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Review

Nanotechnology-based biomaterials for orthopaedic applications: Recent advances and future prospects

Sandeep Kumar[a,*], Monika Nehra[a], Deepak Kedia[b], Neeraj Dilbaghi[a], K. Tankeshwar[a,c], Ki-Hyun Kim[d,*]

[a] Department of Bio and Nano Technology, Guru Jambheshwar University of Science and Technology, Hisar, Haryana 125001, India
[b] Department of Electronics and Communication Engineering, Guru Jambheshwar University of Science and Technology, Hisar, Haryana 125001, India
[c] Department of Physics, Panjab University, Chandigarh 160014, India
[d] Department of Civil & Environmental Engineering, Hanyang University, 222 Wangsimni-Ro, Seoul 04763, Republic of Korea

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ABSTRACT

Bioimplant engineering aims to mature biological alternatives to restore, retain, or modify damaged tissues and/or the functionality of organs. Remarkable advancements in modern material technology have helped the diversity of materials for orthopaedic implant application. As such, nanomaterials can simulate the surface properties of natural tissues, especially with respect to surface topography, surface chemistry, surface energy, and surface wettability. The novel properties of nanomaterials also encourage their use for improving the growth of different tissues. The present review lays the foundation for nanotechnology-driven biomaterials through revelation of fundamental design considerations to determine the performance of an orthopaedic implant in terms of success or failure, their antimicrobial/antibacterial activities, and response to cell adhesion, proliferation, and differentiation. In this context, the nano-functionalization of biomaterial surface has been widely investigated to improve cell adhesion, proliferation, differentiation, and migration for implants with high antimicrobial activity. The potential use of nanomaterials (in terms of nanostructured surface or functional nanocoating over implant surface) can resolve several issues (*e.g.*, corrosion resistance and bacterial adhesion) pertaining to conventional metallic or non-metallic implants, especially for optimization of implant techniques. The future trends of orthopaedic biomaterials (*e.g.*, porous structures, smart biomaterials, and 3D implants) are promising to achieve the desired properties and structure of an implant with stimuli-responsive behaviour. The major challenges in commercialization of nanotechnology-derived biomaterials are finally addressed to help overcome the limitations of pre-existing orthopaedic biomaterials in terms of key variables, *e.g.*, quality, treatment cost, implant life, and pain relief.

1. Introduction

Nanotechnology refers to a multi-disciplinary field in which properties and structures of materials are manipulated at the nanometer scale through physical, chemical, and biological routes. Nanomaterials possess novel size-dependent properties that are usually not detected in their bulk counterparts. Progress in nanotechnology has opened up new opportunities for numerous applications in medicine [1–3],

Abbreviations: BMP, Bone morphogenic protein; CaP, calcium phosphate; CNFs, carbon nanofibers; CNTs, carbon nanotubes; *E. coli*, *Escherichia coli*; FGF, fibroblast growth factor; FMOC, fluorenylmethyloxycarbonyl; GDA, glycerol diglycidyl ether; GelMA, methacrylated gelatin; GMA, glycidyl methacrylate; GO, graphene oxide; HA, hydroxyapatite; HBPU, hyperbranched polyurethane; HIUS, high-intensity ultrasound; LIDC, low-intensity direct current; MeTro, methacryloyl-substituted tropoelastin; MRI, magnetic resonance imaging; MRSE, methicillin-resistant *Staphylococcus epidermidis*; MRSA, methicillin-resistant *Staphylococcus aureus*; MWT, microwave techniques; PCL, polycaprolactone; PCU, polycarbonate-urethane; PEEK, polyether ether ketone; PEG, polyethylene glycol; PGA, polyglycolide; PHA, polyhydroxyalkanoates; PHMGCL, poly(hydroxymethylglycolide-co-ε-caprolactone); PLA, poly(lactic acid); PLGA, poly(lactide-*co*-glycolide); PLLA, poly-L-lactic acid; PMMA, poly(methyl methacrylate); PS, polystyrene; *P. aeruginosa*, *Pseudomonas aeruginosa*; PVA, poly(vinyl alcohol); PVDF, polyvinylidine fluoride; SMAT, surface mechanical attrition treatment; *S. aureus*, *Staphylococcus aureus*; *S. epidermidis*, *Staphylococcus epidermidis*; SPD, severe plastic deformation; SWCNTs, single-walled carbon nanotubes; TCP, tricalcium phosphate; TMPGDE, trimethylolpropane triglycidyl ether; UHMWPe, ultra-high molecular weight polyethylene; USP, ultrasonic shot peening

* Corresponding authors.
E-mail addresses: ksandeep36@yahoo.com (S. Kumar), kkim61@hanyang.ac.kr (K.-H. Kim).

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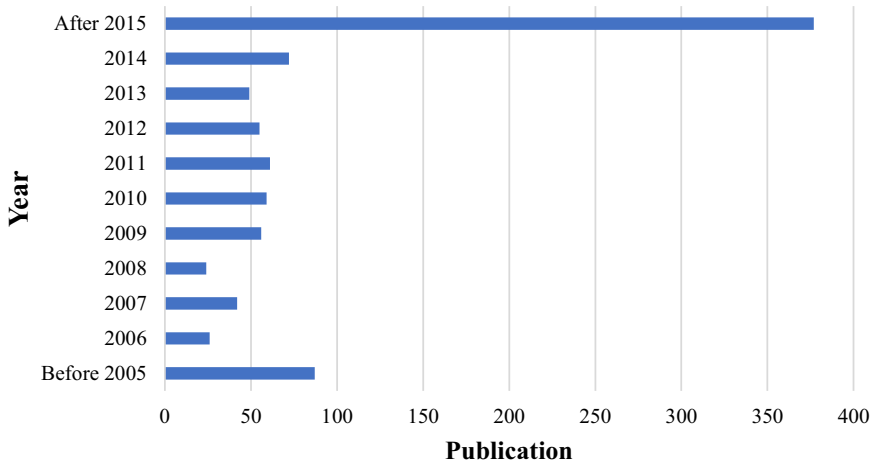

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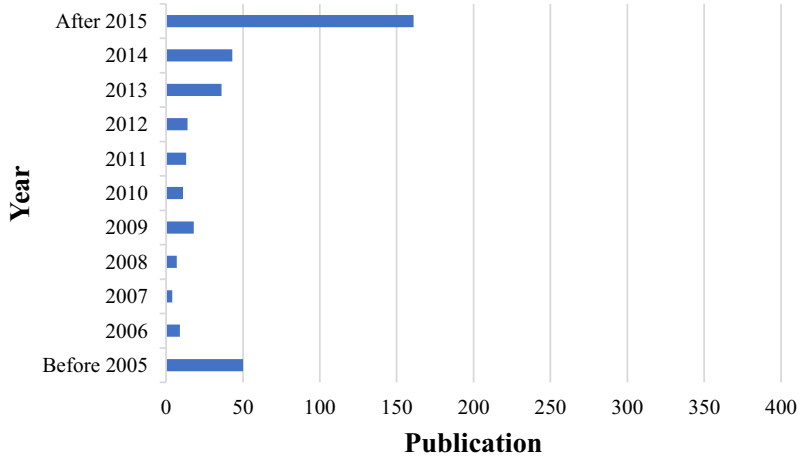

(b)

Fig. 1. Bar diagram describing the basic statistics of publications with the subject "implants": (a) The total number of publications (N = 908) with "nanotechnology for implants" in the title based on PubMed data accessed on July 30th, 2019 and (b) the publications (N = 366) that are cited in this review article.

biotechnology [4,5], molecular biology [6,7], and environmental science [8–10]. The application of nanotechnology to medicine (*e.g.*, nanomedicine) has been realized through the development of several sophisticated techniques for the prevention, diagnosis, and treatment for many diseases including cancer therapy, scaffolds for tissue engineering, medical imaging, drug delivery, and immunotherapy.

