TABLE 25.1
Revision Burdens for Hip Arthroplasty in Various Countries

Country	Period	Revision Burden (%)	Comments
Australia	1999–2002	18.2	—
Canada	2002–2003	13.1	—
Finland	1980–2001	15.7	—
Finland	1990–2001	18.3	—
Norway	1987–1998	15.0	—
Norway	1994–1998	16.4	—
Sweden	1979–2000	7.7	—
Sweden	1992–2000	11.0	—
Sweden	1992–2000	6.4	≥65 years old
United States	1990–2002	17.5	—
United States	1990–2002	16.9	≥65 years old

With the exception of THA performed in Sweden, the revision burden in the United States compared favorably with that in several countries with established total joint registries (Table 25.1) [1,2]. Overall, the THA revision burden of 17.5% in the United States from 1990 through 2002 fell within the range of revision burdens of 15.0%–18.3% observed in Norway, Finland, and Australia. In Canada, the revision burden for THA was lower (13.1% for 2002–2003). The overall revision burden for THA in the United States was substantially greater than the revision burden reported for Sweden (7%–11%).

25.1.4 Problems of Joint Replacement: Osteolysis

Table 25.2 illustrates the reasons for revision in the 14,081 first revisions for THA performed in the previous study [2]. The majority (75.3%) of the revision surgeries were performed because of aseptic loosening with or without focal osteolysis, 7.6% were performed to treat primary or secondary infection, and 8.8% were performed for technical reasons and dislocation that could have been mainly related to misalignment of the implants. Periprosthetic fractures (5.1%), implant fractures (1.5%), and a number of less prevalent reasons constituted the balance of the reasons.

TABLE 25.2
Reasons for Revision THA

Reason	Number	Share (%)
Aseptic loosening	10610	75.3
Primary deep infection	948	6.7
Dislocation	810	5.8
Fracture only	716	5.1
Technical error	425	3.0
Implant fracture	215	1.5
Secondary infection	128	0.9
Polyethylene wear	126	0.9
Pain	46	0.3
Miscellaneous	56	0.4
Missing	1	<0.1
Total	14081	100

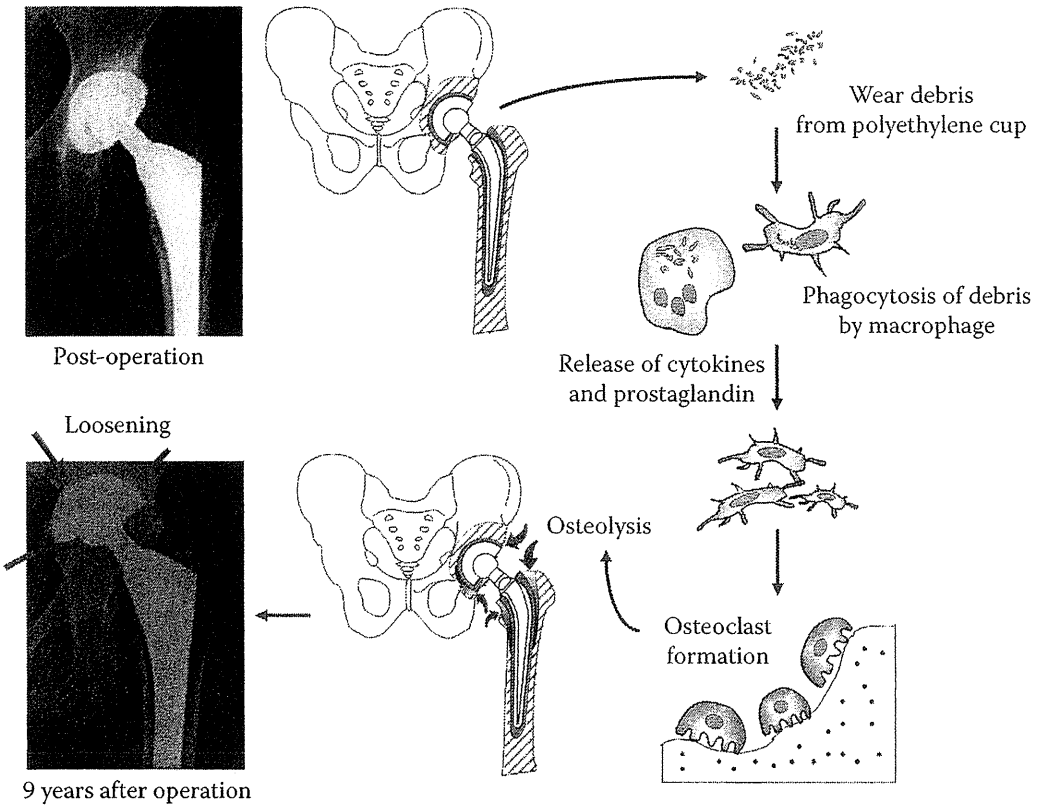

FIGURE 25.4 Schematic model of the mechanisms by which wear debris leads to osteolysis.

As shown in Table 25.2, a consensus statement on total hip joint replacement concluded that the major remaining issues of concern included long-term fixation of the acetabular component, osteolysis due to wear debris, the biological response to debris, and problems related to revision surgery. Although acetabular fixation is no longer a problem, wear and related complications continue to be the major issue affecting the longevity of total hip joint replacements. The bone loss associated with osteolysis can result in pelvic dissociation and instability and major segmental cortical defects in the femur. Young active patients are most at risk for wear and osteolysis.

The precise mechanisms by which wear debris leads to osteolysis will ultimately be determined by defining how specific types of particles combine with environmental factors to permit interactions with specific types of cells that then communicate with each other through the release of soluble mediators (Figure 25.4). Generation of wear debris occurs immediately after implant insertion and ultimately results in a profile of particles that includes all total hip joint replacement materials [6,7]. The extent of bone resorption at the implant–bone interface varies with the severity of the granulomatous tissue response to wear debris and determines the time lapsed before implant loosening occurs. Wear particle-induced macrophage activation plays a role in periprosthetic osteolysis. Essentially, this occurs by two biological mechanisms. First, wear particle-associated macrophages release proinflammatory factors (e.g., cytokines, growth factors, prostaglandins) that enhance the activity of osteoclasts, the cells that carry out bone resorption. Second, osteoclasts are formed from mononuclear precursors that are present in the wear particle-induced macrophage infiltrate. These processes are not mutually exclusive; other stromal and inflammatory cell elements found at the bone–implant interface likely influence both the extent of osteoclast formation and bone resorption.

The contribution of the cells present within the macrophage-rich inflammatory tissue to the induction of bone resorption and implant loosening involves multiple cellular mechanisms. The macrophages are activated by the particles and subsequently release proinflammatory cytokines and other agents that induce bone resorption. Macrophage products capable of inducing

bone resorption include interleukin (IL)-1α, IL-1β, IL-6, tumor necrosis factor (TNF)-α, arachidonic acid metabolites, and degradative enzymes. The existence of multiple factors at one site is likely to accelerate bone destruction. IL-1α, IL-1β, and TNF-α may also induce secondary effects on other cell types (such as osteoblasts) in the interfacial membrane, resulting in the release of matrix-degrading enzymes, including collagenase, stromelysin, gelatinases, and plasminogen activators. Granulocyte/macrophage colony-stimulating factor (GM-CSF) has also been implicated in cellular proliferation in the interfacial membrane around implants. Other cytokines that may exhibit immunomodulatory roles include IL-12, which is increased in the pseudosynovial fluid in patients with aseptic loosening of hip joint replacement. A primary response of macrophages to particulate debris is the increased release of TNF-α. TNF-α release results in part from the exposure of macrophages to particles, which activates the transcription factor NF-κB; this reaction is related to membrane receptor events. Alteration of the bone surface by these proteases may stimulate osteoclast bone-resorbing activity and may influence the recruitment and adhesion of mononuclear phagocyte osteoclast precursors at the bone–implant interface.

A second important mechanism relevant to the role of macrophages in implant loosening is revealed by data demonstrating that wear particle-associated macrophages are capable of differentiating into multinucleated cells that exhibit all the phenotypic features of osteoclasts. Osteoclasts are highly specialized multinucleated cells that are uniquely capable of carrying out lacunar resorption. Osteoclasts are formed by fusion of bone marrow-derived mononuclear precursors that circulate in the monocyte fraction. A number of cellular and humoral factors are known to influence RANKL and osteoprotegerin (OPG) expression. Osteoclast formation in periprosthetic tissues can effectively be viewed as a balance between the productions of these two factors. Various cytokines and growth factors (apart from macrophage CSF) abundant in periprosthetic tissues in aseptic loosening, such as IL-1 and TNF-α, increase the OPG mRNA expression by osteoblasts, suggesting that these factors that stimulate osteoclastic bone-resorbing activity appear to act conversely to downregulate osteoclast formation. Prostaglandins such as PGE2 have also been shown to increase RANKL production and to decrease OPG release, thus stimulating osteoclast formation and bone resorption. Inflammatory cells, such as T-cells, are present in the arthroplasty membrane and may influence osteoclast differentiation and periprosthetic osteolysis by modulating RANKL expression and OPG production. Recent studies have also highlighted the role of certain cytokines (e.g., TNF-α, IL-1β, and IL-1) in inducing osteoclast formation both in the presence and absence of RANKL.

25.2 BEARING MATERIALS FOR JOINT REPLACEMENTS

25.2.1 Polyethylene Bearing Material

Polyethylene is a polymer formed from ethylene (C_2H_4), which is a gas with a molecular weight of 28. The generic chemical formula for polyethylene is $-(C_2H_4)_n-$, where n is the degree of polymerization. For UHMWPE, the molecular chain can consist of as many as 0.2×10^6 ethylene repeat units, i.e., the molecular chain of UHMWPE contains up to 0.4×10^6 carbon atoms.

