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REVIEW ARTICLE

UHMWPE for arthroplasty: past or future?

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Abstract Wear debris related osteolysis is recognised as being the main cause of failure in joint replacements based on UHMWPE inserts. However, many solutions and "new" polyethylenes have been suggested in order to address this issue. This review discusses "historical" issues associated with UHMWPE, such as oxidation, sterilization method and storage, as well as "new" topics, such as crosslinking and stabilization. The final aim is to aid orthopaedic surgeons in their selection of polyethylene inserts and in the information given to the patients. The main problem for the polymer is degradative oxidation, which is caused by the combination of the irradiation used for sterilization and oxygen, and which leads to a decrease in wear resistance and mechanical properties. Irradiation and packaging in the absence of oxygen can only reduce the oxidation, while sterilization with gas (EtO or gas plasma) is the only method that effectively eliminates it. Manufacturing processes are of great relevance to the clinical duration and must be considered by surgeons. Crosslinked polyethylene has been developed for joint inserts due to its superior wear resistance compared to conventional UHMWPE; to prevent the oxidation, crosslinked polyethylene requires post-irradiation thermal treatment, which reduces its mechanical properties and which depends on the producer. Several good clinical results from the use of crosslinked acetabular cups have reported at mid-term, while early results for knee replacements are also encouraging. Recently, the use of the antioxidant vitamin E (alpha-tocopherol) has been introduced for joint prostheses in order to prevent the oxidation of both crosslinked and noncrosslinked UHMWPE.

Keywords UHMWPE · Crosslinked · Vitamin E · Oxidation

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Introduction

Four decades after its introduction for joint arthroplasties, UHMWPE still represents the gold standard as an articulating counterface for arthroplasties, since it combines superior wear resistance along with high fracture toughness and biocompatibility compared to other polymers.

It has been demonstrated that the main factor responsible for the failure of UHMWPE in joint replacements is oxidative degradation, which decreases its mechanical properties [1–3]. Decreased abrasive wear resistance, due to oxidation, leads to the formation of wear debris and consequently to osteolysis, which has been recognized as being the main cause of failure in orthopaedic implants [1–4].

The mechanical properties are of great relevance when the UHMWPE inserts are subjected to high contact stresses that can exceed the yield stress of the UHMWPE, leading to permanent deformation and to the catastrophic rupture and failure of the implant [5].

Oxidation is strictly correlated with the sterilization method: UHMWPE components sterilized with ethylene

oxide (EtO) do not oxidize, while those sterilized using high-energy radiation in air (γ radiation or an electron beam with a dose of 25–40 kGy) are known to show high levels of oxidation [3, 6–9]. Immediate oxidation following the high-energy treatment results in chain scission in the UHMWPE, thus immediately decreasing its molecular mass and therefore its mechanical properties. Moreover, the oxidative degradation proceeds during storage and in vivo, thus further exacerbating the problem [8–10]. Several methods have been applied to reduce the impact of the oxidation on the duration of the implant: thicker inserts have been recommended, the designs of the implants have been improved, and the use of ionizing radiations in air for sterilization has been avoided.

In 1998, in the Safety Notice 9816–1998 (*UHMWPE Components of Joint Replacement Implants*), the British Medical Devices Agency established that UHMWPE components should not be used if they are over five years old and if they have passed their indicated expiry date. In 2005, the Italian Ministero della Salute (see DGFDM/III/7101/P/I.1.c.r. 8/3/2005) recommended that the use of implants sterilized in the presence of oxygen should be avoided.

Recently, radiation crosslinking of the UHMWPE has been applied as answer to the main problem, wear debris related osteolysis [11]. Alternative bearing materials, such as ceramics and metals, are associated with concerns about biocompatibility, duration, carcinogenicity, revision difficulties and costs, which explains why joint replacements using polyethylene inserts are still the ones mostly commonly used in orthopaedics.

