10 Bioceramics for Hip and Knee Implants

Ikra Iftekhar Shuvo
Massachusetts Institute of Technology

Lovely Khandakar
University of Manitoba

Sara V. Fernandez and Canan Dagdeviren
Massachusetts Institute of Technology

10.1 INTRODUCTION

Reconstructive and regenerative orthopedic surgeries have generated considerable interest in fabricating artificial body parts for implants. Medical advancements and developments have heightened the use of biomaterials for reclamation of damaged body parts. Among the different categories of biomaterials, bioceramics have gained popularity in prosthetics (an artificial mechanical device designed to replace the biological part). Bioceramics are biocompatible to humans and other mammals and can therefore be used for repairing any unfixed parts. Since bioceramics closely resemble that of the host tissue, it can promote a regenerative response in the organism (Dorozhkin 2010). Notably, the bioceramics contribute to minimizing exposure to metallic surfaces, thereby augmenting the prosthetic experience of the user by reducing the source of potential sensitizing ions (Piconi and Maccauro 2015).

In orthopedic surgeries, total knee arthroplasty (TKA) and total hip arthroplasty (THA) outpace every other surgery and, therefore, incur high cost and outcome durability (Schwartz et al. 2020). Superior biocompatibility, endurance to a larger degree of torques, load-bearing capacity, low density, and high corrosion/wear resistance of the bioceramic implants have intensified their demand in THA/TKA surgical procedures. While THA requires replacement of the upper femur (thigh bone) and resurfacing/replacement of the mating pelvis (hip bone), TKA refers to the replacement of the diseased cartilage surface of the lower femur, tibia, and the patella (Joseph 2003). Due to the lower reactivity, early stabilization, and longer functional life, bioceramic implants demonstrate the potential to replicate the mechanical behavior of original bones (Shekhawat et al. 2021). Pragmatically, the finite lifespan of the ceramic implants could also necessitate revision surgeries for TKA/THA patients (rTKA/rTHA). In addition, any unexpected mechanical mismatch or infection from ceramic debris could cause premature failure of knee and hip joint implants (Shekhawat et al. 2021). A report by the Department of Orthopedic Surgery of the Emory University

DOI: 10.1201/9781003258353-13

School of Medicine forecasted an increase of 70% and 182% incidents in rTHA and rTKA, respectively, from 2014 to 2030 (Schwartz et al. 2020). Alarmingly, just from prosthetic joint infection, rTHA and rTKA are expected to rise by 176% (from 2,808 cases in 2002 to 16,169 cases in 2030) and 170% (from 9,089 cases in 2002 to 53,569 cases in 2030), respectively. Between 2002 and 2014, rTKA increased three times more than rTHA. Therefore, it is not at all a trivial matter to properly understand the selection criteria, properties, and evidence-driven cases of the bioceramics to help prepare for the growing trends of the knee and hip joint replacement surgeries.

10.2 MARKET SIZE

Dental industries comprise the lion's share of the use of bioceramics, which accounts for about 42% of the total application (Technavio Research 2017). After dental applications, the orthopedic surgeries account for the next largest segment of the global bioceramics market, followed by areas such as cardiovascular, drug delivery, and tissue engineering. The global market value of bioceramics was US$1 billion in 2001 (Vallet-Regí 2001), which reached US$14 billion in 2020 and has been projected to be US$23 billion by 2031 (Fact.MR 2021). The demand for bioceramics materials is propelled by the increase in life expectancy as well as advancements in biological implants. In the USA alone, ~0.5 million total hip arthroplasty (THA) surgeries were done in 2020, and the number is predicted to rise to 1.5 million surgeries/year by 2040 (Transparency Market Research 2022). Approximately 0.5 million total knee arthroplasty (TKA) surgeries/year were performed in the USA as of 2010 at the expense of $15,000 USD/patient, totaling an aggregate of US$9 billion/year (Cram et al. 2012). The number of surgeries surpassed 1 million/year in 2020, and a 401% increase is expected by 2040 to ~4 million replacements/year (Rheumatology Advisor 2019). A study conducted by Mayo clinic, presented at the American Academy of Orthopedic Surgeons (AAOS) annual meeting, revealed that both TKA and THA are comparatively more prevalent in women than in men (3 and 1.4 million women out of 4.7 and 2.5 million US people who underwent TKA and THA in 2014) (Mayo Clinic 2014).

10.3 BIOCERAMIC COMPONENTS FOR HIP/KNEE JOINTS

A recent report has predicted that 30% of hospital beds could soon become occupied by osteoporosis patients, i.e., patients with a porous bone disease that leads to weak and brittle bones. This "silent disease" slows down the body's natural new bone synthesis process (Habraken et al. 2016) to the point where the breakdown process of old bone tissue outpaces the new bone tissue formation process; consequently, bones become fragile and break easily. Unfortunately, 20% of the patients with an osteoporotic hip fracture die within the first year after surgery. Such an alarming number indicates the need for advanced materials for bone replacements.

There are both natural and artificial materials available for bone replacements (Vallet-Regí 2014). The natural option includes autologous bone (self-donor), homologous bone (tissue bank), and heterologous bone (animal sourced). The natural options became less appealing due to their risk of disease transmission or scarcity of materials. The artificial option includes bioceramics. Interestingly, bioceramics are considered materials that exhibit the best resemblance to the mineral components of the bone joints.

Knee and hip joints are among the largest joints in the human body, supporting body weight and locomotion. Unfortunately, hip and knee replacements are the most common arthroplasty surgery. Knee-joint pain can arise from wear and tear from daily activities like walking, jogging, or lifting. Joint fractures, torn ligaments, patellar instability, torn meniscus, or ligaments injuries are also a few of the common causes of knee surgeries. Recent years have seen the burgeoning applications of bioceramics and their composites in implants or orthopedic surgeries: bioactive glasses for cranial repair, zirconia in load-bearing components, alumina for keratoprostheses or orthopedic knee fixation devices, and so on. Bioceramics are also used in condyles and tibial plateau for knee replacement (Antoniac 2016).

Figure 10.1 illustrates the application of a non-metal implant for TKA using bioceramic composites based on alumina (Al_2O_3) and zirconia (ZrO_2). TKA implants typically consist of three main components: femoral, tibial, and patellar part (Piconi and Maccauro 2015). The tibial component is a flat platform with a cushion of wear-resistive solid plastic, polyethylene. Besides a metallic platform, a bioceramic platform could be used for the tibial component. By replacing metal condyles with bioceramic-made condyles, the wear-performance of the polyethylene insert could be augmented. This is due to the higher scratch hardness of bioceramics. Thus, it provides better resistance

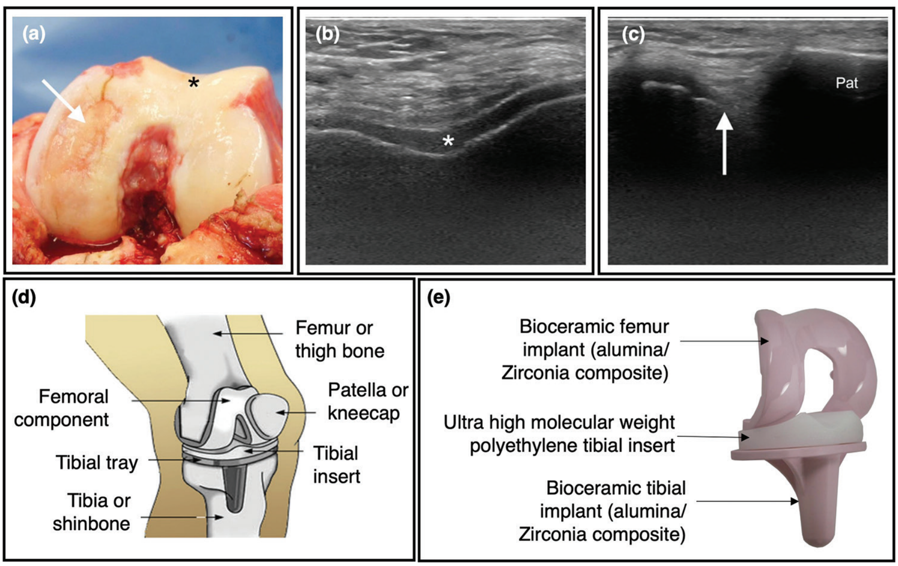

FIGURE 10.1 Cartilage degeneration in late-stage knee osteoarthritis observed during the total knee arthroplasty (TKA). (a) Intraoperative photography of the femoral cartilage exhibits intact (asterisk) and damaged cartilage (arrow) at the femoral sulcus and medial femoral condyle of the knee, respectively (Nevalainen et al. 2018). The corresponding ultrasonographic (b) and radiographic (c) images demonstrate the normal (asterisk) and degenerated (arrow) area of the femoral cartilage. The schematic (d) shows the implant components (femoral, tibial, and tibial insert components) during a TKA (Bahraminasab and Jahan 2011), and the digital photograph (e) displays the non-metal implantable total knee replacement device made of bioceramic composites (from alumina and zirconia) (Meier et al. 2016).

to damage and protects the polished surface of the articulating condyles. Knee arthroplasty is classified into two categories: total and partial knee arthroplasty (TKA/PkA). During TKA, all these three parts are replaced with prostheses. However, for partial knee arthroplasty (PKA), only the affected region of the knee is replaced.

Like knee arthroplasty, hip arthroplasty is also a surgical procedure performed to relieve pain and restore the functionality of the hip using an artificial implant. The need for a total hip arthroplasty may arise from several issues, like injuries/accidents, menopause in the case of women, age-related bone diseases, and bone degeneration among the older populations. Hip arthroplasty can be of two types, which are total and partial hip arthroplasty (THA/PHA). THA includes replacement of both ball (femur head) and socket, while PHA involves replacing only the ball.

Figure 10.2 exhibits a hip stem implant used in THA. The stems are typically made of different alloys of titanium (Ti) or cobalt-chromium (CoCr). The cups could also be made of Ti or polyethylene. For liner, tough plastic materials are generally used, UHMWPE, for instance, which has high wear and abrasion resistance. Alumina and its composites are mainly used for the femoral head; however, CoCr-based and metallic femoral heads are also available. Monoclinic zirconia is used as a coating on the surface of metallic ball heads to better the wear behavior of metal-on-polyethylene (MoPE) implant bearings.

