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An overview of recent advances in designing orthopedic and craniofacial implants

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Abstract

Great deal of research is still going on in the field of orthopedic and craniofacial implant development to resolve various issues being faced by the industry today. Despite several disadvantages of the metallic implants, they continue to be used, primarily because of their superior mechanical properties. In order to minimize the harmful effects of the metallic implants and its by-products, several modifications are being made to these materials, for instance nickel-free stainless steel, cobalt-chromium and titanium alloys are being introduced to eliminate the toxic effects of nickel being released from the alloys, introduce metallic implants with lower modulus, reduce the cost of these alloys by replacing rare elements with less expensive elements etc. New alloys like tantalum, niobium, zirconium, and magnesium are receiving attention given their satisfying mechanical and biological properties. Non-oxide ceramics like silicon nitride and silicon carbide are being currently developed as a promising implant material possessing a combination of properties such as good wear and corrosion resistance, increased ductility, good fracture and creep resistance, and relatively high hardness in comparison to alumina. Polymer/magnesium composites are being developed to improve mechanical properties as well as retain polymer's property of degradation. Recent advances in orthobiologics are proving interesting as well. This paper thus deals with the latest improvements being made to the existing implant materials and includes new materials being introduced in the field of biomaterials.

Keywords

metal alloys; implants; orthopedic; craniofacial; mechanical properties; ceramics; polymers

INTRODUCTION

In 2007, "The Economist" reckoned that humanity is on the verge of biology's "Big Bang," meaning that the most important problems being faced by current society and their solutions are biological. Till date, always the numbers of young children have outnumbered the elderly population; however, in about five years from now, the elderly population will

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CONFLICT OF INTEREST STATEMENT

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outnumber the children younger than five years old.[1] One of the major chronic conditions reported by aging population is arthritis; it is a fact that one in every five adults suffer from it.[2] One of the other major causes of the increased arthritis rates found amongst patients is obesity; about 54% of adults who suffer from arthritis are obese.[3] Treatment for arthritis depends on the type of arthritis, its location, severity, and the medical condition of the patient. Therefore, the treatment procedure can vary from medication, joint injections to surgical operation being the last resort. Osteoporosis and trauma are the other major reasons for joint replacement.

Musculoskeletal disorders are thus the most widespread human health issue, with knee and hip replacements costing around $42.3 billion within US in 2009.[4] Surgical implantation of artificial biomaterials have allowed surgeons to ameliorate the lives of patients by reducing the pain and restoring function to the otherwise functionally compromised structure. Hip, knee, and spine are the body parts being replaced most frequently.

Apart from the increased number of the replacement surgery, there has been a simultaneous and parallel increase in the revision surgery of hip and knee implants.[5] From the year 2000 through 2011, Food and Drug Administration (FDA) gave a premarket approval for more than 150 new high-risk medical devices, and an additional 600 devices were cleared through the 510(k) process.[6] The public directly relates increased flooding of the market with new devices to the demand rate. In 2006, the sales of orthopedic implants and trauma products totaled $12.2 billion, and by 2012, it has increased at a compound annual rate of $18.1 billion.[6] The total cost for hip and knee replacement surgery has increased to 10.2% annually since 2000 and this value outpaces the overall U.S. healthcare expenditure growth of 8%.[7] Various implantable medical devices being used for these applications are constructed from materials like stainless steel (SS), titanium alloys, and cobalt base alloys. But these materials have demonstrated strong tendencies of failure after long-term use thus recommending the need for revision. There are a number of reasons for revision as depicted in Table I.[8] Due to advancement in medical technology, people live longer along with the combined benefit of the increased population of active young adults traumatized by sports injuries, exertive exercise habits, or road accidents appropriating more comfortable living conditions. If this is to be so, the implants have to serve a much longer period without failure or revision surgery. Therefore, it has become necessary to develop implants with superior longevity and biocompatibility.

BIOMATERIALS AND THEIR PROPERTIES

In order to attain optimal osseointegration, the material properties of these biomaterials are of paramount significance. Biocompatibility and mechanical endurance are the most crucial properties for both temporary and permanent implants.[9] Resistance to corrosion also plays a role especially when different implants are combined such as plate and screw for internal fixation of bone fractures.[10] In order for bones to sustain pressurized loads, they must be stiff and able to resist deformation. They must also be flexible in order to absorb energy from possible deformation, shorten and widen when compressed, and to lengthen and narrow through tension without cracking. Implant materials must also be light to facilitate motion. Thus, the implant materials chosen should feature characteristics, which serve these contradictory needs of stiffness yet flexibility and, lightness yet, strength. Apart from these mechanical properties, the material must also be biologically stable because of its interaction with soft and hard tissues, blood, and intra- and extracellular fluids of the human body. Thus, for an implant to serve for an extended period of time, it should possess biomechanical compatibility, biocompatibility, high corrosion and wear resistance, and osseointegration.

These properties and requirements evolved gradually with time leading to the development of innovative devices for improved solutions to clinical issues of implant failure due to infection, corrosion, dislocation etc.[11] The first generation of biomaterials was used with the only requirement to achieve physical properties to match those of the replaced tissue with minimal toxic response to the host.[12] The second generation of biomaterials was defined by their ability to interact with biological environment to enhance tissue bonding as well as progressively degrade while the new tissue regenerates and heals. Today, we are in the era of third generation of biomaterials, which have the additional ability to stimulate specific cellular responses at the molecular level.[13] Despite the tremendous advancement, there is still a need in the industry to develop orthopedic and craniofacial implants, which last longer. There is a need to focus more on the physical, mechanical, and biological properties of the materials being used today to understand their behavior *in vivo* in order to improve their characteristics (Fig. 1).[13] Fig. 1 indicates the mechanical properties of various materials being used for manufacturing orthopedic implants in relation with bone. It is clear that there are very few materials that satisfy all the mechanical properties exhibited by bone. This paper focuses on the various implant materials being used today, especially for orthopedic and craniofacial implants, the problems being faced by these materials and what remedies are being taken to resort those issues.

Metals and their composites

Stainless steel—Majority of the internal fixation devices are currently made from SS. These devices can be roughly classified into few major categories, which include wires, pins, screws, plates, and intramedullary nails or rods (Fig. 2).[14] The advantages associated with the use of SS are the fact that they are relatively low priced, easily available, have excellent fabrication properties, are biocompatible, and have great strength.[15] SS is an alloy consisting mainly of nickel, chromium, and molybdenum. SUS 316 is the only austenitic steel being used for biomedical applications.

