE, Harris WH, Muratoglu OK. α-Tocopherol doped irradiated UHMWPE for high fatigue resistance and low wear. *Biomaterials.* 2004;25:5515-5522.

63. Oral E, Wannomae KK, Rowell SL, Muratoglu OK. Diffusion of vitamin E in ultra-high molecular weight polyethylene. *Biomaterials*. 2007;28:5225-5237.

64. Packer L. Protective role of vitamin E in biological systems. *Am J Clin Nutr*. 1991;53:1050S-1055S.

65. Parth M, Aust N, Lederer K. Studies on the effect of electron beam radiation on the molecular structure of ultra-high molecular weight polyethylene under the influence of alpha-tocopherol with respect to its application in medical implants. *J Mater Sci Mater Med.* 2002;13:917-921.

66. Pruitt LA. Deformation, yielding, fracture and fatigue behavior of conventional and highly

cross-linked ultra high molecular weight polyethylene. *Biomaterials.* 2005;26:905-915.

67. Reno F, Lombardi F, Cannas M. UHMWPE oxidation increases granulocyte activation: a role in tissue response after prosthesis implant. *Biomaterials.* 2003;24:2895-2900.
68. Reno F, Sabbatini M, Cannas M. Surface oxidation of UHMWPE for orthopaedic use increases apoptosis and necrosis in human granulocytes. *J Mater Sci Mater Med.* 2003;14:241-245.
69. Seguchi T, Tamura N. Mechanism of decay of alkyl radicals in irradiated polyethylene on exposure to air as studied by electron spin resonance. *J Phys Chem*. 1973;77:40-44.
70. Sheppard AJ, Pennington JA, Weihrauch JL. Analysis and distribution of vitamin E in vegetable oils and foods. In: Packer L, Fuchs J, eds. *Vitamin E in Health and Disease*. New York, NY: Marcel Dekker, Inc; 1993:9-31.
71. Shibata N, Kurtz SM, Tomita N. Advances of mechanical performance and oxidation stability in ultrahigh molecular weight polyethylene for total joint replacement: highly crosslinked and alpha-tocopherol doped. *J Biomech Sci Eng*. 2006;1:107-123.
72. Shibata N, Tomita N. The anti-oxidative properties of alpha tocopherol in gamma-irradiated UHMWPE with respect to fatigue and oxidation resistance. *Biomaterials.* 2005;26:5755-5762.
73. Shibata N, Tomita N, Onmori N, Kato K, Ikeuchi K. Defect initiation at subsurface grain boundary as a precursor of delamination in ultrahigh molecular weight polyethylene. *J Biomed Mater Res A*. 2003;67:276-284.
74. Sochart DH. Relationship of acetabular wear to osteolysis and loosening in total hip arthroplasty. *Clin Orthop Relat Res*. 1999;363:135-150.
75. Teramura S, Sakoda H, Terao T, Endo MM, Fujiwara K, Tomita N. Reduction of wear

volume from ultrahigh molecular weight polyethylene knee components by the addition of vitamin E. *J Orthop Res*. 2008;26:460-464.

76. Thomas MJ. Physiological aspects of low-density lipoprotein oxidation. *Curr Opin Lipidol.* 2000;11:297-301

77. Tomita N, Kitakura T, Onmori N, Ikada Y, Aoyama E. Prevention of fatigue cracks in ultrahigh molecular weight polyethylene joint components by the addition of vitamin E. *J Biomed Mater Res B.* 1999;48:474-478.

78. Traber MG, Sies H. Vitamin E in humans: Demand and delivery. *Ann Rev Nutr.* 1996;16:321-347.

79. Wang A, Zeng H, Yau SS, Essner A, Manely M, Dumbleton J. Wear, oxidation and mechanical properties of a sequentially irradiated and annealed UHMWPE in total joint replacement. *J Phys D Appl Phys.* 2006;39:3213-3219.

80. Wang XY, Quinn PJ. The location and function of vitamin E in membranes. *Mol Membr Biol.* 2000;17:143-156.

81. Wannomae KK, Christensen SD, Freiberg AA, Bhattacharyya S, Harris WH, Muratoglu OK. The effect of real-time aging on the oxidation and wear of highly crosslinked UHMWPE acetabular liners. *Biomaterials.* 2006;27:1980-1987.

82. Wolf C, Krivec T, Blassnig J, Lederer K, Schneider W. Examination of the suitability of alpha-tocopherol as a stabilizer for ultra-high molecular weight polyethylene used for articulating surfaces in joint endoprostheses. *J Mater Sci Mater Med*. 2002;13:185-189.