There are several kinds of polyethylene, which are synthesized with different molecular weights and chain architectures. Low-density polyethylene (LDPE) and linear low-density polyethylene (LLDPE) generally have branched and linear chain architectures, respectively, each with a molecular weight of typically less than 5×10^4 g/mol. High-density polyethylene (HDPE) is a linear polymer with a molecular weight of up to 0.2×10^6 g/mol. In comparison, UHMWPE has a molecular weight of up to 6×10^6 g/mol. In fact, the molecular weight is so ultra-high that it cannot be measured directly by conventional methods and must instead be inferred by its intrinsic viscosity. Table 25.3 summarizes the physical and chemical properties of LDPE, LLDPE, HDPE, and UHMWPE.

TABLE 25.3
Typical Physical and Chemical Properties of LDPE, LLDPE, HDPE, and UHMWPE

Property	LDPE	LLDPE	HDPE	UHMWPE
Molecular weight (10^6 g/mol)	—	—	0.05–0.25	2–6
Melting temperature (°C)	110–115	110–125	130–137	125–138
Poisson's ratio	—	—	0.40	0.46
Specific gravity	0.910–0.930	0.910–0.925	0.952–0.965	0.932–0.945
Tensile modulus of elasticity (GPa)	0.1–0.4	0.1–1.6	0.4–4.0	0.8–1.6
Tensile yield strength (MPa)	7–14	7–42	26–33	21–28
Tensile ultimate strength (MPa)	3–57	8–46	22–31	39–48
Elongation (%)	145–1000	460–1100	10–1200	350–525
Crystallinity (%)	<50	—	60–80	39–75

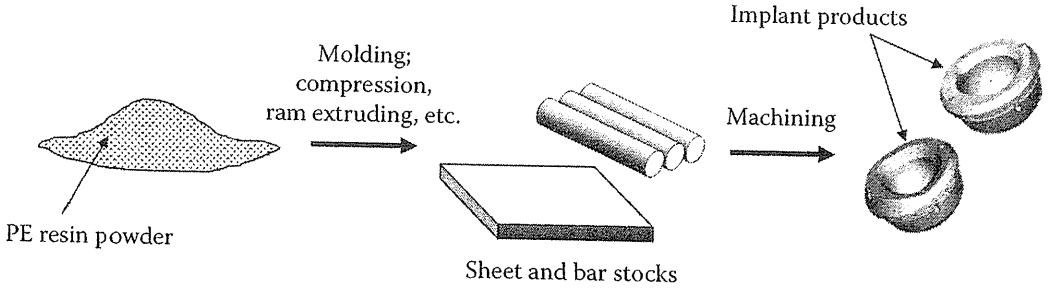

FIGURE 25.5 Typical processing steps in the manufacture of UHMWPE implants.

Three industrial steps are needed to manufacture orthopedic implants. First, UHMWPE must be polymerized from ethylene gas. Second, the polymerized UHMWPE, in the form of resin powder, needs to be consolidated into a sheet (i.e., compression molding), rod (i.e., ram extrusion), or near-net shaped implant (i.e., direct compression molding). Finally, in most instances, the UHMWPE implant needs to be machined into its final shape (Figure 25.5).

Since the 1950s, UHMWPE powders have been produced by Ruhrchemie (currently known as Ticona GmbH, Oberhausen, Germany) using the Ziegler process. The main ingredients for processing UHMWPE are reactive ethylene gas, hydrogen, and titanium tetrachloride catalyst. The polymerization takes place in a solvent used for mass and heat transfer. The requirements for medical-grade UHMWPE powder are specified in the American Society for Testing and Materials (ASTM) standard F648 and the International Organization for Standardization (ISO) standard 5834-1 [8,9].

Historically, the UHMWPE powder has been converted by compression molding since the 1950s, because the industries in the area around Ruhrchemie already were experienced in this processing technique. Today, compression-molded sheets of the UHMWPE are produced commercially by two companies (Orthoplastics, Ltd., Lancashire, United Kingdom, and Meditech Poly Hi Solidur, Ltd., Fort Wayne, IN). One UHMWPE sheet is pressed between the upper and middle plates, and the second is produced between the middle and lower plates. The plates are oil heated and hydraulically actuated from below. The heating and loading systems are all computer controlled. Finally, the entire press is contained in a clean room, to reduce the contamination of extraneous matter into the sheet. In contrast, ram extrusion of UHMWPE was developed by converters in the United States during the 1970s. Today, only few converters supply medical-grade ram extrusion UHMWPE to the orthopedic industry. Medical-grade extrusion facilities are owned by Orthoplastics, Ltd., Meditech Poly Hi Solidur, Ltd., and Westlake Plastics Co. Ltd. (Lenni, PA). The process is as follows. UHMWPE powder is fed continuously into an extruder. The extruder itself consists essentially of a hopper that

allows powder to enter a heated receiving chamber, a horizontal reciprocating ram, a heated die, and an outlet. Within the extruder, the UHMWPE is maintained under pressure by the ram as well as by the backpressure of the molten UHMWPE. The backpressure is caused by frictional forces of the molten resin against the heated die wall surface as it is forced horizontally though the outlet. Beyond the outlet, the UHMWPE rod is slowly cooled in a series of electric heating mantles.

25.2.1.1 History of Polyethylene in the Orthopedic Field

The load-bearing articulating surface materials used in total joint arthroplasty comprise metallic alloys, ceramics, and polymers. The articulating couples of primary concern—those that generate considerable amounts of wear leading to osteolysis—include UHMWPE cups and inserts. Accordingly, in the past several decades, most research and development have been focused on improving the wear resistance of UHMWPE (Table 25.4).

Introduced clinically in November 1962 by Charnley, UHMWPE articulating against a metallic femoral ball remains the gold standard bearing surface combination in total hip joint replacement [11]. Considering how rapidly technology can change in the field of orthopedics, the long-term role that UHMWPE has played in hip joint replacement since the 1960s is fairly remarkable.

In the 1970s, the properties of UHMWPE were modified by including carbon fibers within the matrix of polyethylene, thereby creating a carbon fiber-reinforced UHMWPE, known as Poly II (Zimmer, Inc., Warsaw, IN) [13]. However, this UHMWPE composite was not found to exhibit consistent and improved clinical results relative to the conventional UHMWPE introduced by Charnley. The material was designed with orthopedic bearing applications in mind, under the assumption that increasing the modulus and ultimate tensile strength of the bearing as well as decreasing its creep properties would increase its longevity. This assumption was reasonable, since bearing surfaces are subject to high contact stresses, conditions under which conventional UHMWPE had often been observed to be pitted or delaminated. The inclusion of short chopped carbon fibers in a UHMWPE matrix resulted in a composite material with improved mechanical properties in vitro. Thus, the expectation was that Poly II would be more resistant to the pitting and delamination often seen in

TABLE 25.4
History of UHMWPE Development for Joint Replacement

Year	Comments
1958	Clinical use of polytetrafluoroethylene as bearing material of implants in hip arthroplasty by Charnley et al. [10]
1962	Charnley et al. adopts UHMWPE for use in hip arthroplasty [11]
1969	UHMWPE was gamma-ray sterilized in air with a minimum dose of 25 kGy [12]
1970	Commercial release of the Poly II-carbon fiber-reinforced UHMWPE for hip arthroplasty by Zimmer, Inc. [13]
1971	Clinical introduction of the 100 Mrad PE—extremely highly CLPE by more than 1000 kGy of gamma-ray irradiation in air by Oonishi et al. [16]
1982	Commercial release of alumina ceramic balls articulating against UHMWPE by Kyocera, Corp. [19]
1986	Clinical introduction of silane cross-linked HDPE by Wroblewski et al. [20]
1991	Commercial release of the Hylamer—highly crystalline UHMWPE for hip arthroplasty by DePuy Orthopedics, Inc. [21]
1997	Commercial release of highly CLPE with an energy-ray irradiation of 50–105 kGy by several orthopedic product manufacturers [13,24]
2006	Clinical use of the vitamin E-blended UHMWPE in knee arthroplasty produced by Nakashima Medical, Co. Ltd., as a trial [44]
2007	Clinical use of the PMPC-grafted CLPE in hip arthroplasty produced by Japan Medical Materials Corp. as a trial [42]

joint replacements. Further, wear testing of Poly II conducted by the manufacturer revealed it to have lower wear than conventional UHMWPE, suggesting that the strength benefits would result in longer lasting hip arthroplasties. However, unfortunately, the promise shown by Poly II in vitro was not borne out in the clinical setting, and within a short time after implantation, many patients presented with osteolysis and complete mechanical failure of their bearing surfaces [14]. One possible explanation for the mechanical failure was that the poor crack propagation resistance of Poly II was due to the carbon fibers not bonding with the UHMWPE matrix, instead serving as stress concentrators and crack nucleation sites [15].

In Japan, during the 1970s, an important technological advancement occurred: the clinical introduction of an extremely highly cross-linked polyethylene (CLPE) with more than 1000 kGy of gamma-ray irradiation in air by Oonishi et al., the so-called 100 Mrad PE [16,17]. A similar advancement in extremely highly CLPE also occurred in South Africa during the 1970s, where researchers in Pretoria clinically introduced a UHMWPE that was gamma-ray irradiated with up to 700 kGy in the presence of acetylene [18]. During the 1980s, two other noteworthy developments occurred relative to polyethylene in joint replacements. Chas F. Thackray-DePuy International Ltd. (Leeds, United Kingdom) began the development of an injection-molded HDPE that could be cross-linked by silane coupling. Only 22 of these implants were produced and implanted by Wroblewski et al. starting in 1986 [20]. After an initial wear period (initial bedding-in period), these cross-linked HDPE components have been found to exhibit very low clinical wear rates.

In 1991, a highly crystalline UHMWPE known as Hylamer was patented by Li et al. from E. I. Du Pont de Nemours and Company (Wilmington, DE) and marketed by the DePuy-DuPont Orthopedics joint venture (Newark, DE) [21]. Hylamer is a hot isostatically pressed UHMWPE, leading to the formation of an extended-chain crystallite morphology with thick (200–500 nm) lamellae and higher crystallinity (65%–71%) [13]. In contrast, conventional low-pressure sintered UHMWPE displays a folded-chain crystalline morphology with much thinner lamellae (10–50 nm in thickness) and a crystallinity of 50%–55%. By varying the postconversion heating, pressure, and cooling sequence, a family of materials was developed with varying crystalline morphologies and sizes. Hylamer has a higher density and crystallinity than conventional UHMWPE. Although the yield and ultimate strength of Hylamer are slightly higher, the most noticeable change occurs in the elastic modulus, which is nearly double for Hylamer as compared to conventional UHMWPE. The clinical results for the highly crystalline UHMWPE, which were clarified in the 1990s, have been mixed and are therefore controversial. Although several studies reported worse clinical performance using the Hylamer compared with conventional UHMWPE, other studies reported several satisfactory or even improved performances [13].