Studies have shown that 90% of implant failures of 316L SS are due to pitting and crevice corrosion arising by the presence of chloride ions and reduced sulfur compounds in bodily fluids leading to the release of elements like nickel and chromium, which have a toxic effect.[16–22] Corrosive properties of these alloys have been worked on, and they have increased the levels of chromium, molybdenum, and nitrogen in order to increase its corrosion resistance.[23,24] SS are also being coated with transition metal nitrides like TiN, VN, TiAlN etc. which act as protective coating against wear and corrosion thus increasing life expectancy of the implants.[25] The major concern in using SS for biomedical applications is the presence of large amounts of nickel content. Nickel has been reported as a toxic substance to human body. Therefore, great deal of research is being focused on developing nickel-free SS, one of the approaches being the addition of large amounts of nitrogen, which is an austenite stabilizing element instead of nickel (which is also an austenite stabilizing element). Studies have compared the cytocompatibility of thus produced nickel-free SS (one containing Fe–Cr–Mo–N and the other containing Fe–Cr–Mo) with 316L SS, and results indicated that cell viability of nickel-free SS Fe–Cr–Mo–N is the best.[26,27]

The primary cause of response of immune system of the host against the biomaterial is the adhesion of proteins to its surface through interactions such as electrostatic or hydrophobic forces. Therefore, surface modification to generate protein-resistant surface is being accepted as a promising technology. Surfaces are being treated with chemical groups like epoxides and then grafted with various polymers such as polyethylene glycol, poly (dimethylsiloxane) etc., which increase surface hydrophilicity, thereby decreasing protein adsorption.[28,29]

Infection caused at the site of surgery can also lead to implant failure. Decreasing antibacterial activity exhibited by different materials is given in the following order gold> titanium>cobalt>vanadium>aluminium>chromium>iron showing little resistance of SS to microbial attack.[30] The most extensive remedy for this problem is being sort by implanting SS with silver/copper ions, which show strong antimicrobial properties to both *Staphylococcus aureus* and *Aspergillus niger*.[31,32] Titanium based biomaterials have shown better behavior in all the above-mentioned aspects.[33] But still SS continues to be used for manufacturing implants due to their cost aspect and will be used in future as well, and thus, its fatigue corrosion behavior should be studied well and resolved.[34,35] But, when a situation arises where a larger implant is required, such as joint replacements due to high elastic modulus possessed by SS as shown in Table II, the material is stiffer, and thus demands the use of other appropriate implant materials.[36]

Cobalt based alloys—Cobalt–chrome alloy is ubiquitously used in knee and hip replacement implants, particularly in the ball and socket joint where the motion occurs. In hip anthroplasty, it is generally the femoral head component that is hard and Co-Cr is used as a very smooth and scratch resistant surface. Other applications of this alloy include implants like tibial trays, acetabular cups, dental parts, pacemaker lead casings, as well as cardiovascular stents. All of these alloys are primarily composed of cobalt and chromium, but they may also include other metals like molybdenum to refine grain size, enhance solid solution strength, as well as increase corrosion resistance while nickel increases plasticity, fatigue crack growth resistance, and malleability of the alloy.[37,38] These alloys are known to possess high wear resistance and good mechanical properties under static loadings.[39] In the beginning stellite series of Co–Cr, alloys were developed composed of base material cobalt, 27–32% Cr, 4–6% W, 0.9–1.4% C and later vitallium composed of 62 % cobalt, 30% chromium, 6% molybdenum, 2% other elements (silicon, manganese, carbon) were patented. Since then, there has not been a significant change in the composition of the alloy, except for the carbon content. There has been a strict regulation on the percent of carbon and the homogeneous distribution of hard carbide grains, which increases the abrasion resistance of the alloy. Cast and wrought alloys are primarily used with identical composition but different microstructure. The cast iron exhibits a heterogeneous, large-grained, and cored microstructure, while the later one has a face-centered cubic structure with an austenitic microstructure and a finely distributed small block of carbides.[40] These properties make it one of the toughest materials available (Table II).[41]

Despite the corrosion resistance provided by both cobalt and chromium, biocorrosion is one of the major issues this alloy possesses.[42] Metal on metal implants are known to create 10^{12}–10^{14} nanoparticles of cobalt–chromium (Co–Cr) alloy per year in the size range of 20–60 nm. The presence of these nanoparticles near the implant site has an antibacterial characteristic preventing formation of biofilms. Research has shown that metal on metal wear debris and metal on polymer wear debris accelerate the growth of common organisms that infect prosthetic hip joints, but the clinical significance of this result is still uncertain. In isolation, the heavy metals contained within the wear debris (cobalt and nickel) have shown to retard the growth of bacteria, particularly nickel. Therefore, nanoparticles in the wear debris do not possess the toxic effects of its constituent metals on bacteria. This reinforces the safety of wear debris but also shows the potential for antibacterial effects to be harnessed.[43] Studies have shown that increased levels of cobalt and chromium in the serum can also be related to implant loosening.[44,45] Inflammatory responses are observed near the implant showing tissue necrosis, ulceration, and allergic reactions.[46] Numerous animal studies have also shown carcinogenicity.[47–48] Therefore, nowadays, Co–Cr–Mo alloy is being used in collaboration with ultrahigh molecular weighted polyethylene (UHMWPE) to reduce corrosion and wear.

Nickel is also often employed as an alloying element as it increases the stacking fault energy of the alloy and thus stabilizes the γ phase rather than the ε phase, thereby achieving higher ductility.[49] However, it is well known that nickel is a very toxic element. Therefore, Ni-free cobalt alloys are being developed for biomedical applications. In order to maintain good mechanical properties as well as to remove Ni for cobalt alloys, N is being used as a substitute under hot compression.[50,51]

Lack of integration of the Co–Cr alloy into the bone also leads to implant failure. Efforts are being made to modify its surface including covalent protein grafting and self-assembled monolayers of certain chemicals, to mention few. Studies have shown that osteoblasts attach, proliferate and differentiate better on these surfaces thus providing a potential solution for tissue integration.[52,53]

Titanium and its alloys—The application of titanium and its alloys in the medical area is truly astonishing as through its utilization in craniofacial implants, dental implants, joint replacement parts for hip, knee, shoulder, spine, elbow, and wrist, and bone fixation materials like nails, screws, nuts, and plates have been possible. This wide variety of applications can be attributed to its excellent characteristics as indicated in Table II such as high strength, low density, high specific strength (strength per density), good resistance to corrosion due to formation of an adhesive titanium oxide layer at the surface, inertness to body environment, enhanced biocompatibility, moderate elastic modulus, and high rate of integrity with the bone.[54–56] Titanium is commonly used in either grade 4 (G4Ti) or 5 (Ti-6Al-4V) forms because of their excellent chemical and mechanical properties. There are four types of titanium alloys-α, near α, $\alpha+\beta$, and β alloys based on their chemical composition, the content and nature of alloying elements, and the resulting microstructure.[57]