While marketing any prostheses or bone implants, the morphological study of the target market is crucial for successful engineering design. For instance, a study

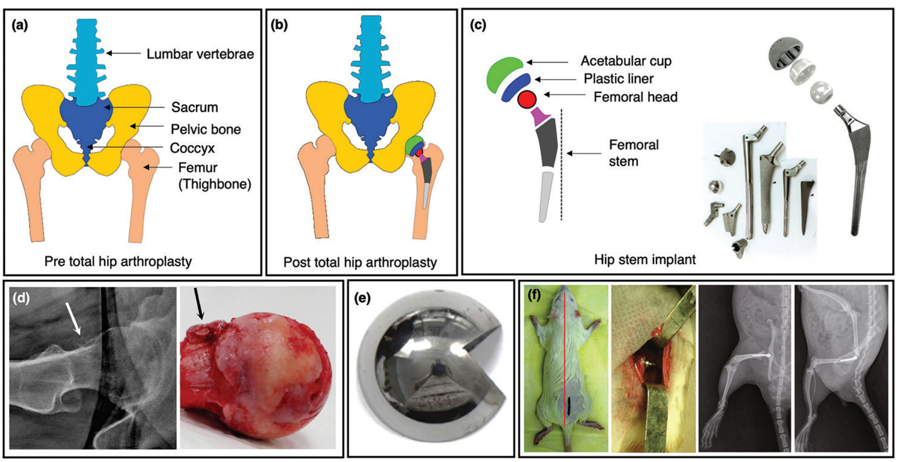

FIGURE 10.2 Hip stem prosthesis for total hip arthroplasty (THA) (or replacement) shown in the (a–c) schematics with photographic image of a commercial femoral hip implant (c) (Murr et al. 2012). Radiographic image demonstrates the presence of osteophytes (bone lumps causing painful joints) (white arrowhead) (d) in a patient with late-stage hip osteoarthritis, which is clearly distinguishable (black arrowhead) in the femoral head removed during THA (Nevalainen et al. 2020). As implants, metallic femoral heads (e) could be used in a metal-on-polyethylene (MoPE) implant framework (Cui et al. 2016). (f) Rat models are used in alumina or different material-based THA experiments to investigate osteolysis in aseptic loosening by implanting man-made prostheses (Li et al. 2018).

was conducted in 2007, which was aimed to compare the need for a revision TKA (rTKA) surgery between people of two ethnic background: 73 Japanese and 76 Americans with TKA (Iorio et al. 2007). This study showed that the longevity of the implants and the needs for revision surgeries for the two groups were different. The mean implant longevity for the Japanese patients was 6.6 years, with 4.1% of patients requiring revision surgery, while only 2.6% of the American patients needed revision surgery, demonstrating a mean 9 years of the longevity of their prostheses. The study hypothesized that the anomalies of the implant performance between two test subject groups could be attributed to the flawed marketing campaign of the prosthetic implants without considering their morphological differences.

10.4 CLASSIFICATION OF BIOCERAMICS

Biomaterials are any synthetic materials used for making devices to replace part of a living system or to function in direct contact with living tissue (Wong and Bronzino 2007; Agrawal 1998). In the field of regenerative medicine, biomaterials play a vital role in cell proliferation, adhesion, spreading, differentiation, and tissue formation in all three space dimensions (Antoniac 2016). Superior biocompatibility and relevant mechanical performance are the two critical reasons for which biomaterials are becoming popular in clinical applications (Kumar and Baino 2020). Biocompatibility of the biomaterials comes from their specific chemical compositions and topographical features which directs the cellular response toward tissue regeneration. Some other preferable qualities of biomaterials include osteo-inductivity (ability to induce osteo-genesis, i.e., bone formation), osteo-conductivity (ability to grow bone on a osteo-conductive surface and conform to it), and osteo-integration or osseo-integration (ability to fuse so strongly with the bone that it cannot be disintegrated without fracture) (Stevens 2008). In contrast to these highly biocompatible biomaterials, low-biocompatible prosthesis materials like Cu, Ag, or bone cements exhibit very low to zero osteo-conduction (Albrektsson and Johansson 2001). Generally, biomaterials are divided into four types: (i) biometals, (ii) biopolymers, (iii) bioceramics, and (iv) biocomposites (Dorozhkin 2011). The following discussion will focus mainly on bioceramics and their applications for knee and hip joint implants.

Typically, bioceramics can be categorized into three classes: (i) bioinert, (ii) bioactive, and (iii) bioresorbable materials. However, it must be noted that there are numerous studies where authors study bioactive and bioresorbable materials together – calcium phosphate (CaP) and hydroxyapatite (HAp) for instance – and categorize them as second-generation bioceramics, in contrast to first-generation bioinert and third-generation scaffolds for tissue engineering (Punj et al. 2021). Among the bioceramics, bioinert materials (e.g., alumina or zirconia) can co-exist with the tissues without causing much noticeable change; however, bioactive materials (e.g., glass ceramics) can form direct biochemical bonds with the tissue (Dubok 2000). Bioresorbable materials, on the other hand, undergo gradual dissolution in the biosystem of the organism and are replaced by bone tissues without toxicity or rejection. Table 10.1 gives a summary of these three categories of bioceramics, and Figure 10.3 illustrates a comparison of the different mechanical properties of ceramic and glass materials.

TABLE 10.1
Summary on the Three Categories of Bioceramics

Subjects	Bioinert Materials	Bioactive Materials	Bioresorbable Materials
Reactivity with the host	Physical and mechanical properties remain constant and do not exhibit any reactivity with the host tissues.	Undergoes osteo-conduction and able to form direct chemical bond with host tissue and, thus, enables fixation of the implant within host skeletal system	With time they get absorbed and replaced by bone in the bone tissue, i.e., the resorbed ceramics are replaced by endogenous tissue
Applications	Typically used as bearing surface for joint prostheses and in making bone plate, bone screw, femoral head, and parts of knee, hip, shoulder, wrist, elbow, tooth, etc.	Bone grafts and coating material for metallic prosthetics or implants	In bone defect or void fillers in the form of granules, bone grafts and replacement of the surrounding tissue
Examples[b]	Alumina, zirconia	Bioglass®, apatite-wollastonite (AW) containing glass ceramics	Calcium sulfates (CaSs), calcium phosphates (CaPs), hydroxyapatite (HA)
Incorporation into bone	Following the pattern of "contact osteogenesis"	Following the pattern of "bonding osteogenesis"	Similar to "contact osteogenesis"
Major advantage	High strength, non-toxicity, excellent corrosion resistance, superior stability, and in-vivo biocompatibility	In-vivo biocompatibility and rapid tissue bonding	Eliminates the need of surgical revisions or second surgery it
Major disadvantage	Material never transforms into bone, and sometimes may cause negligible foreign body reaction	Low fracture toughness and mechanical strength	Low interfacial stability between bone tissues and bioresorbable materials
Hardness (HV)[a]	High (e.g., 1,200 – 2,000)	Low (e.g., 350 – 600)	–
Tensile strength (GPa)[a]	High (250 – 400)	Low (e.g., 0.12 – 122)	Lower (0.03 – 0.2)
Compressive strength (MPa)[a]	1,600 – 4,000	600 – >2,000	20 – 900
Fracture toughness (MPa. $m^{1/2}$)[a]	5.0 – 12.0	0.6 – 1.0	< 1.0

[a] Shekhawat et al. (2021).
[b] Punj et al. (2021).

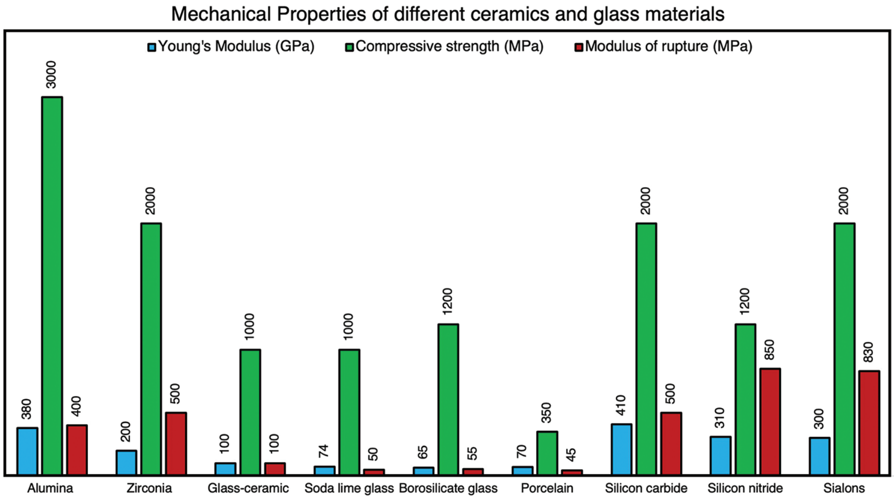

FIGURE 10.3 Mechanical properties of different ceramics and glasses. (Based on data from Park (2009).)

10.5 OVERVIEW OF DIFFERENT TYPES OF BIOCERAMICS

A critical review of different types of bioceramic materials used in hip and knee implants is discussed in the following sections.

10.5.1 Bioinert Ceramics

It is hard to say whether any material exists that is completely inert or 100% safe (to be used as body implant – can we use?) for body implants; however, bioinert ceramic materials do have comparatively stable physiochemical properties (Kumar et al. 2018). Oxide ceramic materials, for example, are stable, inorganic, bioinert materials: they do not undergo further oxidative processes and stay chemically inert the entire time they reside inside an organism (Piconi and Sprio 2021). Hence, the chemical stability of oxides makes them an ideal choice for bioceramics. Alumina (Al_2O_3), zircona (ZrO_2), and their composites are the major classes of bioinert materials widely used in orthopedics and have gained popularity for applications in arthroprosthetic surgeries for joint replacements. Table 10.2 synopsizes the results from different clinical trials and case studies that incorporated bioinert ceramics for hip and knee implants.

10.5.1.1 Alumina (Al_2O_3)

Al_2O_3 is the most widely used bioinert ceramic for THA (Vallet-Regí 2001). Alumina displays good performance under compression, although it is brittle under tension. The tensile strength of alumina is better at a higher density and smaller grain size. By incorporating low-melting magnesium oxide (MgO) into the ceramics, full density at a lower temperature can be reached, thus decreasing grain growth and increasing ceramic strength. Unfortunately, the addition of MgO reduces the hardness – a setback that could be solved by adding small amount of chromia (Cr_2O_3) (Piconi et al. 2003).

