Polymeric Biomaterials for Load-bearing Medical Devices

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This paper aims to give a broad overview of the challenges that are faced in load-bearing medical devices and focuses specifically on the challenges faced in utilizing polymeric materials in such applications. Three specific cases are given in the field of polymeric biomaterials. These cases build in complexity and initiate with examination of the evolution of intravascular catheter design in which the materials, properties, and processing have been optimized to develop a system that can be used in an angioplasty procedure with little concern of clinical failure.

INTRODUCTION

In the field of biomaterials there are a number of challenges that must be addressed for successful design of a medical implant.[1–5] First, all biomaterials must be biocompatible and, unless the material is designed to degrade in the body, it must offer long-term resistance to biological attack in vivo. Biocompatibility is a complex issue in that both the composition and size scale of the biomaterial can dictate the cellular response in vivo. Bulk materials that are considered biocompatible can become bioactive or trigger an inflammatory response if the material is present in small enough particles to be ingested by macrophages or elicit cellular interactions.[6,7] Many implants can be susceptible to premature failures due to biological attack, and this limits the choice of materials that can be safely used in the body. In fact, much of the material evolution in metals used in the body is built upon the improvement of corrosion resistance. Load-bearing devices face the challenge of a coupled effect between the structural requirements of the implant and the aggressive environment of the body. Many metallic systems employed today are still susceptible to stress corrosion cracking or crevice corrosion when the stress state, implant design, and biological environment are coupled.[8] Polymers offer the benefit of being intrinsically resistant to environmental attack; however, polymeric biomaterials face unique demands when utilized in load-bearing medical devices in that the mechanical stresses in which they function often put them at direct risk for yield, fatigue, wear, creep, and fracture. Figure 1 illustrates how many polymers are loaded to a stress value near their yield strength when subjected to the physiological stress state of the implant; this is in contrast to metals and ceramics that typically operate well below their strength levels.

Medical devices composed of polymers, like other biomaterial systems, are not immune to mechanically induced biological failures.[1,2] The functional demands placed on an implant may elicit mechanical damage that is sufficient to liberate particulates or other constituents that can trigger a chronic inflammatory response in vivo, ultimately leading to the biological failure of the device. The performance of a medical device is quite complicated as there are several contributing and related factors, including the implant design, material selection, structural requirements of the device, processing or manufacturing modality of the implant, and clinical issues. Figure 2 illustrates the contributing factors that affect device performance. These issues contribute to

How would you…

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Medical implant design is a multifactorial process involving the interplay of material structure and properties, processing, biocompatibility concerns, and long-term mechanical reliability. Design iterations may have unforeseen clinical consequences that necessitate further analysis or development. This paper introduces biomedical polymers and describes the incremental design evolution and material optimization of three polymeric medical devices.

…describe this work to a materials science and engineering professional with no experience in your technical specialty?

Load-bearing polymeric medical implants can be expected to function for decades, while experiencing stresses near or beyond their strength. Further, mechanical damage can release particulate debris or leached constituents that may elicit a severe immune response from the body. The interplay of mechanical, biological, and material performance in a medical implant is sophisticated, particularly given that the environment in the body is difficult to model. This paper describes the design evolution of and performance trade-offs in three polymeric medical implant systems.

…describe this work to a layperson?

Medical implants made of polymers (plastics) are often subjected to relatively severe forces. These forces may break down the material over time, possibly causing the implant to break or resulting in a biological reaction that causes the body to reject the implant. This paper describes the design evolution of three polymeric medical implant systems, based on incremental improvement and trade-offs.

a multifactorial problem that often requires numerous iterations in the device design with a continuous feedback process that relies on assessment of device performance in its clinical application. An additional challenge in the medical device field is that it is extremely difficult to model the actual in-vivo conditions and thus bench tests rarely predict clinical performance of the implant.

In the past several decades a plethora of research has addressed the role of processing and microstructure on mechanical behavior of polymers that are utilized in the body.[1] However, a paucity of studies have addressed the intricate relationships that exist between structure, properties, processing, clinical conditions, and device design. Thus while some aspects of medical device design are well established others remain inchoate. Often device manufacturers seek to improve a specific property or function of a device without appreciating the tradeoffs in other areas of performance. For instance, a change in material can result in unpredicted failures of an implant if the device design is not updated and/or verified to meet its functional requirements. In general any time one factor is shifted there is a tradeoff elsewhere.