25.2.1.2 Cross-Linked Polyethylene

High-energy ray irradiation cross-linking and thermal treatment of UHMWPE has aroused intense scientific and commercial interest within the orthopedic field since the late 1990s (Figure 25.6). For decades, the cross-linking of polyethylene has been known to improve the abrasion resistance of the polymer for industrial applications. However, only a few applications of this technology have been reported in orthopedics literature [13,22,23]. All high-energy ray irradiation, including the standard 25- to 40-kGy dose of gamma-ray irradiation used for sterilization, leads to the formation of free radicals in polymeric materials through homolytic chain cleavage. In UHMWPE, some of these free radicals recombine with each other to form cross-links or trans-vinylene bonds, while others remain as highly reactive species in the structure for extended periods of time. Although the gel content of UHMWPE may be increased to 80% by an average gamma-ray radiation dose of 25 kGy, the polymer becomes highly cross-linked (corresponding to a gel content of 90%–100%) after an absorbed dose of 50 kGy [13,24]. Despite the plateau in gel content, the cross-linking density in UHMWPE did not reach an asymptotic value until a dose of 100–150 kGy had been absorbed. Therefore, several CLPEs, irradiated with 50–105 kGy, have been launched since 1998 and used extensively.

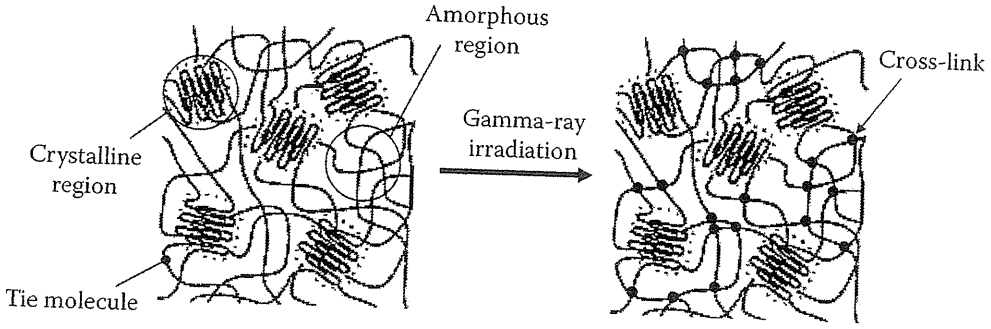

FIGURE 25.6 Schematic illustration of cross-linking induced by gamma-ray irradiation.

TABLE 25.5
Wear Reductions in Early- and Mid-Term Clinical Studies of CLPE Cups Compared with Conventional UHMWPE Cups

Manufacturing Process for CLPE	Mean Follow-Up Period (Years)	Wear Reduction (%)	Reference
Cold-irradiated and annealed	2.0	85	[27]
	2.3	42	[28]
	2.3	94	[23]
	4.0	58	[29]
	4.9	60	[30]
Cold-irradiated and remelted	2.8	72	[31]
	3.2	45	[32]
	5.3	73	[24]
	5.5	95	[33]
Warm-irradiated and remelted	2.0	54	[34]
	2.6	94	[35]
	2.9	44	[36]
	3.0	23	[37]
	3.8	83	[38]
	5.0	55	[39]

In several independent reviews of the literature, it was found that osteolysis is rare in patients in whom the UHMWPE cup is wearing at a rate of less than about 0.1 mm/year, but osteolysis becomes much more frequent and extensive as the wear rate increases substantially above this "threshold" value [25,26]. In several studies with a mean duration of follow-up of ~5 years or longer, the mean rates of wear of CLPE cups (Table 25.5) were all well below 0.1 mm/year [23,24,27–39].

On the other hand, the osteolysis threshold of 0.1 mm/year was established for hip joints with conventional UHMWPE cups—i.e., those that either were not cross-linked or were moderately cross-linked during gamma-ray sterilization. Some investigators have reported that the mean particle size is smaller with CLPE and that, in equivalent volumes, smaller particles tend to be more likely to cause osteolysis [40]. If that is correct, these factors could lead to the osteolysis threshold being somewhat lower for CLPE. We are aware of only one published case report of clinically relevant osteolysis in a hip with a CLPE cup [41]. However, the hip in question also had a forged-steel surface-grit-blasted femoral component that, at revision, was found to be loose at the stem–cement interface. Because the osteolysis in this hip joint occurred endosteally around the loosened stem, with no acetabular osteolysis, it is highly possible that the lesions were primarily due to debris produced at the stem–cement interface rather than from the CLPE cups. Continued close monitoring

of patients with CLPE cups is essential to determine if the improved wear resistance that has been observed in the mid-term, as summarized here, will translate into a substantial reduction in the prevalence and severity of osteolysis at long-term follow-up.

25.2.1.3 Antioxidants for Polyethylene

Recently, there has been an explosion of interest in the research and development of vitamin E as an antioxidant for UHMWPE in the orthopedic field. The primary role of vitamin E (α-tocopherol) is to stabilize the active free radicals resulting from oxidation. The antioxidant activity of vitamin E is due to hydrogen abstraction from the –OH group on the chroman ring by a peroxy free radical, which can combine with another free radical (Figure 25.7). In a gamma-ray irradiated UHMWPE with vitamin E, peroxy free radicals abstract a hydrogen from vitamin E, forming hydroperoxides. The oxidative degradation cascade in the gamma-ray irradiated UHMWPE is hindered in the presence of vitamin E.

The idea of vitamin E-blended UHMWPE is popular in the industrial field: the first widespread applications of the vitamin E-blending technology actually appeared in food packaging since the 1980s. In the orthopedic field, Tomita et al. demonstrated the use of vitamin E-blended UHMWPE in order to prevent delamination by reducing crack formation at the grain boundaries of UHMWPE in 1998 [43]. Then, they demonstrated that the vitamin E-blended UHMWPE with gamma-ray sterilization exhibited a higher resistance to oxidation and fatigue wear compared with conventional UHMWPE. In light of its acceptance as an effective antioxidant, the vitamin E-blended UHMWPE

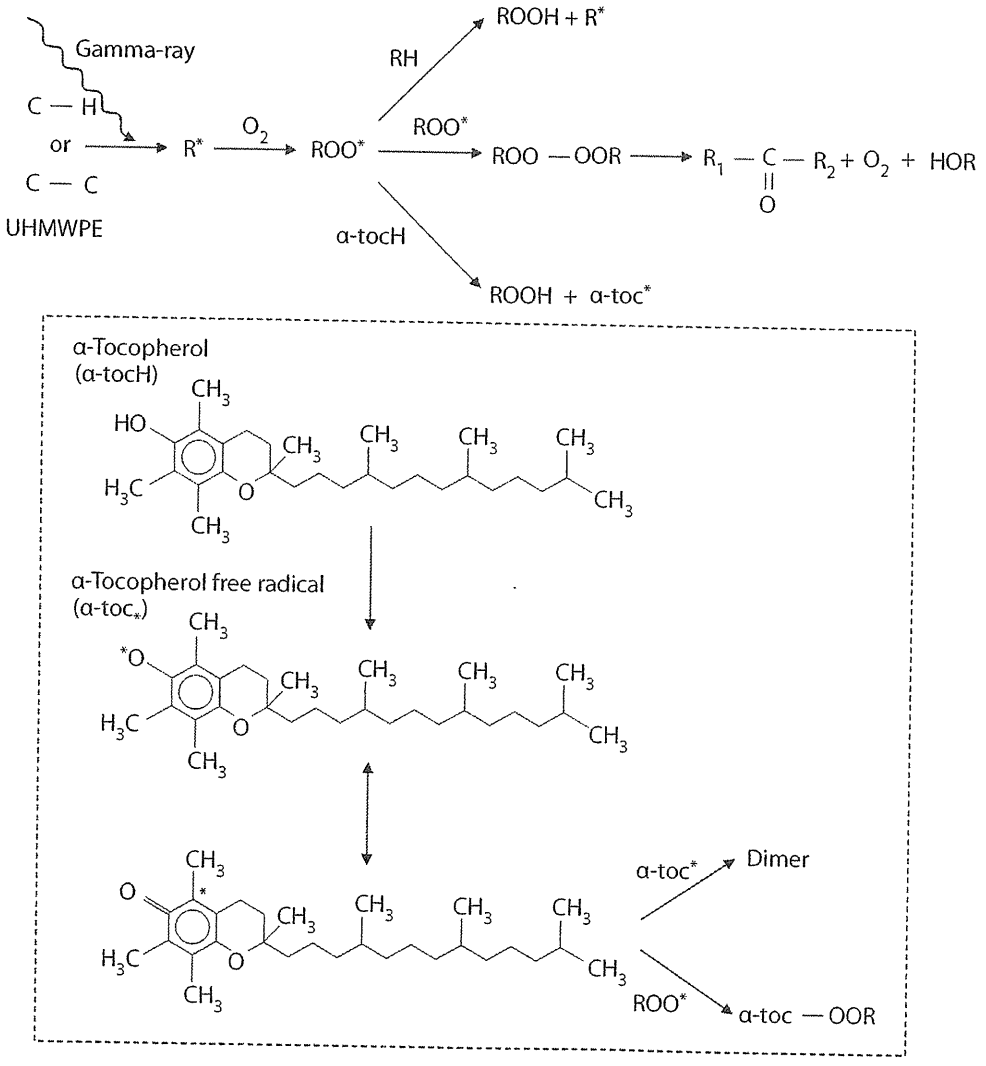

FIGURE 25.7 Schematic illustration of reaction of vitamin E (α-tocopherol).

insert in TKR was produced by Nakashima Medical Co. Ltd. (Okayama, Japan) and is being used in a clinical trial in Japan since 2006 [44]. Although this trial has taken place, the clinical results have not been published yet.