Of the different types of titanium alloys found, β phase titanium alloy tends to satisfy most of the requirements for an orthopedic implant application in contrast to an α phase alloy.[58]

The third generation titanium alloys are focused on developing porous structures to allow penetration of the vascular system for total integration of metal and bone.[59,60] Titanium fiber meshes with a porosity of 86% with an average pore size of 250 μm have been used in ex vivo studies in rats.[61] Titanium foams were used in vitro with human osteoblasts showing that the cells colonize and differentiate into mature bone cells and also possess osteoinductive properties, the only metal to possess this property.[62,63] Titanium is one of the few materials that do not contain calcium phosphate and has been shown to calcify when exposed to simulate body fluids and therefore is expected to calcify *in vivo* also.[64]

Despite all these advantages, long-term performance of these alloys has raised some concerns. This is due to the release of metals like aluminum and vanadium from Ti64 alloys that have been shown to be associated with health problems like Alzheimer's disease (although recent finding do not support this), neuropathy, and osteomalacia.[65,66] Vanadium alone is toxic in both elemental and oxide states at the surface of the implant.[67] Therefore, V-free Ti alloys such as Ti-6Al-7Nb and Ti-5Al-2.5Fe were developed. Then, V-and Al-free Ti alloys such as Ti-Zr and Ti-Sn alloys were developed.[68–70]

Titanium alloy also undergoes severe wear when it comes in contact with other metal surfaces due to a high coefficient of friction. This leads to the inflammation of the surrounding tissues and as a consequence loosening of implants.[71] Therefore, in order to increase wear resistance, thermomechanical processing of titanium microstructure is being studied as temperature is found to play a crucial role in the evolution of microstructures.[72,73]

Stress shielding is another major issue with metallic implants given the difference in the Young's modulus of the implants and bone. Young's modulus or the tensile modulus or elastic modulus is a measure of inherent stiffness of the material. It defines as a ratio of uniaxial stress to strain. This leads to bone absorption followed by loosening of the implant or refracture after removal of the implant. Therefore, it becomes necessary to lower the modulus of metallic implants to match the modulus of the bone. Studies showed that the additions of non-toxic elements like Nb, Zr, Mo, and Ta to titanium decreases the modulus of elasticity without compromising its strength.[74–76] Very recently, elements such as Fe, Cr, Mn, Sn, and Al are being proposed instead of rare metals like Nb, Zr, Mo, and Ta in order to lower the cost of the implant.[77–80] The lowest Young's modulus thus obtained for β-type Ti alloy is 35 GPa and is thus similar to the top range of bone which is 30 GPa.[81]

Spine fixation implants need to be bent to reproduce the curvature of patient's spine. In such cases, it is necessary to have a Ti alloy that has Young's modulus low enough to avoid stress shielding but high enough to suppress spring back that will cause trouble in patients. Therefore, a novel type of Ti alloy with low Young's modulus before deformation but increasing during deformation (self-tuning Young' modulus) has been developed and includes Ti–Cr, Ti–Mo, Ti–Zr–Cr, Ti–Zr–Mo, and Ti–Zr–Mo–Cr.[82,83]

Among several types of shape memory alloys, the NiTi alloy is considered the best biomaterial for orthopedic implants. The austenite form is quite strong and hard like titanium.[84] NiTi has an elastic modulus much similar to that of bone, it also has unique fatigue resistance and ductile properties while wear resistance is high and comparable to the Co–Cr–Mo alloy.[7] But, due to the toxicity of Ni, various studies are being carried out to develop Ni-free Ti-shape memory alloy. Currently, there are four categories of Ni-free Ti-shape memory alloys: Ti–Cr alloy system, Ti–Nb alloy system, Ti–Ta alloy system, and Ti–Mo alloy system.[85–88] Addition of small amounts of oxygen and nitrogen have been found to enhance super-elastic behavior of Ni-free Ti alloys as they lower the starting temperature of the martensite transformation. Temperature has been found to play an important role in functionality and strength of shape memory alloys.

Another approach being used for improving biocompatibility of Ti is provided by the surface modification approach based on controlling surface topography, ceramic coating, physicochemical, or inorganic modification and very recently biochemical modification of titanium surfaces.[89–91] In this recent approach, proteins, enzymes, glycosaminoglycans, chondroitin sulfate, collagen, and hyaluronic acid have been found to influence bone remodeling by improving osteointegration.[92,93] In the above-mentioned materials, the adjuvant remains only superficially associated with Ti. However, it is difficult to make these coatings remain adherent to Ti due to differences in mechanical moduli with eventual failure either at bone–implant interface or implant–coating interface.[94,95] There have also been attempts in which materials are impregnated into the core material, like calcium phosphate crystals within titanium and the results showed that there was an improved cell differentiation, bone bonding to implant, and osseoactivity.[96] Modification of topography of the Ti surface has also been shown to be a promising method.[97] Roughness has been established as an important character that determines and enhances osteoblast proliferation, adhesion, alkaline phosphatase activity, and mineralization.[98] However, principle contents of bone either organic (collagen) or inorganic [hydroxyapatite (HA)] are nanophase materials.[99,100] Thus, nanostructured materials are being studied as they provide a completely different sort of interaction between implant and cell, increasing surface area for cell attachment, cell proliferation, and mineralization.[101,102]

Knee joints operate similarly to a dynamically loaded bearing with about 10^8 cycles of loading in a 70-year lifespan. The average coefficient of friction of a load bearing synovial joints like hips and knees is about 0.02 with an average wear factor of about 10^6 mm^3/N. (wear properties of knee joint are always greater than that of the hip, given its polyaxial movement with flexion extension rotation and translation).[7] On the contrary, the coefficient of friction lies in between 0.16 and 0.05 depending on implant material and lubricant used. Commonly, prosthetic hip joints consist of a femoral head articulating against an UHMWPE. Of the metals used for femoral head construction, titanium was found to possess maximum wear followed by 316L SS, with the least observed in Co–Cr–Mo alloys.