This review discusses the "historical" issues associated with polyethylene, such as oxidation, sterilization method and storage, as well as "new" topics, such as crosslinking and stabilization. The final aim is to aid the orthopaedic surgeons in the selection of the implant and polyethylene insert, the information given to the patient, and when signing contracts.

UHMWPE: the material and its properties

Medical-grade polyethylene (UHMWPE with an average molecular mass of >2,000,000 a.m.u.) is a semicrystalline polymer that can be depicted as a set of ordered regions (crystalline lamellae) embedded in a disordered amorphous phase [12]. The degree of crystallinity is an important parameter: higher crystallinity gives a larger modulus of elasticity, superior yield strength, improved resistance to creep deformation and enhanced fatigue strength, all of which are desirable properties for joint components. The degree of crystallinity, within the range commonly used for medical-grade UHMWPE, does not substantially affect the wear resistance, which is related to the molecular mass [3]. The resistance to creep deformation of the UHMWPE is important to evaluations of the relative contribution of deformation or wear to the penetration of the femoral head into the insert. The fatigue strength is also very important, since it relates to the ability of UHMWPE to resist cyclic damage modes, which are very common in knee components and also in hip components, although prevalent in the rims of malpositioned cups.

Medical-grade UHMWPE orthopaedic implants are machined from stocks and sheets made from UHMWPE powders by compression moulding or ram extrusion and subsequent annealing [1]; the ASTM F 648-07 designation (standard specification for UHMWPE powder and fabricated form for surgical implants) defines the characteristics required for medical-grade orthopaedic UHMWPE: density excluded, there are no upper limits on any of the starting parameters, and the characteristics of the material are determined before processing and sterilization. It is clear that commercially available UHMWPE inserts can be very different from each other after processing, sterilization and packaging, which is very relevant to their clinical applications.

Oxidative degradation

When a polymeric material is exposed to a stronger energy than that of the chemical bonds, the consequence is bond scission and the formation of free radicals; this chain fragmentation modifies the mechanical properties of the polymer [13]. High-energy radiation (γ-rays, X-rays and electron beams), heat and strong mechanical stress are all examples of energies that can break chemical bonds. Even if only a single C–C bond of the polymer chain in UHMWPE is broken and two $^{\cdot}CH_2-$ radicals are formed, the molecular mass decreases; as a consequence, many of the chemical and physical properties of the polymer begin to worsen.

In orthopaedics, this issue is mainly associated with the γ radiation and electron beams commonly used during sterilization, and the process is known as degradation. If oxygen is present when the degradation process occurs, it is called oxidative degradation (oxidation). Once the oxidation process (which is also a function of the temperature) has been initiated, it cannot be interrupted, and its rate increases continuously with a series of reactions that involve free radicals and oxygen. The extent of the oxidative process depends on the number of radicals formed during sterilization and on the amount of oxygen, which can be either atmospheric, present at the sterilization, or it can be oxygen that penetrated by diffusion into the polymer during processing and storage or while the joint is being

used in vivo. Therefore, the oxidative degradation can continue during storage and in vivo implantation [14, 15].

Sterilization and packaging issues

Sterilization of UHMWPE components deserves a special mention since, as described above, it is known that this process can modify the mechanical and wear properties of UHMWPE [1, 6–9, 16].

Obviously, finished UHMWPE orthopaedic components must undergo sterilization before clinical use. High-energy radiation represents the most common sterilization technique: the source of γ radiation is the decay of an unstable ^{60}Co nucleus, while electron beams are generated from the electrons emitted by a thermally excited tungsten filament, which are accelerated by electric fields. The dose absorbed by the material during sterilization depends on the geometry of the sample and its position in relation to the source. The electron beam is easier to control and requires a shorter period of treatment (seconds).

UHMWPE components are usually stored on the shelf for long durations prior to implantation (periods of six months or longer); in addition, UHMWPE inserts of total joint replacements have historically been packaged in air and thereafter sterilized by γ radiation. It is well established that such irradiation, as well as electron beam irradiation, causes crosslinking, chain scission and long-term oxidative degradation of polyethylene, and that long-term post-irradiation aging can have detrimental effects on the morphology and mechanical properties of UHMWPE [1, 14, 16, 17].