TABLE 10.2
Overview of Different Studies on Bioceramics Used in Clinical Trials and Experimental Research Works

Material	Application	Strength	Limitation	Additional Remarks	Ref.
Third-generation cementless alumina CoC (ceramic-on-ceramic) bearings	Total hip arthroplasty	Wear-resistance, excellent implant survival rate, and low osteolysis and ceramic fractures	Squeaking was identified due to edge loading and lubrication loss	94.2% survival rate at 20 years	Xu et al. (2022)
Alumina sandwich liner	Total hip arthroplasty	Stable formation of bone without any infections	High risk of liner fracture at a mean 7.3 years follow-up due to design defects	91.4% survival rate at 12 years	He et al. (2022)
Oxidized zirconium (Oxinium)	Femoral component for total knee arthroplasty	Applicable as an alternative to cobalt-chromium bearing surface that could undergo up to 1,000 lbf (68,400 psi) fatigue load reduces mechanical failures	Femoral component fracture and debonding due to poor osteotomy and cementing technique at the implant interface	First reported failure case of the Oxinium-based femoral implant	Ichimura et al. (2022)
Magnesia partially stabilized zirconia (MgPSZ)	Femoral component for revision total knee arthroplasty	Bearing surfaces made of MgPSZ are known to prevent the release of any metallic ions or debris	Less information is available to draw any conclusion because of the proprietary nature of the implant designed with the MgPSZ materials	A good candidate as implant components for patients displaying clinical signs of metal allergy or sensitivity	Whiteside (2022)
Alumina-toughened zirconia (ATZ)	Arthroplasty for hip resurfacing	Improved fixation stability due to increased contact area by 1.8 times with the bone material	Titanium-based inner layer is required to improve the stability	The fixation stability could be optimized by carefully choosing the bone material and specimen size	Vogel et al. (2022)

Alternatively, mechanical property could be improved through a hot isostatic pressing (HIP) process, which involves shaping at a high pressure and temperature and produces a high-density ceramic having limited grain growth (López 2014).

Al_2O_3 can also be added to different bioceramics to improve their performance; examples include β-tricalcium phosphate (β-$Ca_3(PO_4)_2$ or β-TCP), which displays excellent osteo-conductivity and biocompatibility with the physiological environment. Its bone-like chemical composition makes it a suitable alternative for bone graft. However, its application in the human body is limited by its reputation of having weak rupture resistance (Sprio et al. 2013). Barkallah et al. demonstrated the potential of Al_2O_3 to improve the overall mechanical properties of β-TCP-based composites (Barkallah et al. 2018). This collaboration between French and Tunisian researchers showed that the addition of Al_2O_3 with 10 wt% TCP and 5 wt% titania (TiO_2) powder improved the overall mechanical properties of the bioceramics, leading to a compressive strength of 352 MPa, flexural strength of 98 MPa, tensile strength 86.65 MPa, and fracture toughness of 3 MPa $m^{1/2}$. In 2021, these researchers studied the tribological (i.e., friction, wear, lubrication, and design) behaviors of the composites, using 2D profilometer and SEM analysis to measure wear volume and associated mechanism, respectively (Barkallah et al. 2021). The result showed that the combination of β-TCP, 10 wt% Al_2O_3, and 5 wt% TiO_2 produced the best composites: the best wear resistance and microhardness with the lowest friction coefficient (Figure 10.4).

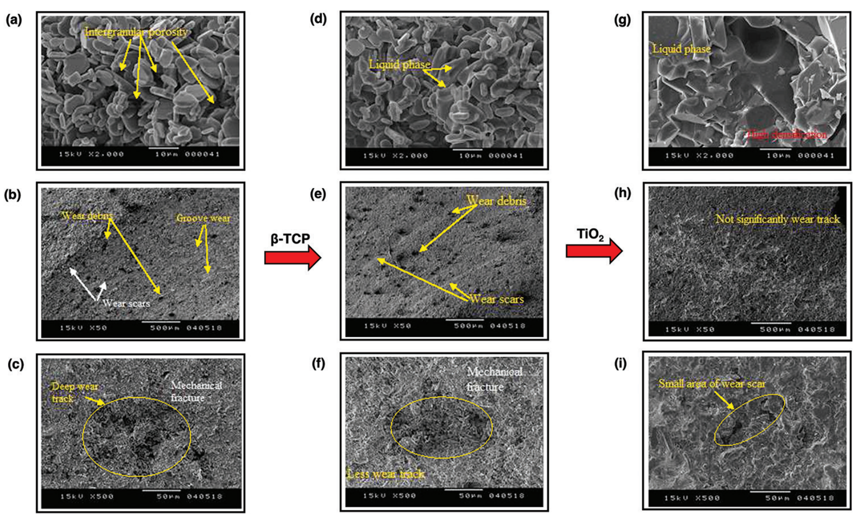

FIGURE 10.4 SEM micrographs of alumina Al_2O_3 and its composites with β-tricalcium phosphate (β-TCP) and titania (TiO_2) (Barkallah et al. 2021). (a) Unworn intergranular porous and (b, c) worn surface of 100% pure Al_2O_3. (d) Adding 10 wt% β-TCP with the Al_2O_3 produces composites with finer microstructures as a liquid phase emergence on the unworn surface, and consequently, a reduced widths of wear scars are seen on the (e, f) worn surface, improving its fracture toughness property. (g) Further addition of the 5 wt% TiO_2 enhances the liquid phase between TCP and TiO_2 as seen in the unworn surface of the composite. (h, i) As a result, the specimens become more dense, compact, and the debris are less deep, leading to an overall improvement of the tribological properties, i.e., lower wear volume and friction coefficient.

10.5.1.2 Zirconia (ZrO_2)

ZrO_2 exists in three different crystalline structures at ambient pressure: monoclinic, tetragonal, and cubic (Weng et al. 2021). At 1,000°C–1,200°C, zirconia undergoes an allotropic phase transition from monoclinic to tetragonal, and at 2,370°C, the phase changes from tetragonal to cubic (Park 2009a,b). During the manufacturing stages, ball milling hours can have significant effect on the crystallite size and lattice strain of the zirconia (Elsen et al. 2017). Prolonged ball milling results in reduced crystallite size. For example, ball milling of 4, 6, or 8 hours will produce a crystallite size of 34, 28, and 25 nm, respectively, with a corresponding lattice strain of 0.000236, 0.000157, and 0.000104 (unit paper also have no unit).

Pure ZrO_2 is not suitable for direct application due to the difficulty of transformation from one form to another (López 2014). Any change in shape and volume during the transformation process can easily lead to material degradation and cracking. Furthermore, ZrO_2 manifests comparatively higher level of wear during in-vivo studies compared to in-vitro studies (Dawson-Amoah et al. 2020). The underlying causes are attributed to the presence of proteins, pH of bodily fluids, and salts in contrast to the artificial ageing simulations using autoclaves. Figure 10.5 summarizes the THA case study of a 50-year-old female with a 5-year history of right-hip pain, a non-trivial family history of father with colon cancer and mother with breast cancer and Alzheimer's. The patient underwent a ceramic-on-polyethylene THA.

The mechanical performance of zirconia can be improved by adding stabilizing agents such as MgO, CaO (calcium oxide) or Y_2O_3 (yttrium oxide), during the fabrication process to limit the phase transformation. For instance, a high degree of flexural strength and fracture toughness of zirconia can be observed when it is partially stabilized with Y-TZP (yttrium tetragonal zirconium polycrystal) (Park 2009). The increase in the fracture toughness is a result of the cessation of crack propagation during the phase transformation. On the other hand, yttrium magnesium oxide-stabilized zirconia (Y-Mg-PSZ) could be added for higher Weibull modulus compared to Y-TZP.

The size of the pore is an important factor for bone growth: it should be sufficiently large to accommodate development of the organic and inorganic

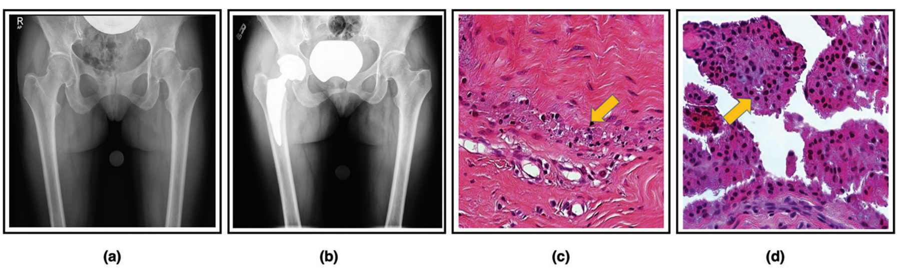

FIGURE 10.5 Radiographs of the THA implant on the right-hip of a female patient and pathologic evaluation during the revision period (Dawson-Amoah et al. 2020). (a, b) The radiographs exhibit the pre- and post-operative THA of the right-hip. (c, d) During the revision surgery, histological investigation of the synovium tissues confirms the macrophagic infiltration of ZrO_2 debris (shown in arrow) from the ceramic head.

components of the bone along with the bone cells (Klawitter and Hulbert 1971). Optimum pore size allows mineralization and provides space and a smooth path for growth of vascular tissue. Pore size of approximately 200 μ must be provided for proper development of osteons. Increasing the pore size and surface area of the bioceramics may increase bone-forming bioactivity by accelerating biological apatite deposition (Antoniac 2016). Research conducted in 2016 using 3Y-TZP and steric acid found that differing contents of stearic acid powder can be used to achieve the desired mechanical property and pore size in zirconia (Li et al. 2016). In addition to pore size, the inter-connectivity among the pores plays a major role in bone growth; therefore, both the pore size and the overall pore structure need to be taken into consideration.

Proper porosity plays a vital role in providing the template for cell attachment on the surface and allows formation of the three-dimensional spreading-out structure (Li et al. 2016). A study using 0, 5, and 10 wt% stearic acid with 3Y-TZP resulted in 1.1%, 5.8%, and 16% porosity, respectively. The 16% porosity proved to have superior biocompatibility as it allowed high cell proliferation. Both porosity and a lightweight structure of superior properties are essential. A study conducted in 2018 found that adding 15%–20% of silicon nitride to zirconia effectively reduced the density of the composite, lowering the weight of the finished product (Renoldelsen and Vivekananthan 2018). Interestingly, addition of silicon nitride to zirconia also improves the sintering property of zirconia.