Tantalum and its alloys—With the increasing number of young, active population undergoing arthroplasty, the need for a material, which has adequate biological and mechanical properties, is apparent. Porous tantalum has been identified as a potential alternative given its ability to integrate with the tissue allowing bone–tissue ingrowth, biomechanical properties, inert nature *in vivo*, and excellent chemical stability.[103] As indicated in Table II, the microhardness value for porous tantalum ranged from 240 to 393, the compressive strength was 60 ± 18 MPa, the tensile strength was 63 ± 6 MPa, the bending strength was 110 ± 14 MPa, and modulus of elasticity on the order of 3 GPa (similar to trabecular bone).[104] The ductility of this material is less in comparison with the metal implants but is high in comparison with other naturally occurring substances, ceramics, composites, and bone itself. The compressive fatigue endurance was 23 MPa at 5×10^6 cycles.[105] Tantalum implant possesses porosity of 400–600 μm with a volume porosity of 75–85% in comparison with Co–Cr (30–35%) and fiber metal (40–50%).[106] Distal femoral and proximal femoral components and patella have been designed using porous tantalum. Studies have revealed that there have not been any early failures in clinical performance of porous tantalum even in some harsh mechanical circumstances in cases of hip and knee revisions. But it still remains ascertained whether the theoretically advantageous mechanical compatibility of porous tantalum with bone will cause less-stress shielding and disuse atrophy of the surrounding bone.[107] Studies have indicated excellent stability during early bone development with bone ingrowth and minimal stress shielding problems.[108]

Niobium and zirconium alloys—Niobium alloys are very recently being proposed for biomedical applications. Nb-2Zr that has been recently introduced has been reported to exhibit excellent corrosion resistance, fatigue strength, and crack propagation in simulated body fluids.[109]

Zirconium belongs to the same group as titanium and exhibits similar properties as indicated in Table II.[110] But, zirconium is found to possess lower magnetic susceptibility (1.3×10^{-6} cm^3g^{-1}) than paramagnetic Ti (3.2×10^{-6} cm^3 g^{-1}). This property has been found to be important, because an insertion of metallic implants into patients undergoing magnetic resonance imaging (MRI) may increase probability of defects and distortions of this analysis. Therefore, Zr-based alloys have been developed like Zr–Nb and Zr–Mo.[111]

Ceramification of zirconium niobium alloy (Zr-2.5Nb) is being considered to improve the alloys wear and scratch resistance. Roughened-oxidized zirconium (OxZr) surface resulted in 61% less wear than roughened CoCr surface.[112] OxZr is also found to possess increased hardness and wettability, which supports formation of a lubrication film. It also supports higher adhesion in comparison with TiN coating.[113]

Mg alloys—Magnesium alloys are being sorted as a promising candidate for fracture fixation because magnesium possesses mechanical properties very similar to those of the bone (Table II). Its tensile strength in wet conditions is 230 MPa and Young's modulus is 45 GPa.[114] Some of the commercially available magnesium alloys include WE43 [Mg-Y-RE (rare earth)-Zr system], AZ91 (Mg–Al–Zn alloy system), AZ 31 (Mg–Al–Zn–Mn alloy system) and LAE442 (Mg–Li–Al–RE–Mn alloy system).[115–117] Magnesium is the fourth most abundant element in the human body; therefore, degraded products of this alloy can either be stored in fracture callus or new bone or eliminated into blood to be excreted by urine, without causing hyper-magnesium.[118] However, its corrosion resistance is far less than Ti and Co–Cr alloys, and therefore, magnesium is being considered as biodegradable material. Because of rapid degradation, magnesium alloys lead to formation of gaps at the interface of bone and implant; therefore, significant effort is applied to develop methods preventing fast degradation *in vivo*. Addition of alloying elements was one of the first approaches, but due to restrictions on usage of certain elements like Ni, other alternatives were sought. Surface modification of magnesium by chemical, physical, and a combination of both were used for treating it. Chemical modification included procedures like acid etching, fluoride treatment, alkaline treatment, anodizing coating, ion implantation etc. Physical modifications included apatite coating, implantation of metal oxides, and laser surface processing. Chemical and physical modification processes were also combined to improve corrosion resistance of magnesium alloys.[119]

Ceramics and their composites

Inert Ceramics—Alumina and zirconia are the two most widely used inert ceramics in hip and knee arthroplasty, maxillofacial reconstructions, ossicular bone substitutes, keratoprostheses, blade screws, bone screws, and post dental implants. The wide usage of these biomaterials can be attributed to their inertness (no formation of direct bone-material interface) and desirable mechanical properties, as they possess high compressive strength, elastic modulus, and hardness. They also possess excellent corrosion resistance, biocompatibility, low friction, high wear resistance, and stability in a physiological environment. The surface groups promote interaction with bodily fluids.[120] Alumina has been used for nearly 20 years now owing to its favorable characteristics. Polycrystalline α-Al_2O_3 (alumina) when mixed with small amounts of MgO has exceptionally low coefficients of friction making it suitable as a bearing surface. Alumina also has excellent biocompatibility with tissue aging not affecting the material structure or strength.[121] The current fracture rates of ceramics is negligible in comparison with overall failure rates of implants, though it must be kept in mind that the current use of ceramics has been restricted to limited number of which demand less mechanical stress. For femoral heads, fine-grained alumina fitted with Ti–Al–V stem is theoretically established as the best material combination for hip replacement surgeries.[122]

Despite these advantages, alumina femoral heads and acetabular liners are found to be associated with catastrophic failures.[123,124] The surface of the bearing must be perfectly spherical and congruent for hip prosthesis, thus emphasizing on the finalizing steps of its manufacturing. Due to its bioinert characteristic, there is always a soft tissue interlayer between the bone and the implant leading to stress-shielding problems causing troubles amongst the elderly population with osteoporosis and rheumatoid arthritis leading to loosening of the alumina acetabular cap. Thus, only under high compression, the fibrous tissue growth at the interface can be restricted with successful bone ingrowth. Therefore nowadays, ceramics are being fixed inside a taper lining of titanium acetabular shell rather than directly interfacing with the bone.