Because of the capability to mimic or replicate the constituent organs of a natural bone, nanomaterials are highly promising candidates for the construction of future orthopaedic implants [11,12]. In orthopaedic applications, the demand of bone substitutes is indispensable to cure irreversible damage of the natural and healthy bone. In this respect, nanomaterials can play a significant role not only by providing structural support for the cell (*e.g.*, nanofunctionalized scaffolds) but also by regulating cell proliferation, differentiation, and migration [13,14]. Fig. 1(a) shows that the annual growth of publications with "nanotechnology for implants" in the title (N = 908, source: PubMed data) is rapidly growing. Fig. 1(b), shows the same search results, but only the references cited in this review are depicted (N = 366).

The bioimplant market is increasing exponentially with the growth of the aging population, changes in lifestyle (especially those that promote and perpetuate chronic diseases such as osteoarthritis and cardiovascular diseases), technological advancements in bioengineering, and increased awareness of cosmetic implants. According to market survey reports, the global bioimplant market is expected to grow to $115.8 billion by 2020 with a compound annual growth rate (CAGR) of 10.3% during the estimated period (2014–2020) [15]. Bioimplants have emerged as a promising solution for neurological disorders, visual impairments, cardiovascular disease, orthopaedic issues, disfigurement, dental disorders, and other conditions (Fig. 2) [16–21]. Different bioimplants such as joint replacements, vascular grafts, bone plates, sutures, heart valves, ligaments, dental implants, intraocular lenses, and many more, are commonly used to (i) replace or re-establish the function of devastated or disintegrated tissues, (ii) modify the functions of a body part, (iii) assist in healing, and (iv) correct irregularities for cosmetic purposes [22]. Different engineering technologies have been reported in order to mimic the physical properties, chemical characteristics, and gradient architecture of organs or tissues through the use of conventional metallic/non-metallic materials. However, the major limitations of conventional bioimplants are that they do not always conform to the tissues, they are not always compatible with the tissues, and they are not always accepted by the human body [23].

Over the past few years, the impact of nanotechnology on implant field has begun to rise in a significant manner. Especially,

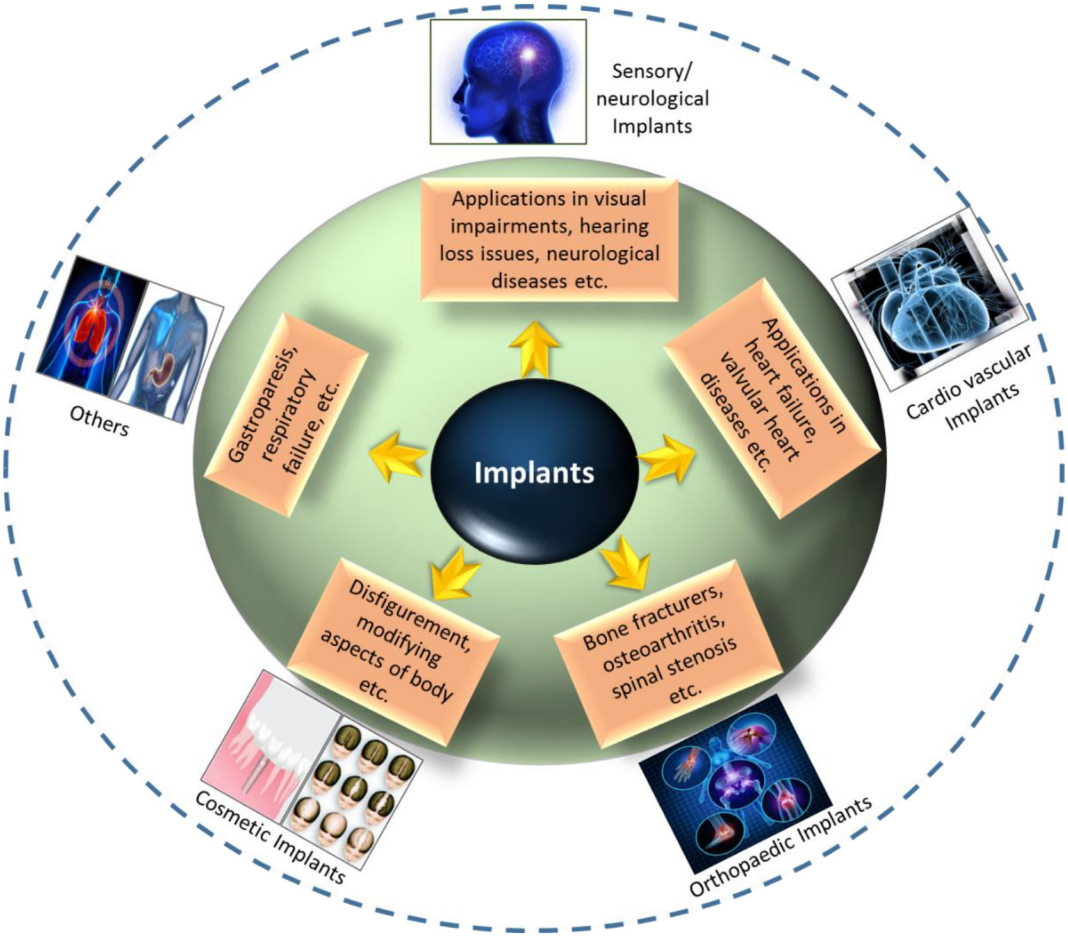

Fig. 2. Application-oriented classification of bioimplants into sensory/neurological implants, cardiovascular implants, orthopaedic implants, cosmetic implants, and others.

nanomaterials with biological-inspired features are motivating the researchers to explore their role in performance improvement of conventional implants. This review covers the historical development of biomaterials from conventional (*i.e.*, metallic and non-metallic) materials to nanomaterials in orthopaedic applications. In addition, the diverse surface modification techniques (*e.g.*, nano-engineered surface structuring and treatments) are discussed here. This review also puts emphasis on antibacterial surface treatment strategies for bioimplants. Diagnosis of the healing sites and effective implantation are the major issues in orthopaedic therapies. To provide a comprehensive review on this highly growing scientific area, the recent trends in the major orthopaedic biomaterials including porous materials, smart biomaterials, and 3D printable nanocomposite implants are also discussed along with commercial challenges. This review establishes a sound platform for the integration of nanotechnology-driven orthopaedic implants into human body.