Subsequently, many orthopedic manufacturers have developed CLPE with vitamin E for joint replacements. However, several new problems have arisen, in particular for the procedures of introduction of vitamin E into the polyethylene as follows: (1) blending during compression molding or extrusion before the cross-linking and (2) diffusion after the cross-linking and machining [45]. The disadvantages of the former are that the cross-link density is suppressed to a low value during the cross-linking procedure with (e.g., gamma-ray) irradiation (Figure 25.8). On the other hand, those of the latter are that it is difficult to control the concentration and distribution of diffused vitamin E.

In both the cases, the hypothesized advantage of the vitamin E-blended/diffused CLPE is that the vitamin E protects the CLPE against oxidative degradation (Figure 25.9).

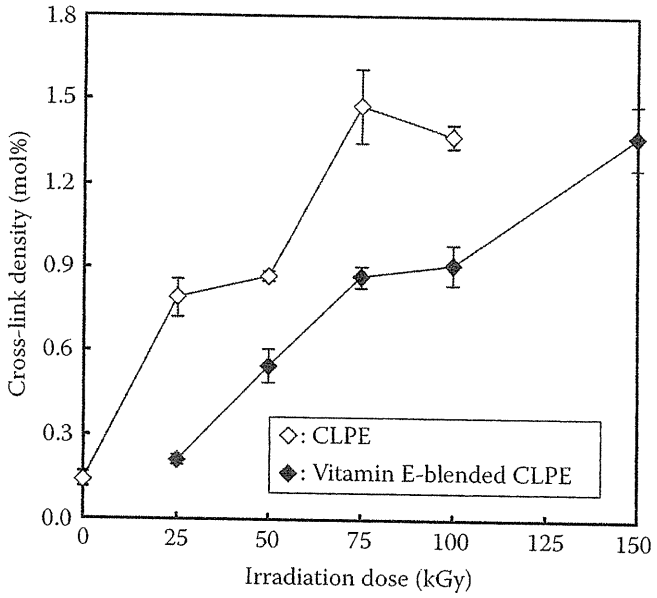

FIGURE 25.8 Cross-link density of vitamin E-blended CLPE as a function of the gamma-ray irradiation. Bar: Standard deviations.

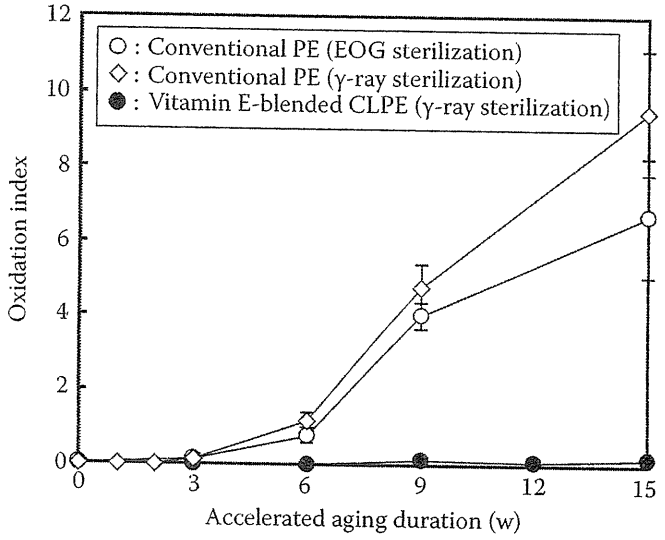

FIGURE 25.9 Oxidative degradation (oxidation index) of vitamin E-blended CLPE as a function of the accelerated aging duration in air at 80°C. Bar: Standard deviations.

25.2.2 Phospholipid Polymers for Mimicking Articular Cartilage

25.2.2.1 Hydration Lubrication

Water attracted by hydrophilic macromolecules in the surface layer plays an important role in lubrication. As macromolecules are flexible, they cannot support a load by themselves. The water in the surface layer would support most of the load because the water is attracted by the macromolecules. Frictional forces arise due to the adhesion of macromolecules to the counter surface. The time-dependent properties of friction forces can be interpreted as follows (Figure 25.10) [46]. Under a load, water exudes slowly from the surface layer with or without sliding. As the result of water loss, the thickness of the surface layer reduces and the water content of the surface layer decreases. Consequently, the degree of adhesion to the opposite bearing surface increases and the frictional force also increases. Therefore, it may be concluded that friction depends essentially on the water content of the surface layer. This hydration would lead to low friction and wear, by acting as "hydration lubrication."

25.2.2.2 Articular Cartilage and Material Design

Although the lubrication mechanism of human joints has been studied since the 1930s, it has not yet been understood clearly. However, it is well known that the composition elements of the articular cartilage surface consist of the collagen network, hyaluronic acid, and proteoglycan subunits. The proteoglycan subunits form a gel-like surface layer due to hydration along with the joint synovia. Although the binding between the proteoglycan subunits and hyaluronic acid can be visible [47], the binding between hyaluronic acid and the collagen network has not yet been confirmed. It was reported by Obara et al. [48] that the friction coefficient of joints increases when the gelled material on the cartilage surface is removed by gauze. After this, the joint surface is lubricated only by joint synovia or hyaluronic acid, i.e., following the loss of the gel comprising proteoglycan subunits, the friction coefficient of the joint cannot be lowered again. This fact indicates that the proteoglycan aggregates are not combined with the collagen network by physical adsorption and that the hydrophilic macromolecules on the joint surface play an important role in keeping the friction at low levels. A previous study reported that the hydrophilic macromolecules of the cartilage surface are assumed to have a brush-like structure: a part of the proteoglycan aggregate brush is bonded with the collagen network on the cartilage surface (Figure 25.11) [49]. The rest of the proteoglycan aggregate floats freely in joint synovia.

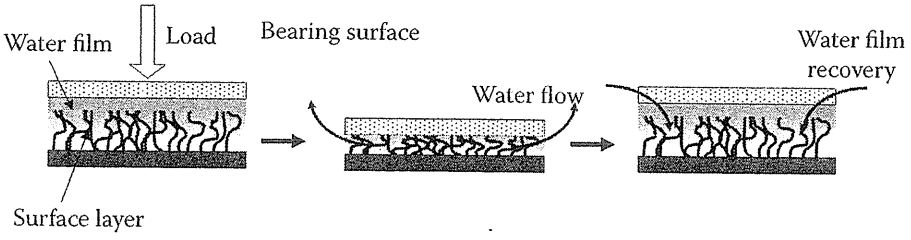

FIGURE 25.10 Schematic model of hydration lubrication.

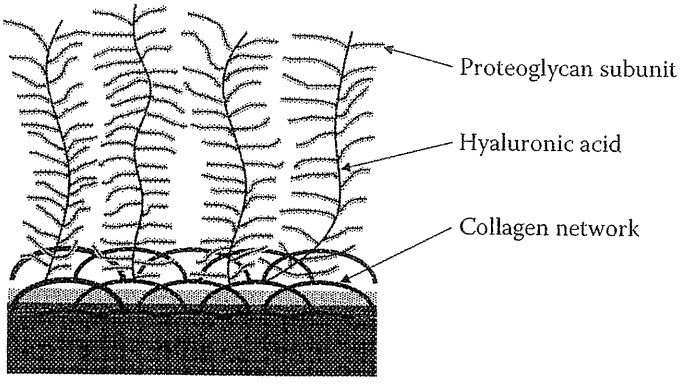

FIGURE 25.11 Schematic model of the brush-like structure of the cartilage surface.

Longfield et al. [50] and Ikeuchi et al. [51] reported that the lubrication mechanism of joints mainly comprises hydration lubrication. Hydrophilic macromolecules induce low friction by promoting the formation of a fluid film that is retained by the water molecules' attraction forces, indicating that the water molecules' attraction forces are important for realizing low friction. The lubrication of the human joint appears to occur by hydration lubrication because the surface layer of the joint resembles the structure of the gelled material in the human joint. Sasada et al. proposed a new idea for joint lubrication, named "Surface gel hydration lubrication" [49] for a lubrication mechanism peculiar to such hydrophilic macromolecules. A bearing surface with a brush-like structure comprising hydrophilic macromolecules in artificial hip joints was therefore assumed to be similar to that of articular cartilage. The hydration lubrication interface can also be regarded to mimic the natural joint cartilage in vivo. The novel material design with this hydration lubrication should be necessary.

25.2.2.3 Photo-Induced Surface "Grafting from" Polymerization

The grafting of polymers onto various surfaces has been studied for over 50 years and has played an important role in many areas of biomaterial science and technology, e.g., colloidal stabilization, adhesion, lubrication, tribology, and rheology. Recent work has focused on the synthesis of so-called polymer brushes whereby the polymer chains stretch out away from the surface or substrate [52,53]. There are three primary methods for modifying a planar substrate with an organic polymer: (a) physical coating, (b) chemical coating and/or "grafting to," and (c) "grafting from" (Figure 25.12). This includes physical coating such as spin or dip coating; however, the polymer is merely adsorbed onto the substrate and may diffuse away when the substrate is immersed into a solvent in which it is soluble. Chemical coating utilizes the functional group of the polymer to chemically attach onto the substrate via several coating techniques. Robust layers may be created by utilizing a self-assembled monolayer (SAM) in order to immobilize a reactive functionality. Thus, the polymer can be attached to the surface, provided the preformed polymer possesses a functional group that is capable of bonding with the surface (e.g., a polymer containing a primary amine could form an amide bond with a carboxylic acid-terminated SAM). This approach

