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

Running title: Vitamin E-stabilized UHMWPE for Arthroplasty

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This work was performed at Università di Torino and at Massachusetts General Hospital.

1 **Abstract**

2 *Background* Osteolysis due to wear of UHMWPE limits the longevity of joint replacement.

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

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

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

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

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

22 mechanical, wear, and oxidation properties.

23 *Clinical Relevance* Vitamin E-stabilized, irradiated UHMWPEs were recently introduced

24 clinically. The rationale behind using vitamin E and in vitro tests comparing its performance to

25 older materials is of great interest.

26 **Introduction**

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

30 Sterilization of UHMWPE with gamma radiation in air was common practice until the late
31 1990s, but it was proven to induce severe oxidation of the polymer. Oxidation and subsequent
32 embrittlement of UHMWPE decrease the abrasive wear resistance and increase the wear debris
33 associated with the polymer [9, 27, 28, 49]. Radiation crosslinking of UHMWPE reduces wear *in*
34 *vitro* [48, 50, 51, 53] and *in vivo* [29, 47]; but also induces free radicals, which can cause
35 oxidation. Postirradiation melting renders crosslinked UHMWPE oxidation resistant by allowing
36 these residual free radicals trapped in the crystalline regions [8, 40] to recombine. However, the
37 postirradiation melting step reduces the fatigue strength of irradiated UHMWPE [34], which is
38 already decreased by crosslinking [58], due to a decrease in crystallinity that accompanies
39 postirradiation melting.

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

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

48 vitamin E with UHMWPE powder before consolidation. Once consolidated, the blend can be
49 crosslinked with the use of ionizing radiation. The presence of vitamin E in UHMWPE during
50 irradiation protects the polymer from oxidation but reduces the efficiency of crosslinking [56, 57,
51 65] while the vitamin E itself is reacted; therefore, the vitamin E concentration and the
52 subsequent radiation dose must be optimized to obtain a simultaneously wear- and oxidation-
53 resistant UHMWPE. The alternative method is the diffusion of vitamin E into UHMWPE after
54 radiation crosslinking [62, 63]. The crosslinking efficiency of UHMWPE is not adversely
55 affected in this method since vitamin E is not present during irradiation. Therefore, the amount
56 of vitamin E that can be incorporated into the material is not limited by concerns for crosslink
57 density. On the other hand, the polymer remains unprotected against oxidation during irradiation
58 and following storage, until vitamin E is incorporated. Furthermore, a homogenization step is
59 required after incorporation to obtain adequate antioxidant concentration throughout the
60 implants.

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

66 **Search Strategy and Criteria**

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

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

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

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

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

92 appropriate.

93 **The Rationale in using the Antioxidant Vitamin E**

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

97 Tocopherol compounds were proposed as stabilizers for polyolefins in the 1980s [31] but did not
98 include orthopaedic implants. In 1994, Hoechst researchers (now Ticona, Kelsterbach, Germany)
99 described consolidated forms of UHMWPE with antioxidants for orthopaedic implants [7]. To
100 stabilize UHMWPE, Brach del Prever et al. [13] also described vitamin E-blended UHMWPE
101 for orthopaedics. In 1998, a gamma-sterilized UHMWPE blended with 0.1% wt% α -tocopherol
102 was developed by Sulzer (Winterthur, Switzerland) in collaboration with Lederer et al. [65, 82–
103 85]. For reasons unknown to the authors, this UHMWPE (VITASUL[®]) was never released. In
104 Japan, the research of Tomita et al. resulted in a vitamin E-blended UHMWPE for total knee
105 implants [71–73, 75, 77] (Nakashima Medical Ltd, Okayama, Japan) which have been in clinical
106 use in Japan since 2006 [71]. In 2007, ASTM published a standard specification for medical-
107 grade UHMWPE blended with vitamin E [3] followed, in 2009, by commercialization by Ticona
108 of the first vitamin E-containing UHMWPE resins for use in orthopaedics. Also in 2007, the first
109 vitamin E-diffused, irradiated UHMWPE hip implant was clinically introduced in the US
110 (Biomet, Warsaw, IN), followed by knees in 2008.