2. Orthopaedic biomaterials: Classification and their associated challenges

Biological tissues can be classified into two basic categories: hard tissues (including bone, cartilage, teeth, and nails) and soft tissues (including skin, ligaments, fibrous tissues, and synovial membranes)—with or without mineral components. The shortage of donor organs placed an impetus on researchers to discover new ways to either mimic or replicate organs [24,25]. To meet such demand, bioimplants have been introduced to restore, support, or enrich the functions of human tissues. Biomaterials developed for implant applications are nonetheless different from biological materials such as bone and tissues. These biomaterials are either synthetic or natural materials that are intended to perform appropriately in a biological environment.

In orthopaedic applications, the aim of biomaterials is either to re-establish the structural integrity of injured bone or to replace it. There are major necessities to be considered in the design of each biomaterial such as appropriate mechanical properties (*e.g.*, specific weight and elastic modulus), biocompatibility, good bio-stability (resistance to corrosion, oxidation, and hydrolysis), osseo-integration (in the case of bone prosthetics), high wear resistance, high bio-inertness (non-irritant, and non-toxic), and ease of surgical application (Fig. 3) [26,27]. Biomaterials have shown success in cell proliferation and tissue remodeling [28].

Over time, significant research efforts have been made to devise and regulate the biomaterial properties to obtain the specific application-oriented biological response [29,30]. For instance, it is possible to optimize the growth of muscle cells by modulating the stiffness of the cell substrate [31]. In a modern context, orthopaedic biomaterials can be classified into two major categories: classical biomaterials and nanophase biomaterials (Fig. 4). The classical biomaterials can be further classified into: (i) metals and their alloys and (ii) non-metallic materials (such as polymeric, amorphous glasses, crystalline ceramics, and carbon composites). In this section, classical biomaterials are discussed along with their associated challenges for orthopaedic implant applications.

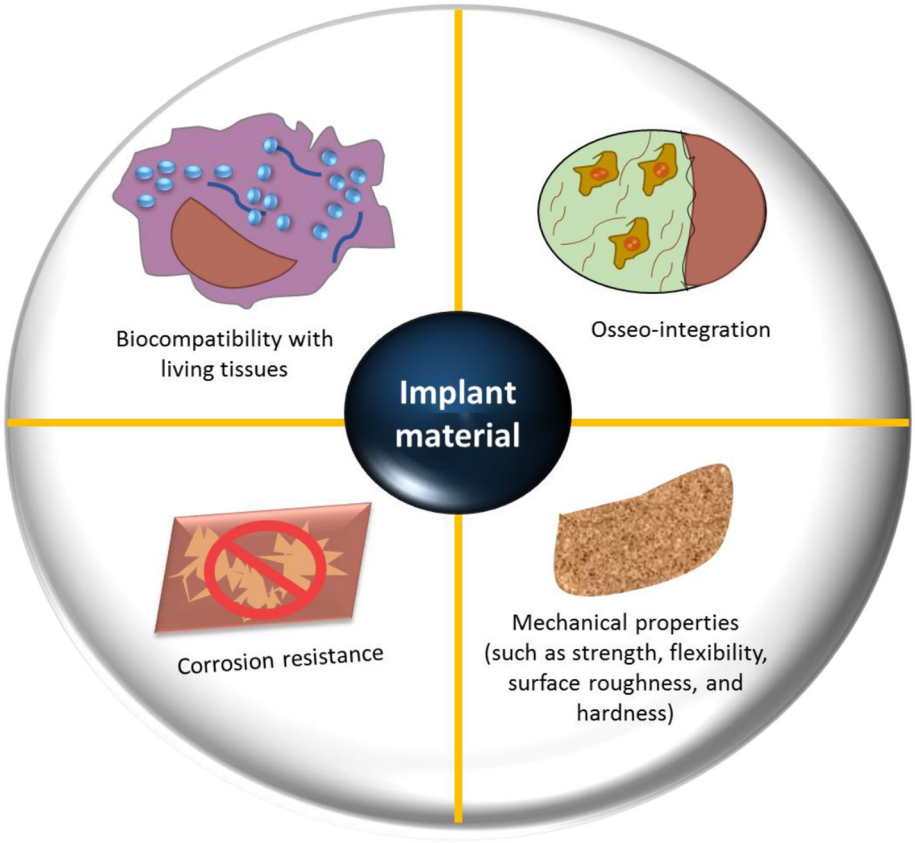

Fig. 3. Considerable factors in design of the orthopaedic biomaterial such as biocompatibility with living tissues, corrosion resistance, osseo-integration, and mechanical properties (such as strength, flexibility, surface roughness, and hardness).

2.1. Metals and alloys

Metals and alloy materials are usually preferred for load-bearing and internal fixation orthopaedic implants. Such implants are strongly bound to bones to ensure minimal movement between the host tissue and the implant as well as load-bearing capabilities at the implantation site. Although the availability of such materials is high, only a few materials are biocompatible and thus capable of long-term success in implant applications, *e.g.*, magnesium in biodegradable orthopaedic implants for load-bearing [32], titanium in bone and joint replacement [33,34], surgical grade stainless steel (usually 316 L) in temporary implants (such as hip nails and fracture plates) [35], and cobalt-based alloys in orthopaedic prostheses (for hip, shoulder, and knee) [36]. The mechanical properties and clinical orthopaedic applications of metallic materials are listed in Table 1 (section A) [37–40]. In orthopaedic applications of biomaterials, specific mechanical properties are required for (i) stabilizing or promoting the fracture integrity, (ii) joint replacements, and (iii) realigning the bone fragments. The use of metallic biomaterials began in the 1860s when the metal industry started to grow during the industrial revolution [41]. Metallic materials occupy a significant place in biomedical implant engineering due to the uniformity of their properties (*e.g.*, high strength, toughness, and durability), ease of manufacturing, and reasonable biocompatibility, all of which are desirable to achieve longevity of implants [42–45].

Titanium (Ti) and its alloy Ti6Al4V are common bioimplant materials that possess good fatigue strength, corrosion resistance, excellent biocompatibility, light weight, and low cost [46]. The formation of an oxide layer on the metallic surface offers significant resistance against corrosion. The stability of the oxide layer has been considered one of the major issues of bioimplants, as it may change due to the reactions between the metallic surface and living tissues [47]. Most of the metallic materials experience chemical and/or electrochemical dissolution under the environment of the human body that have an oxygenated saline solution along with a 0.9% salt content at pH 7.4 and 37 °C temperature (Fig. 5) [48]. In this oxygenated saline solution-containing biological environment, these metallic biomaterials have a tendency to lose electrons in solution. As a result, these biomaterials generally exhibit a high likelihood of corrosion in such an environment; corrosion, in turn, can lead to inflammation and loosening of the implants [49,50]. The complex interaction in between the corrosive biological environment and physiological stresses may cause premature failure of the metallic bioimplants. The reason behind this premature failure is stress corrosion cracking of biodegradable metallic implants that can induce significant damage to the implant material while shortening its life span [51]. In orthopaedic implants, a permanent failure of 316 L stainless steel has been reported due to their poor fatigue strength and/or liability to undergo plastic deformation [52,53].