83. Wolf C, Lederer K, Muller U. Tests of biocompatibility of α-tocopherol with respect to the use as a stabilizer in ultrahigh molecular weight polyethylene for articulating surfaces in joint endoprostheses. *J Mater Sci Mater Med*. 2002;13:701-705.

84. Wolf C, Macho C, Lederer K, Accelerated ageing experiments with crosslinked and conventional ultra-high molecular weight polyethylene (UHMW-PE) stabilised with alpha-tocopherol for total joint arthroplasty. *J Mater Sci Mater Med.* 2006;17:1333-1344.

85. Wolf C, Maninger J, Lederer K, Fruhwirth-Smounig H, Gamse T, Marr R. Stabilisation of crosslinked ultra-high molecular weight polyethylene (UHMW-PE)-acetabular components with alpha-tocopherol. *J Mater Sci Mater Med*. 2006;17:1323-1331.

Table 1. Mechanical properties and fatigue strength of crosslinked UHMWPEs

UHMWPE	UTS (MPa)	EAB (%)	WF (kJ/m^2)	ΔK_i ($MPam^{1/2}$)
Conventional (25 kGy)	46 ± 2	376 ± 20	2237 ± 148	1.19 ± 0.04
First-generation crosslinked (100 kGy + melting)	39 ± 3	225 ± 9	1206 ± 67	0.54 ± 0.02
Second-generation crosslinked (100 kGy + vitamin E diffusion)	43 ± 2	256 ± 17	1240 ± 151	0.72 ± 0.02

Values are expressed as mean ± SD; UTS = Ultimate Tensile Strength; EAB = Elongation at break; WF = Work to failure; ΔK_i = Stress factor range at fatigue crack inception.

Legends

Fig. 1 A flowchart shows the processing steps for the incorporation of vitamin E into UHMWPE: blending versus diffusion.

Fig. 2A–B A diagram illustrates the oxidation scheme of UHMWPE and stabilizing mechanisms of vitamin E.

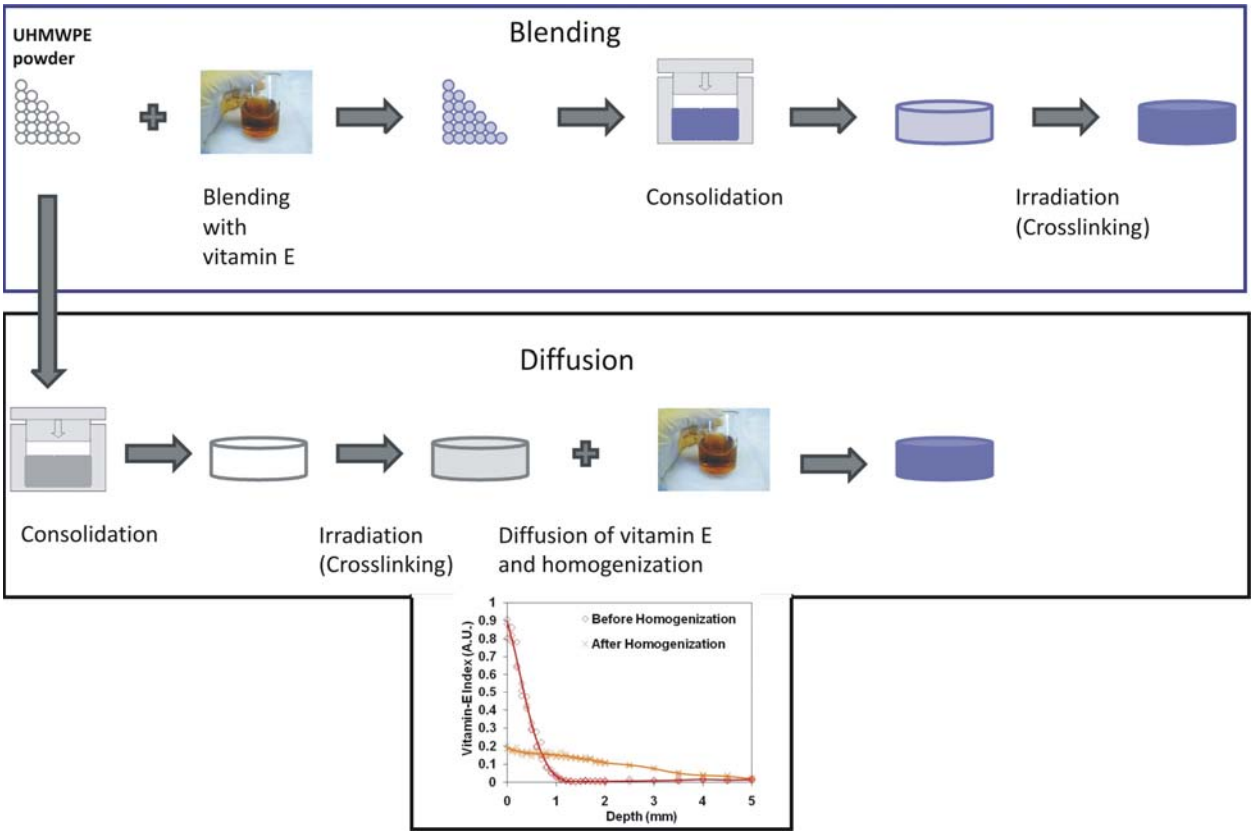
UHMWPE
powder
Blending
Blending
with
vitamin E
Consolidation
Irradiation
(Crosslinking)
Diffusion
Consolidation
Irradiation
(Crosslinking)
Diffusion of vitamin E
and homogenization
Before Homogenization
After Homogenization
Vitamin-E Index (A.U.)
Depth (mm)