Macroscopic evidence for the oxidative degradation caused by γ-sterilization in air can be seen on a UHMWPE section, where it looks like a white halo and is called the "crown effect" or white band; this is a zone where a critical molecular mass decrease has occurred, and which therefore has very low mechanical properties, resulting in the well-known effects of delamination and fracture that are typical of such components [18]. It was previously erroneously believed that oxidation was associated with fatigue damage mechanisms; however, it has since been established that there is a correlation between the rate of abrasive wear and the post-oxidative reduction in molecular weight [2, 3].

In response to these oxidation issues, some manufacturers now sterilize UHMWPE using non-radiation-based methods, such as ethylene oxide (EtO) or (more recently) gas plasma sterilization (GP); sterilization by steam is not feasible because the temperatures required—about 135°C—could result in modifications to the material.

EtO is used to sterilize UHMWPE components sealed in gas permeable packages. The treatment is continued for as long as needed for the gas to diffuse inside the containers; the packages are then left under vacuum for enough time to allow the complete elimination of EtO. Prosthetic UHMWPE sterilized with EtO does not undergo any variation in chemical and physical structure.

Gas plasma is a surface sterilization method based on the action of ionized gas (i.e., hydrogen peroxide or peracetic acid), which deactivates biological organisms. Commercially available GP sterilization methods are usually carried out at low temperatures (below 50°C) and do not significantly affect the physical, chemical and mechanical properties of UHMWPE.

A detailed mechanism for the oxidation for orthopaedic implants has been described, and it has been demonstrated that oxidation can also occur under certain conditions in ethylene oxide sterilized UHMWPE, albeit to a much smaller extent than for γ-radiation-sterilized UHMWPE. However, this phenomenon has been related to the presence in the pristine resin of calcium stearate, which is no longer used in contemporary medical-grade UHMWPE [7–9].

As another response to long-term post-irradiation ageing and oxidation, some manufacturers have recently shifted to sterilization with high-energy radiation performed in vacuum or under inert gases (nitrogen or argon).

The material used for the envelope or packaging itself—which can classified into the following categories: (a) gas-permeable packaging; (b) polymer barrier packaging, and; (c) aluminium barrier packaging—is clearly important.

The gas-permeable packaging used is usually a PET (polyethylene terephthalate) blister with a Tyvek® cover, which allows the diffusion of gases (oxygen included); it is therefore indicated for EtO or gas plasma sterilization, but it does not prevent oxidative degradation when used for radiation sterilization.

Polymer barrier packaging is based on a series of multilayer plastic bags with gas-barrier properties, and therefore has a limited but measurable permeability to oxygen; it does not exclude the presence of oxygen during and after the radiation sterilization.

Aluminium barrier packaging is virtually impermeable to gases, and so only oxygen already dissolved in the UHMWPE prior to irradiation can be present.

A complete absence of sterilization-induced oxidation can only be guaranteed by gas sterilization, particularly because the extent to which in vivo oxidation rates affect the clinical performance of conventional UHMWPE packaged in low-oxygen environments and then sterilized using γ radiation is still unclear.

Wear and debris

Abrasion wear is the process of removing parts of a material from the surface during reciprocal movement

along another surface with greater hardness. In orthopaedic joint components, the UHMWPE is removed because the interactions of its chains are weak compared to those between the metal or ceramic atoms in femoral head and femoral knee components.

The particles of polyethylene removed induce aseptic loosening, through a mechanism involving the formation of reactive tissue and consequently osteolysis, which has been recognized as being the main cause of implant failure [4, 19]. The exact immune reaction that occurs in periprosthetic osteolysis of joint replacements is still unclear: it is known that several types of immune processes appear to be relevant. A foreign-body, granulomatous response to UHMWPE particles denotes a nonspecific chronic inflammatory reaction involving activated mononucleated macrophages and fibroblasts but few T lymphocytes [20].