10.5.1.3 Different Composites of ZrO_2 and Al_2O_3 Ceramics

Bioinert material has both benefits and drawbacks when considered for hip or knee arthroplasties. There are ways to enhance its beneficial characteristics, such as improving mechanical properties using bioceramic composites. For example, higher content of silicon oxide makes the composite bioinert in its behaviors: it induces the formation of a fibrous capsule at the interface of tissue and implant (Dubok 2000). Similarly, Homerin et al. studied two different fabrication methods that exhibited superior fracture toughness (FT) of biocomposites like zirconia toughened alumina (ZTA): (i) attrition milling and hot-pressing and (ii) electrochemical dispersion (Homerin et al. 1986). Such composite structures are used in joint replacement surgeries (Piconi et al. 2003). A study shows that an addition of ZrO_2 up to 25% (wt) into the alumina matrix results in increased fracture toughness as a result of the phase transformation of the zirconia particles. The performance of the ZTA composites could be further improved by introducing stabilizers as they prevent microcrack formations inside the composite structures (Trabelsi et al. 1989). Homerin et al. showed the impact of stabilizer concentrations (1 and 3 mol% Y_2O_3) on FT. The 3 mol% concentration showed a constant and steady increase in the FT; however, 1 mol% showed a dramatic effect in its fracture toughness properties, to a maximum at 10 vol% ZrO_2, and then decreasing (Homerin et al. 1986). While the improvement of the FT is due to the increase in phase transfer volume, the linkage between microcracks of neighboring ZrO_2 particles causes its drop after reaching the maximum. A separate study by Trabelsi et al. also revealed that when the amount of ZrO_2 exceeds 10 vol%, microcracks are formed in the sintered materials due to phase transformation (Trabelsi et al. 1989). Besides improved mechanical properties, combining ZrO_2 with Al_2O_3 also reduces the water corrosion in Al_2O_3; however, in this process, the wear resistance is reduced due to the reduced hardness, which arises from adding excessive ZrO_2.

Thermal fatigue resistance of bioceramics materials developed for joints or implants is another important attribute, especially when compliant with the human body temperature. ZTA composites, for instance, present better thermal fatigue resistance compared to the pure Al_2O_3 (Orange et al. 1992). Hence, the composition of the bioceramics, stabilizer concentration, and environmental parameters could be strategically selected to engineer the optimum composite performance for suitable orthopedic or biomedical end-applications.

10.5.2 Bioresorbable Ceramics

After implant, bioresorbable ceramics slowly disappear within a given period of time, while their physiochemical properties enable restoration of the target bone along with the growth of blood vessels and nerve fibers (Dubok 2000). Calcium sulfate (CaS) and calcium phosphate (CaP) are the major bioresorbable materials (Punj et al. 2021). While the CaS-based bone grafts degrade rapidly, CaPs degrade slowly (Ferguson et al. 2017). Among the widely used CaP ceramics (Figure 10.6a and b), tricalcium phosphate (TCP), hydroxyapatite (HA) (Figure 10.6c and d), and biphasic calcium phosphate (BCP) are the most common materials (Punj et al. 2021). α-TCP and β-TCP are two phases of TCP, but both of them dissolve faster than the HA. Nearly, all CaPs undergo biodegradation to varying degrees, but in an analogous form in the following order: α-TCP > β-TCP>>HA (Hench 1991).

The underlying mechanism of the resorption (biodegradation) process of this class of bioceramics is interesting. CaP ceramics, for instance, could be an ideal candidate to manifest such a phenomenon in three different stages: (i) physiochemical dissolution, (ii) physical disintegration into tiny particles, and (iii) biological factors (Hench 1991). At first, the pH of the surrounding environment and the solubility of the ceramic product propagate the physiological dissolution process which initiates a phase transition, e.g., amorphous CaP, dicalcium phosphate dihydrate, octa-CaP, and anionic hydroxyapatite (HA). Next, during the physical disintegration stage, the product breaks down into tiny particles as a result of the chemical attack of grain boundaries. Finally, biological factors such as phagocytosis cause a decrease in the surrounding pH.

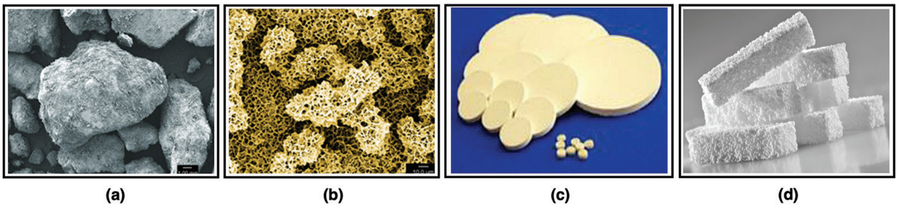

FIGURE 10.6 Calcium phosphate (CaP) ceramics. (a, b) SEM micrographs of β-tricalcium phosphate (β-TCP) (magnification level: 50×) and hydroxyapatite (HA) (magnification level: 5,000×) (Sheikh et al. 2015). (c, d) Dense (nonporous) and porous (by adding pore-generating additives) HAs produced by sintering the ceramic powders inside electric furnace at varying temperatures (Fiume et al. 2021).

CaP commonly refers to the calcium cations (Ca^{2+}) with negative anions of phosphates like orthophosphate (PO_4^{3-}), metaphosphate (PO^{-3}), or pyrophosphate ($P_2O_4^{-7}$). Bovine milk typically contains this principal form of calcium; 90% of tooth enamel is based on CaP. Hydroxyapatite (HA or HAP) (aka hydroxylapatite) is a type of CaP mineral that has 65% intrinsic compound resemblance to the mammalian bone structure (Fernando et al. 2016), with a Ca:P atomic ratio of 1.67. Bioresorbable materials form HA and promote bone tissue formation. The resorption rate could vary for different HA-based bioceramics. For instance, a 12-week slow resorption rate was reported after implanting femoral bone inside a rabbit (Tan et al. 2013); however, the resorption rate for bioresorbable materials could be accelerated by increasing their surface area and reducing the crystallinity or grain size (Hench 1991).

Since the bioresorbable materials take part in the formation and resorption process of the bone tissue, they are highly effective as scaffolds and filling spaces. For example, HA is used as bone filler for small defects that may arise from fractures in tibia (Quarto et al. 2001). Interestingly, bioresorbable bioceramics can be distinguished from bioactive bioceramics mainly by their structural factors (Antoniac 2016). A good example would be the nonporous HA, which is a bioactive material that is retained within the organism for at least 5–7 years without change. On the other hand, HA applied as a highly porous form-factor behaves as a bioresorbable ceramic that can be resorbed within a period of 1 year (Antoniac 2016). Several techniques are used for depositing bioresorbable coating into metal implants such as thermal spraying, sputter coating, pulse laser deposition, dynamic mixing method, dip coating, sol-gel technique, electrophoretic deposition, biomimetic deposition, hot isostatic pressing, and electrochemical deposition (Yang et al. 2005).

Highly porous composite ceramics are also employed for orthopedic applications by mixing bioresorbable HA with bioinert and bioactive ceramics: α-Al_2O_3-HA-bioactive glass, for instance. Wet chemical precipitation, sol-gel, and conventional melting-quenching processes could be employed to mix HA, α-Al_2O_3, and bioactive glass powders (Yelten and Yilmaz 2019). Such fabrication techniques often introduce unnecessary biproducts during the sintering process and lower the mechanical strength of the composites due to the highly porous structure of the sintered composites. However, researchers point out that this class of biocomposites performs better in terms of transmitting nutrient supply or body fluids due to the high (28%–30%) porosity. Further, the CaP molar ratio is around 1.65 for this new class of HA composite pellets, making them much more compatible with body fluids compared to traditional bioceramics (Ratner 1996).

10.5.3 Bioactive Ceramics

Bioactive materials, ones that react with bone tissue, could be considered "midway" between bioinert and bioresorbable materials. They have the capacity to react with the living cells and tissues inside the body and evoke a very specific biological response leading to the formation of a bond between the (introduced) material and the body tissue (Agrawal 1998). They are called osteo-conductive materials, as they stimulate the differentiation process of the stem cells to bone building osteoblast cells. Highly bioactive materials allow osteoprogenitor (i.e., the potential to form new bone) cells to colonize on its surface. Soluble ions released by the bioactive materials stimulate cell division and trigger growth factor and extracellular matrix protein production (Antoniac 2016).

The formula for bioactive glass ceramics was developed by Hench et al. in the 1970s and was named Bioglass® 45S5 (Hench et al. 1971). Hench et al. presented all the possible bonds formed between bone and biomaterial surfaces, including direct ionic covalent, electrostatic ionic, hydrogen, and van-der-Waals bond. The researchers divided the requirements of the biomaterial model into three criteria: chemical, crystallography, and microstructural. The study concluded that glass ceramics was the best-fit to meet all three requirements and had unique bone-forming properties, which is why it gained significant attention from researchers and scientists (Borden et al. 2021). Further, its chemical requirement can be achieved for end-use applications as it is possible to incorporate any element of the periodic table in any percentage into the glass. It displays a rapid rate of surface reactivity, giving it fast tissue-bonding properties (Ducheyne et al. 1993). Properties like in-vivo dissolution, ion release, and interparticle spacing can be used to determine the effectiveness of bioactive glass as bone graft (Borden et al. 2021). The study reported that a spherical shape is the optimum geometry for bioactive glass bone formation as the spherical particles displayed a more uniform shape and smooth surface compared to the irregularly shaped particles. Another study showed the evidence of new mineralized bone tissue formation surrounding the ceramic prosthesis after just 4 weeks of implanting (Barros et al. 2002). In the first week, there were appearances of bone mineralizing at the interface of the bioactive glass (Ducheyne et al. 1993). On the fourth week, the interface was completely bonded to the bone with no intervening fibrous tissue. Figure 10.7 displays the fundamental building blocks of new bone formation at the 45S5 bioactive glass material interface (Brézulier et al. 2021). The mineral component of bone includes $Ca_{8.3}(PO_4)_{4.3}(CO_3)_x(HPO_4)_y(OH)_{0.3}$ (Vallet-Regí 2001). These mineral component makes up two-third of the dry weight of the bone. Ionic substitution of the mineral component of bone includes CO_3^{2-}, Na^+, and Mg^{2+}. Collagen and water collectively make up the 43% of the remaining portion of bone.

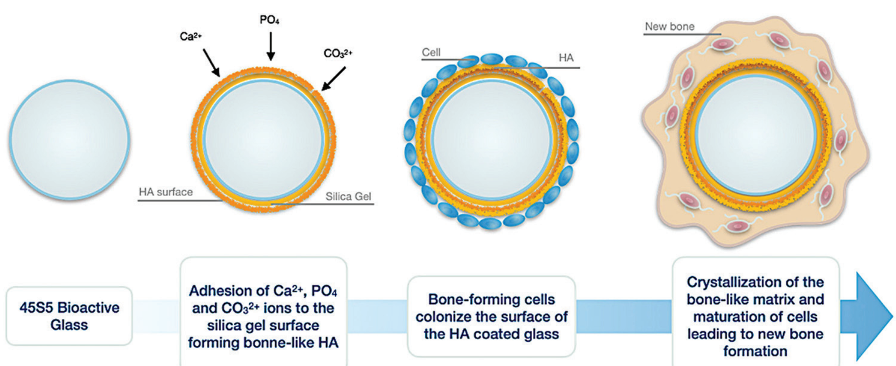

FIGURE 10.7 Bone formation mechanism after inserting bioglass 45S5 into a bone defect. The bone tissue minerals are formed on its surface, HCA (hydroxy-carbano-apatite) (HA, hydroxyapatite) (Brézulier et al. 2021).