Other metallic implants have other limitations. Cobalt-based alloys have replaced stainless steel for application in permanent implants due to their resistance to corrosion. Nonetheless, cobalt-based alloys release carcinogenic ions *in vivo* [54]. Titanium and its alloys promote a titanium oxide layer, and abrasion of the titanium oxide layer can lead to the release of debris particles into the surrounding tissues [55]. These particles may cause an undesirable tissue response along with sudden long-term aseptic loosening of the implant. Similarly, magnesium implants suffer from a high corrosion rate along with continuous generation of hydrogen gas in contact with fluids [56]. Another major limitation of metallic implants is their longevity (mainly limited to 20–25 years), which is much shorter than a human's lifespan, but could be useful for elderly patients [57]. The metallic biomaterials in orthopaedic implant applications (like bone fixation devices) have a limited implant lifetime (approximately 10 to 15 years); after this time period, its durability has been reported to be unsatisfactorily low [58]. The hazards of implant materials (*e.g.*, the metal-related toxicity, lifespan,

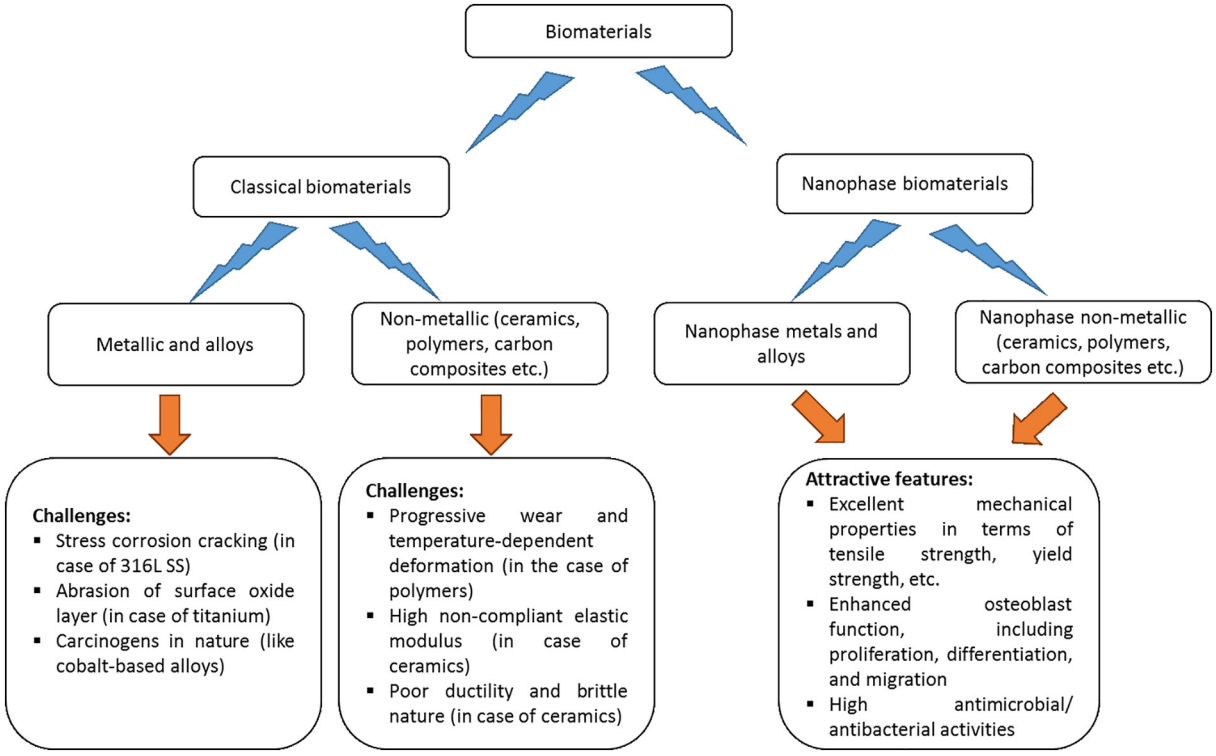

Fig. 4. Classification of orthopaedic biomaterials into two major categories: classical and nanophase biomaterials. The former can be divided further into (i) metallic and alloys and (ii) non-metallic biomaterials. Similarly, the latter can be classified into (i) nanophase metals (and alloys) and nanophase non-metallic biomaterials. The classical biomaterials suffer from several challenges for implant applications such as stress corrosion cracking (in the case of 316 L stainless steel), progressive wear, and temperature-dependent deformation (in the case of polymers). In contrast, nanomaterials offer several attractive features such as enhanced osteoblast functions and excellent mechanical properties (in terms of tensile strength, yield strength, *etc.*).

and corrosion behaviour) led to the development of other alternative options [59].

2.2. Non-metallic materials

There are different types of non-metallic materials that have advanced features for structural implantation such as polymeric, amorphous glasses, crystalline ceramics, and carbon composites. The use of these materials was not widespread because of their inherent bio-incompatibility or deficient mechanical properties. Over the time, significant efforts have been put forth for their refinement as structural implants [60,61]. Polymeric materials are preferred options for: (i) porous scaffolds for tissue engineering (due to enhanced capabilities of osseo-integration and bone regeneration) and (ii) controlled drug

Table 1
Properties and clinical orthopaedic applications of classical biomaterials.

Material	Mechanical properties	Clinical applications	Ref.
Natural bone	EM: 1–20 GPa; TS: 120–170 MPa; 0.2% YS: 110–200 MPa; Density: 1.8–2.01 g/cm^3; Elongation: 1.5%	–	37
A. Metallic and alloys			
Mg alloy	EM: 41–45 GPa; TS: 87–280 MPa; 0.2% YS: 20–246 MPa; Density: 1.74–2.0 g/cm^3; Elongation: 13%	Potential biodegradable implant materials for orthopaedic applications, such as fracture fixation	38,39
Ti alloy	EM: 110–117 GPa; TS: 240–1800 MPa; 0.2% YS: 170–1060 MPa; Density: 4.4–4.5 g/cm^3; Elongation: 10–25%	Commonly used in producing pins, posts, rods, bone plates, screws, expandable rib cages, and toe replacements	38,40
Stainless steel	EM: 189–205 GPa; TS: 490–1350 MPa; 0.2% YS: 200–700 MPa; Density: 7.9–8.1 g/cm^3; Elongation: 10–40%	Excellent material for long-term implant devices	38,40
Co-Cr alloy	EM: 230 GPa; TS: 900–1800 MPa; 0.2% YS: 500–1500 MPa; Density: 8.3–9.2 g/cm^3; Elongation: 10–50%	Excellent material choice for total joint replacements due to superior fatigue resistance	40
B. Non-metallic			
PLA	T/FM: 3.0 GPa; TS: 50–70 MPa; Elongation: 4.0%; MP: 150–162 °C	Excellent material used (i) to produce biodegradable screws, (ii) for fixation of pin, plates, and (iii) for suture anchors	62
PGA	T/FM: 6.5 GPa; Elongation: 15–20%; MP: 225–230 °C	Promising material as a porous scaffold, bioactive agent, and extracellular matrix component	68
UHMWPe	T/FM: 0.8–1.5 GPa; TS: 21–48 MPa; Elongation: 200–350%; MP: 141.2 °C	Most promising material as a bearing surface in total joint devices due to low coefficient of friction with metals	70
Aluminium oxide	T/FM: 0.4 GPa; TS: 490 MPa; CS: 3055–3413 MPa; MP: 2072 °C	Good choice as joint-replacement material due to low friction and wear	73
Zirconia	T/FM: 1.0 GPa; TS: 190 MPa; CS: 2000 MPa; MP: 2715 °C	Adequate for use as a prosthetic clinical material	75

EM- Elastic modulus, TS- Tensile strength, YS- Yield strength, T/FM- Tensile/Flexural modulus, CS- Compressive strength, MP- Melting point, PLA- Poly(lactic acid), PGA- Polyglycolide, UHMWPe- Ultra-high molecular weight polyethylene.