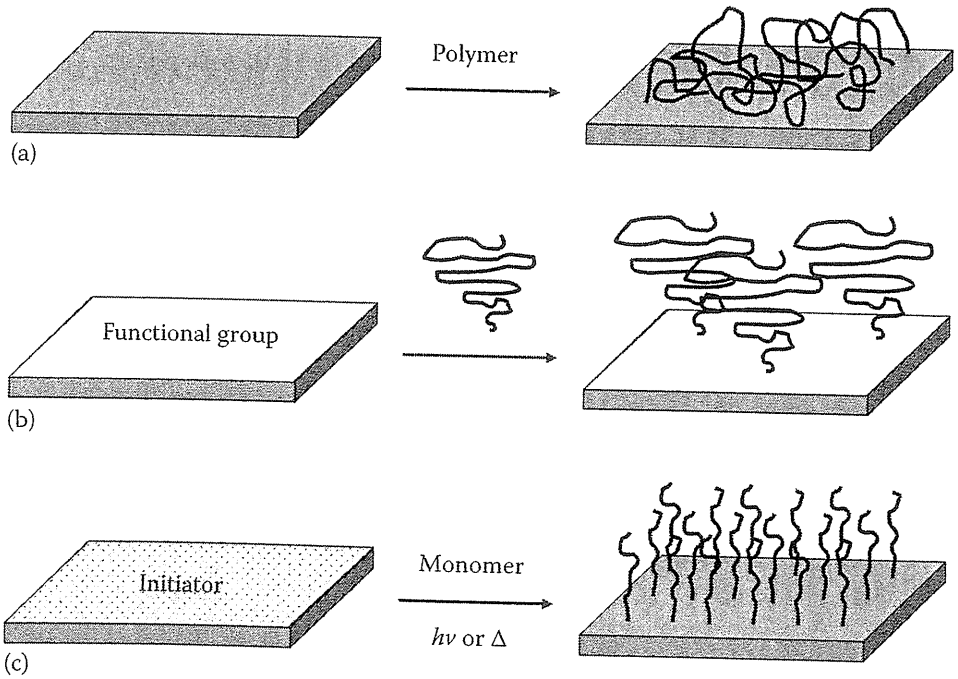

FIGURE 25.12 Approaches for modifying a substrate with a polymer: (a) physical coating (adsorption), (b) chemical coating (immobilization) and/or "grafting to," and (c) "grafting from."

is known as the "grafting to" technique and has been considerably successful at synthesizing robust layers of 1–50 nm in thickness. However, the "grafting to" technique is limited by diffusion barriers that prevent the preformed polymer from intercalating through the tethered polymer to the reactive substrate. Therefore, the "grafting to" method yields a low-density brush. In contrast, the "grafting from" approach has been utilized to synthesize high-density polymer brushes [54]. The conformation of these polymer brushes in a solvent can dramatically change with the graft density. At low-graft density, they will assume a "mushroom" conformation with a coil dimension similar to that of free chains. With increasing graft density, the graft chains will be obliged to stretch away from the substrate, forming a "polymer brush." These high-density brushes can be much thicker and range in size from a nanometer-scale to greater than a micrometer-scale. The great increase in thickness for "grafting from" layers is due to much higher grafting densities compared to those of "grafting to" layers.

Photochemical initiation has several advantages over thermal initiation. First, certain functional groups are not thermally stable; therefore, it is desirable to activate polymerization at room temperature. This also simplifies manufacturing processes. Furthermore, most alkylthiolate SAMs are not stable above 70°C and may begin to degrade at the temperatures required for most thermal initiations. Second, photoinitiation is generally faster than thermal initiation. Third, the initiation process may be activated at almost every temperature; this yields great flexibility when controlling the reactivity and processability of a layer. Surface-initiated polymerization has been carried out with a variety of initiators, and Figure 25.13 describes some of the most common photoinitiators [55]. For surface-initiated polymerization applications, these initiators are typically modified and covalently bonded to the substrate to yield a "grafting from" polymerization. Alternatively, photo-sensitizers can be added to bulk solutions in order to abstract hydrogen atoms from the substrate. For example, benzophenone (BP, Figure 25.13d) is converted to a reactive triplet state after ultraviolet (UV) irradiation; this triplet is capable of abstracting hydrogen atoms from various moieties. Tertiary amines or thiolene systems have been activated with photo-sensitizers, but until recently have not been used for surface-initiated polymerization. Other photoinitiators include peroxides (Figure 25.13a) and benzoin derivatives (Figure 25.13c); of the two, only peroxides have been used for surface-initiated polymerization. The most common free radical photoinitiators are derivatives of 2,2′-azobisisobutyronitrile (AIBN, Figure 25.13b), and these have been used by several research groups for "grafting from" polymerizations from various substrates. Recently, controlled free radical polymerizations have gained much recognition owing to their low polydispersities and "living"-like properties [55]. Indeed, "living" polymerizations have a tremendous advantage for surface-initiated polymerization since it is possible to grow block copolymers and to terminate the polymerization with specific end-groups. However, most living free radical polymerizations utilize thermal initiation; for example, atom transfer radical polymerization may be

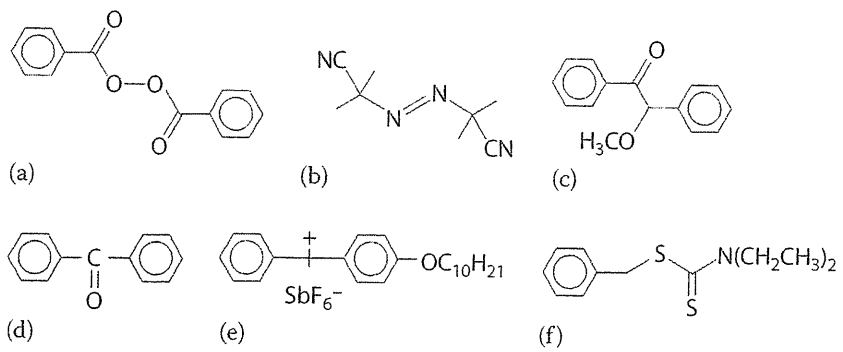

FIGURE 25.13 Various types of photoinitiators: (a) benzoylperoxides, (b) 2,2′-azobisisobutyronitrile compounds based on AIBN, (c) benzoin methylethers, (d) triplet photo-sensitizers, benzophenone (e) onium salts for cationic polymerization, and (f) controlled free radical polymerization with photoiniferters.

used for surface-initiated polymerization, but the rate of initiation and propagation is relatively slow as compared to that of photoinitiation and typically leads to layers that are less than 50 nm thick. Thus, there is a rich variety of photopolymerization strategies that may be utilized in the future, although very few examples of photosurface-initiated polymerization have been reported to date.

25.2.2.4 Poly(MPC)-Grafted Polyethylene

Surface modification is important for improvements in bearing materials. Moro et al. have demonstrated the creation of an artificial hip joint based on the novel concept of "hydration lubrication" by using poly(MPC) (PMPC)-grafted onto the surface of CLPE (PMPC-grafted CLPE); this device is designed to reduce wear and suppress bone resorption [56–58]. A previous study has reported that the hydrogel cartilage surface is assumed to have a brush-like structure: a part of the proteoglycan aggregate brush is bonded with the collagen network on the cartilage surface [49]. Therefore, the bearing surface with PMPC in artificial hip joints is assumed to have a brush-like structure similar to that of articular cartilage (Figure 25.14). The hydration lubrication interface can therefore be regarded to mimic the natural joint cartilage in vivo.

MPC, a methacrylate monomer with a phospholipid polar group in the side chain, is a novel biomaterial designed and developed by Ishihara et al. that mimics the neutral phospholipids of cell membranes [59]. MPC polymers are one of the most common biocompatible and hydrophilic polymers studied thus far, which have potential applications in a variety of fields, such as biology, biomedical science, and surface chemistry, because they possess the unique properties of good biocompatibility, high lubricity and low friction, anti-protein adsorption, and cell membrane-like surface [59–62]. Hence, MPC is hydrophilic and can form a thin film of free water under physiological conditions. Several medical devices have already been developed by utilizing the MPC polymers. These devices have been subjected to clinical use with the approvals of the Ministry of Health, Labour and Welfare (MHLW) of Japan and the Food and Drug Administration (FDA) of the United States; therefore, the efficacy and safety of the MPC polymer as a biomaterial are well established (Table 25.6) [63–82].

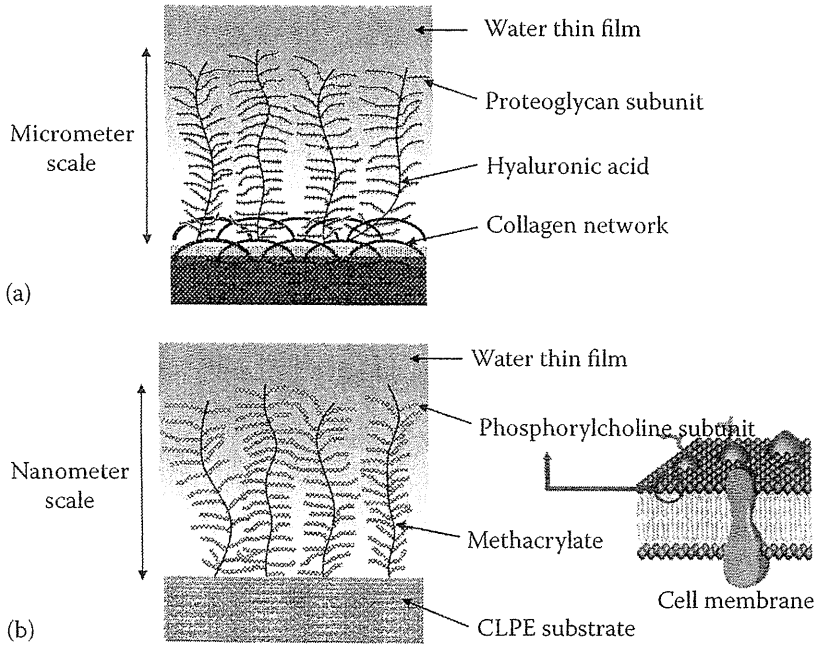

FIGURE 25.14 Schematic model of PMPC-grafted CLPE surface mimicking cartilage. (a) Cartilage. (b) PMPC-grafted CLPE.