Bioglass® 45S5 is considered the gold standard in bioactive materials for clinical applications, with the highest bioactivity index (I_B) of 12.5. On the other hand, 45S5 (NovaBone) or S53P4 (AbminDent1) have the highest level of bioactivity index (class A), indicating its ability to bond with bone and connecting soft tissues through osteo-conduction and osteo-stimulation; glass-ceramic materials (e.g., A/W glass ceramics) have a relatively lower level of bioactivity (class B) demonstrating the ability to bond only with the bone through osteo-conduction. Figure 10.8a displays the compositions of different bioactive glass and glass-ceramic materials for clinical applications. Gao et al. have outlined a comprehensive review of the applications of scaffolds made of different bioactive ceramics for bone repairs and regenerations (Gao et al. 2014). Additive manufacturing techniques like powder bed-selective laser processing (PBSLP), binder jetting, material extrusion, and sheet lamination are few of the fabrication techniques for bioactive ceramics (Kamboj et al. 2021).

A disadvantage of bioactive materials is mechanical weakness due to the low fracture toughness (FT) and crack growth from cyclic fatigue, resulting from the two-dimensional amorphous glass network. However, in terms of mechanical strength, it is weaker than bioinert ceramics (Poitout 2004). Therefore, they are not suitable for load-bearing applications (Ducheyne et al. 1993). Even though the mechanical weakness of bioactive glass does not allow use in repairing a large osseous defect, it is an excellent choice for filling small defects (Vallet-Regí 2014). Research conducted at the Universiti Sains, Malaysia, demonstrated that by varying the Al_2O_3 concentration at a high heat treatment of 950°C, mechanical compressive strength could be improved (from ~4 to 10.7 MPa) for SiO_2-CaO-Na_2O-P_2O_5 bioactive glass (Oh et al. 2020). X-ray diffraction (XRD) revealed that a new and larger crystalline phase was developed that was attributed to the formation of $Na_2CaSi_2O_6$ crystalline structures. Figure 10.8b demonstrates a comparison of mechanical properties among three different commercial bioactive glass ceramics: Cerabone® A/W, Ceravital®, and Bioverit®.

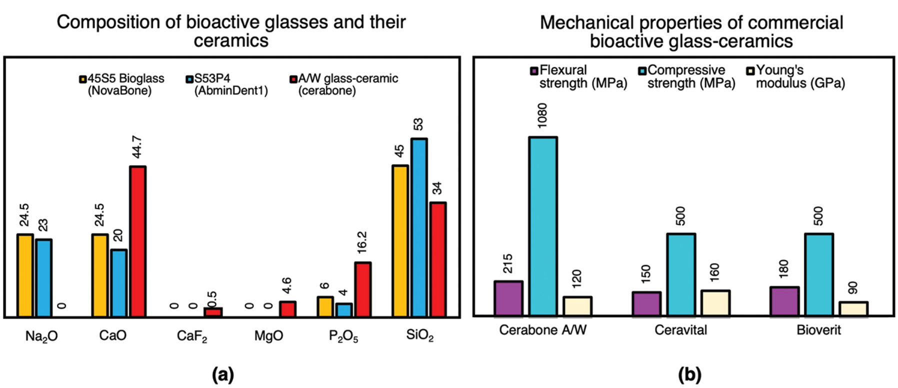

FIGURE 10.8 Bioactive glass materials and their properties. (a) Compositions of different bioactive glass and glass-ceramic materials for clinical applications. (Based on data from Hench (2016).) (b) Comparative performance among different bioactive glass ceramics. (Based on data from Siqueira and Zanotto (2011).)

10.6 IMPORTANCE OF BIOCOMPATIBILITY OF IMPLANTS

The reaction between the body and foreign materials is a critical challenge for the fixation of orthopedic devices (Hench et al. 1971). The chemical and physical nature of the bioceramics determine the kind and the extent of tissue response that will be triggered following implantation (Ravaglioli and Krajewski 1992). A study conducted in Tokyo, Japan, to test blood compatibility of sputter-deposited alumina films showed that incorporating alumina films is promising for developing blood-compatible and durable materials. The study found a 50% reduction in the platelet adhesion on the implant surface when the surface was coated with alumina film; there was a 50% reduction in the platelets adhesion on the implant surface and lowered intrinsic coagulation factor XI1 (Yuhta et al. 1994).

A serious challenge for joint arthroplasty is periprosthetic (body structure close to the implant) joint infection caused by microorganisms. A study found that Gram-positive *Cocci* are the most common infectious pathogen for periprosthetic infection, namely, *Staphylococcus aureus* and *Staphylococcus epidermis* (Pulido et al. 2008). The first step of infection is bacterial adhesion to the implant surface followed by the formation of biofilms leading to a complex interaction among the host-defense system, implant, microorganisms, and their by-products (Romanò et al. 2016). Therefore, it will be wise to find ways to eliminate infection from its root by finding ways to prevent microorganisms from adhering to implant surfaces. In such context, Pezzotti et al. developed a way to investigate the bacteriostatic response of ZTA and silicon nitride (Si_3N_4) using molecular biology characterization and advanced Raman Spectroscopy (Pezzotti et al. 2018). The research group concluded that non-oxide Si_3N_4 performs better at inhibiting bacterial infection due to its surface chemistry against bacterial loading.

There are several variables that determine bacterial adhesion and proliferation in the biomaterial implant surface, such as pathogen types, physiochemical properties, environmental factors, and surface morphology (Kumar et al. 2018). Bioceramics can prevent bacterial adhesion as they contain nanocrystals of a diameter between 1 and 3 nm. Incorporating fluoride ions into the bioceramics formulation can also improve the antibacterial property (Hermansson 2015). Ion doping mechanisms can further enhance certain properties of biomaterials like biodegradation abilities, biomechanical properties, and biocompatibilities (Xie et al. 2012). Potassium and strontium ions (K/Sr) doped into calcium polyphosphate (CPP) for bone tissue regeneration have better compatibility when compared to CPP and HA scaffolds. Another study found that incorporation of trace elements like Sr, zinc (Zn), magnesium (Mg), and silicon (Si) into bioactive materials will give improved ability to control the osteogenic property of bone-forming cells (Zhang et al. 2012).

10.7 BIOCOMPATIBILITY TESTS

Researchers at University of Leeds (UK) employed histological tests to analyze some retrieved tissues from an artificial ceramic-on-ceramic hip joint following a rTHA (Hatton et al. 2002). TEM (transmission electron microscopic) tests of the laser-captured micro-dissected tissues showed the presence of bioceramic particles in the size range of 5–90 nm, and SEM micrographs showed particles in the 0.05–3.2 μm size, presenting the possibility of two different size ranges of wear particles from the bioceramic prosthesis. This wear debris could cause health risks based on the level of reactivity or constituents and could limit their medical relevance. Hence, it is highly recommended to conduct biocompatibility tests for any medical devices that would come into contact with the patient (Ramakrishna et al. 2015). ISO 10993 is recognized by the FDA (Food and Drug Administration) for biocompatibility testing to ensure the safety of the medical devices. ISO 10993-1 lists the tests to be conducted for tissue and bone implants, considering the area of contact and duration of contact in the patient body. Initial evaluation tests for bone and tissue implant include cytotoxicity, sensitization, and irritation (intracutaneous reactivity). Additional tests such as systematic/acute toxicity, subacute and sub-chronic toxicity, and genotoxicity are required for prostheses with prolonged contact (1–30 days) or permanent implants.

Toxic materials are those that trigger a macro-scale rejection in the form of inflammatory or carcinogenic response or both (Hench et al. 1971). Hence, for safety of the patient and to avoid unnecessary revision surgeries following the TKA/THA, the toxicity level of the bioceramics should be tested at a cellular level prior to any clinical applications. Tests should be conducted on the implants for their biological, morphological, and phytochemical behaviors to avoid any traces of systematic or local toxicity to ensure safety of the patients (Kumar et al. 2018). Cytotoxicity test (i.e., tissue culture test) is test done in-vitro to determine if the medical device will cause any cell death from direct contact or as a result of leaching of a toxic substance (Ramakrishna et al. 2015). Some common cytotoxin assays include Trypan blue, MTT, MTS, XTT, WST-1, LDH, NRU, GSH, and AlamarBlue (Thrivikraman et al. 2014). Genotoxicity (i.e., toxic to DNA) tests are usually performed after the cytotoxicity tests (Thrivikraman et al. 2014). Genotoxins are chemical agents that have the potential to cause DNA or chromosomal damage (Phillips and Arlt 2009): damage of DNA can lead to malignant transformation (i.e., cancer). Nano particles resulting from implant wear get into the cytoplasmic space (Thrivikraman et al. 2014) and induce oxidative stress at the cellular level, which leads to the production of reactive oxygen species (ROS). These ROS disturb the intra- and inter-cellular signaling pathways (Zuberek and Grzelak 2018). As a result, cells start to behave abnormally and may cause cancer.