Predicting the ultimate consequences of performance tradeoffs is rarely a simple task, given the complex interplay of variables, and yet it is critical to the development of devices that offer long-term performance in vivo. Thus, there is a need for a fundamental, mechanistic understanding of polymeric biomaterials science and how it is tied to processing, properties, device design, and clinical performance. This work addresses the general functional requirements for a number of medical device applications utilizing polymers. Three specific examples in the medical device field are examined where the design, material, process, or properties have evolved in a systematic way.

MEDICAL POLYMERS IN LOAD-BEARING DEVICES

Medical polymers are used in a broad range of applications including tissue repair and replacement, drug delivery, and wound healing.[1] Polymers are capable of a wide range of structural properties that depend on backbone structure, molecular weight, entanglement density, degree of crystallinity, and degree of crosslinking.[9] In general, polymers exhibit time-dependent mechanical behavior and are known to be viscoelastic. For example, the elastic modulus and yield strength of a polymer generally increases with increasing strain rate while the strain to failure typically decreases with increased loading rates. Similarly, sustained loads can result in time-dependent strain or creep in polymers. Time-dependent material properties render the prediction of in-vivo performance challenging, particularly when the load conditions become complex. In fact, load-bearing medical devices often subject the polymer components to their limits of yield, fracture, wear, and fatigue resistance. Table I presents several applications of polymers in load-bearing implants.

Table I. Examples of Polymers used in Load-bearing Medical Devices

Application	Devices	Polymers	Performance Requirements
Vascular	Balloons/catheters	Nylon/polyester/HDPE	Rupture, flexibility, friction
	grafts	e-PTFE	compliance, tissue integration
Soft Tissues	Suture anchors	PLDLA, PLLA, PEEK	Resilience, strength
	sutures	Polyester, PLLA, PGA	Tensile strength
	Breast implants	Silicone	Burst strength, leak resistance
Dental	Crown/filling	Acrylic resins	Wear, fatigue, thermal stress
Orthopedics	Total joint replacements	UHMWPE	Fracture, wear, fatigue, creep
	bone cement	PMMA/PS	Interface fracture, fatigue

STRUCTURE-PROPERTY-DESIGN RELATIONSHIPS

Understanding structure-property-design relationships is essential for the successful performance of a medical implant. Yet, implants often undergo iterative changes in design, materials selection, and processing, resulting from the study of their overall clinical performance. Sometimes challenges can be adequately addressed in the laboratory, but often feedback from the clinical use of the device is key to understanding the factors at play. In this section we detail three cases where the design, material, process, or functional properties have evolved in a systematic way in the medical device industry. These cases include an intravascular balloon catheter in which the materials, properties, and processing have been optimized to develop a system that can be used in an angioplasty procedure with little concern of clinical failure; silicone breast implants, which have utilized a shift in design and materials to develop more robust and leak-resistant implants; and total hip replacements, where a shift in material properties without a change in design enabled catastrophic fracture of the polymer bearing component.

Intravascular Balloon Catheters

Intravascular catheters are widely used in both diagnostic and interventional procedures. Balloon catheters are probably best known for their clinical success in coronary angioplasty.[10] In such applications the balloon at the distal end of a catheter is inflated to open an occluded blood vessel afflicted with heart disease. Such systems are also used in stent deployment and Figure 3 shows a rendition of a catheter balloon used in the deployment of a coronary stent for the repair of an occluded artery.[11] There are a few important functional requirements for the polymeric balloon: its profile must be small enough to be navigated through the coronary arteries; it must provide sufficient radial force to open an occluded vessel, deploy a stent, or in some instances it may need to exert a radial force on a highly calcified plaque; and it must withstand the inflation pressures necessary for the clinical procedure without rupturing. For these reasons most polymeric catheter balloons are typically made of polyester or nylon due to their tensile strengths and ease of processing.