In response to the concerns regarding Al_2O_3 femoral fractures, yttria-stabilized zirconia (Y-TZP) was introduced. Due to the excellent mechanical properties of zirconia, it is called "cement steel".[125] Zirconia has the characteristic property of changing its crystalline reticulation when force is applied to its surface. This force on the crystal surface causes a volumetric change thus sealing the crack caused by the stress.[126] Y-TZP has about two to three times larger fracture toughness and flexural strength than Al_2O_3, making it one of the strongest ceramics for medical use. Zirconia has been shown to be non-cytotoxic, with no mutagenic effect.[127–129] Zirconia has been shown to support growth of blood vessels, but in comparison with titanium based implants, it shows lower inflammatory infiltrate, micro vessel density, and vascular endothelial growth factor characteristics.[130] Zirconia was also found to influence the gene expression of the cells, thus acting as a self-regulatory material.[131] Zirconia heads are used widely against UHMWPE bearings in Total Hip Arthroplasty and Total Knee Arthroplasty. But, despite these characteristics, recent studies have shown low temperature degradation for Y-TZP, including the temperature used for steam sterilization (140°C) and body temperature (37°C).[132] In Y-TZP, the presence of numerous vacancies in its lattice (trivalent) makes the diffusion of water higher than in normal zirconia, which ultimately leads to micro cracking.[133] Studies have also shown aging on the surface of the Y-TZP implants and predicting failures from low temperature degradation in the large number of zirconia implants used in the last decade (>500,000).[134] To overcome these limitations, two kinds of materials are considered: (1) alumina-zirconia composites – doping zirconia with alumina strongly reduces the number of vacancies in the lattice thus preventing the uptake of water molecules and improving crack resistance (there are already some implants in the market with SrO and Cr_2O_3 addition to zirconia-alumina grains); and (2) ceria and magnesia doped zirconia (Ce-TZP, Mg-PSZ) – these dopants were found to increase the toughness of the material.

Bioactive ceramics—This category of ceramics include calcium phosphate, glass, glass–ceramic, and composites, as these materials have the capability to interact with the biological environment to improve host response as well as bind the injured tissue. These materials also undergo progressive degradation while the new tissue regenerates.[135]

Natural bone can be viewed as a composite made from biopolymer (mainly collagen) and bioceramic [calcium phosphate (CaP)]. A total of 69% of the mineral content of the natural bone is composed of CaP in the form of carbonated apatite. The organic matrix of the bone consist of proteins (22%), type I collagen (90% of organic matrix) with some non-collagenous proteins (proteoglycans), lipids, and osteogenic factors.[99] Though CaP itself is not an osteoinductive material, it can be combined with materials like growth factors, bioactive proteins, or osteogenic drugs, and osteoinductivity can be induced.[136–139] Depending on temperature, impurities, and the presence of water, they exhibit different physical and chemical properties.[140–142] CaP has always showed excellent biocompatibility, bioactivity, biodegradability, and osteoinductive ability.[143–146] Of the different types of calcium phosphate, HA and β-tricalcium phosphate (β-TCP) are the most commonly used biomaterials because of their osteogenic properties, degradation properties, and their ability to form strong bond with bones. HA is a naturally occurring mineral form of calcium apatite. β-TCP is more soluble than HA and thus is called bioresorbable ceramic.[147,148] Some studies have shown that β-TCP supports cells better when compared to HA, while other studies have shown HA to be a better supporter.[149–151] The biological property of CaP can be attributed to the liberation of Ca^{2+}, PO_4^{3-}, HPO_4^{2-} to the surrounding environment which causes super saturation of the nearby fluid causing precipitation of carbonated apatite thus incorporating ions like Mg^{2+}, Na^+, CO_3^{2-} as well as proteins and other inorganic compounds.[142,152] They also provide nucleation sites for deposition of apatite layer containing organics. Porous ceramic scaffolds have shown to better support bone formation in comparison with dense sintered scaffolds. This is because the pores help in the invasion of blood vessels into the scaffold which brings nutrients and oxygen supply very essential for metabolism of cells.[153–155] The mechanical properties of this material depend on a number of factors including crystallinity, porosity, composition, and grain size. When comparing the mechanical properties of bone (Table III), we find that HA has higher compressive strength than bone, but bone has higher fracture toughness than HA. Despite the excellent biological and mechanical properties, HA cannot be used for all bone–tissue growth, especially at load bearing sites due to its low mechanical strength. They have also shown slow biodegradation.

Glass-based scaffolds can be classified into two main groups: (1) glass/glass–ceramic porous scaffolds (2) glass–polymer porous composites. Silicon found in glass has been found to greatly upregulate the gene expression in osteoblasts that regulate osteogenesis and production of growth factors.[156] Silicon has also been found to play a role in bone mineralization.[157] Recent work has shown that bioglass can also induce neovascularization promoting the formation of blood vessels *in vitro*.[158] Studies have shown that silicon substituted HA granules have higher bone ingrowth when compared to pure HA.[159] Phase transformations occur during thermal treatment leading to a high versatility of the final component which cannot be obtained in CaP ceramics. One of the main drawbacks of bioactive glass is its low fracture toughness and mechanical strength, especially in porous forms (Table III). Thus, similar to HA, these materials also have limitations in usage as substitutes in load bearing positions.

Non-oxide ceramics—This category of materials includes silicon nitride (Si_3N_4) and silicon carbide (SiC). They can be considered as glass–ceramic composites as they contain partially crystalline grain and amorphous boundary phases. They possess a combination of properties such as good wear and corrosion resistance, increased ductility, good fracture and creep resistance, and relatively high hardness in comparison to Al_2O_3.[160]

Despite these advantages, studies have found that silicon oxide layer, which forms by super oxidation of Si_3N_4 and SiC surface, may chip off over time resulting in significant increase in wear, as indicated in Table III.[161,162] Also despite high fracture toughnesss and strength, these materials have shown catastrophic *in vivo* failure. Therefore, efforts are being made to overcome these issues by working on their microstructure development and design and fabrication techniques. In the microstructure development, β-Si_3N_4 can be formed with a perfect circular cross-section and aspect ratio which are major factors contributing to the toughness and strength of a material. Designing of a concentric ring-structured implant consisting of alternate layers of Si_3N_4 and partially porous interface, which eliminates the direction of easy crack propagation and offers high damage tolerance.[163]

Apart from the high mechanical strength, these materials have also exhibited excellent cytocompatibility *in vitro*.[164] Studies have also found that Si_3N_4 showed better resistance to bacterial film formation in comparison with Ti and polyether-ether ketone (PEEK). This difference can be attributed to the surface chemistry and surface nanostructure properties of the material.[165]

Polymers and their composites

For orthopedic and craniofacial applications, polymers currently used are acrylics, polyamides, silicones, polyurethanes, PEEK, UHMWPE, and polypropylene (PP).[166] The main advantages of these materials include the possibility to tailor their composition and structure according to the specific needs. In addition, bioresorbable polymers are being used in both orthopedic and craniofacial bone regeneration. Polymethyl methacylate (PMMA) commonly referred to as bone cement, continues to play a vital role as synthetic biomaterial used in orthopedic surgery due to a comparable elastic modulus to that of the bone. It is the only implant that is manufactured in the operating room. It functions as a supportive material that forms a mechanical bond between the cement and bone ad cement and prosthesis. Another important polymer to consider is poly-hydroxyethylmethacrylate (poly-HEMA), as it is the only polymer possessing osteoinductive capability *in vivo* till date. However, composites of polymers and HA possess osteoinductive property.[101,167] Even in the absence of osteoinductive factors like bone morphogenic proteins (BMPs), these materials were successful in bone formation in pigs.[168] This phenomenon was explained by the fact that bone formation can be induced by tendons and arteries only if they were first calcified and the CaP formed plays a role in osteoinduction.[169] Thus polymers with growth factors incorporated are being evaluated as promising material for tissue regeneration.[170] Polymers can also be fused with bioactive peptides like arginine–glycine–aspartic acid (RGD), which help in cell migration onto the surface. Despite these efforts, polymers still face the problem of interfacial adhesion at tissue and implant junction.[171]