10.8 IMPLANT FAILURE PREVENTION

Success of bioceramic implants depends mainly on their biocompatibility, mechanical properties, and engineering design (Wong and Bronzino 2007). Implant failures, in general, depend on several factors as shown in Figure 10.9i and could include carcinogenicity or bacterial colonization. Hence, it is significant to ensure that the implant has sufficient load-bearing capacity for its purpose, and its design framework fits into the biological system properly. In-vivo degradation of prosthetic implants is considered one of the primary factors limiting the longevity of the total joint arthroplasty (TJA) (Jacobs et al. 1994). Such degradation could arise from wear and corrosion. Wear happens due to the loss of materials resulting from the relative motion between two surfaces (via adhesion, abrasion, or fatigue) (Jacobs et al. 1994). Wear generates debris that can trigger a local host response and may eventually cause osteolytic cavity due to osteolysis (i.e., periprosthetic bone loss or bone resorption

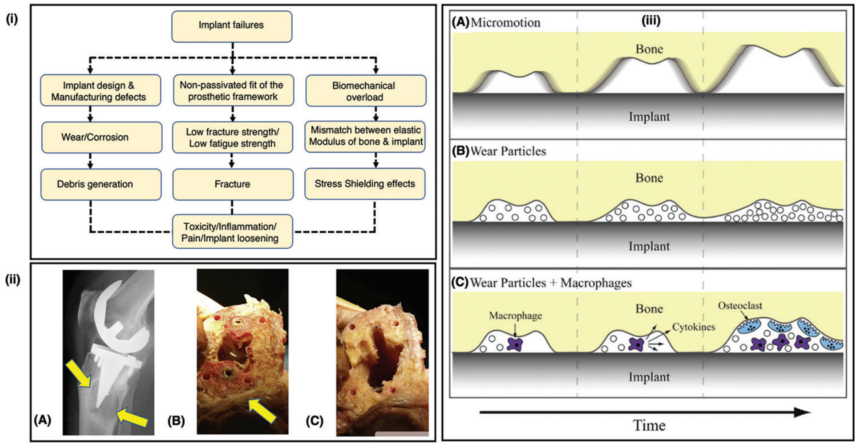

FIGURE 10.9 (i) Different factors leading to implant failures. (Modified from Priyadarshini et al. (2019).) (ii) (a–c) Screw track osteolytic cavity from osteolysis (marked with white arrows) after cementless total knee replacement (Klutzny et al. 2019). Radiograph exhibits tibial osteolysis in the screw fixation area (ii-a) and the intraoperative photographs shows the femoral stems before (ii-b) and after (ii-c) the revision surgeries demonstrate the extent of bone loss defect. (iii) (a–c) The aseptic loosening mechanism at the interfacial gaps between bone and implant (Raphel et al. 2016). As implant moves relative to the bone, the overall micromotion worsens gradually (iii-a) and becomes instable as wear debris consumes the interfacial space (iii-b), which subsequently activates the macrophages, cytokines, and consequently leads to osteoclast bone-resorbing cells (iii-c).

surrounding an implant) and could compromise the implant fixation (Purdue et al. 2006) (Figure 10.9ii), resulting in aseptic loosening (i.e., implant failures without any mechanical reason or evidence of infection, which typically arise from osteolysis) (Figure 10.9iii) or chronic inflammation (Abu-Amer et al. 2007). Wear can be reduced by improving the bearing characteristics of the femoral head, condyle counter face, and by improving the stability of the molecular connection.

Failures from fixture (or locking mechanism) fretting is another crucial aspect, which is often ignored while choosing the replacement devices. In 2021, a study reported the fretting of fixture pins due to mechanical mismatch with the tibial baseplate, leading to knee-joint instability and severe bone loss of a 46-year Caucasian woman and, thereby, necessitated a revision surgery (Figure 10.10) (Lamba et al. 2021). The rTKA revealed the total loss of lateral collateral ligament, femoral condyle, and popliteus tendon due to poor prosthetic design, material selection, and locking mechanism. Hence, sufficient micro-scale and ultra-scale bonding at the material–bone interface could solve the orthopedic fixation problem associated with the loosening of nails, screws, plates, and hip prostheses. Furthermore, the application of composite structures improves the tribological properties and mechanical strength of the implants (as discussed in the earlier segments). Other factors relating to success and failure of the implants are beyond the control of the engineering design, such as surgical technique during implanting, health condition of patient, mode of physical activities of the patient. Hence, a holistic knowledge framework

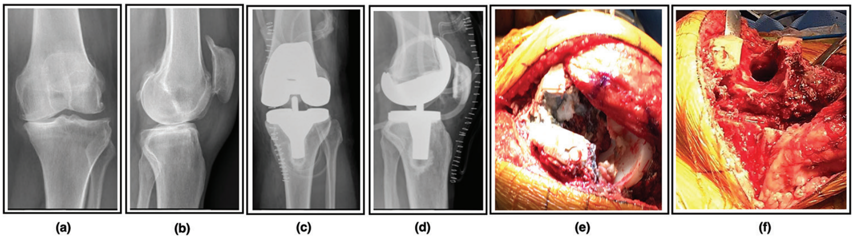

FIGURE 10.10 Failure in the bio-implantable TKA device (Lamba et al. 2021). TKA was conducted for a woman suffering from symptomatic osteoarthritis, which could be seen from the radiographs of pre-TKA anteroposterior and lateral views (a, b). Implanted TKA device is shown in the radiographs (anteroposterior and lateral views) of the post-operative TKA (c, d). While replacing the femoral implant, device residue (gray and white fibrous material) (e) was identified in the implanted region that caused the complete loss of lateral femoral condyle (f).

based on physiology of bone (composition and mechanics), material science, surgical expertise, immunology, design manufacturing, diet, and awareness should be implemented to improve the knee/hip joint arthroplasty procedure.

10.9 CONCLUSIONS AND FUTURE PROSPECTS

The application of bioceramics is expected to increase due to their unique functionalities. Bioceramic-based implants or prostheses have seen dramatic growth in knee/hip replacement surgeries in the last few decades due to their biocompatibility, low density, and ease of fabrication. However, it is also essential to understand the evolving nature of bioceramics and evaluate their medical performance through clinical trials. For this, scientists continue to investigate novel bioceramic composites. A conformable decoder based on piezoelectric bioceramic composites is an arena that engineers could explore to innovate new-generation-integrated medical devices for bone joints. As the world is moving toward the Internet of Health Things (IoHT), it could be naturally expected that the futuristic knee/hip bioceramic prostheses will soon have conformable decoding abilities that would connect with the patients for them to continuously monitor the health of their knee/hip prosthetic components. Such technology could ameliorate the implantable experience of the patients. The conformable decoding system could also host microfluidic actuators as drug carriers. By combining machine learning technologies with such smart knee/hip joint prostheses, doctors (or users) will soon predict and prevent periprosthetic knee/hip joint infections by triggering the actuators and administering on-demand drug delivery. Since the bone tissues intrinsically constitute piezoelectric components, the synergy between bone and piezoelectric bioceramics could also boost the antibacterial performance of the implant sites of bioceramic knee/hip joints and, ultimately, augment the implant lifespan.

REFERENCES

Abu-Amer, Y., I. Darwech, and J.C. Clohisy. 2007. Aseptic loosening of total joint replacements: Mechanisms underlying osteolysis and potential therapies. *Arthritis Research & Therapy* 9 (Suppl 1): S6. https://doi.org/10.1186/ar2170.

Agrawal, C.M. 1998. Reconstructing the human body using biomaterials. *JOM* 50 (1): 31–5. https://doi.org/10.1007/s11837-998-0064-5.

Albrektsson, T., and C. Johansson. 2001. Osteoinduction, osteoconduction and osseointegration. *European Spine Journal* 10 (October): S96–S101. https://doi.org/10.1007/s005860100282.

Antoniac, I.V. 2016. *Handbook of Bioceramics and Biocomposites*. edited by I.V. Antoniac. Cham: Springer International Publishing. https://doi.org/10.1007/978-3-319-12460-5.

Bahraminasab, M., and A. Jahan. 2011. Material selection for femoral component of total knee replacement using comprehensive VIKOR. *Materials & Design* 32 (8–9): 4471–77. https://doi.org/10.1016/j.matdes.2011.03.046.

Barkallah, R., R. Taktak, N. Guermazi, K. Elleuch, and J. Bouaziz. 2021. Mechanical properties and wear behaviour of alumina/tricalcium phosphate/titania ceramics as coating for orthopedic implant. Engineering Fracture Mechanics 241 (January): 107399. https://doi.org/10.1016/j.engfracmech.2020.107399.

Barkallah, R., R. Taktak, N. Guermazi, F. Zaïri, J. Bouaziz, and F. Zaïri. 2018. Manufacturing and mechanical characterization of Al_2O_3/β-TCP/TiO2 biocomposite as a potential bone substitute. *The International Journal of Advanced Manufacturing Technology* 95 (9–12): 3369–80. https://doi.org/10.1007/s00170-017-1434-3.

Borden, M., L.E. Westerlund, V. Lovric, and W. Walsh. 2021. Controlling the bone regeneration properties of bioactive glass: Effect of particle shape and size. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, December. https://doi.org/10.1002/jbm.b.34971.

Brézulier, D., L. Chaigneau, S. Jeanne, and R. Lebullenger. 2021. The challenge of 3D bioprinting of composite natural polymers PLA/bioglass: Trends and benefits in cleft palate surgery. *Biomedicines* 9 (11): 1553. https://doi.org/10.3390/biomedicines9111553.

Cram, P., X. Lu, S.L. Kates, J.A. Singh, Y. Li, and B.R. Wolf. 2012. Total knee arthroplasty volume, utilization, and outcomes among medicare beneficiaries, 1991–2010. *JAMA* 308 (12): 1227. https://doi.org/10.1001/2012.jama.11153.

Cui, Z., Y-X. Tian, W. Yue, L. Yang, and Q. Li. 2016. Tribo-biological deposits on the articulating surfaces of metal-on-polyethylene total hip implants retrieved from patients. *Scientific Reports* 6 (1): 28376. https://doi.org/10.1038/srep28376.

Dawson-Amoah, K.G., B.S. Waddell, R. Prakash, and M.M. Alexiades. 2020. Adverse reaction to zirconia in a modern total hip arthroplasty with ceramic head. *Arthroplasty Today* 6 (3): 612–6.e1. https://doi.org/10.1016/j.artd.2020.03.009.

Dorozhkin, S. 2011. Medical application of calcium orthophosphate bioceramics. *BIO* 1 (1): 1–51. https://doi.org/10.5618/bio.2011.v1.n1.1.

Dorozhkin, S.V. 2010. Bioceramics of calcium orthophosphates. *Biomaterials* 31 (7): 1465–85. https://doi.org/10.1016/j.biomaterials.2009.11.050.

Dubok, V.A. 2000. Bioceramics – Yesterday, today, tomorrow. *Powder Metallurgy and Metal Ceramics*. https://doi.org/10.1023/A:1026617607548.

Ducheyne, P., M. Marcolongo, and E. Schepers. 1993. Bioceramic composites. In *An Introduction to Bioceramics*, 281–97. World Scientific. https://doi.org/10.1142/9789814317351_0015.

Elsen, S.R., K. Jegadeesan, and J.R. Aseer. 2017. X-ray diffraction analysis of mechanically milled alumina and zirconia powders. *Nano Hybrids and Composites* 17 (August): 96–100. https://doi.org/10.4028/www.scientific.net/NHC.17.96.

Fact, M.R. 2021. Bioceramics market.