An intravascular balloon catheter system used in coronary angioplasty is typically inserted through the femoral artery and then it is navigated through the tortuous vasculature to its final destination in the heart. Due to the anatomical requirements there are a number of unique functional requirements for intravascular catheter systems. Intravascular catheters are generally construct-

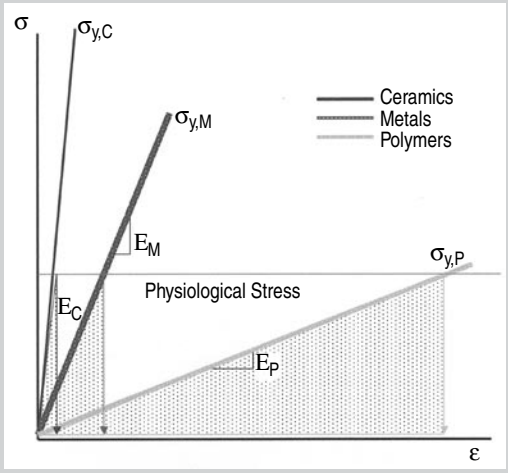


Figure 1. A schematic illustration showing relative elastic range of ceramics, metals, and polymers in the realm of the applied physiological stress on the implant.

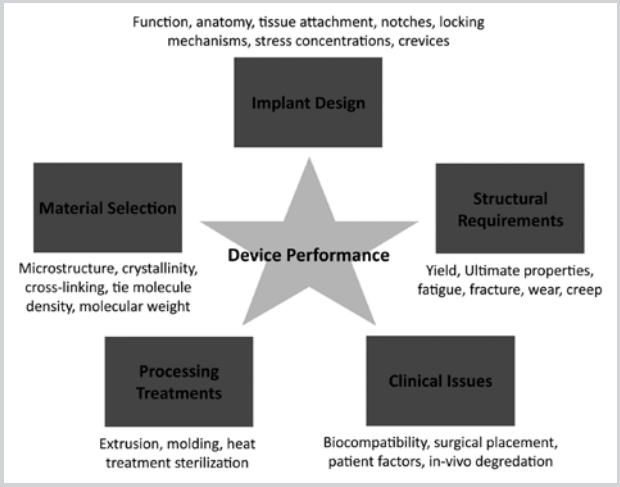


Figure 2. A schematic illustration showing the complex factors contributing to medical device performance.

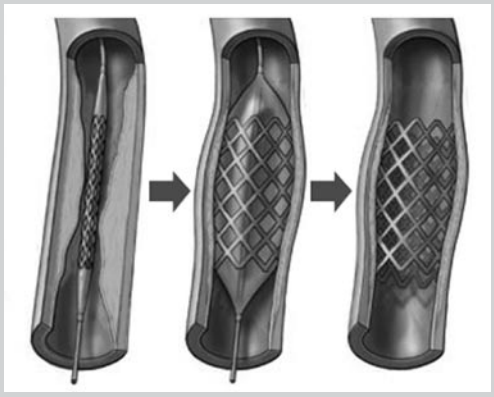
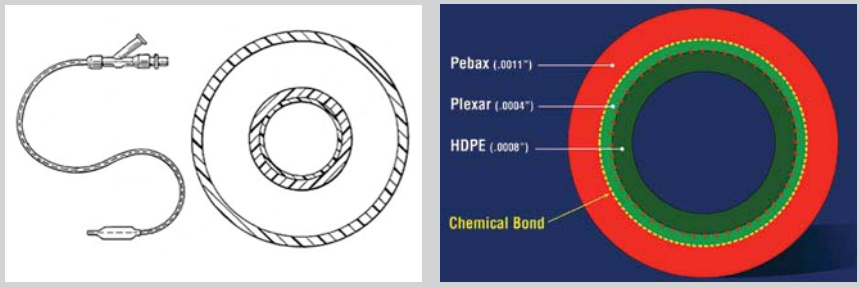


Figure 3. A polymer balloon used in deployment of a coronary stent.



a **b**

Figure 4. A schematic illustration of (a) a balloon catheter system and its cross section showing the inner lumen and (b) a cross section of a modern implant using a Pebax® polyester for the outer tube and an HDPE polymer for the inner tube. Chemical bonding is achieved with a functionalized LDPE Plexar® tie layer that provides covalent bonding (yellow dashes) between the Pebax and Plexar® layer and the chain entanglement between the inner HDPE and tie layer.

ed of a long tube with an inner opening or lumen that accommodates the guide wire that delivers the balloon to its final destination and that facilitates an inflation mechanism. Figure 4a shows a schematic illustration of a balloon catheter system and its cross section and Figure 4b shows a specific cross section in a modern catheter comprised of a high-density polyethylene (HDPE) inner layer, an outer layer of polyester (Pebax®), and a functionalized low-density polyethylene tie layer (Plexar®) that facilitates bonding between the two layers.