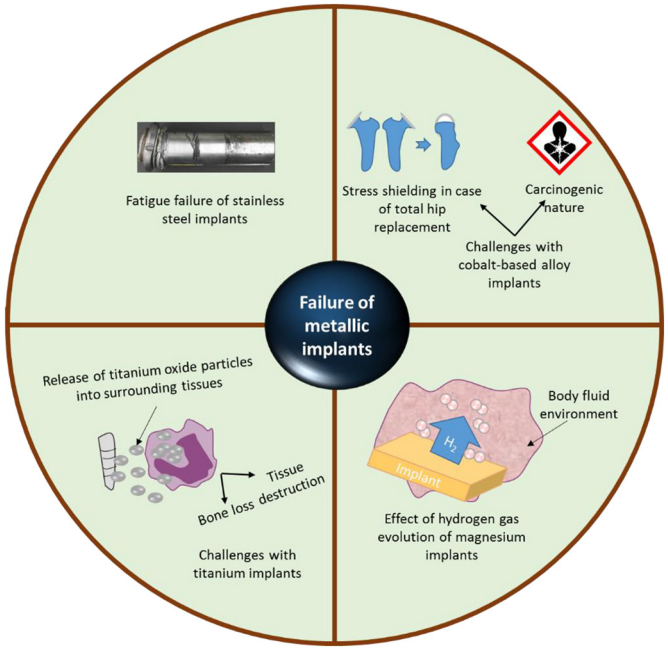

Fig. 5. Challenges associated with classical metallic orthopaedic implants: (i) fatigue failure of stainless steel implants, (ii) stress shielding and carcinogen nature of cobalt alloys, (iii) oxide particles released from titanium implants into surrounding tissues to cause bone loss or tissue destruction, and (iv) effect of hydrogen gas evolution of magnesium implants.

delivery vehicles (due to their flexibility, ease of fabrication, biocompatible nature, and good electro-mechanical properties) (Table 1, section B) [62,63]. In comparison to metallic implants, polymers have the ability to (i) transfer stress over time to a damaged area, allowing the proper healing of tissues [64] and (ii) gradually recover tissue function without using enzymes or catalysis [65]. Initially, unreinforced biodegradable polymers exhibited 36% better tension and 54% better bending than those of annealed stainless steel. The strength of polymeric materials can be raised with fibre reinforcement; 62% and 15% stiffness of polymeric materials (in comparison to stainless steel) can be achieved by reinforcing polymers with non-degradable carbon fibre and degradable inorganic fibre, respectively [66]. Before installation of implants in the human body, there is a need to carefully select the packaging material that interfaces the implant device and the human body. Such materials should be capable of preventing the movement of waste materials between them. The most common polymers used for packaging of orthopaedic implants are as poly(lactic acid) (PLA), polyglycolide (PGA), ultra-high molecular weight polyethylene (UHMWPe), polyhydroxyalkanoates (PHAs), polyether ether ketone (PEEK), and polyvinylidine fluoride (PVDF) [67,68]. The major concerns with polymers are progressive wear and temperature-dependent deformation under loading conditions, which is analogous to corrosion in case of metallic implants [69]. The most common problem with UHMWPe is oxidative degradation during shelf aging, which requires further improvement (*e.g.*, by some appropriate crosslinking technique). Nonetheless, they appear to be more promising as a bearing surface in total joint devices due to their low coefficient of friction with metal [70].

Other non-metallic materials such as ceramics have received considerable attention for such applications due to their enhanced biocompatibility, excellent corrosion and wear resistance, good chemical stability in the physiological environment, and high compressive strength under load-bearing conditions inside the human body [71,72]. The most common ceramics in orthopaedic implants are aluminium oxide, calcium phosphates (CaP), zirconium oxide, silicon oxide, hydroxyapatite (HA), and bioglass [73–75]. CaP ceramics are also highly attractive as implant coatings due to their high reactivity and biocompatibility. The CaP porous implant coatings help in strong implant fixation and early bone growth. These materials are highly resistant to compression and are not brittle. The most common issue with ceramics is their high noncompliant elastic modulus in comparison to bone, which may cause either fracture or loosening of acetabular sockets. The success of these materials depends on their ability to prompt bone regeneration and bone growth at the tissue-implant interface [76]. They have not yet been applied for fracture fixation due to their poor ductility and brittle nature.

As of now, several attempts have been made to adapt conventional biomaterials for bone regeneration and integration with surrounding bone tissues [77]. However, further improvements are still needed in terms of their capacity to selectively guide and influence the cell and tissue functions for implantation at a particular site. Over the past decade, nanotechnology has gained significant attention with a variety of nanomaterials produced *via* different physical, chemical, and biological routes, as discussed in detail in Section 3. Because natural tissues and organs have different dimensions, they can easily interact with nanostructured extracellular matrices [78,79].

3. Nanotechnology for orthopaedic implants

Nanomaterials have been examined for bioimplant applications due to their tunable surface properties and bioactive nature. The nanomaterials offer increased surface area, effective stiffness, roughness, and altered physiochemical properties to enhance (i) adhesion, (ii) proliferation, (iii) synthesis of bone-related proteins, and (iv) deposition of calcium-contained minerals [80–82]. Because nanomaterials can mimic the proportions of constituent components of biological bone, these materials are promising candidates in orthopaedic implants. For example, nanostructured polymers and composites have been widely investigated in bone tissue engineering to enhance osteoblast functions, to promote osteointegration, and to support healing of bone-related diseases [83]. The choice of nanostructures like quantum dots [84], nanotubes [85], nanocubes [86], nanoflowers [87], nanopillars [88], nanorods [89], metal-organic frameworks [90], *etc.* is significantly important to consider in order to ensure the functionality and reliability of implants. A number of studies have been carried out to explore the favourable surface properties of nanostructured materials that may promote or facilitate: (i) a large amount of specific protein interactions, (ii) better osteoblast attachment, and (iii) good osteoblast differentiation and migration for more efficient growth of new bone than conventional materials, as shown in Fig. 6 [91–93].

3.1. Implantable nanomaterials

With the advent of nanotechnology, various forms of nanophase (< 100 nm grain size) materials including metals, polymers, ceramics, and composites have emerged with novel surface properties; many exhibit an enhanced potential to support osseo-integration as well as to stimulate the new bone growth [94]. An increase in cell proliferation by a factor of 20 was reported due to a decrease in titanium grain size from 4.5 μm to 200 nm (processed by equal channel angular pressing) [95]. Nanophase materials have a vast number of grain boundaries associated with a unique atomic structure. Nanocrystalline materials are found to have high strength and/or hardness with low ductility and/or brittleness [96–98]. Note that the brittle nature of nanostructured materials can cause insuperable problems in advanced structural applications. There are several reasons behind this brittle nature of nanostructured materials such as compact production of materials and their fundamental nature [99,100].