The activation of macrophages has been related to the size, shape, volume and number of radiation-sterilized UHMWPE debris particles: those 0.3–10 μm in size are phagocytable and are therefore the most biologically active [21, 22]. An influence of the chemical composition of the UHMWPE particles has recently been suggested: the reactivity might be related to the composition of the surfaces of the particles themselves (superficial reactivity), and in particular to the level of oxidation of the UHMWPE itself [23, 24]. Oxidized particles from γ-irradiated UHMWPE inserts would be more effective at activating the macrophages than the unoxidized particles from EtO-sterilized UHMWPE. The surface reactivity of the particles also depends on the properties of the absorbed molecules, their hydrophilic/phobic character, and the release of radicals which can react with human tissues [24]. Many modifications can occur: freshly detached particles are different from particles that have been in contact with biological tissues for some time [23], and the debris may be not only fragments of UHMWPE but fragments of an oxidized, lower molecular mass polyethylene [24].

Actually, catastrophic failures due to extreme wear and heavy oxidation are quite uncommon; nevertheless, wear is also a function of time, and therefore abrasion and the production of abraded particles remains a problem in young, active patients with long life expectancies. Crosslinked UHMWPE appears to be the answer to the wear issue.

Crosslinked UHMWPE

Polymer "crosslinking" is a well-known process in chemistry: it involves the linking of two or more molecular chains through chemical covalent bonds. Amongst the several methods that can be employed to achieve this, crosslinking is obtained in orthopaedics by high-energy irradiation, which leads to the formation of radical species that react with chain imperfections and other radicals. Such reactions result in polymer chains with stable C–C chemical bonds, theoretically increasing the molecular mass to infinity [13, 25]. Basically, crosslinked UHMWPE (XPE) has much better wear resistance and decreased mechanical properties compared to conventional UHMWPE [26].

The potential benefits of reduced particulate wear generation led to the introduction of crosslinked UHMWPE in orthopaedics during the late 1970s [27]. Following laboratory wear tests that confirmed the theoretical decrease in the wear rate, XPE has been widely used since the late 1990s as a bearing surface for orthopaedic implants [28, 29].

Medical-grade crosslinked polyethylenes for orthopaedics are processed with radiation doses of 60–100 kGy at different temperatures and are then thermally treated to remove residual radicals. These processes vary depending on the manufacturer. The thermal treatment involves ''remelting'' when the temperature is above the melting point (150°C) and ''annealing'' when below. One of the major advantages of post-irradiation thermal treatment is that it also imparts oxidation resistance to the material, due to the removal of detectable amounts of residual free radicals and hydroperoxides. Nevertheless, only melting is completely effective at eliminating the residual free radicals and the hydroperoxides formed during radiation sterilization, and therefore at preserving UHMWPE from radiation-related oxidative degradation [30, 31]. In contrast, the problem with complete melting is the resulting deterioration in mechanical properties like elongation-to-break, tensile modulus, tensile strength [28, 32] and J-integral fracture toughness [32], and resistance to fatigue crack propagation [33–37].

UHMWPE melting erases the thermal history induced by ram extrusion and compression moulding; since cooling or recrystallization after melting are carried out without applying any pressure, the process decreases the overall degree of crystallinity of radiation-crosslinked UHMWPE. In theory, one possible method of restoring crystallinity in crosslinked UHMWPE would be to utilize high-pressure crystallization, but this is not possible using current processing technology.

Several new methods are now currently used in order to resolve the crystallization issue and to impart higher mechanical properties to the crosslinked polyethylene, like annealing close to but below the melting temperature of crosslinked UHMWPE [37], solid-state deformation followed by annealing [38], and repetitive subsequent annealings. All of these processes have the advantage of substantially decreasing the free radical concentration. However, detectable levels of free radicals still persist in the material, and so it still has a lower resistance to

oxidation than remelted crosslinked UHMWPE; this is undesirable, since it would expose the material to degradative oxidation, which can also be very effective at causing dramatic insert failures for crosslinked materials.