TABLE 25.6
Medical Devices with MPC Polymer

Medical Device	Product Name	Manufacturer	Clinical Introduction	Reference
Artificial heart	Evaheart	Sun Medical	Current trial	[63]
Artificial joint	Aquala	Japan Medical Materials	Current trial	[42]
Artificial lung	Mimesys	Sorin Biomedica	2002	[64]
	Synthesis	Sorin Biomedica	2003	[65]
	Physio	Sorin Italia	2005	—
Catheter	Eliminate	Clinical Supply	—	MHLW approval
Contact lens	Proclear	Cooper Vision	1998	FDA approval
Guide wire	Aqua diver	Clinical Supply	—	MHLW approval
	Inter through	Clinical Supply	—	—
	Hunter	Biocompatible	1997	FDA approval
Micro catheter	Londis	Clinical Supply	2005	MHLW approval
Stent	Endeavor	Medtronic	Current trial	[66]
	Endeavor I	Medtronic	Current trial	[67,68]
	Endeavor II	Medtronic	Current trial	[67–69]
	Endeavor II CA	Medtronic	Current trial	[67,68]
	Endeavor III	Medtronic	Current trial	[67,68,70]
	TriMaxx	Abbott Laboratories	2005	[71]
	ZoMaxx	Abbott Laboratories	—	[72]
	Biodiv Ysio	Biocompatible	2000	[73–82]
Tympanostomy tube	—	Gyrus, Grace Medical	2000	FDA approval

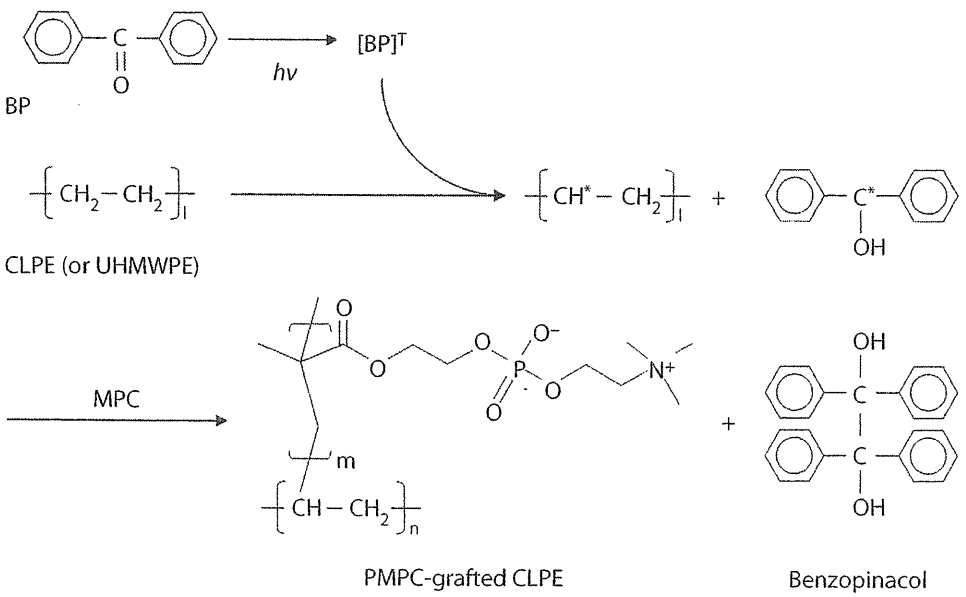

FIGURE 25.15 Schematic illustration of MPC graft polymerization by using the BP system.

The grafting of biocompatible and hydrophilic PMPC with CLPE has been accomplished by using a photo-initiated "grafting-from" polymerization. The photo-initiated "grafting-from" polymerization reaction by using a typical BP photoinitiator is shown in Figure 25.15. First, the physically coated BP on CLPE is excited by UV irradiation. The BP excited to the triplet state extracts a hydrogen atom from the $-CH_2-$ group and then generates a radical that is capable of initiating the graft polymerization of MPC.

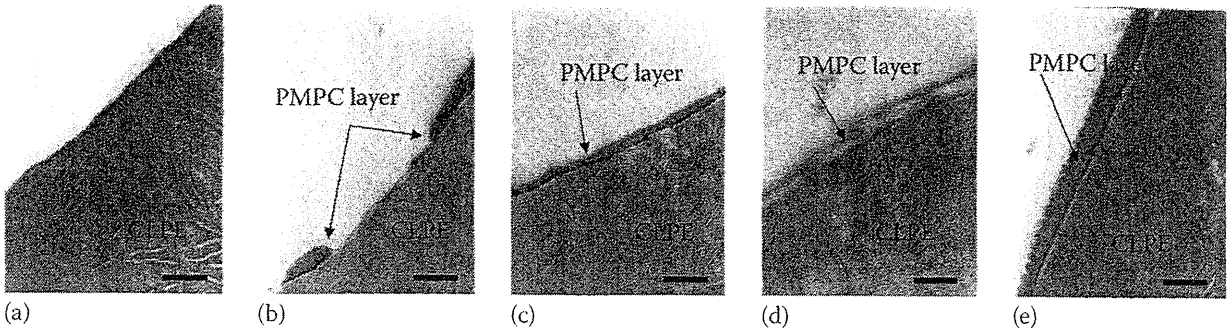

FIGURE 25.16 Cross-sectional TEM images of PMPC-grafted CLPE obtained with a 0.5 mol/L MPC concentration and various photo-irradiation times. Bar: 200 nm. (a) 11 min. (b) 23 min. (c) 45 min. (d) 90 min. (e) 180 min.

This technique has several important benefits as follows: direct grafting of PMPC to CLPE—thereby forming C–C covalent bonding between the PMPC and CLPE substrate, high mobility of the chains of the PMPC, a high density, and controlling the length of the introduced PMPC.

Figure 25.16 shows cross-sectional transmission electron microscope (TEM) images of PMPC-grafted CLPE produced with various photo-irradiation times during polymerization [83]. With photo-irradiation times longer than 45 min, a 100- to 200-nm-thick PMPC-grafted layer was clearly observed on the surface of the CLPE substrate. The MPC-covered region was coexistent with uncovered regions after a photo-irradiation time of 23 min, although the thickness of the covered region on the PMPC layer remained the same (100–200 nm). With photo-irradiation for 11 min, no PMPC layer was observed on the surface of the CLPE. These results indicate that the density of the grafted PMPC can be controlled by the polymerization time. This is attributable to the fact that the number of polymer chains produced in a radical polymerization reaction is generally correlated with the photo-irradiation time.

Figure 25.17 shows the static water-contact angle of PMPC-grafted CLPE as a function of the photo-irradiation time used for polymerization (0.50 mol/L MPC concentration) [83]. The static water-contact angle of untreated CLPE was 90° and decreased markedly with a decrease in the photo-irradiation time. The static water-contact angle decreased as the irradiation time was increased.

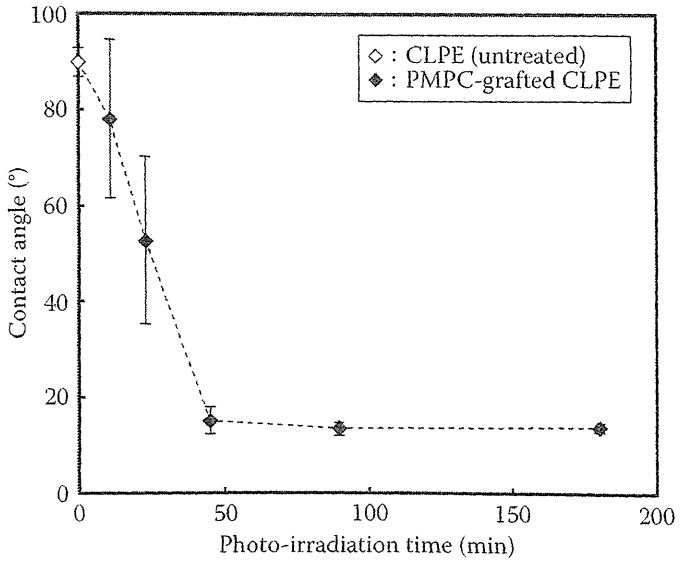

FIGURE 25.17 Static water-contact angle of PMPC-grafted CLPE as a function of the photo-irradiation time with a 0.5 mol/L MPC concentration. Bar: Standard deviations.

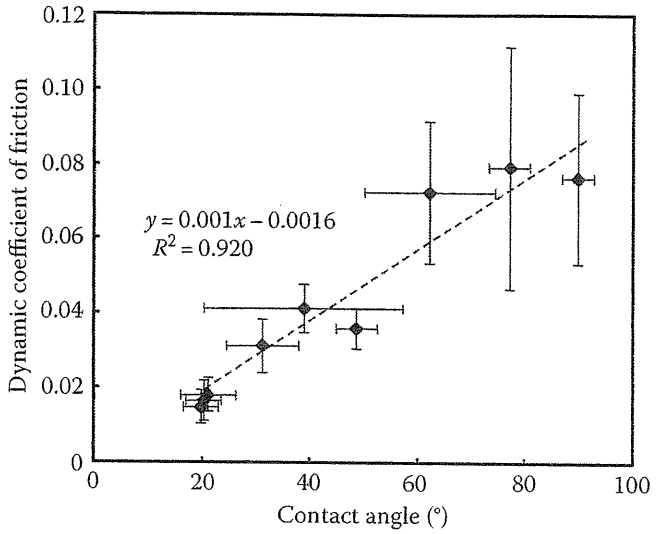

FIGURE 25.18 Relationship between dynamic coefficient of friction and contact angle in the PMPC-grafted CLPE surface. Bar: Standard deviations.

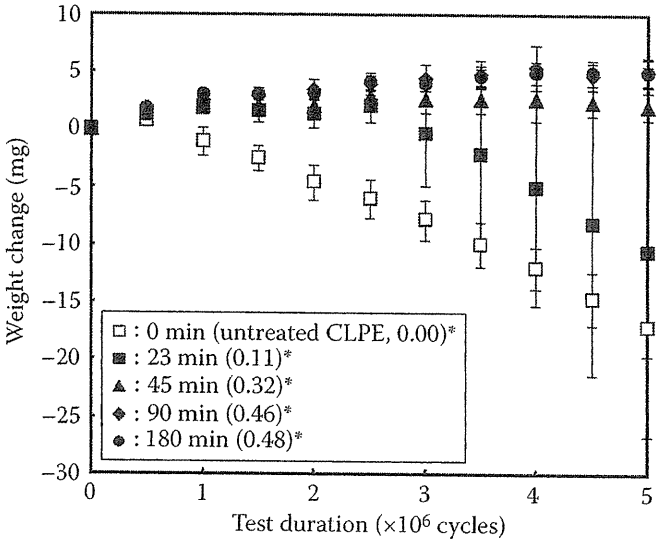

FIGURE 25.19 Weight change (gravimetric wear) of the PMPC-grafted CLPE cups obtained with a 0.5 mol/L MPC concentration and various photo-irradiation times in the hip joint simulator wear test. Bar: Standard deviations. *P–O group indexes are in parentheses.

