Update on UHMWPE research
From the bench to the bedside

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ABSTRACT Ultra-high molecular weight polyethylene (UHMWPE) is the key material for achieving excellent long-term results in total joint arthroplasties. Despite the fact that there has been a substantial amount of research and development over the years, new aspects of this material are still controversial and the most recent innovations have had a variable reception regarding clinical use. Advancements in conventional UHMWPE in the 1990s (nitrogen atmosphere irradiation, barrier package) were further improved by introduction of first-generation crosslinked polyethylene, as seen both from laboratory findings and clinical results. However, while clinical data on first-generation highly crosslinked polyethylene (HXLPE) showed reduced wear in the medium-term, academic and industrial research have helped to refine the material further, to overcome criticisms regarding residual oxidation and potential material fracture. Present concerns, although less nowadays, relate to the post-irradiation techniques used to stabilize the crosslinked polyethylene, namely annealing and remelting. Current topics of research interest include in vivo oxidation, second-generation highly crosslinked polyethylene, vitamin E doped or blended polyethylene, fracture mechanics, and consequences of wear. Some of these improvements derived from recent research are already available to the orthopedic community, and others will appear in the next few years. This review gives an overview of these topics, and the latest advancements are described in detail with a view to help the orthopedic surgeon make scientifically sound decisions when selecting material for total-joint implants. We conclude the review by affirming that today’s state-of-the-art material is no longer conventional UHMWPE, but HXLPE.

As a material for prostheses, polyethylene has been the key to the success of total joint replacements since it was first used by Sir John Charnley (1961), after the early failure of polytetrafluoroethylene (PTFE, Teflon). It has thus accompanied the development of many past and present designs of replacement systems for most joints. In particular, the hip and the knee have benefited from the outstanding tribological and mechanical properties of UHMWPE as an interposition material. The microstructure of polyethylene entails a semicrystalline polymer with a crystalline phase of lamellar crystals and an amorphous one of entangled molecular chains. Advantageous mechanical properties are then sustained on long molecular chains connecting different lamellae through the amorphous phase. The recognized biocompatibility of its bulk form and the outstanding material performance...
have led to the extensive use of UHMWPE. Today, it remains the essential interposition material in total knee replacements (TKRs), and from registry data it is the most frequently used material in total hip replacements (THR)s (Lidgren et al. 2005, Karrholm et al. 2006). According to registry data (CIHI 2007), two-thirds of THR bearings have been metal-on-polyethylene, without any appreciable variability from 2003 through 2006. This confirms the important role of this material in today’s implant surgery.

The long-term service of UHMWPE and thus the lifespan of the whole joint replacement system are, however, compromised by material limitations. In the hip, wear of the polyethylene has been accepted as the most prominent drawback, with subsequent generation of debris, osteolysis, and aseptic loosening of the implant (Santavirta et al. 1990, Willert et al. 1990) related to submicron particles (McKellop et al. 1995, Sabokbar et al. 2003, Goodman 2005, Konttinen et al. 2005) from different polyethylenes (Galvin et al. 2007). The main issues in the knee are not wear-related, but include material fatigue, delamination, and fracture—particularly in component designs in which there is thin material in some regions. The classical recommendation of a minimum 6- to 8-mm thickness for polyethylene components (Bartel et al. 1986) is occasionally disregarded due to design constraints, and early failure may be the consequence (Bono et al. 1994).

Irradiation of UHMWPE to sterilize the material, while improving its wear resistance due to crosslinking, introduces material degradation through an oxidation process. Oxidation induced by irradiation was found to be due to interaction between the free radicals in the material and surrounding oxygen. The result of degradation was polyethylene embrittlement. As this type of degradation happens in the subsurface material, the so-called white band (Figure 1), material failure is also fostered when mechanical stresses on the UHMWPE components, particularly in the knee, become concentrated in this region. Thus, the combination of poor material properties in the long term and high mechanical requirements sooner or later leads to prosthesis failure and revision surgery. Thus, substantial changes in the irradiation process and uncoupling of the sterilization process led to the development of highly crosslinked polyethylenes (HXLPE). Thermal treatments were incorporated to control the undesirable consequences of high-dose irradiation, although subsequent structural changes may modify mechanical properties.