Typical nanostructures reported in orthopaedic implants are shown in Table 2 [101–127]. Zhang et al. [112] observed improved mechanical properties (i.e., hardness of 31.7 GPa and a Young's modulus of 314 GPa) of nanostructured $MgAl_2O_4$ ceramics (having a grain size of

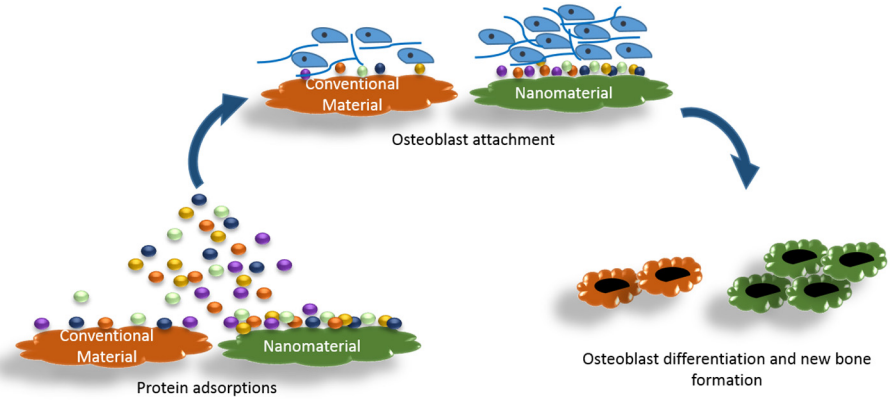

Fig. 6. Schematic presentation of bone generation using both nanomaterials and conventional materials. Nanomaterials exhibit better protein adsorption, osteoblast attachment, and differentiation for new bone generation than conventional materials.

~40 nm), fabricated *via* high pressure and temperature sintering. Serra et al. [121] were able to produce nanostructured Ti6Al4V alloy through severe plastic deformation of pure titanium. The nanostructured Ti6Al4V alloy exhibited better mechanical properties over conventional titanium including: (i) ultimate tensile strength of 1240 MPa over 700 MPa, (ii) a yield stress of 1200 MPa over 530 MPa, and (iii) elongation of 12% over 25% of pure titanium. Regardless of material chemistry, the nanometer surface roughness exerted a great impact on osteoblast function; the surface roughness values of conventional titanium and three nanostructured materials (*i.e.*, Ti, Ti6Al4V, and CoCrMo alloy) were measured as 4.9, 11.9, 15.2, and 356.7 nm, respectively. The increased osteoblast functions have been confirmed by a wide range of nanostructured materials (*e.g.*, Ti, Ti6Al4V, and CoCrMo) along with reduced functions of competitive cells [102]. Enhancement in osteoblast proliferation (determined after 5 days in terms of cells/square cm) was observed from all forms of the nanophase materials including alumina (~6000), titania (~8000), and HA (~9000) relative to conventional borosilicate glass (~5000) [122].

The carbonaceous materials have not been fully explored for orthopaedic applications due to the doubt of their safety. Hence, only a few studies have explored the appropriate synthesis procedures for carbon nanotubes/nanofibers (CNTs/CNFs) for orthopaedic prosthetic devices [128]. However, the structural and mechanical properties of CNTs make them promising for implants. Further, CNT-based composites are found to possess fewer toxic effects than asbestos [129]. The incorporation of CNTs into polycaprolactone (PCL), polycarbonate-urethane (PCU), or polystyrene (PS) matrixes has been proposed to enhance the mechanical properties (in terms of tensile and compressive moduli) of the composite scaffolds [130–132]. In one study, the incorporation of single-walled CNTs (SWCNTs) into poly-L-lactic acid (PLLA) composites offered a decrease (~5%) in polymer crystallinity, while offering an increase (~12%) in tensile strength and a reduction in degradation rate [133]. CNFs/polycarbonate urethane composites were reported to have good mechanical properties such as a tensile strength of 9 MPa, an elastic modulus of 22 MPa, along with an elongation of 452% (for 90:10 wt%) [125]. These structural properties are very useful for delivery of structural organs and bone regeneration while offering good support for surrounding tissues [134]. In comparison to other materials, the superiority of nanocomposites is often recognized in terms of better chemical, physical, and mechanical properties due to additive contributions from each component.

Due to the flexible nature of nanocomposites, it is possible to optimize their properties for specific applications. For instance, the tensile strength is different among different forms of PLA-HA nanocomposites, for example 770 ± 350 N/mm^2 for PLA, 840 ± 330 N/mm^2 for PLA-HA (20 wt%), and 1030 ± 390 N/mm^2 for PLA-HA (50 wt%). Similarly, the porosity of these three forms was also clearly distinguished as 80 ± 3%, 91 ± 2%, and 70 ± 4%, respectively [123]. Elangomannan et al. [127] fabricated CNF/PCL/mineralized HA nanofibrous scaffolds on a Ti substrate to exploit the biodegradable nature of the polymer and the excellent mechanical properties of the CNFs to result in a good elastic modulus and adhesion strength of the scaffold.

4. Nanotechnology-derived surface modifications

Surface modification of structural materials is a potential way to improve the performance and durability as well as modulate the unsafe side effects that may occur in the degradation of bioimplants. Surface properties of the implants play a determinant part in biological interactions. In particular, the nanoengineered surfaces have the capacity to exert a direct impact on the molecular and cellular events; this property helps in determining the inclusive biological response for an implant (*e.g.*, cell adhesion, protein adsorption, and proliferation). To this end, different strategies have been developed to engineer nanosurfaces for orthopaedic implants, such as the electrochemical method (like anodic oxidation) [135], electrochemical plating [136], plasma electrolytic oxidation [137], physical vapour deposition (PVD), chemical conversion coating [138], laser surface alloying [139], thermal spraying [140], organic coating [141], and microwave-derived coatings [142] (Refer to Fig. 7). These techniques offer novel implant surfaces with controlled features at the nanometer scale. The specific technique can be selected depending on a number of parameters, such as (i) to achieve complex geometries and (ii) to integrate in the industrial process line [143].

4.1.1. *Surface nanostructuring*

Nanocrystalline metallic surfaces have demonstrated success for improving the cell-substrate interface and healing bone. In recent years, growing attention has been paid to severe plastic deformation (SPD) [144,145] of bulk billets in comparison to other synthesis techniques such as high-energy ball milling [91], the gas-phase evaporation method [146], and physical/chemical deposition approaches [147] (Table 3). This is because the majority of these techniques results in low ductility, residual porosities, and other dimensional issues. On the other hand, the SPD technique is based on heavy straining under very highly imposed pressure. The main feature of the obtained nanostructures is their ultrafine grain characteristics along with enhanced mechanical strength and biological characteristics [148]. Plastic deformation can be easily achieved in metallic materials by twinning, phase transformation, or grain boundary sliding at low temperatures and relatively high strain rates [149,150].