Ferguson, J., M. Diefenbeck, and M. McNally. 2017. Ceramic biocomposites as biodegradable antibiotic carriers in the treatment of bone infections. *Journal of Bone and Joint Infection* 2 (1): 38–51. https://doi.org/10.7150/jbji.17234.

Fernando, S., M. McEnery, and S.A. Guelcher. 2016. Polyurethanes for bone tissue engineering. In *Advances in Polyurethane Biomaterials*, 481–501. Elsevier. https://doi.org/10.1016/B978-0-08-100614-6.00016-0.

Fiume, E., G. Magnaterra, A. Rahdar, E. Verné, and F. Baino. 2021. Hydroxyapatite for biomedical applications: A short overview. *Ceramics* 4 (4): 542–63. https://doi.org/10.3390/ceramics4040039.

Gao, C., Y. Deng, P. Feng, Z. Mao, P. Li, B. Yang, J. Deng, Y. Cao, C. Shuai, and S. Peng. 2014. Current progress in bioactive ceramic scaffolds for bone repair and regeneration. *International Journal of Molecular Sciences* 15 (3): 4714–32. https://doi.org/10.3390/ijms15034714.

Habraken, W., P. Habibovic, M. Epple, and M. Bohner. 2016. Calcium phosphates in biomedical applications: Materials for the future? *Materials Today* 19 (2): 69–87. https://doi.org/10.1016/j.mattod.2015.10.008.

Hatton, A., J.E. Nevelos, A.A. Nevelos, R.E. Banks, J. Fisher, and E. Ingham. 2002. Alumina-alumina artificial hip joints. Part I: A histological analysis and characterisation of wear debris by laser capture microdissection of tissues retrieved at revision. *Biomaterials* 23 (16): 3429–40. https://doi.org/10.1016/S0142-9612(02)00047-9.

He, B., X. Li, R. Dong, P. Tong, and J. Sun. 2022. A multi-center retrospective comparative study of third generation ceramic-on- ceramic total hip arthroplasty in patients younger than 45 years with or without the sandwich liner: A ten-year minimum. *Journal of Orthopaedic Surgery* 30 (2): 102255362211099. https://doi.org/10.1177/10225536221109960.

Hench, L.L. 1991. Bioceramics: From concept to clinic. *Journal of the American Ceramic Society* 74 (7): 1487–510. https://doi.org/10.1111/j.1151-2916.1991.tb07132.x.

Hench, L.L. 2016. Bioactive glass bone grafts: History and clinical applications. In *Handbook of Bioceramics and Biocomposites*, 23–33. Cham: Springer International Publishing. https://doi.org/10.1007/978-3-319-12460-5_5.

Hench, L.L., R.J. Splinter, W.C. Allen, and T.K. Greenlee. 1971. Bonding mechanisms at the interface of ceramic prosthetic materials. *Journal of Biomedical Materials Research* 5 (6): 117–41. https://doi.org/10.1002/jbm.820050611.

Hermansson, L., ed. 2015. *Nanostructural Bioceramics Advances in Chemically Bonded Ceramics*. Jenny Stanford Publishing.

Homerin, P., F. Thevenot, G. Orange, G. Fantozzi, V. Vandeneede, A. Leriche, and F. Cambier. 1986. Mechanical properties of zirconia toughened alumina prepared by different methods. *Le Journal de Physique Colloques* 47 (C1): C1-717–C1-721. https://doi.org/10.1051/jphyscol:19861108.

Ichimura, R., T. Minamikawa, H. Nakagawa, A. Mori, K. Midorikawa, K. Sakuragi, and H. Minamikawa. 2022. Fracture of the oxidized zirconium femoral component after total knee arthroplasty. *The Knee* 36 (June): 27–32. https://doi.org/10.1016/j.knee.2022.03.014.

Iorio, R., S. Kobayashi, W.L. Healy, A.I. Cruz, and M.E. Ayers. 2007. Primary posterior cruciate-retaining total knee arthroplasty: A comparison of American and Japanese cohorts. *Journal of Surgical Orthopaedic Advances* 16 (4): 164–70.

Jacobs, J.J., A. Shanbhag, T.T. Glant, J. Black, and J.O. Galante. 1994. Wear debris in total joint replacements. *Journal of the American Academy of Orthopaedic Surgeons* 2 (4): 212–20.

Joseph, D., ed. 2003. *Handbook of Materials for Medical Devices*. ASM International.

Kamboj, N., A. Ressler, and I. Hussainova. 2021. Bioactive ceramic scaffolds for bone tissue engineering by powder bed selective laser processing: A review. *Materials* 14 (18): 5338. https://doi.org/10.3390/ma14185338.

Klawitter, J.J., and S.F. Hulbert. 1971. Application of porous ceramics for the attachment of load bearing internal orthopedic applications. *Journal of Biomedical Materials Research* 5 (6): 161–229. https://doi.org/10.1002/jbm.820050613.

Klutzny, M., G. Singh, R. Hameister, G. Goldau, F. Awiszus, B. Feuerstein, C. Stärke, and C.H. Lohmann. 2019. Screw track osteolysis in the cementless total knee replacement design. *The Journal of Arthroplasty* 34 (5): 965–73. https://doi.org/10.1016/j.arth.2018.12.040.

Kumar, A., and F. Baino. 2020. Editorial: Bioceramics and bioactive glasses for hard tissue regeneration. Frontiers in Materials 7 (September). https://doi.org/10.3389/fmats.2020.593624.

Kumar, P., B.S. Dehiya, and A. Sindhu. 2018. Bioceramics for hard tissue engineering applications: A review title. *International Journal of Applied Engineering Research* 13 (5): 2744–52.

Lamba, C., K. Denning, E. Ouellette, S. Kurtz, and M. Bullock. 2021. An interesting case of osteolysis with accompanying metallosis in a primary total knee arthroplasty. *Arthroplasty Today* 11 (October): 81–7. https://doi.org/10.1016/j.artd.2021.07.002.

Li, D., C. Wang, Z. Li, H. Wang, J. He, J. Zhu, Y. Zhang, et al. 2018. Nano-sized Al_2O_3 particle-induced autophagy reduces osteolysis in aseptic loosening of total hip arthroplasty by negative feedback regulation of RANKL expression in fibroblasts. *Cell Death & Disease* 9 (8): 840. https://doi.org/10.1038/s41419-018-0862-9.

Li, J., X. Wang, Y. Lin, X. Deng, M. Li, and C. Nan. 2016. In vitro cell proliferation and mechanical behaviors observed in porous zirconia ceramics. *Materials* 9 (4): 218. https://doi.org/10.3390/ma9040218.

López, J.P. 2014. Alumina, zirconia, and other non-oxide inert bioceramics. In *Bio-Ceramics with Clinical Applications*, 153–73. Chichester, UK: John Wiley & Sons, Ltd. https://doi.org/10.1002/9781118406748.ch6.

Mayo Clinic. 2014. First nationwide prevalence study of hip and knee arthroplasty shows 7.2 million Americans living with implants. https://www.mayoclinic.org/medical-professionals/orthopedic-surgery/news/first-nationwide-prevalence-study-of-hip-and-knee-arthroplasty-shows-7-2-million-americans-living-with-implants/mac-20431170.

Meier, E., K. Gelse, K. Trieb, M. Pachowsky, F.F. Hennig, and A. Mauerer. 2016. First clinical study of a novel complete metal-free ceramic total knee replacement system. *Journal of Orthopaedic Surgery and Research* 11 (1): 21. https://doi.org/10.1186/s13018-016-0352-7.

Murr, L.E., S.M. Gaytan, E. Martinez, F. Medina, and R.B. Wicker. 2012. Next generation orthopaedic implants by additive manufacturing using electron beam melting. *International Journal of Biomaterials* 2012: 1–14. https://doi.org/10.1155/2012/245727.

Nevalainen, M.T., K.V. Kauppinen, T. Niinimäki, and S.S. Saarakkala. 2020. Comparison of ultrasonographic, radiographic and intra-operative findings in severe hip osteoarthritis. *Scientific Reports* 10 (1): 21108. https://doi.org/10.1038/s41598-020-78235-z.

Nevalainen, M.T., K. Kauppinen, J. Pylväläinen, K. Pamilo, M. Pesola, M. Haapea, J. Koski, and S. Saarakkala. 2018. Ultrasonography of the late-stage knee osteoarthritis prior to total knee arthroplasty: Comparison of the ultrasonographic, radiographic and intra-operative findings. *Scientific Reports* 8 (1): 17742. https://doi.org/10.1038/s41598-018-35824-3.

Oh, H.J., D-K. Kim, Y.C. Choi, S-J. Lim, J.B. Jeong, J.H. Ko, et al. 2020. Fabrication of piezoelectric poly(l-lactic acid)/BaTiO3 fibre by the melt-spinning process. *Scientific Reports* 10 (1): 16339. https://doi.org/10.1038/s41598-020-73261-3.

Orange, G., G. Fantozzi, P. Homerin, F. Thevenot, A. Leriche, and F. Cambier. 1992. Preparation and characterization of a dispersion toughened ceramic for thermomechanical uses (ZTA). Part II: Thermomechanical characterization. effect of microstructure and temperature on toughening mechanisms. *Journal of the European Ceramic Society* 9 (3): 177–85. https://doi.org/10.1016/0955-2219(92)90003-V.

Park, J. 2009a. *Bioceramics: Properties, Characterizations, and Applications*. In *Lecture Notes in Economic and Mathematical Systems*. New York: Springer. https://books.google.com/books?id=bWMLpUyZCFgC.

Park, J. 2009b. *Bioceramics*. New York, NY: Springer. https://doi.org/10.1007/978-0-387-09545-5.

Pezzotti, G., R.M. Bock, B.J. McEntire, T. Adachi, E. Marin, F. Boschetto, W. Zhu, O. Mazda, and S.B. Bal. 2018. In vitro antibacterial activity of oxide and non-oxide bioceramics for arthroplastic devices: I. In situ time-lapse Raman spectroscopy. *The Analyst* 143 (15): 3708–21. https://doi.org/10.1039/C8AN00233A.

Phillips, D.H., and V.M. Arlt. 2009. Genotoxicity: Damage to DNA and its consequences. 87–110. https://doi.org/10.1007/978-3-7643-8336-7_4.

Piconi, C., and G. Maccauro. 2015. Perspective and trends on bioceramics in joint replacement. In *Handbook of Bioceramics and Biocomposites*, 1–37. Cham: Springer International Publishing. https://doi.org/10.1007/978-3-319-09230-0_41-1.

Piconi, C., G. Maccauro, F. Muratori, and E.B.D. Prever. 2003. Alumina and zirconia ceramics in joint replacements. *Journal of Applied Biomaterials & Functional Materials* 1 (1): 19–32. https://10.1177/228080000300100103.