In spite of these problems, which certainly raise some concern in the orthopedic community, the use of UHMWPE is justified because of the effectiveness of the material in providing not only relevant tribologic and mechanical properties, but also because of the ease with which it can be molded or machined as final components of any design, its properties as a shock absorber, its tolerance to edge loading, its forgiveness under mild malalignment, and its relatively low price—features that maintain the popularity of the material. However, disadvantages have been stressed when the accession of metal-on-metal (MOM) and ceramic-on-ceramic (COC) friction pairs of newer generations, presently in use for the hip, provide harsh competition to the conventional metal-on-UHMWPE joint. In view of these alternative bearings, where different complications may appear due to clearance (Brockett et al. 2008), ion release (Witzleb et al. 2006, Luetzner et al. 2007), or even potential fracture (Barrack et al. 2004, Popescu et al. 2008), research has been increased to meet challenges developed over the three facets of the current UHMWPE paradigm of the polyethylene over 3 axes (Figure 2). These challenges include (1) achieving enough wear resistance to avoid or delay osteolysis and (2)
ensuring the oxidative stability of the material—and all that without appreciable loss in mechanical performance (3). UHMWPE-related research has offered the orthopedic community substantial breakthroughs, but many issues remain open and under debate.

UHMWPE wear

Wear, the main disadvantage of UHMWPE, has been the driving force behind the search for alternative bearings. Early hip components showed significant adhesive wear at the hip, while abrasion and occasional delamination (Figure 3) were the main findings at the knee. Most commercial companies originally used ethylene oxide for sterilization of their components. Later, manufacturers turned to irradiation at doses between 25 and 40 kGy as a cost-effective sterilization strategy, with the advantage of reducing wear due to crosslinking. The disadvantage of this popular strategy appeared in the 1990s, when gamma irradiation in air was found to cause material oxidation due to generation of free radicals within the implants and chemical interaction with oxygen (Costa et al. 1998b), which jeopardized the assumption of wear reduction.

A more definite approach to wear reduction was to generate higher crosslink density in the amorphous part of the polyethylene using higher doses of irradiation, with the potential advantage of increasing wear resistance. While a low degree of polyethylene crosslinking was obtained at sterilization dosage, basically by gamma irradiation, extensive crosslinking could be obtained at a dose range of 50–100 kGy using gamma irradiation or high-energy beta irradiation (electron beam), to obtain the first generation of highly cross-linked polyethylene. Early precedents dated from the 1970s (Grobbelaar et al. 1978), when irradiation was recognized as an improvement for UHMWPE implants. The clinical consequences were appreciated in the long term (Kyomoto et al. 2007).

Gamma irradiation is a penetrating and inexpensive method, which is widely available but relatively slow, requiring hours to sterilize a batch. Electron beam irradiation is faster (in the order of minutes), but an accelerator is needed and it is thus not as widely available. Irradiation causes the radiolytic scission of molecular chains by cleavage of C-C and C-H bonds, generating radicals within the material. In the amorphous region, the mobility of the free radicals is higher than in the crystalline region and can recombine (leading to crosslinking, branching, and the formation of double bonds), stabilize, or react with either incoming oxygen or oxygen that is already present. In the crystalline phase, radicals are long-lasting. Due to increased crosslinking at high-dosage irradiation, early data from simulators (McKellop et al. 1999) showed dramatic increases in the wear resistance of the material to virtually no wear, comparing conventional polyethylene with...
HXLPE. The dark side of this irradiation leading to HXLPE is the induction of a complex oxidation process, which leads to deleterious degradation of the material that may jeopardize the progress made in wear control due to crosslinking. To control subsequent oxidation of the material, changes in the material based on temperature were devised—to obtain commercial HXLPE during the past decade (Table). These thermal treatments, aimed at reducing free radicals, were an attempt to minimize oxidation of UHMWPE and its consequences, and will be discussed below.

Clinical results regarding wear performance of this first generation of HXLPE are now in medium-term follow-up. A common trend of reduction in wear rate compared with conventional UHMWPE is found in many hip systems at 4 to 5 years (Dorr et al. 2005, Manning et al. 2005, Engh et al. 2006, Geerdink et al. 2006), and even at 6 years (Bragdon et al. 2007b), with marked reduction of early femoral head penetration (Krushell et al. 2005). More precise techniques such as radiostereometric analysis (RSA) showed 62% less proximal penetration and 31% less 3-dimensional penetration in prospective randomized clinical studies at 2 years (Digas et al. 2004), reducing the wear by more than 95% at 5 years (Digas et al. 2007). RSA also confirmed that, after bedding-in, no further head penetration was detected with 28- and 36-mm heads at 3 years (Bragdon et al. 2007a). The low in vivo wear rate for highly crosslinked cups was not at the expense of higher migration or less favorable clinical outcome (Rohrl et al. 2005), without any differences in other clinical respects such as range-of-motion, complications, or clinical satisfaction.

While other wear problems may raise concern (e.g. back-side wear and counterface roughness), wear is a less frequent cause of failure as observed in retrieved polyethylene components obtained at revision surgery than it was with conventional polyethylene with comparable follow-up. Based on in vivo wear data from series followed in the medium term, wear may no longer be the main issue in total joint failure. Wear remains a potential problem to be controlled, however, and the low wear rate with HXLPE should be at least matched, if not improved, by new developments in materials. This is increasingly important when more challenging cases are treated—including younger, more active, and obese patients—with wear rates that are above average. Modular designs that focus on large-diameter femoral heads to reduce other complications such as hip dislocation increase the risk of wear and failure when thin polyethylene components are used to locate large heads in small cups. Thus, wear is less of a problem than it used to be, but it may affect the survivorship of prostheses in the future if disregarded.