In designing the catheter shaft it is ideal to make the system in such a way that it can readily navigate the tortuosity inherent to the vascular system without kinking or penetration of the tissue. In order to maneuver through the anatomy, the catheter tube needs to provide flexibility to follow the desired path of the surgeon. This functional property is referred to as "trackability." The catheter tube must also have sufficient axial stiffness to travel along the winding path of the vasculature. Additionally the catheter tube should offer resistance to twisting or in transmitting torque from the proximal to distal (balloon) end; this property is termed "torqueability."[11]

Initial catheter tubes were made of a single polymeric material such as nylon, polyethylene, or polyethylene terephthalate, but these polymers were limited by their relatively high coefficients of friction. In an iteration of design, these polymers were coated with silicone to achieve the desired coefficient of friction, however, these systems were limited in their ability to deliver sufficient trackability and torqueability. Subsequent designs moved toward a co-extruded system using two different polymers: HDPE for the inner tube that rides over the guide wire and a nylon or polyester outer tube that can be chemically or thermally bonded to the distal balloon. In its basic form HDPE does not form a chemical bond with a nylon or polyester material, and consequently these systems were also prone to delamination. In order to solve this material-processing-performance problem, the use of a chemical functional group that could be copolymerized with the HDPE was used to achieve a chemical bond between the two distinct

polymers. The use of functional groups or tie layers evolved the intravascular catheter tube into a system that could offer the required functional properties without delamination and could be readily manufactured using a co-extrusion process (Figure 5).

Modern vascular catheters either use functional groups or tie layers to facilitate bonding between the inner HDPE and the outer polyester or nylon material, as shown in Figure 4b. Such systems offer good structural integrity, deliver the required functional properties, and minimize complications due to delamination between the materials. Thus, the design evolution of the modern catheter system involved several iterations of materials selection, processing, and design to achieve the functional requirements of the intravascular balloon catheter in a clinical setting. This is an example of where design iterations that have transpired over several decades have resulted in the evolution of a very reliable biomedical device.

Silicone Breast Implants

Silicone has been utilized in breast implants since 1962; however, early designs were prone to rupture and leaking.[12] The first implants utilized low viscosity forms of silicone gel encased in a solid silicone elastomer shell but were prone to failure through tissue contracture around the implant or rupture.[12–14] Rupture of the implant shell enabled the silicone to leak into the surrounding tissue, which could then elicit a chronic inflammatory response. Over the next 20 years, second and third generations of breast implants experimented with different silicone gels and encasement designs to minimize or prevent leaks and inflammatory complications. While these implants were a vast improvement over previous design iterations, leakage and rupture were still major problems.

Many of the early designs and materials used were prior to the 1976 Medical Device Act that provided the Federal Drug Administration (FDA) the authority to review and regulate medical devices.[4] Without any formal regulation, companies could switch materials used in their devices without the need of FDA approval. Thus, the earlier silicone breast implant designs were not subjected by the FDA to the scrutiny of structural assessment and biocompatibility testing that newer devices must undergo prior to approval for clinical use. In the early 1990s, extensive litigation and research into the realm of silicone breast implant safety ensued with great controversy. The premise of these lawsuits was that leaking of silicone would lead to connective tissue disease, immune reactions, and ultimately autoimmune disorders.[15]

The FDA put together a scientific committee to assess the integrity and medical concerns surrounding breast implants in 1991, while mandating the withdrawal of silicone implants for cosmetic use until the investigation of the scientific committee was complete.[14] In 1999, the scientific committee concluded that silicone breast implants were not responsible for the immunological diseases that had been rampant in many patients who had the silicone implants.[15] In 2006, the FDA approved the re-release of silicone breast implants utilizing a crosslinked form of the polymer, under the conditions that patients must be at least 22 years of age and would require an MRI in the first 3 years and then every 2 years thereafter. The current view is that these implants will not likely last a "lifetime" as initially promised in the early release of silicone implants, and women should plan to have multiple surgeries.[16]