Piconi, C., and S. Sprio. 2021. Oxide bioceramic composites in orthopedics and dentistry. *Journal of Composites Science* 5 (8): 206. https://doi.org/10.3390/jcs5080206.

Poitout, D.G., ed. 2004. *Biomechanics and Biomaterials in Orthopedics*. London: Springer. https://doi.org/10.1007/978-1-4471-3774-0.

Priyadarshini, B., M. Rama, Chetan, and U. Vijayalakshmi. 2019. Bioactive coating as a surface modification technique for biocompatible metallic implants: A review. *Journal of Asian Ceramic Societies* 7 (4): 397–406. https://doi.org/10.1080/21870764.2019.1669861.

Pulido, L., E. Ghanem, A. Joshi, J.J. Purtill, and J. Parvizi. 2008. Periprosthetic joint infection: The incidence, timing, and predisposing factors. *Clinical Orthopaedics & Related Research* 466 (7): 1710–15. https://doi.org/10.1007/s11999-008-0209-4.

Punj, S., J. Singh, and K. Singh. 2021. Ceramic biomaterials: Properties, state of the art and future prospectives. *Ceramics International* 47 (20): 28059–74. https://doi.org/10.1016/j.ceramint.2021.06.238.

Purdue, P.E., P. Koulouvaris, B.J. Nestor, and T.P. Sculco. 2006. The central role of wear debris in periprosthetic osteolysis. *HSS Journal(r): The Musculoskeletal Journal of Hospital for Special Surgery* 2 (2): 102–13. https://doi.org/10.1007/s11420-006-9003-6.

Quarto, R., M. Mastrogiacomo, R. Cancedda, S.M. Kutepov, V. Mukhachev, A. Lavroukov, E. Kon, and M. Marcacci. 2001. Repair of large bone defects with the use of autologous bone marrow stromal cells. *New England Journal of Medicine* 344 (5): 385–86. https://doi.org/10.1056/NEJM200102013440516.

Ramakrishna, S., L. Tian, C. Wang, S. Liao, and W.E. Teo. 2015. Safety testing of a new medical device. In *Medical Devices*, 137–53. Elsevier. https://doi.org/10.1016/B978-0-08-100289-6.00006-5.

Raphel, J., M. Holodniy, S.B. Goodman, and S.C. Heilshorn. 2016. Multifunctional coatings to simultaneously promote osseointegration and prevent infection of orthopaedic implants. *Biomaterials* 84 (April): 301–14. https://doi.org/10.1016/j.biomaterials.2016.01.016.

Ratner, B.D. 1996. Biomaterials science: An interdisciplinary endeavor. In *Biomaterials Science*, 1–8. Elsevier. https://doi.org/10.1016/B978-0-08-050014-0.50005-5.

Ravaglioli, A., and A. Krajewski. 1992. *Bioceramics*. Dordrecht: Springer Netherlands. https://doi.org/10.1007/978-94-011-2336-5.

Renoldelsen, S, and M Vivekananthan. 2018. A preliminary study on the physical and biocompatibility characteristics of zirconia-silicon nitride bio-ceramics. *IOP Conference Series: Materials Science and Engineering* 402 (September): 012031. https://doi.org/10.1088/1757-899X/402/1/012031.

Rheumatology Advisor. 2019. Increased rate of total joint replacements predicted from 2020 to 2040. *Rheumatology Advisor*. 2019. https://www.rheumatologyadvisor.com/home/topics/osteoarthritis/increased-rate-of-total-joint-replacements-predicted-from-2020-to-2040/.

Rocha Barros, V.M. da, L.A. Salata, C.E. Sverzut, S.P. Xavier, R. van Noort, A. Johnson, and P.V. Hatton. 2002. In vivo bone tissue response to a canasite glass-ceramic. *Biomaterials* 23 (14): 2895–900. https://doi.org/10.1016/S0142-9612(01)00417-3.

Romanò, C.L., D. Romanò, I. Morelli, and L. Drago. 2016. The concept of biofilm-related implant malfunction and 'low-grade infection'. 1–13. https://doi.org/10.1007/5584_2016_158.

Schwartz, A.M., K.X. Farley, G.N. Guild, and T.L. Bradbury. 2020. Projections and epidemiology of revision hip and knee arthroplasty in the United States to 2030. *The Journal of Arthroplasty* 35 (6): S79–85. https://doi.org/10.1016/j.arth.2020.02.030.

Sheikh, Z., S. Najeeb, Z. Khurshid, V. Verma, H. Rashid, and M. Glogauer. 2015. Biodegradable materials for bone repair and tissue engineering applications. *Materials* 8 (9): 5744–94. https://doi.org/10.3390/ma8095273.

Shekhawat, D., Amit Singh, M.K. Banerjee, T. Singh, and A. Patnaik. 2021. Bioceramic composites for orthopaedic applications: A comprehensive review of mechanical, biological, and microstructural properties. *Ceramics International* 47 (3): 3013–30. https://doi.org/10.1016/j.ceramint.2020.09.214.

Siqueira, R.L., and E.D. Zanotto. 2011. Facile route to obtain a highly bioactive SiO_2-CaO-Na_2O-P_2O_5 crystalline powder. *Materials Science and Engineering: C* 31 (8): 1791–99. https://doi.org/10.1016/j.msec.2011.08.013.

Sprio, S., S. Guicciardi, M. Dapporto, C. Melandri, and A. Tampieri. 2013. Synthesis and mechanical behavior of β-tricalcium phosphate/titania composites addressed to regeneration of long bone segments. *Journal of the Mechanical Behavior of Biomedical Materials* 17 (January): 1–10. https://doi.org/10.1016/j.jmbbm.2012.07.013.

Stevens, M.M. 2008. Biomaterials for bone tissue engineering. *Materials Today* 11 (5): 18–25. https://doi.org/10.1016/S1369-7021(08)70086-5.

Tan, L., X. Yu, P. Wan, and K. Yang. 2013. Biodegradable materials for bone repairs: A review. *Journal of Materials Science & Technology* 29 (6): 503–13. https://doi.org/10.1016/j.jmst.2013.03.002.

Technavio Research. 2017. High demand from emerging economies to boost the bioceramics market: Technavio. https://www.businesswire.com/news/home/20170918005941/en/High-Demand-from-Emerging-Economies-to-Boost-the-Bioceramics-Market-Technavio.

Thrivikraman, G., G. Madras, and B. Basu. 2014. In vitro/in vivo assessment and mechanisms of toxicity of bioceramic materials and its wear particulates. *RSC Advances* 4 (25): 12763. https://doi.org/10.1039/c3ra44483j.

Trabelsi, R., D. Treheux, G. Orange, G. Fantozzi, P. Homerin, and F. Thevenot. 1989. Relationship between mechanical properties and wear resistance of alumina-zirconia ceramic composites. *Tribology Transactions* 32 (1): 77–84. https://doi.org/10.1080/10402008908981865.

Transparency Market Research. 2022. Femoral head prostheses market – Global industry analysis, size, share, growth, trends, and forecast, 2019–2027. https://www.transparencymarketresearch.com/femoral-head-prostheses-market.html.

Vallet-Regí, M. 2001. Ceramics for medical applications. *Journal of the Chemical Society, Dalton Transactions* 2: 97–108. https://doi.org/10.1039/b007852m.

Vallet-Regí, M., ed. 2014. *Bio-Ceramics with Clinical Applications*. Chichester, UK: John Wiley & Sons, Ltd. https://doi.org/10.1002/9781118406748.

Vogel, D., P. Henke, A. Haenel, J. Mokros, M. Liebelt, and R. Bader. 2022. Experimental evaluation of the primary fixation stability of uncemented ceramic hip resurfacing implants. *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine* 236 (4): 496–503. https://doi.org/10.1177/09544119211070892.

Weng, W., W. Wu, M. Hou, T. Liu, T. Wang, and H. Yang. 2021. Review of zirconia-based biomimetic scaffolds for bone tissue engineering. *Journal of Materials Science* 56 (14): 8309–33. https://doi.org/10.1007/s10853-021-05824-2.

Whiteside, L.A. 2022. Clinical results of revision TKA in patients with presumed metal and cement allergy. *The Journal of Arthroplasty* 37 (6): S250–57. https://doi.org/10.1016/j.arth.2022.02.052.

Wong, J.Y., and J.D. Bronzino. 2007. *Biomaterials*. edited by J.Y. Wong and J.D. Bronzino. CRC Press. https://doi.org/10.1201/9780849378898.

Xie, H., Q. Wang, Q. Ye, C. Wan, and L. Li. 2012. Application of K/Sr Co-doped calcium polyphosphate bioceramic as scaffolds for bone substitutes. *Journal of Materials Science: Materials in Medicine* 23 (4): 1033–44. https://doi.org/10.1007/s10856-012-4556-z.

Xu, J., T. Oni, D. Shen, Y. Chai, W.K. Walter, and W.L. Walter. 2022. Long-term results of alumina ceramic-on-ceramic bearings in cementless total hip arthroplasty: A 20-year minimum follow-up. *The Journal of Arthroplasty* 37 (3): 549–53. https://doi.org/10.1016/j.arth.2021.11.028.

Yang, Y., K. Kim, and J. Ong. 2005. A review on calcium phosphate coatings produced using a sputtering process? An alternative to plasma spraying. *Biomaterials* 26 (3): 327–37. https://doi.org/10.1016/j.biomaterials.2004.02.029.

Yelten, A., and S. Yilmaz. 2019. A novel approach on the synthesis and characterization of bioceramic composites. *Ceramics International* 45 (12): 15375–84. https://doi.org/10.1016/j.ceramint.2019.05.031.

Yuhta, T., Y. Kikuta, Y. Mitamura, K. Nakagane, S. Murabayashi, and I. Nishimura. 1994. Blood compatibility of sputter-deposited alumina films. *Journal of Biomedical Materials Research* 28 (2): 217–24. https://doi.org/10.1002/jbm.820280212.

Zhang, M., C. Wu, K. Lin, W. Fan, L. Chen, Y. Xiao, and J. Chang. 2012. Biological responses of human bone marrow mesenchymal stem cells to Sr-M-Si (M = Zn, Mg) silicate bioceramics. *Journal of Biomedical Materials Research Part A* 100A (11): 2979–90. https://doi.org/10.1002/jbm.a.34246.

Zuberek, M., and A. Grzelak. 2018. Nanoparticles-caused oxidative imbalance. 85–98. https://doi.org/10.1007/978-3-319-72041-8_6.ssfffffffB