Figure 1

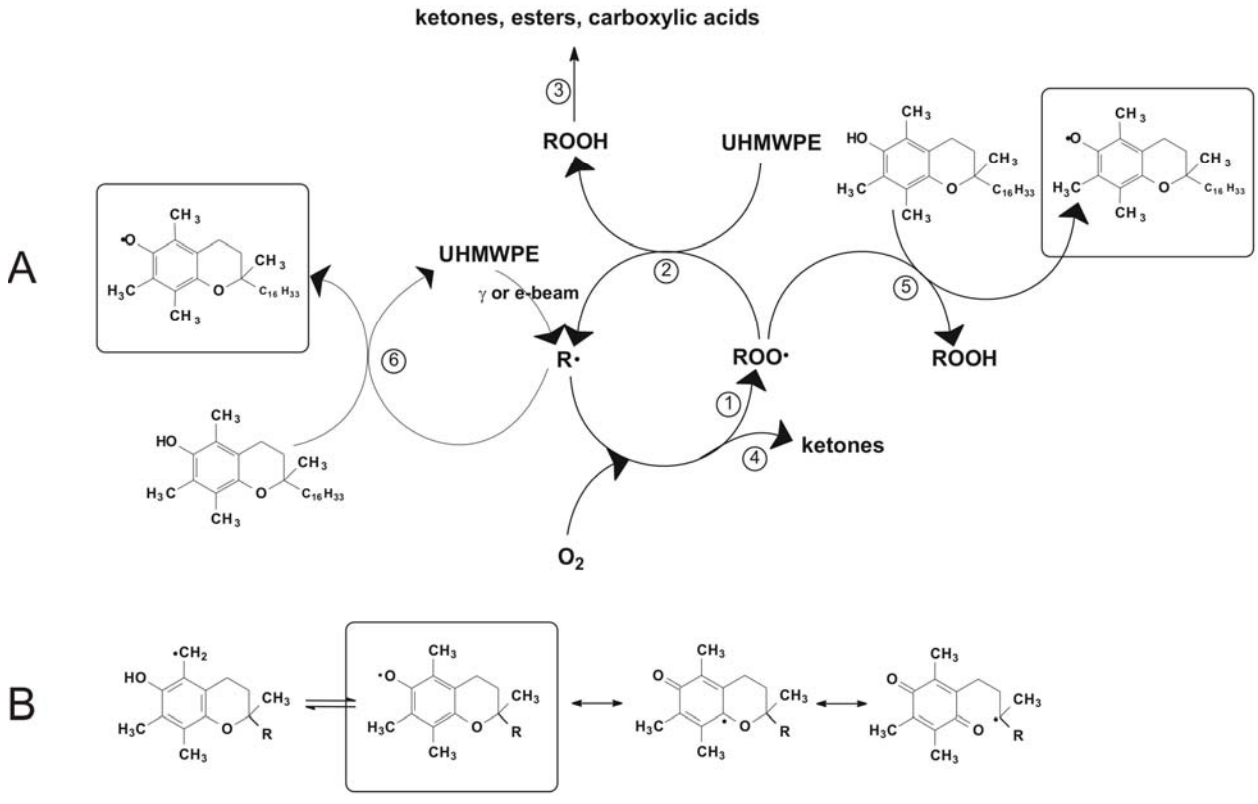
ketones, esters, carboxylic acids
ROOH
UHMWPE
UHMWPE
γ or e-beam
R·
ROO·
ROOH
ketones
O2
A
B

Figure 2