The main advantage of using polymers is that they can be injected into the defect site thus reducing the cost and pain that follows surgery. One approach to do this is to design photopolymerizable materials, such as Poly(sebacic acid) (PSA), poly [1,3-bis(p-carboxyphenoxy) propane], and poly[1,6-bis(p-carboxyphenoxy] hexane, which can be injected as liquid and once in the bone defect site; they can be solidified by exposure to light. Since these materials can absorb water, they undergo degradation at their surface. In order to avoid these troubles, scientists are exploring polymers which can cross-link *in vivo* such as poly (propylene fumarate) and polyanhydrides. These polymers have showed the ability to control polymerization and form three-dimensional structures, along with the ability of controlled degradation rate.[172–176]

New processing techniques and composite materials are being used such as polyvinyl alcohol (PVA)/polyvinylpyrrolidone (PVP) hydrogels and PVA melted on titanium mesh to resolve the issues of mechanical instability.[177] Composite consisting of polyethylene (PE), younger cross-linked variant of polyethylene (XPE), and CoCr grafted with 2-methacryloxyloxethyl phosphorylcholine polymer are being designed which mimic the neutral phospholipids of biomembranes having coefficient of friction in the range of cartilage–cartilage articulation thus minimizing the wear debris, thereby reducing the chances of implant failure due to implant loosening.[178]

Polymers also have been found to lack mechanical stability as shown in Table IV.[179] To overcome this, fiber-reinforced polymer composites are being used widely in orthopedics.[180] These materials have the required strength (Fig. 1) to match the properties of bone which include low elastic modulus as well as high strength, corrosion, and fatigue resistance. Also the properties of the composites can be adapted according to the requirements by varying the arrangement or volume fraction of the fibers.[181]

A number of studies have been conducted on ceramic–polymer composites and polymer–polymer composites. But, despite tremendous efforts to improve their mechanical properties, disastrous failures have been reported. Therefore, efforts are being made to design polymer/magnesium composites.[182] The polymer matrix will benefit from magnesium which possesses high mechanical strength and fracture toughness, while the magnesium can benefit from polymer which will prevent its degradation and will give the strength required by the composite to reach the values of cortical bone.[183,184] Magnesium and polymer being degradable can degrade with time as the tissue heals.

Orthobiologics

Orthobiologics include resorbable calcium salt bone void fillers, few of which contain demineralized bone matrix (DBM), which is processed from human bone tissue and contains a number of bone growth stimulators, BMPs, stem cells, gene therapy etc. They are among the cutting edge technologies for musculoskeletal treatments. They possess tissue regeneration characteristics which include osteoconduction, osteoinduction, osteogenesis, and osteocompatibility. Apparent differences in the mechanisms of osteoinduction have been shown between BMPs and inorganic biomaterials: (1) bone induced by biomaterials is always intramembranous, that is, direct bone formation without cartilage intermediate at heterotropic sites, while bone formed by BMP induction is mostly endochondrial; (2) in small animals, bone formation is rarely induced by biomaterials in contrast to BMPs; (3) in larger animals, bone induction by biomaterials is relatively slow and requires few months to be accomplished, whereas for BMPs, it takes 2–3 weeks; (4) in biomaterials, bone formation is seen mostly in the porous area of the scaffold, whereas BMPs-induced bone formation is seen in the periphery as well as in the soft tissue away from the carrier.[137,185–195] Due to these advantages, several studies have been focused on growth factor incorporating biomaterials. CaP matrices and scaffolds have been used to deliver growth factors locally, in the defect site, which is more effective as compared to the methods of systemic delivery used for treatment of majority musculoskeletal disorders. CaP cements, CaP coated metallic implants, and several other custom-designed implants with growth factors incorporated are being used in clinics.[196–199]

An optimum concentration level of DBM and carrier is required in order to resist the migration from graft site. Cortical and cancellous bone chips are used to provide the three-dimensional scaffold for osteoconduction and mechanical strength. The orthobiologics are stored in dry form in sterilized condition, and when they need to be used, they are mixed with blood or autogenous bone grafts and delivered into the bone defect using a syringe or can be molded into a shape and fixed at that site. These substances are made water insoluble to prevent flowing off from the graft site.

Type I collagen along with bone mineral has been proven to be osteoconductive. The limitations of using these new technologies are the delivery of these materials to the specific site of implantation and to study the specific response from these products. Fibrous textile materials have been designed for use as composites with the orthobiologics to bridge this gap. The fabric structures can be formed from polyglycolides, poly-L-lactic acid, and similar materials. And they are given a structural design by either of the technologies: weaving, braiding, and knitting to obtain a unique design feature that allows resorption of the polymer within the structure to coincide with the repair rate of the biological material.

RECENT IMPROVEMENTS IN COMMERCIALLY AVAILABLE IMPLANTS

Knee replacements

Knee joint is composed of tibia, femur, and patella. In order to provide pain-free motion, the ends of bones are covered with cartilage, which is a lubricating tissue that prevents friction between the bones. The most common form of cartilage wear-osteoarthritis results in irritation, swelling, stiffness, and discomfort urging them to resort to cartilage replacements.

Several other alternatives are thought before considering knee replacement. Minimally invasive surgery, arthroscopy, replacing the worn out cartilage with either tissue engineered cartilage or cartilage transplant, and microfracture arthroplasty are some of the methods. But, if the surgeon recommends knee replacement, then the implants are typically made of metal alloy on the end of thighbone and PE on top of the tibia and underneath the kneecap. The word replacement does not mean removing the entire joint, but it includes removal of the damaged bone and cartilage at the end of the joints.

When designing a knee implant, the most advantageous method is to consider the individual’s joint anatomy. Indeed, many manufacturing companies are nowadays offering customized personal implants by utilizing MRI or CT scan technology to create three-dimensional joint reconstruction. This allows for better implant positioning and alignment with other joint components.