Table 2
Examples of implantable nanomaterials used in orthopaedic applications.

Material	Processing technique	Structure	Outcomes	Ref.
A. Metal and alloys				
Ti alloys	Anodization processes	Nanotubular, nanorod, and nanotextured	High corrosion resistance and high osseointegration	101,102
Stainless steel	Phase-reversion	Ultra-fine grain	High strength/weight ratio and superior wear and corrosion resistance for long-term stability of implants	103
Co-Cr-Mo alloys	Heat treatments	Nanostructures	High wear and corrosion resistance and good biocompatibility	104
Tantalum	Microemulsion technique	Nanoparticles	Outstanding biocompatibility and anticorrosive behaviour	105
B. Ceramics				
HA	Sol-gel synthesis, hydro-thermal reactions, solid state reactions	Nanorods, nanowires, and nanoparticles	Improved sinterability, enhanced densification, good biocompatibility, and bone integration ability	106–108
CaP	Sol-gel combustion method	Nanoparticles	Good cytophilicity, cell viability, proliferation, and bone/enamel integration	109
Forsterite	Sol-gel process	Nanomaterials	Apatite-formation ability for its use in preparing new biomaterials	110
Bioactive glass	Sol-gel process	Nanoparticles	Despite inherent brittleness, ability to promote neovascularization for bone regeneration	111
$MgAl_2O_4$	High pressure-temperature sintering	Nanostructured (grain size of 40 nm)	Excellent mechanical properties in terms of hardness (31.7 GPa) and Young's modulus (314 GPa)	112
C. Polymers				
Collagen	Electrospin method	Nanofibers	Good for growth of mesenchymal stem cells without compromising osteogenic differentiation capability	113
Chitosan	Sol-gel method	Nanomaterials, nanofibers	Biodegradable, biocompatible, and non-toxic nature	114
PLA	Thermally induced phase-separation method	Nanopores	Thermoplastic possibility, excellent biocompatibility, and biodegradability	115
PMMA	Radical-mediated dispersion polymerization technique	Nanofibers	Biocompatible and brittle in nature; employed as bone cement	116
D. Carbonaceous materials				
CNTs	Vapour-growth method, co-catalyst deoxidization process	Nanotubes, nanofibers	Good mechanical properties, direct integration into bone tissues, and low inflammatory response	117,118
Graphene	Hummers's method	Nanosheets	Excellent mechanical properties in terms of elastic modulus and tensile strength, high electrical conductivity, and good biocompatibility	119
Diamond	Detonation technique	Nanoparticles	Excellent mechanical and tribiological properties along with increased mineralization capability	120
E. Composites				
PLA-HA nanofiber scaffolds	Electrospin technique	Nanofiber reinforced composites	Good osteogenic and osteoclatogenic differentiation as well as heterotypic interactions between osteoblast and osteoclasts	123
Multifunctional TiO_2/high density-polyethylene	Lamination templating method	Nanoparticles reinforced composites	Super-hydrophobic in nature, self-cleaning properties, and UV-induced reversible wettability	124
CNFs/polycarbonate urethane	Chemical method	Nanofibers reinforced composites	Tailorable mechanical properties along with enhanced osteoblast and fibroblast interactions	125
Graphene/HA composites	Spark plasma sintering	Nanosheets reinforced composite	~80% improvement in fracture toughness in comparison to pure HA, improvement in apatite mineralization, and osteoblast adhesion	126
CNF/polycaprolactone/mineralized HA	Electrochemical deposition	Nanofibrous scaffolds	Good adhesion strength and elastic modulus, high cell viability, and favourable for load-bearing applications	127

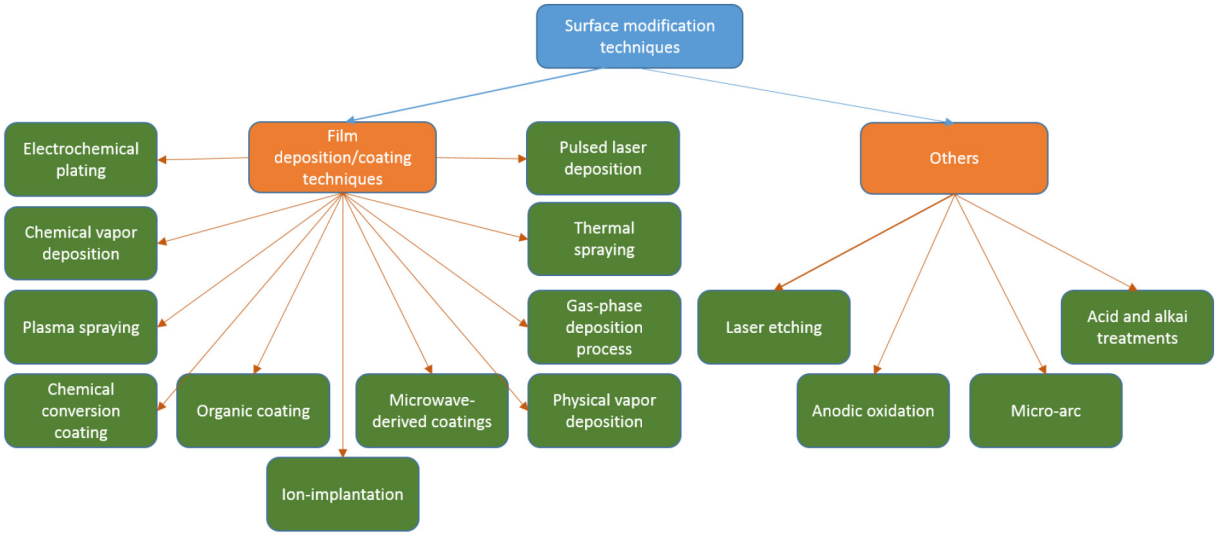

Fig. 7. Different techniques for surface modification of implantable orthopaedic biomaterials.

A number of parameters (including the grain structure, surface roughness, wettability, and surface functional groups) play significant roles in mediating the cell activities at the cell-substrate interface [151]. Osteoblasts adhere specifically to grain boundaries of the nanophase materials; thus, by increasing the proportion of grain boundaries, cell adhesion to nanophase material can be improved significantly [152]. Zhang et al. [153] fabricated a clustered nanorod structure over an acid-etched titanium surface through the use of hydrogen peroxide to support enhanced initial adhesion activity and osteogenic differentiation of rat bone marrow mesenchymal stem cells. Misra et al. [103] observed a different cellular response with diverse grain structures (*i.e.*, from nanosized grain regime to coarse-grained regime) in 316 L stainless steel through a phase reversion approach. They reported highest cell attachment (~15,000 cells/cm^2) on the substrate with the smallest grain size (320 nm).

