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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

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

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

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

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

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

The fatigue strength increases with crystallinity and decreases with crosslinking [5, 34, 45, 79, 81]. While conventional UHMWPE has high crystallinity and fatigue strength in its unaged form, its fatigue resistance is severely deteriorated due to oxidation [58, 66]. Irradiated and melted UHMWPEs have low fatigue strength, caused by crosslinking and the loss of crystallinity during melting [4, 46, 53, 62]. The fatigue strength loss due to postirradiation melting has been recovered by vitamin E stabilization due to the maintenance of crystallinity. The fatigue strength 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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Table 1. Mechanical properties and fatigue strength of crosslinked UHMWPEs

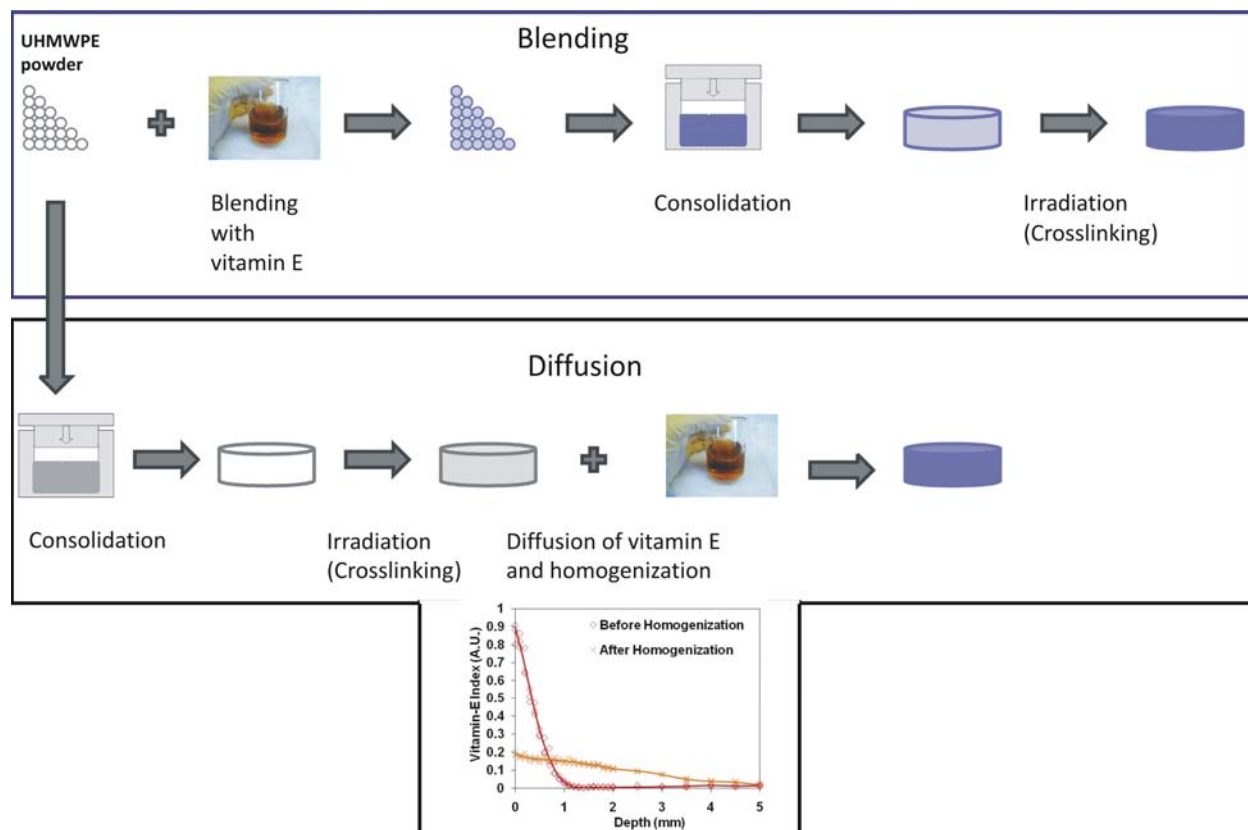
UHMWPE	UTS (MPa)	EAB (%)	WF (kJ/m ²)	ΔK_i (MPam ^{1/2})
Conventional (25 kGy)	46 ± 2	376 ± 20	2237 ± 148	1.19 ± 0.04
First-generation crosslinked (100 kGy + melting)	39 ± 3	225 ± 9	1206 ± 67	0.54 ± 0.02
Second-generation crosslinked (100 kGy + vitamin E diffusion)	43 ± 2	256 ± 17	1240 ± 151	0.72 ± 0.02

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**