Figure 25.18 shows the relationship between the dynamic coefficient of friction and the contact angle [84]. The dynamic coefficient of friction tended to increase with the contact angle. This increase was linear to a degree of accuracy, and the correlation coefficient was 0.920.

Figure 25.19 shows the gravimetric wear of PMPC-grafted CLPE with various photo-irradiation times during the hip joint simulation test. The PMPC-grafted CLPE cups were found to wear significantly less than the untreated CLPE cups. The wear of the PMPC-grafted CLPE cups subjected to 23-min photo-irradiation time started to increase after 2.5×10^6 cycles. The PMPC-grafted CLPE cups exhibited a slight increase in weight. This was partially attributable to enhanced fluid absorption in the tested cups than in the load-soak controls. When using the gravimetric method, the weight loss in the tested cups is corrected by subtracting the weight gain in the load-soak controls; however, this correction cannot be perfectly achieved because only the tested cups are continuously subjected to motion and load. Fluid absorption in the tested cups is generally slightly higher than that in the load-soak controls. Consequently, the

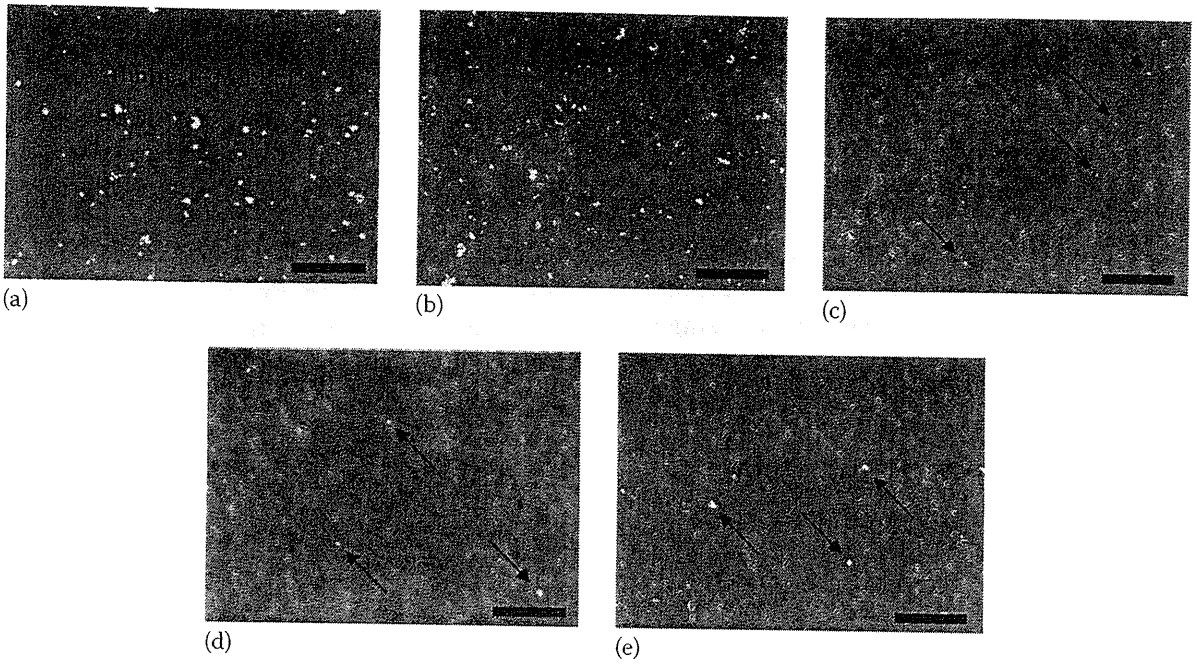

FIGURE 25.20 FE-SEM images of wear particles of the untreated CLPE and PMPC-grafted CLPE with various photo-irradiation times during the 4.5×10^6–5.0×10^6 cycles of the hip joint simulation test. Arrows: wear particles. Bar: 5 μm. (a) 0 min. (b) 23 min. (c) 45 min. (d) 90 min. (e) 180 min.

correction for fluid absorption by using the load-soak data as the correction factor leads to a slight underestimation of the actual weight loss. The initial wear rate is defined as that from the start to 0.5×10^6 cycles, and the steady wear rate is considered as that from 4.0×10^6 to 5.0×10^6 cycles. All the untreated CLPE and PMPC-grafted CLPE cups showed low initial wear rates of −1.42 to −3.74 mg/10^6 cycles. The steady wear rate of the untreated CLPE cups and the PMPC-grafted CLPE cups with a low P–O group index of 0.11 (23-min photo-irradiation time) increased to 5.11 and 5.48 mg/10^6 cycles, respectively. In contrast, the wear rates of the PMPC-grafted CLPE cups with high P–O group indexes, i.e., 0.46 (90-min photo-irradiation time) and 0.48 (180-min photo-irradiation time), were markedly lower at 0.32 and −0.02 mg/10^6 cycles, respectively.

Figure 25.20 shows field emission scanning electron microscope (FE-SEM) images of wear particles of the untreated CLPE and PMPC-grafted CLPE with various photo-irradiation times during the 4.5×10^6–5.0×10^6 cycles of the hip joint simulation test. The wear particles of the untreated CLPE and PMPC-grafted CLPE cups, as characterized by FE-SEM, were predominantly submicrometer-sized granules. The wear particles of the PMPC-grafted CLPE cups with 45-, 90-, and 180-min photo-irradiation times were found to be significantly lesser than those for the untreated CLPE cups and the PMPC-grafted CLPE cups with 23-min photo-irradiation time.

In summary, an artificial hip joint based on the novel concept of "hydration lubrication" was created by using PMPC grafted onto the surface of CLPE for reducing the wear debris of UHMWPE. The approach using "hydration lubrication" is surely novel in the field of orthopedic biomaterials science, and joint replacement with hydration lubrication can pioneer the "next generation" artificial joint. Furthermore, these joint replacements have the potential to be applied in the orthopedic field in the near future [85]. The clinical trial for such joint replacements with hydration lubrication (i.e., PMPC-grafted CLPE acetabular cup) has been started at the University of Tokyo and other hospitals in Japan since 2007. For this novel PMPC-grafted CLPE material, close monitoring of clinical performance and accurate quantification of wear rates would be essential for the early recognition of unforeseen problems.

25.2.3 Poly(Ether-Ether Ketone) Bearing Materials

25.2.3.1 Structure and Properties

Poly(aryl-ether-ketone) (PAEK), including poly(ether-ether-ketone) (PEEK), is a new family of high-performance thermoplastic polymers, consisting of an aromatic backbone molecular chain interconnected by ketone and ether functional groups, i.e., a BP unit is included in its molecular structure. Polyaromatic ketones exhibit enhanced mechanical properties, and their chemical structure is stable, resistant to chemical and radiation damage, and compatible with several reinforcing agents (such as glass and carbon fibers; carbon fiber-reinforced PEEK [CFR-PEEK], Figure 25.21). Therefore, they are considered to be promising materials for not only industrial applications but also biomedical applications.

In the 1980s, the in vivo stability of various PAEK materials and the tissue response to the same were investigated [86]. Recently, PEEK has emerged as the leading high-performance super-engineering plastic candidate for replacing metal implant components, especially in the field of orthopedics and spinal surgery (Table 25.7) [87]. In recent studies, the tribological and bioactive properties of PEEK, which is used as a bearing material and flexible implant in orthopedic and spinal surgeries, has been investigated [88–90]. However, conventional single-component PEEK cannot satisfy these requirements (e.g., antibiofouling, wear resistance, and fixation to a bone) for use as an artificial joint or intervertebral body fusion cage [87]. For further improving the capabilities of PEEK as an implant biomaterial, various studies have focused upon the lubricity and antibiofouling of the polymer, either via reinforcing agents or surface modifications [91,92]. Therefore, multicomponent polymer systems have been designed in order to synthesize new multifunctional

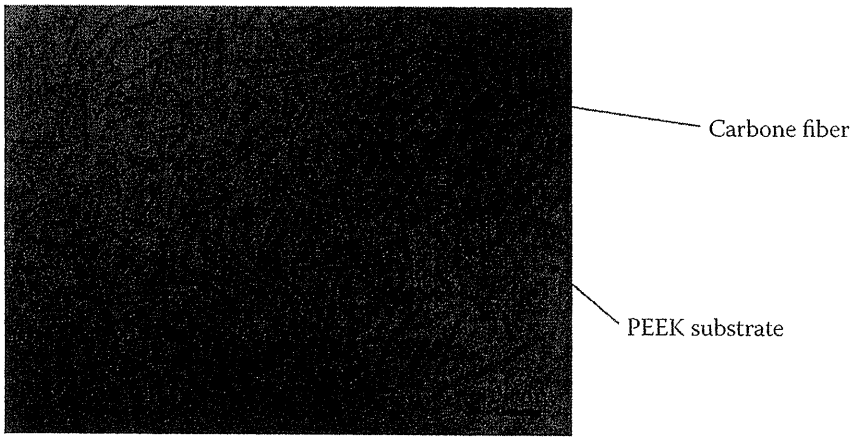

FIGURE 25.21 Fluorescence microscopic images of CFR-PEEK. Bar: 100μm.

TABLE 25.7
Typical Physical and Chemical Properties of PEEK and CFR-PEEK

Property	PEEK	30% CFR-PEEK	60% CFR-PEEK
Molecular weight (10^6 g/mol)	0.08–0.12	0.08–0.12	0.08–0.12
Melting temperature (°C)	343	343	—
Poisson's ratio	0.36–0.40	0.40–0.44	0.38–0.44
Specific gravity	1.3	1.4	1.6
Flexural modulus (GPa)	4	20	135
Tensile ultimate strength (MPa)	93–97	170–228	>2000
Elongation (%)	30–40	1–2	1
Crystallinity (%)	30–35	30–35	30–35

biomaterials. In order to use PEEK and related composites in the implant applications, they can be engineered to have a wide range of physical, mechanical, and surface properties.