Modern silicone breast implants have evolved in design to ensure safety against rupture and leakage. The primary mechanical design requirement of a breast implant is resistance to rupture. This is typically modeled as a thin-walled pressure-vessel to address the stress resulting from peak compressive forces. The primary design change from the first implants has been in the utilization of a crosslinked form of silicone that does not leak if the surrounding shell is ruptured or torn. Figure 6 shows the design evolution of silicone implants and provides an image showing the consequences of rupture when the silicone has low viscosity. In the modern silicone implant the implant retains its structural integrity and does not leak into adjacent tissue.

However, several concerns linger in the wake of the recent FDA approval of silicone implants. One concern is founded upon prior clinical complications of leaking and association with autoimmune disease. While scientific studies have shown no link between silicone and autoimmune disease, much of the public at large remains cautious. Also, while a large number of clinical studies have been undertaken to demonstrate the safety of silicone implants, the long-term performance of these implants has not been established.

This is an example of a design iteration process where the clinical performance has driven the research for optimization of materials selection and design of the implant to ensure safety. As with all devices, the clinical performance drives a continuous feedback loop, and it will be years before the long-term performance of crosslinked silicone breast implants is understood.

Ultra-High-Molecular-Weight Polyethylene in Total Hip Replacements

The designs and materials used in total hip replacements have been under steady improvement for nearly 50 years, and currently enjoy a high degree of success with an estimated 90% survival rate after 10 years in vivo as the result of this effort.[17] In total hip arthroplasty, the bearing system typically employs an ultra-high-molecular-weight polyethylene (UHMWPE) insert that articulates against a cobalt-chromium alloy or ceramic in order to restore function to a damaged or diseased joint. The majority of total hip replacement systems in use today utilize a modular design, where the UHMWPE bearing is assembled to a metal shell that integrates with the bone of the acetabulum of the pelvis (Figure 7). The UHMWPE component must be held in place by a combination of locking mechanisms and interference fitting. Locking mechanisms often take the form of notches or grooves that cause a stress concentration during loading of the implant, and are located where the component can experience substantial tensile stress. Such design features are a potential structural concern, particularly for a relatively flaw-intolerant material such as UHWMPE.

One of the primary clinical concerns in total hip replacements is wear-mediated osteolysis, in which inert microscopic wear debris from the bearing cause an acute immune response that

results in bone lesions that can compromise the implant.[18–20] In the last decade, the mitigation of wear volume has been the main focus of technical development, and the principal breakthrough in that area has been the use of ionizing radiation to crosslink the UHMWPE bearing for improved wear resistance. Crosslinking of UHMWPE has been shown to reduce the volume of evolved wear particles in pin-on-disc and in vitro implant simulator studies, with a dose-dependent relationship, as shown in Figure 8a.[21] This effect saturates around 100 kGy of radiation, when the polymer is termed highly crosslinked. Combined with a post-irradiation annealing or melting step to eliminate free radicals, crosslinking substantially reduces the strength, ductility, toughness, and fatigue crack propagation resistance of UHMWPE.[22] Thus, mitigating wear via radiation crosslinking results in a tradeoff against other material performance characteristics, such as fatigue crack propagation resistance (Figure 8b).[22]

Performance Tradeoffs in Total Hip Replacements

There are performance tradeoffs in total hip replacements owing to the benefit of improved wear resistance at the expense of fatigue fracture in crosslinked UHMWPE. In fact, recent failure analyses of highly crosslinked UHMWPE hip replacement components have indicated that these systems are susceptible to fracture in a clinical environment.[23,24] The authors analyzed the clinical failure of four catastrophically fractured, crosslinked acetabular liners to elucidate this performance tradeoff.[24] Each implant was designed and manufactured by a different device manufacturer, but shared similar design features: an unsupported rim outside the main weight-bearing region containing notches or interfaced with a notch in the metal shell. Another critical aspect these implants shared was that they were all developed originally for uncrosslinked UHMWPE, and subsequently deployed with crosslinked UHMWPE without updating the design to reflect the consequent reduction in defect tolerance.