**UHMWPE oxidation**

The production of UHMWPE is based on the synthesis of a so-called resin (UHMWPE powder) that is extruded in a bar or compacted in a material sheet, or even molded in a sheet or in a final component. The final shape is obtained by machining the material if it is not directly molded. The fact that the material resin is not perfectly compacted caused some controversy when fusion defects were identified, but subsequent studies could not establish that these defects play a deleterious role in
wear or survivorship (Gómez-Barrena et al. 1998). Instead, oxidation was found to be associated with damage to UHMWPE components (Li et al. 1995, Sutula et al. 1995, Bell et al. 1998).

Oxidation has been highlighted recently because the disadvantage of crosslinking is the formation of free radicals arising from irradiation. The residual radicals that remain in the polyethylene after quenching lead to chain reactions and subsequent degradation of the (initially) high-quality UHMWPE implant. This is caused by residual alkyl-free radicals, which upon contact with molecular oxygen produce oxygen-induced peroxyl free radicals. These can abstract hydrogen from the polymer chain, which produces hydroperoxides and carbon-centered free radicals. At the end of the chain reactions, the material also contains degradation products such as ketones, acid groups, and esters (Costa et al. 1998b). Thus, the presence of oxygen—together with free radicals formed inside the material—may eventually lead to oxidation and degradation of the material, with loss of molecular weight and impairment of mechanical properties. This occurred when irradiation was performed in air and the packaging was not impermeable to atmospheric oxygen. The material was well on its way to oxidation, with a shelf life of over 5 years, and most manufacturers now include a last implantation date on their UHMWPE components to reduce the risk of oxidation during storage. Major advances in the field were prompted by the knowledge of the oxidation map in depth at the polyethylene components (Costa et al. 1998a) by Fourier-transformed infrared spectroscopy (FTIR) and electron spin resonance (ESR). Furthermore, an oxidation index (OI) was established (ASTM-F2102) by comparing the fingerprint of chemical species related to oxidation (carbonyl peak) and a reference species (methyl/methylene peak). However, the OI indicates the presence of oxidation but does not give information on oxidation potential in the future. This has been accomplished by studying the hydroperoxides in the implant; thus enables the performance of quality controls on the potential oxidation of a batch of UHMWPE components.

Early polyethylene components did not show any relationship between time in service and oxidation, so it was concluded that oxidation after implantation was not a major problem (Gomez-Barrena et al. 1998). However, further studies showed that UHMWPE components do become oxidized in vivo (Kurtz et al. 2005, 2006). Thus, early components, frequently based on early resins that are no longer available (RCH1000 or Himont 1900) and ethylene oxide sterilization, showed mainly wear while oxidation-related problems predominated when irradiation became more popular. Different degrees of oxidation were observed across different regions of the retrieved implants. The higher oxidation at the most vulnerable areas of the component, such as the rim at the hip and the knee, or the central post at the posterior cruciate-substituting knee, may even complicate modular junction or implant stability. In vivo oxidation may also be related to the individual patient and the oxidative potential of the joint, as oxygen dissolved in synovial fluid and surrounding tissues is present in a non-uniform manner. However, future oxidation of the material mainly depends on the potential for oxidation of the component, and can be determined by means of titratable hydroperoxides and other radical species according to ASTM 2003.

In the first generation of commercial HXLPEs, the residual free radicals after crosslinking by irradiation were originally controlled by different thermal treatments. These stabilization methods can be classified into two groups, depending on whether the stabilization temperature falls below (annealing) or above (remelting) the melting transition temperature of the polymer, which is around 137°C. Although a consensus has been established on the fact that both methods ensure wear resistance, differences may exist—in that remelting stabilizes the polymer against oxidation, whereas annealing is not fully effective. Both methods introduce changes in the microstructure, however—particularly in the crystallinity content and the lamellar size, which are more pronounced after remelting than after annealing. This generates negative effects on the capability to absorb energy before the fracture (toughness), and even on the fatigue resistance. Thus, research efforts have been placed on securing a better post-treatment that would permit the elimination of free radicals while maintaining key mechanical properties. In this scenario, sequential annealing, and the use of antioxidants such as alpha-tocopherol (vitamin E) or nitroxide (RRNO) scavengers, have been inves-
tigated to control the radicals and improve oxidation stability.