Partial knee replacement is considered when only one compartment of the three compartments in the knee is affected by arthritis and the other two are healthy. The advantages of this procedure are smaller incision, lesser bone removal, better natural motion, and faster recovery of the patient. The disadvantage of this procedure is that partial knee replacement does not last as long as total knee replacement surgery. The New Zealand National Joint Registry reviewed the rate of revision of unicompartmental knee replacements (UKR) between 1999 and 2008 and found that the rate of revision for the UKR to a total knee replacement (TKR) was four times higher than that for primary TKR.[200]

Complete knee replacement needs to take many factors into consideration before designing the implant for an individual like their gender, age, weight, medical condition, activity levels etc. But, generally, for the manufacturing companies, the important consideration is how the kneecap moves against the femoral component. The kneecap moves in the groove provided in the implant during the flexion and extension movement. The angle of movement has to be crafted individually because it differs among individuals.

Hip replacements

The hip is a ball and socket joint with the femoral head (ball) sitting in the acetabulum (socket) with a cartilage in-between (Fig. 3). Constant motion and pressure on the joints can result in continuous wear and tear of the cartilage.

Customized implants are also available to ensure better implant-bone match. Also in implants where highly cross-linked polyethylene is being used, they are preparing vitamin E induced polyethylene, as it is found that polyethylene gets oxidized in presence of polyethylene and with time becomes weak. Vitamin E acts like an antioxidant and protects the polyethylene from oxidation thus increasing its life.

Future development

The promise of the biomedical implants in eliminating some of the intricate issues of middle-and old-age population has led to outpouring of demands for new procedures. The major reason for the torrent of demand is prolonged average life expectancy of the population. However, the current generation of implants still faces certain issues during the long-term performance. By the extensive studies carried out till date, we can provide a theoretical answer to the properties required by these biomaterials, but still we are unable to design materials that can provide us desired results in vivo. The main reason is that properties of the end product greatly depend on the process parameters, which greatly influence various characters like macroporosity, grain size, surface roughness etc, which in turn determine the mechanical and biological properties of that material. These parameters are often missing in the publications and thus should be standardized and studied carefully. There is also an increasing need for understanding the basic interaction of the biomaterials with the implant surface, the host, and the biological environment at atomic levels as well as to know all types of micromotions executed by the implant inside the host, in order to develop implants which can last longer in the human body. Intense studies should be carried out to understand aspects like wear of the implant under pressurized loads, biologic response to wear and corrosion debris, the effect of biologic medium surrounding the implant etc. In the end, one has to accept the fact that humans have been diligently working and in many ways have succeeded in relieving many people from the sufferings and have increased their longevity, but the mission is still unaccomplished.

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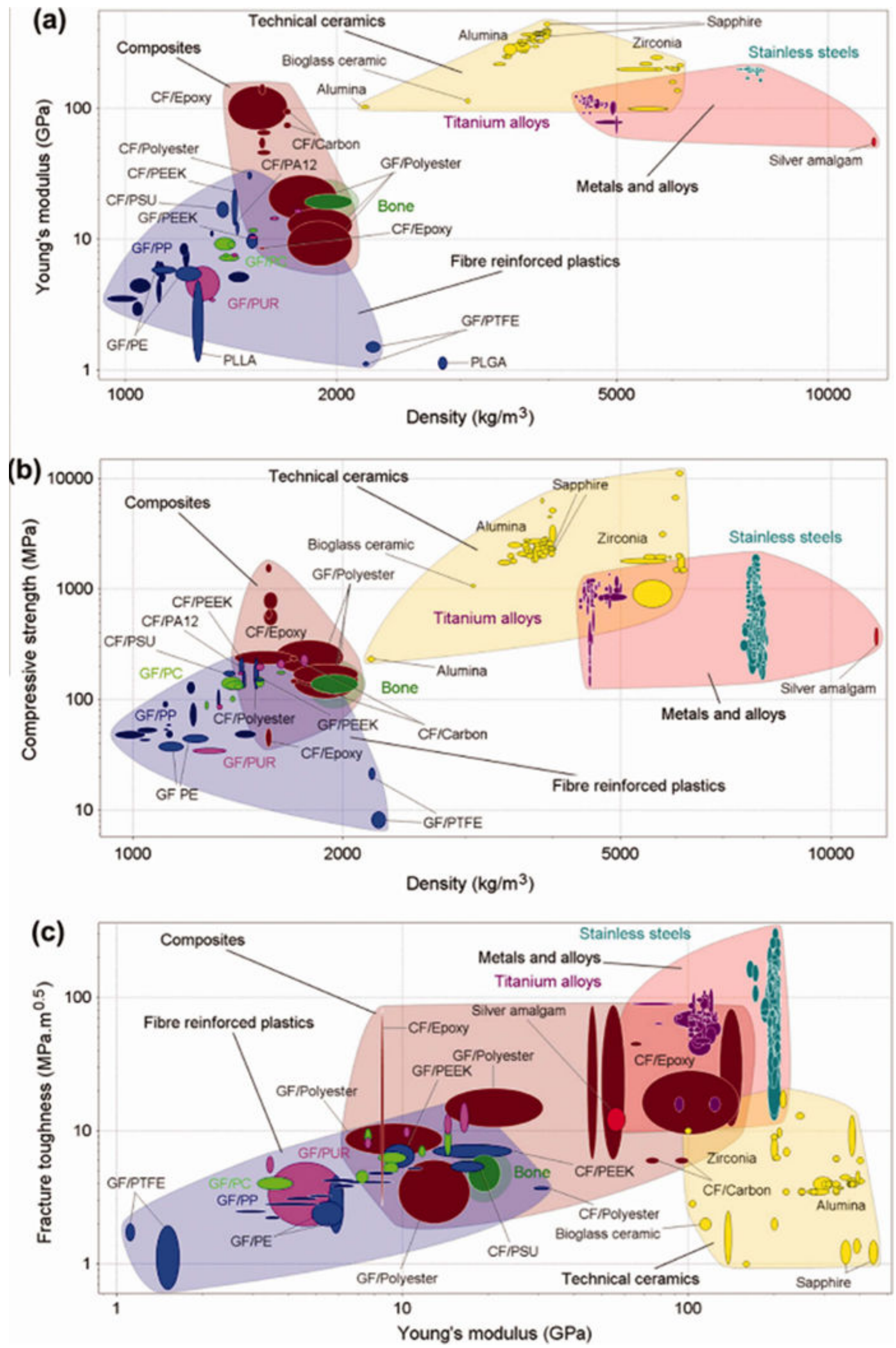

FIGURE 1.