In conclusion, crosslinked polyethylenes can have very different mechanical properties due to the different crosslinking processes that are possible, while UHMWPE, if processed and sterilized correctly, always has the mechanical property values required by the ASTM. Despite the variability, it should be noted that crosslinked UHMWPE inserts have better mechanical properties than the standard required. The mechanical properties, and the resistance to fatigue crack propagation in particular, are important in joint component applications, and so it is still unclear whether the benefits of wear resistance due to crosslinking would outweigh the risk of fatigue failure over the long term; to our knowledge, there are no reports of fatigue failures of crosslinked implants. Concerns remain about the oxidation rate of the nonremelted crosslinked inserts.

It has been demonstrated that wear particles generated by crosslinked polyethylenes play a different role in biological reactions than those generated by conventional polymers, although why this is so is not clearly understood. Crosslinking would generate a larger percentage of small particles [39, 40], which would lead to a higher release of tumor necrosis factor-alpha and therefore to a higher reactivity [41]. However, crosslinked and conventional polyethylenes would cause similar levels of cytokines, IL-6, IL-1α, IL-1β and TNF-α [42], and the degree of crosslinking-related osteolysis would be reduced compared to conventional osteolysis [43]. Regardless, radiation-crosslinked UHMWPE acetabular cups and tibial plateaus are now in clinical use, and it is still to be determined whether they will lead to a higher survivorship over the long term compared to conventional noncrosslinked UHMWPE, as expected.

Another advantage of using crosslinked polyethylene is the possibility, thanks to its resistance to abrasion, of reducing the thickness of the insert and consequently using larger femoral heads in THA, which reduce the dislocation rate and improve range of motion [44]. In contrast, fractures of the superior rim of the cup have been correlated to excessive thinness of the polyethylene [45].

Actually, assessments of the clinical behaviour of crosslinked UHMWPE depend on radiographic measurement analyses: these demonstrate an initial penetration of the femoral head into the crosslinked insert, followed by a decreased penetration after the first year compared to conventional inserts. The initial penetration observed in crosslinked inserts, in vivo and not in laboratory wear tests, has been explained as creep deformation and not as wear. The results indicate decreased wear for crosslinked UHMWPE compared to conventional UHMWPE. To our knowledge, most studies have reported good crosslinked insert performance regardless of the manufacturer [11, 46–51]; moreover, there is no evidence of large-scale failures of knee or hip implants with crosslinked components due to particle-induced osteolysis, only sporadic case reports [52] of fatigue failure [45, 53].

Surface cracking, abrasion, scratching and pitting have been reported on the articular surfaces of retrieved crosslinked acetabular liners, and these features have been explained as being due to the decreased ductility and fatigue resistance associated with extensive crosslinking [53]. In contrast, some studies state that the abovementioned microscopic damage to the surfaces of retrieved crosslinked inserts is a sign of load-induced plastic deformation of the surface, not an early sign of a future failure [54–57].

One final unclear issue regarding crosslinked polyethylene is its third-body wear resistance: it has been supposed that XPE, due to its micromorphology, could be less resistant to such wear than UHMWPE, which may be a problem when third bodies like bone fragments are present in revisions or microparticles of PMMA are present in cemented implants. Nevertheless, to our knowledge, there are no laboratory wear tests that report such a problem, and there are no reports of failures related to the presence of third bodies, so more studies are needed to clearly understand this issue.

Future directions and stabilization against oxidation

In the near future, we can expect radiation crosslinking processes to be optimized to improve the resistance to particulate wear without significantly decreasing mechanical properties [58]; these developments are of particular importance for knee arthroplasties, where high cyclic stresses can lead to fatigue wear mechanisms.

Despite the several thermal treatments proposed, as discussed above, oxidation can be a problem for crosslinked UHMWPE inserts, although to a degree that depends on the processing procedure [38, 49].