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

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

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

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

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

129 **Effects of Vitamin E on Periprosthetic Tissue**

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

135 **Discussion**

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

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

149 The main purpose of using vitamin E in UHMWPE is to prevent oxidative degradation. Due to
150 radiolytic bond scission, free radicals are produced in irradiated UHMWPE [15, 18, 20, 30, 38],
151 which react with oxygen and trigger the oxidation cascade [2, 16, 17, 20, 22, 25-27, 54, 69] (Fig.
152 2A, Reactions 1-4). Oxidation is accompanied by chain scissioning, deteriorating its mechanical
153 properties [19, 24, 43]. The stabilization mechanism of α -tocopherol (vitamin E) in UHMWPE
154 was studied [11, 20, 23, 85]. It is believed that α -tocopherol can stabilize peroxy radicals formed
155 by oxidation and can also directly react with alkyl macroradicals (Fig. 2A, Reactions 5 and 6)
156 [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

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

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

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

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

208 In conclusion, vitamin E-stabilized UHMWPEs are good alternative bearing surfaces. Vitamin E
209 protected UHMWPE from oxidative degradation *in vitro* resulting in improved mechanical and
210 wear properties. *In vitro* and animal studies did not register adverse biologic responses to vitamin
211 E-stabilized UHMWPE. The clinical performance of these materials will best be determined by
212 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 ^{13}C 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, Dalleria 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 peroxy radicals in γ -irradiated polyolefins. *Macromolecules.* 1990;23:4934-4938.
 17. Carlsson D, Dobbin C, Wiles D. Direct observations of macroperoxy 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 Polym 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.