Comparison of (a) stiffness, (b) strength, (c) fracture toughness for metals, technical ceramics, composites, and fiber reinforced plastic with respect to bone. CF- carbon fibre, GF – glass fibre, PA12: polyamide12, PC – polycarbonate, PE – polyethylene, PEX – poly ether ether ketone, PLGA – poly(l-lactic-co-glycolic acid), PLLA (poly(1-lactic acid), PP – polypropylene, PSU – polysulfone, PTTE – polytetrafluoroethylene, PUR – polyurethane. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

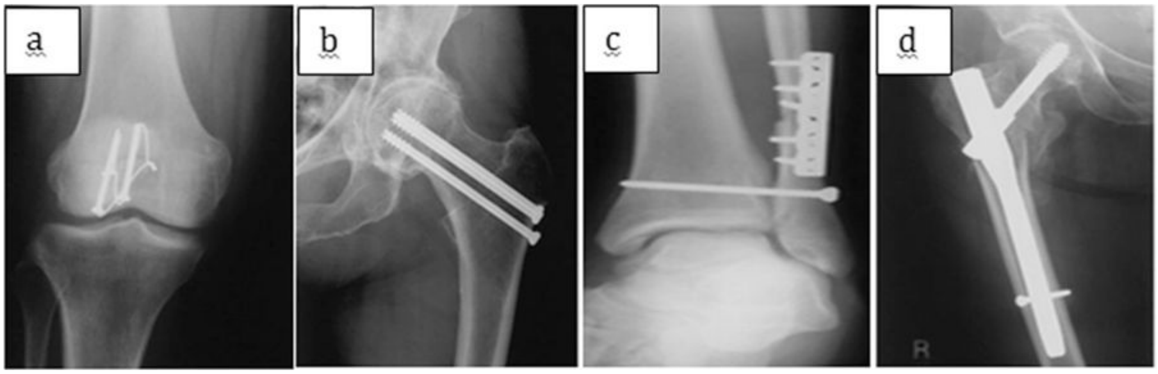

FIGURE 2.

a) Transverse patellar fracture (knee) transfixed with a tension band wire b) Subcapital proximal femoral fracture (hip) transfixed with screws c) Distal fibular shaft fracture (ankle) transfixed with plate and screws d) Intertrochanteric fracture (hip) transfixed with intramedullary femoral rod with an interlocking screw.

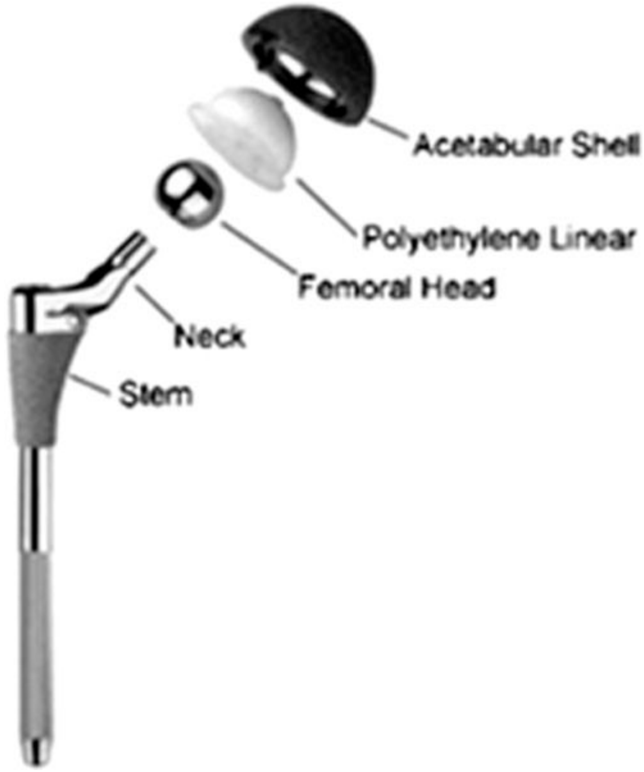

FIGURE 3.
Total Hip Replacement implant with metal on polyethylene.

TABLE I

Major Reasons for Revisions in Orthopedic Surgeries

Reasons for Revision	Number According to Kaiser Permanente Total Joint Replacement Registry	%
Infection	464	40.4
Instability	233	20.3
Pain	212	18.5
Aseptic loosening	143	12.5
Anthrofibrosis	124	10.8
Fracture	33	2.9
Others (include extensor mechanical failure, osteolysis, hematoma, polylinear wear, ingrowth failure)	78	6.9

TABLE II

Mechanical Properties of Metallic Materials used for Orthopedic Implants. The Range of Values is Dependent on the Composition of the Material and Testing Conditions

Material	Elastic Modulus (GPa)	Fracture Toughness (MPa)	Hardness (MPa)	Compressive Strength (MPa)	Density (g cm^{-3})
Human cortical bone	3–20	3–6	300–480	90–120	1.8–2.1
Stainless steel	190	50–200	130–180	170–310	7.6
Co–Cr alloys	200–300	N/A	300–400	450–1000	8.9
Ti and Ti alloys	110–116	55–115	310	758–1117	4.5
Tantalum and alloys	3	96–124	240–393	42–78	–
Zirconium	96–100	–	210–235	276–345	6.51–6.64
Magnesium	41–45	15–40	–	65–345	1.74–1.84

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TABLE III

Mechanical Properties of Ceramics. The Range of Values is Dependent on the Composition of the Material and Testing Conditions

Ceramics	Compressive Strength (MPa)	Tensile Strength (MPa)	Elastic Modulus (GPa)	Fracture Toughness (MPa)
Hydroxylapatite	>400	~40	~ 100	~ 1
45S5	~500	42	35	0.5–1
Glass–ceramic	1080	215	118	2.0
Porous bioactive glass 70S30C (82%)	2.25	–	–	–
Porous bioglass derived glass ceramic (>90%)	0.2–0.4	–	–	–
Porous HA (82–86%)	0.21–0.41	–	0.002–0.83	–
Non-oxide ceramic	4000–4500	450–1200	175–250	2.8–12

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TABLE IV

Mechanical Properties of some Polymers

Polymer	Young's Modulus (GPa)	Compressive or Tensile Strength (MPa)
ultrahigh molecular weighted polyethylene (UHMWPE)	0.495	231.1
Poly(glycolic acid) – PGA	7–14 (FIBRE)	340–920 (FIBRE)
poly(L-lactic acid) – PLLA	10–16 (FIBRE)	870–2300 (FIBRE)
poly(L-lactic-co-glycolic acid) – PLGA	1.4–2.8	41.4–55.2
Poly(anhydrides)	0.14–1.4	25–27