The failure analysis sought to clarify whether the mechanical compromise resulting from crosslinking might have been sufficient to enable the observed fractures. Fractography results demonstrated that the fractures in each case initiated in a microscopically similar manner, at the root of a stress-concentrating feature, despite their different designs and clinical case histories. The fracture surfaces exhibited faint lines parallel to the advancing crack front, originating at a point on the outside surface of the component near the focus of a stress concentration. Near the initiation site, these surface features were prominent and resembled clamshell markings, propagating in a roughly radial or thumbnail morphology. A representative initiation site is shown in Figure 9, where the procession of clam shell markings is distinctly visible.[24] The apparent fractographic similarity of the crack initiation sites was taken as strong evidence in support of a common failure mechanism among the four components, and thus the failures were likely derivative of their common material and design attributes.

A finite element analysis was then conducted of each liner to predict the stress generated during a 500 N direct loading event of the exposed rim. One representative result is given in Figure 10.[24] This analysis showed that the resultant maximum principal stress

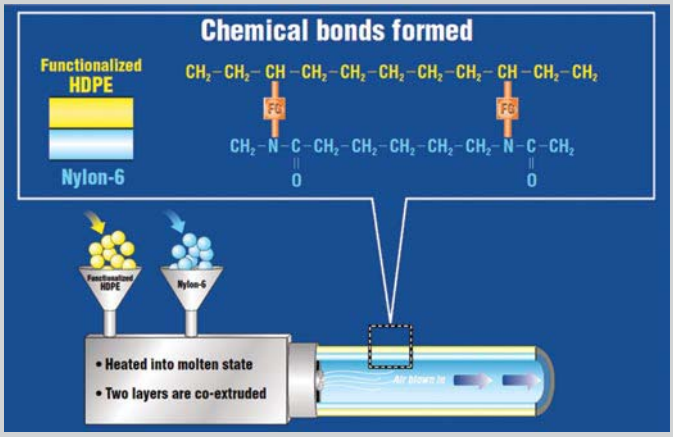


Figure 5. A schematic illustration depicting the use of functional groups (FG) to facilitate chemical bonding between HDPE and Nylon-6 in the co-extrusion process of the balloon catheter.

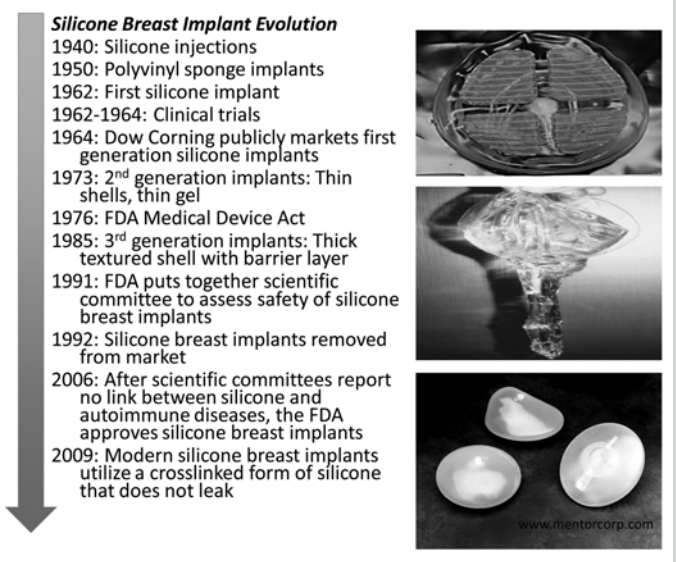


Figure 6. The historical evolution of silicone breast implants.

Figure 7. A total hip replacement employing UHMWPE as the acetabular cup articulating against a Co-Cr head.

peaked at the root of the notches, near where the cracks initiated. This principal stress exceeded that necessary for incipient propagation of a 2 mm deep notch with an incipient crack in each case, using a stress intensity inception value to depict the conditions for the onset of crack growth. This finding was interpreted to indicate that the peak principal stress was sufficient to propagate initiated cracks at the observed initiation sites. Thus the authors concluded that direct rim loading is a sufficient condition to propagate cracks beyond a rim notch and lead to the observed catastrophic fractures.