25.2.3.2 Tribological Properties

In the 1990s, CFR-PEEK was evaluated as a bearing material for hip and knee joint replacement [88]. Wang et al. carried out a more comprehensive tribological investigation of PEEK composites for both hip and knee joint replacements. CFR-PEEK formulations were blended with 20%–30% mass discontinuous polyacrylonitrile (PAN) or pitch fibers. Under higher stress, cylinder-on-flat loading conditions, the PEEK composites exhibited higher wear rates than conventional UHMWPE. In contrast, under the lower stress hip simulator test conditions, all the PEEK composites had substantially lower wear rates than conventional UHMWPE, with the lowest wear observed between 30% pitch CFR-PEEK against ceramics. In contrast, unreinforced PEEK wore at six times the rate of UHMWPE. The results of this study underscored the importance of fiber reinforcement in lowering stress and conforming contact applications and provided a further basis for exploring PEEK composites for hip joint replacements, especially in combination with ceramics as opposed to Co-Cr heads. Therefore, alumina became the femoral head material of choice for THA applications with CFR-PEEK. Co-Cr heads, when used in conjunction with CFR-PEEK liners, exhibited substantially higher wear, with observations of scratching of the metallic surface by the carbon fibers. On the other hand, this study also suggested that PEEK composites were unsuitable for knee applications, regardless of the fiber content of the composite or the type of the counter surface. The authors recommended that the composite materials should not be used as a tibial insert for knee joint replacement.

To validate the in vivo wear behavior and compatibility of CFR-PEEK wear debris, a clinical study was initiated in Italy starting in 2001 using the ABG II total hip system (Stryker SA, Montreux, Switzerland). The CFR-PEEK liners were fabricated from injection-molded PEEK blended with 30% pitch fibers, and the bearing surfaces were machined to achieve the desired final tolerance. After a mean follow-up period of 3 years, none of the liners needed to be revised due to aseptic loosening. This clinical trial is still ongoing, and the detailed results have not yet been published. Overall, the available preliminary clinical data support the short-term effectiveness of CFR-PEEK as a bearing material for hip joint replacement. However, in a conventional hip joint replacement design, the current data do not yet demonstrate a long-term clinical advantage of CFR-PEEK over other well-established bearing alternatives, such as CLPE.

25.2.3.3 Surface Modification

On the other hand, surface modification is one of the most important technologies for the preparation of new multifunctional biomaterials for satisfying several requirements. Surface modifications used today include coating, blending, and grafting.

It is well known that when BP is exposed to photo-irradiation such as ultraviolet-ray (UV)-irradiation, a pinacolization reaction is induced; this results in the formation of semi-benzopinacol radicals (i.e., ketyl radicals) that act as photo-initiators. Therefore, in this study, we have focused upon a BP unit in PEEK and formulated a novel self-initiated surface-graft polymerization method that utilizes the BP unit in "graft from" polymerization (Figure 25.22) [93,94]. This polymerization reaction involving free radicals is photoinduced by UV-irradiation. Under UV-irradiation, a BP unit in PEEK can undergo the following reactions in monomeric aqueous solutions [95–101] as follows: the pinacolization reaction (photoreduction by H-abstraction of a BP unit in PEEK) results in the formation of a semi-benzopinacol radical, which can initiate the graft-from polymerization of the feed monomer as the main reaction, and the graft-to polymerization (the radical chain end of the active-polymer couples with the semi-benzopinacol radical of the PEEK surface) as a subreaction. In addition, a photoscission reaction occurs as a subreaction, which may not need a hydrogen (H) donor. The cleavage reaction induces recombination and graft-from polymerization. When water polymerization is performed in the presence of an H-donor, a phenol unit may be subsequentially formed due to H-abstraction. This technique enables the direct grafting of the functional polymer

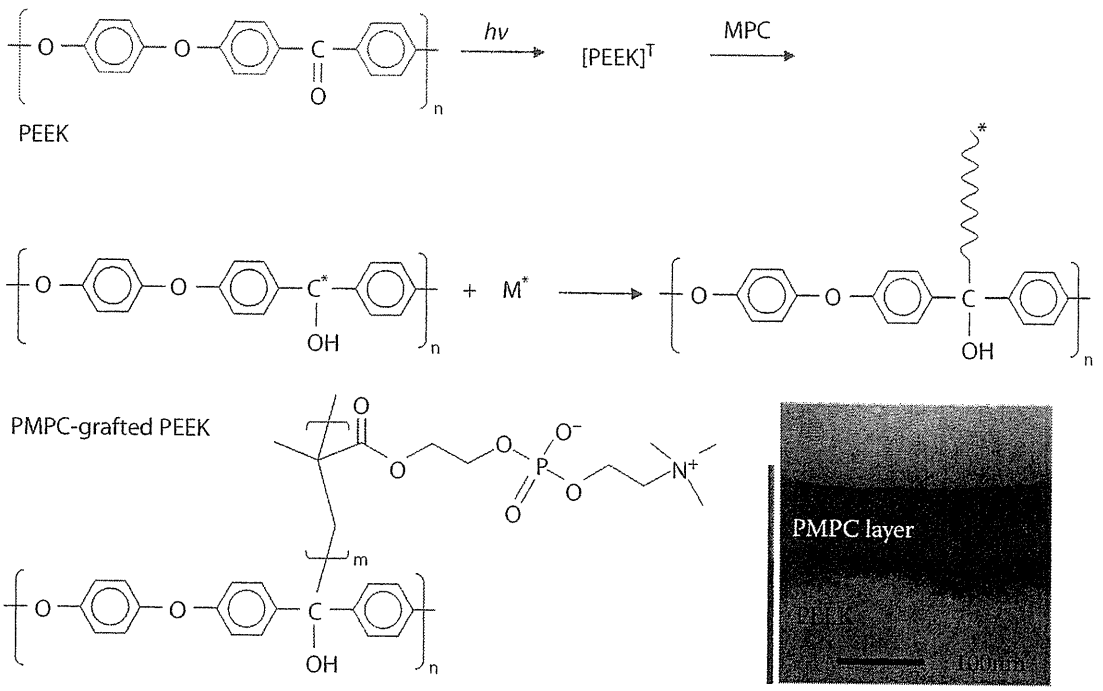

FIGURE 25.22 Schematic illustration for the preparation and cross-sectional TEM image of PMPC-grafted PEEK.

onto the PEEK surface in the absence of a photoinitiator, thereby resulting in the formation of a C–C covalent bond between the functional polymer and PEEK substrate.

Kyomoto et al. demonstrated the fabrication of a biocompatible and highly hydrophilic nanometer-scale-modified surface by PMPC-grafting onto the self-initiated PEEK surface using a photo-induced pinacolization reaction (Figure 25.22) [93,94].

This novel and simple self-initiated surface-graft polymerization on the PEEK surface induces unique properties such as lubricity and anti-protein adsorption by PMPC grafting, which are novel phenomena in the field of orthopedic and spinal surgery (Figure 25.23). Moreover, the fabrications of the PMPC-grafted PEEK and CFR-PEEK can result in next-generation orthopedic and spinal applications.

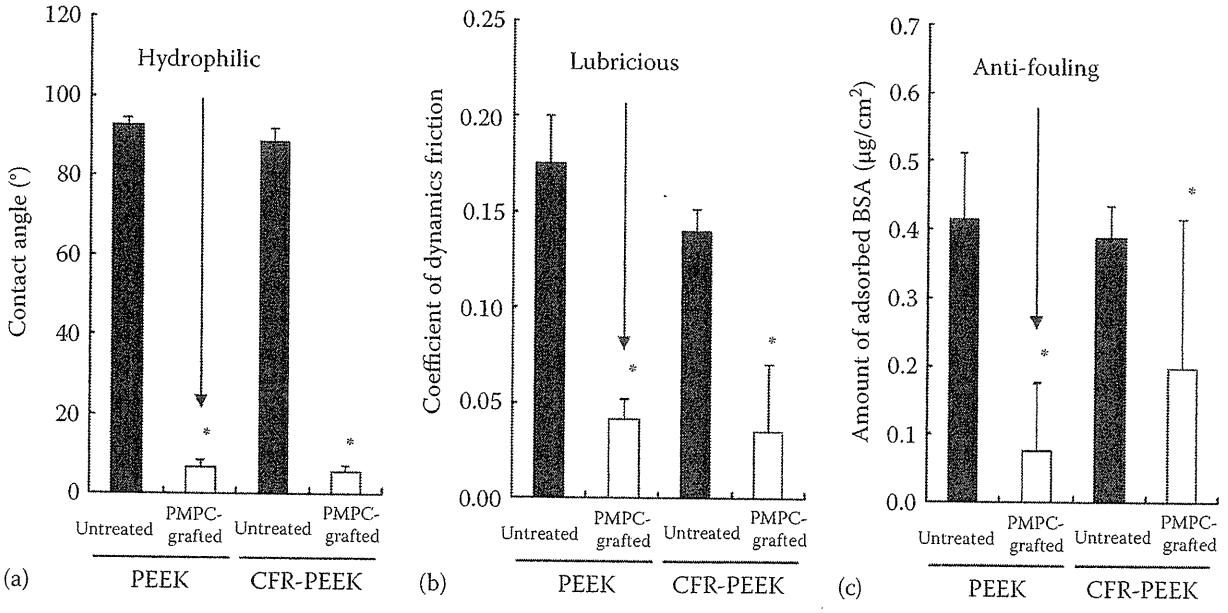

FIGURE 25.23 (a) Static water-contact angle, (b) coefficient of dynamic friction, and (c) amount of adsorbed BSA of PMPC-grafted PEEK and CFR-PEEK. *t-test, significant difference ($p < 0.05$) as compared to the untreated PEEK and CFR-PEEK, respectively.