In several applications, such as food packaging and preservation, polyethylene is currently stabilized against oxidative degradation by adding a suitable biocompatible stabilizer: vitamin E or (better) its synthetic derivative, alpha-tocopherol [59, 60]. Therefore, in order to combat oxidation in irradiated crosslinked UHMWPE, the use of a biocompatible and nontoxic antioxidant such as vitamin E has also been proposed [61]. This would lead to the double advantage of preventing the long-term oxidation associated with the presence of free radicals and preserving mechanical properties [62–65]; nevertheless, the use of any

additive, including antioxidants, in medical-grade UHMWPE (ASTM F648) is prohibited, which has hindered the use of vitamin E in joint replacements for a long time.

A new standard related to the conditions required for the addition of vitamin E has been approved (ASTM Standard F 2695 2007: *Standard Specification for Ultra-High Molecular Weight Polyethylene Powder Blended With Alpha-Tocopherol [Vitamin E] and Fabricated Forms for Surgical Implant Applications*, ASTM International, West Conshohocken, PA, USA, see http://www.astm.org), even though the old regulation has not yet been cancelled.

Recently, given the efficacy of alpha-tocopherol in stabilizing UHMWPE against oxidative degradation, and due to its proven biocompatibility, vitamin E has been introduced at an experimental level by the FDA (regulation 510K) in order to develop orthopaedic implants that are resistant to oxidation [60, 66].

Many manufacturers are now developing crosslinked UHMWPE inserts containing vitamin E; however, some new concerns have arisen, in particular about the method by which the antioxidant is introduced into the polymer: it can be added before the irradiation [63, 67], during moulding or extrusion; or by diffusion after irradiation [62]. The disadvantages of these two methods are that, in the former, crosslinking is suppressed to a minor degree during irradiation, and in the latter, it is difficult to control the concentration and the distribution of the antioxidant. In both cases, the hypothesized advantage is that the vitamin E protects the crosslinked polyethylene against oxidation [68, 69]. At the moment, the elimination of post-irradiation melting in order to optimize the mechanical properties is just a fascinating hypothesis.

However, it must be noted that the use of vitamin E does not completely suppress oxidation during sterilization with high-energy radiation; it only retards the process. It should also be underlined that, even though the safety and biocompatibility of vitamin E is well known, this is still an additive with no clinical history in joint replacement components.

Conclusions

UHMWPE liners can serve well as bearing surfaces for joint replacements. In particular, if the sterilization and packaging processes are carried out correctly, the material has tribological and mechanical properties that can ensure long in vivo service as an articulation, greatly reduced wear, and particle biocompatibility, all without causing catastrophic ruptures and tissue reactions. In fact, to our knowledge, there are no reports of failures related to the mechanical properties of components made of EtO-sterilized UHMWPE and used for arthroplasties. Since the processing techniques play a fundamental role in the durability of implants, the manufacturer could be considered to be the main agent responsible implant durability.

For the same reasons, orthopaedic surgeons must pay careful attention to the processes to which the insert have been subjected: for example, γ and electron beam irradiation can further produce oxidation, even when conducted in the absence of oxygen. The full processing history (sterilization, packaging, time of storage) of the implant, an indication of its integrity, must be present by law on the labels accompanying it, and must be considered when selecting the joint prosthesis, both before and during surgery. In fact, in cases where the surgeon is called upon to explain his choice of implant, a complete knowledge of the materials involved and the reasons for choosing the particular implant selected can be helpful.

New and promising materials, like crosslinked and vitamin E charged polyethylenes, are now considered safe but innovative and are therefore handled cautiously: many in vitro tests and several in vivo demonstrations have confirmed the validity of these materials, but it is important to remember that they do not yet have long-term clinical histories.

Open issues include: the role of debris of crosslinked polyethylene, the quantity and reactivity of which are still to be elucidated, the long-term behaviour of crosslinked material under the kinds of mechanical stresses encountered in knee arthroplasties, and the interaction of vitamin E with the surrounding tissues as well as its long-term effects on crosslinked and noncrosslinked polyethylene.

In conclusion, surgeons can use the innovative and promising products available on the market, but they should also be aware that some products have been tested over the long term and are safe for clinical use while others have short clinical histories and require caution.

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