The finite element analysis also predicted that the stress rapidly decayed with depth from the surface of the rim notch in each case (Figure 10). Thus, while the stress was severe enough for incipient propagation near the surface, a short distance of growth could put a crack outside the notch-affected zone and lead to crack arrest. As the majority of acetabular liners experience substantial rim loading events,[25] we therefore hypothesized that a substantial fraction of intact crosslinked acetabular liners should harbor at least one initiated fatigue crack near an elevated rim notch. A subsequent investigation of intact retrieved crosslinked liners reported that six of nine inspected liners harbored initiated cracks.[26] These results motivate the need to understand crack initiation in existing and future designs of UHMWPE acetabular liners.

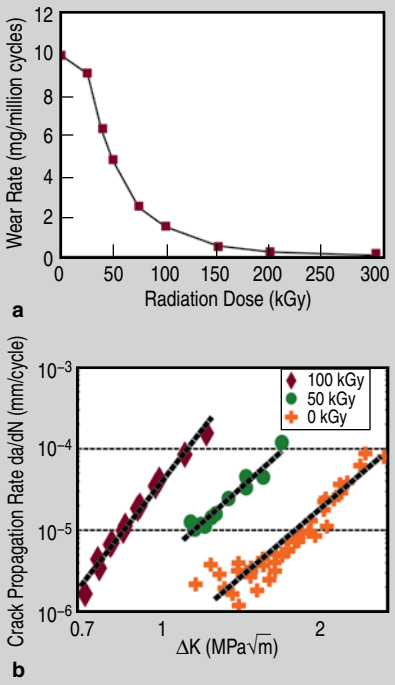


Figure 8. The effect of UHMWPE crosslinking (as measured by radiation dose) on the (a) wear rate and (b) fatigue crack propagation resistance. Note the trade-off in these two material properties: wear resistance comes at the expense of fatigue fracture resistance.

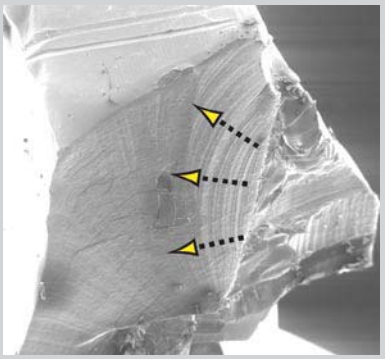


Figure 9. A scanning electron micrograph of the initiation site of a rim fracture in a crosslinked UHMWPE hip replacement bearing.[24] Clam shell markings on the surface originate at the corner of a sharp notch machined into the component. Arrows indicate the direction of propagation from the initiation site.

Design for Crack Initiation Resistance

The crack initiation resistance of a UHMWPE component is governed by intrinsic material behavior, extrinsic design, and clinical factors. The material and design characteristics of importance depend on the physical model used to describe crack initiation. The viscous flow of the highly stressed material at a notch or crack tip has been proposed as the dominant deformation fracture mechanism in UHMWPE.[27,28] A crack initiation framework, based on viscoplastic behavior,[29] can be used to evaluate tradeoffs in performance related to material behavior and design features. For materials that obey a power-law creep relation, a constant load yields the same time dependence of energy release rate (J-integral) at a crack tip or notch root. This equation, shown below, implies that the J-integral monotonically increases with time under load, such that a sub-critical value will eventually overcome a threshold for crack initiation, J_c. Thus, one can find the time under a constant load required to surpass the crack initiation criterion, called the initiation time, t_i:

$$C = \frac{1}{E_0}\left(\frac{t}{\tau_0}\right)^d \Rightarrow J = J_0\left(\frac{t}{\tau_0}\right)^d \Rightarrow \frac{t_i}{\tau_0} = \left(\frac{J_c}{J_0}\right)^{1/d}$$

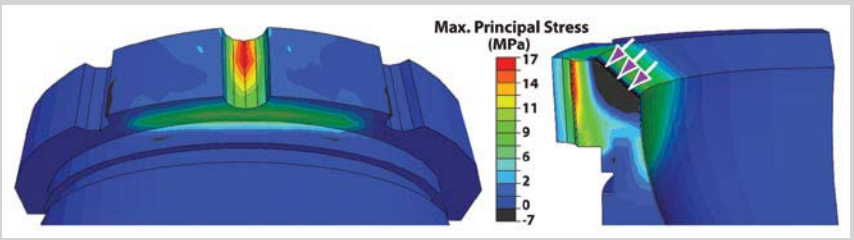


Figure 10. A finite element analysis prediction of maximum principal stress (i.e., maximal tensile stress) during a 500 N rim loading event.[24] Arrows in (b) indicate the distributed load on the rim. (a) The tensile stress peaks at value of 17 MPa at the root of a semi-cylindrical notch in the rim. (b) A cross section through the center of the notch shows that the stress is localized near the notch, and decays rapidly with depth.