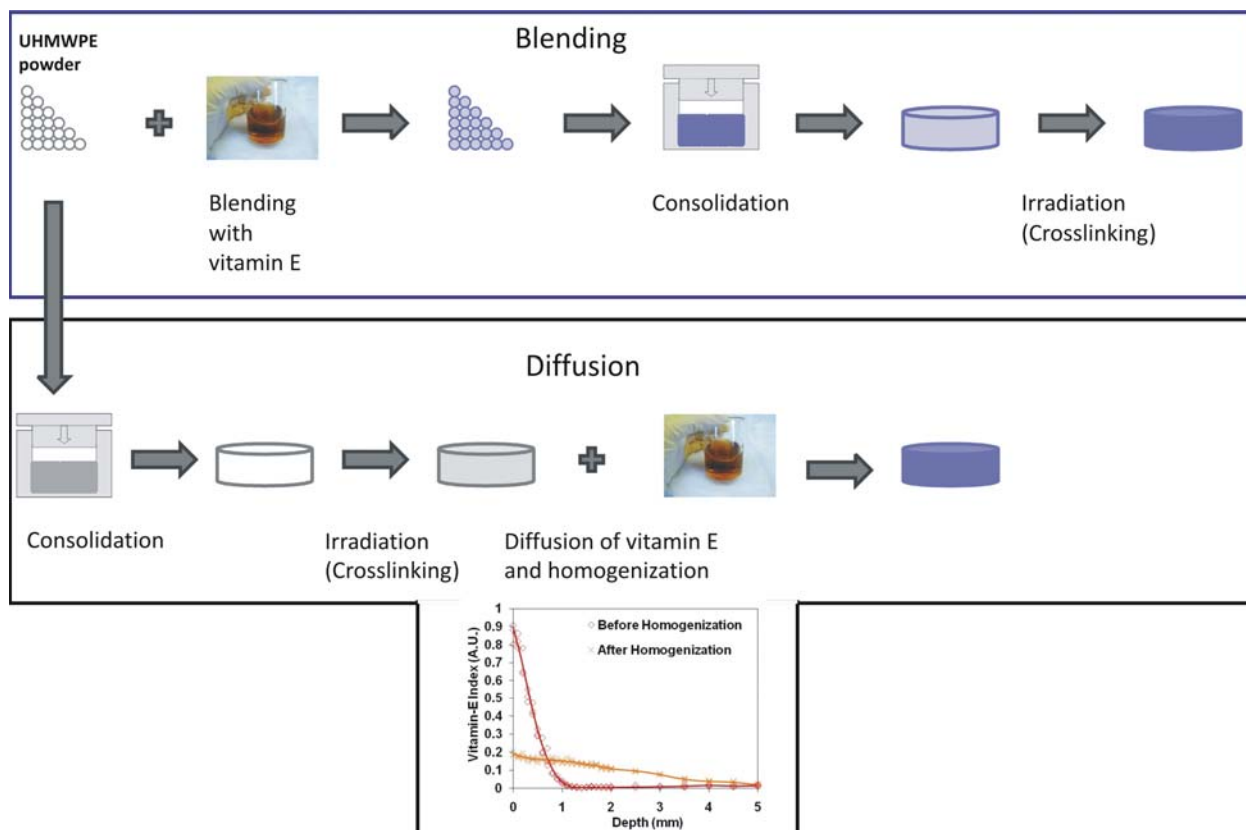


Figure 1

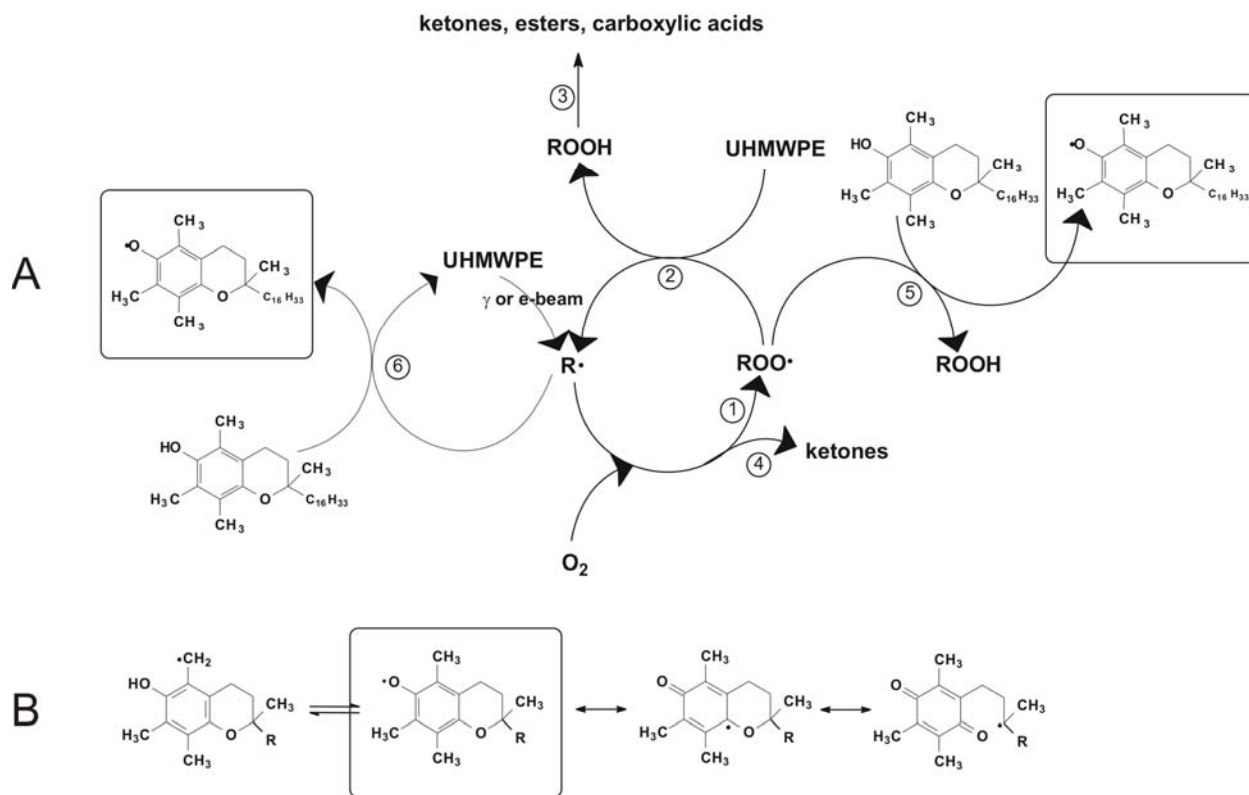


Figure 2