In the clinical application, attempts have been made to develop the so-called second-generation highly cross-linked UHMWPE, addressing in particular the use of sequential annealing steps (Dumbleton et al. 2006) where each step includes an irradiation process at 30 kGy followed by annealing at 130°C for 8 h. This method aims the maintenance of suitable mechanical properties observed in the annealed HXLPEs while improving the oxidation resistance by a free radical reduction in each cycle. Since the density of crosslinking obtained with each irradiation process is not modified with the annealing process, the total dosage of 90 kGy at the end of 3 sequential steps is enough to obtain HXLPE. In vitro data on this technique have confirmed that wear resistance is enhanced (Tsukamoto et al. 2008), while there is resistance to oxidation and the tensile mechanical properties of the material are maintained (Yau et al. 2005). Clinical data are not yet available.

A second powerful strategy to reduce oxidative potential while maintaining the mechanical properties of the material is based on blending of vitamin E with the resin before molding of the material, or doping of the material with vitamin E after consolidation via diffusion. Vitamin E is a fully biocompatible additive that is frequently used in the food industry, due to its antioxidant properties. Both techniques introduce vitamin E at trace concentrations (at a dose range under 500 ppm), and where crosslinking is not significantly affected (Oral et al. 2005). Consequently, the wear resistance is reduced (Teramura et al. 2008) while the microstructure changes, originated during thermal treatments, should be avoided due to the deleterious effects on UHMWPE mechanical properties. The market penetration of these second-generation HXLPE materials—and also their performance—will become apparent in due course.

**UHMWPE: material fracture**

Apart from oxidation, mechanical degradation is a key factor in the failure of UHMWPE implants. With conventional polyethylene sterilized by gamma irradiation in air, post-irradiation aging may originate both mentioned material degradation types. The increase in crystallinity content in the degraded material provokes an increase in the elastic modulus, and more critically a loss in ductility and toughness, leading to embrittlement and subsequent delamination and polyethylene fracture during service in vivo.

Highly crosslinked UHMWPE—and more specifically, post-treatment by annealing or remelting in the first generation HXLPE—affects mechanical resistance of the components as the microstructure is altered, while the degree of crosslinking is not affected. Comparing both thermal processes, remelting causes more severe changes in microstructure, particularly with a decrease in crystallinity, with derived yield and fracture stress reduction after remelting but not after annealing (Kurtz et al. 2002). In both cases, studies based on standardized tests have shown a strong reduction in HXLPE toughness compared to the un-irradiated material (Medel et al. 2007). However, annealing preserved the mechanical properties of resistance to fatigue and fracture better than remelting (Medel et al. 2007). Due to these changes, material fracture may occur, particularly in areas where the thickness of the component is less because of design considerations (modular fixation, rim, etc.). This suspicion has been fostered by early case reports of occasional early component fracture at the hip (Halley et al. 2004). Research has also been intensified regarding another mechanical property seriously affected by thermal treatments: fatigue resistance. Fatigue crack propagation after an initial defect, but also fatigue experiments without initiators (stress-life curves) show decreased fatigue strength and crack propagation resistance after the two thermal treatments, especially after remelting (Puértolas et al. 2006), when comparing the treated material to the virgin material. Changes in the fatigue resistance of crosslinked material have also been found to depend on the irradiation technique (gamma or beta) and the applied stress (Urries et al. 2004).

These mechanical findings introduce a new question. Are remelted and annealed HXLPEs equally suitable for hips and for knees or other joints? To date, this question remains unanswered. UHMWPE used in different locations is subjected to different mechanical requirements, and changes in the mechanical properties of the material.

The mechanical challenge with today’s polyethylene is to maintain the favorable wear properties
obtained with highly crosslinked material, while increasing the mechanical resistance to fracture and fatigue. However, fracture and fatigue resistance is a compromise between material and design factors, and these should be adapted to the limitations of mechanical properties.

**Future directions**

Significant efforts are being made with the so-called second-generation HXLPE, and while sequential annealing is now available for implantation, other important strategies are being developed such as the addition of oxygen scavengers—mainly vitamin E. Surface modifications are being investigated using different ion implantation techniques with N, He, C + H, C + H + Ar, or diamond-like coating (DLC) in an attempt to obtain harder and more resistant surfaces. Another nanoscale modification uses photo-induced polymerization of radicals to graft 2-methacryloyloxyethyl phosphorylcholine polymer onto the polyethylene surface (Mor et al. 2006, Kyomoto et al. 2007b, 2008). Innovations to potentially improve mechanical properties using composite materials have been reported, where multiwalled carbon nanotubes are added as a reinforcing component for different polymers and fibrous materials (Polizu et al. 2006, Cao et al. 2007). However, the biocompatibility of nanotubes is still in question (Lam et al. 2006, Zhu et al. 2007).

Significant research supports new proposals of UHMWPE and recent data reviewed above suggest that UHMWPE will probably remain the reference material in total joint replacements. Undergoing innovation will help to improve the past material and design limitations to successfully compete with alternative bearings and their drawbacks.

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