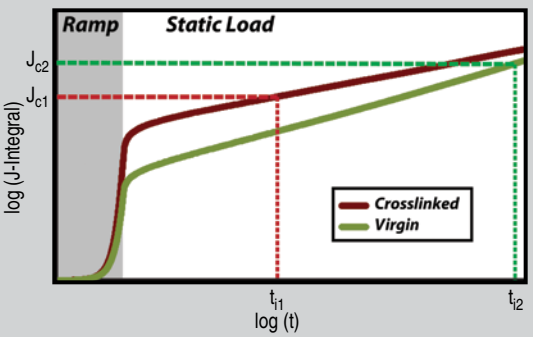


Figure 11. The predicted energy release rate (J-integral) at the root of a notch under a static load for a power-law creeping material model of UHMWPE.[27,29] Compared to untreated UHMWPE, crosslinked UHWMPE has a lower fracture toughness (J_c), greater creep resistance (lower rate of increase in J), and lower elastic modulus (greater J_0 after ramp). In combination, these altered material properties are predicted to result in a substantially shorter crack initiation time (t_i) for crosslinked UHMWPE.

Thus, this model gives the initiation time as a function of intrinsic material parameters (through J_c, t_0, and d) and the extrinsic loading and geometry dependent contributions (contained in J_0). This closed-form prediction of the initiation time provides a means to evaluate how material and design characteristics can directly interact. For instance, a reduction in material toughness could be offset with either alterations to the design or creep resistance. Figure 11 depicts an example of how crosslinking, which affects toughness, elastic modulus, and creep resistance, can result in a substantial reduction in the initiation time with modest changes in individual material parameters.[27]

Specifying a minimum value of initiation time as a design requirement would provide an industry standard for safety against crack initiation without undue restriction of flexibility in the development of new components. The above model also suggests future directions of research for material optimization against crack initiation. For instance, it is desirable for UHMWPE to exhibit both a high creep resistance and fracture toughness, while an increased elastic modulus beneficially depresses J_0 for a given applied load. As crosslinking generally both increases creep resistance and depresses toughness, its overall influence on crack initiation could be difficult to predict. Melting crosslinked UHMWPE reduces its crystallinity and stiffness, thus elevating J_0. Some highly crosslinked UHMWPE formulations are oxidatively stabilized without remelting, and these newer formulations exhibit improved fracture toughness and elastic modulus; however, their relative crack initiation performance is yet unknown. The lesson implied by this analysis is that notch fatigue in UHMWPE is likely not only governed by fracture toughness or crack propagation resistance, but could be dominated by viscous and elastic effects, and that improved UHMWPE formulations could exploit this phenomenon.

RECOMMENDATIONS

Fractures have been observed in crosslinked UHMWPE acetabular liners in total hip replacements, and are likely attributable to the adoption of a more flaw-intolerant material in a design containing notches in highly stressed locations of the component. Investigation of similar intact components has revealed that a majority of these types of device designs using the crosslinked formulation of UHMWPE harbored initiated cracks at the same locations where fractures were previously observed to initiate. The prevalence of initiated cracks in these case series recommends the prevention of crack initiation as a means to control fatigue failure in total hip replacements. The time-dependent analytical crack tip model presented here provides a simple framework for evaluating the inherent impact of material or design alterations on crack initiation performance.

CONCLUSION

The clinical performance of a medical device depends on many factors and an understanding of the structure-property-design relationships is essential for the clinical success of the implant. The clinical evolution of the three systems presented in this work were chosen to illustrate the sophisticated interplay between design, material selection, structural properties, processing and clinical demands; and to illustrate these effects on the performance of medical device implants utilizing polymeric materials.

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