The ultrafine grain nanostructures are efficient at promoting osteoblast differentiation and increasing bone integration by forming nano-defects, affecting surface energy, and other effects. The degree of wettability is directly correlated to the solid surface's ability to decrease the surface tension in the liquid phase (in contact with the implant material). (Note that the small contact angles ($\ll 90^\circ$) of liquid to the interface correspond to a high degree of wettability [154].) Nanotopography is beneficial in provoking down regulatory effects on early conscription and activity of inflammatory cells, while enhancing the osteogenic activity and early woven bone formation [155,156]. Dang et al. [157] prepared nanotubular strontium-loaded structures on Ti implants that showed high osteogenic capability for improved and fast osseointegration under osteoporotic as well as normal conditions. The nanotubes were fabricated *via* electrochemical anodization at 10 V and 40 V along with controlled amount of loaded strontium. Bahl et al. [158] fabricated a nanocrystalline surface over 316 L stainless steel through surface mechanical attrition treatment (SMAT); they observed high corrosion-fatigue strength in the saline surface (an increase of 50% in comparison to microcrystalline surface), better protein adsorption, and thereby improved cell response. These enhancements can be credited to the changes in nature of the oxide layer on the metallic surface due to nanocrystallization [159]. Yin et al. [160] fabricated a novel 'net-like' nanostructured surface on 316 L stainless steel through ultrasonic shot peening. *In vitro* study confirmed significant enhancement in the attachment, spreading, and proliferation rate of human osteoblast cells (Saos-2) on such substrate. Likewise, Guo et al. [161] synthesized nanostructures for a titanium-alloy implant by ultrasonic shot peening (USP) as a means to promote cell adhesion, proliferation, and differentiation of osteoblasts. The formation of a nanofoam structure over the surface of the implant can lead to superhydrophilic bio- and cytocompatible surfaces *via* high intensity ultrasound (HIUS) treatment of material for a short duration [162].

4.1.2. Functional nanocoating

Surface coating can efficiently modify the surface-dominant properties (*e.g.*, ion release or wear), resistance to corrosion, and biological properties without compromising the properties of the bulk material [163]. The coatings applied to orthopaedic implants help encourage the bioactivity so that the implants fuse with the bone and other tissues to ensure proper implant fixation and longevity. The dissolution of metal ions can be reduced with the help of suitable biocompatible inorganic coatings [164]. The coating can also increase the hardness of the implants and provide excellent surface finishing while helping reduce the friction and wear rate of the implant.

The adhesion of coatings to the substrate highly affects the interaction of chemical bonds in between the material layers. The different parameters of coatings (such as hardness, thickness, and surface finish) should thus be defined carefully for the protection of substrate from fatigue, abrasive, and corrosive wear. There are diverse coating methods such as the sol-gel technique [165], electrophoresis deposition [166], laser surface melting [167], sputtering [168], plasma spraying [169], physical vapour deposition [170], and pulsed laser deposition [171]. However, out of these conventional coating methods, many of them suffer from operational defects (*e.g.*, high set-up cost, low deposition rates, and microstructural inhomogeneity) [172]. More specifically, elevated temperatures in the plasma spraying process can alter the structural properties, cause peeling, and subsequently dissolve the coating, ultimately leading to the reduction in the bond strength between the coating material and the implant substrate [173]. To improve the chemical, mechanical, and biological properties of metallic implants, advanced coating techniques (*e.g.*, the use of TiO_2, ZrO_2, and Al_2O_3 as bond coats/composite coats with HA) are needed to enhance the properties of HA coatings [174]. Several attempts have been made for ceramic coatings (from micro- to nanoscale) to improve the surface properties of metallic implants and create new possibilities for bone regenerative technologies [175–177]. The use of ceramic coatings is preferable to minimize the corrosion rate and to capture the release of metal ions (or corrosion products). A proprietary flame-spray system was developed to deposit HA and HA-TiO_2 coatings on Ti6Al4V alloys to improve the bond strength (67.8 MPa for flame-sprayed HA and 37.6 MPa for HA-TiO_2 coatings) and the corrosion resistance (the corrosion current density of the uncoated, HA coated, and HA-TiO_2 coated Ti6Al4V alloys is 906, 120, and 150 nA/cm^2, respectively) [178].

Table 3
Mechanical properties of orthopaedic biomaterials having nanostructured surface.

Material	Surface modification approach	Average grain size of nanostructured surface (nm)	Finding(s)	Ref.
316 L stainless steel	Phase-reversion method	320 ± 5	Good mechanical properties (yield strength of 768 ± 3 MPa, and elongation of 34 ± 2%) and superior cellular response due to high hydrophilicity of nanograined structure and the substrate	103
Pure Ti	High pressure torsion (5 GPa)	100	Ultrafine grained structure after hydrofluoric etching treatment, enhanced hydrophilic wettability, high texture energy state, and good cell adhesion and proliferation after grain refinement	152
AISI 316 L stainless steel	Severe shot peening	25 ± 5	Enhanced mechanical properties, extended functionality of materials for orthopaedic implants, and a good option for large amplitudes of static and dynamic loading	154
HA/β-TCP	Microwave processing	22 ± 2	Fine-tuned solubility and correspondingly biological lifetime of biphasic calcium phosphate through variation in HA/β-TCP ratios	155
3D screw-shaped Ti implants	Colloidal lithography	75 ± 8	Higher osteogenic activity and early formation of osteoid and woven bone	156
316 L stainless steel	Surface mechanical attrition treatment	< 50	Increased corrosion-fatigue strength of 316 L stainless steel in silane by 50%, enhanced osteoblast attachment and proliferation	158
AISI 304 stainless steel	Surface mechanical attrition treatment	11–25	Beneficial nanostructuring in terms of promoting passivation, increased wettability, good surface roughness, and high corrosion resistance in Ringer's solution	159
316 L stainless steel	Ultrasonic shot peening	326 ('net-like' nanostructured surface)	Enhanced cell functions and cell proliferation	160
Titanium alloy	Ultrasonic shot peening	57–88	Promoted *in vivo* and *in vitro* cell adhesion, proliferation, and differentiation of osteoblasts	161
Titanium	High intensity ultrasound treatment	3–7 (thickness of nanofoam layer)	Superhydrophilic bio- and cytocompatible surfaces with short-time ultrasonic treatment	162

Further, CaP coatings can promote bone healing and lead to the rapid fixation of orthopaedic implants [179]. CaP scaffolds were found to have some similarities in inorganic components of bone in terms of chemical or crystallographic properties to support stem cell proliferation and osteogenic differentiation [180]. Numerous studies revealed the use of CaP-based HA as bioactive coatings on metallic substrates for orthopaedic applications [181]. The HA coating with suitable binders can lead to a delay in corrosion and wear and also minimize the chances of implant loosening from bone [182]. The selection of a particular binder material is significantly important for binding the reinforcement phase, and this can directly affect the strength and corrosion resistance of the implant. Denissen et al. [183] reported HA [$(Ca_{10}(PO_4)_6(OH)_2)$] as a bio-medical material with excellent biocompatibility and bioactivity. The excellent properties of HA might be credited to its chemical as well as structural similarities to the bone and tooth minerals. However, the use of HA in clinical applications is limited due to its poor mechanical reliability (*e.g.*, weak tensile strength, low corrosion-fatigue resistance, elastic modulus mismatch, weak tensile strength, stress shielding, and robustness) to withstand physiological loads without fragmentation [184]. Table 4 summarizes the already-reported nanomaterial coatings for orthopaedic implant surfaces [185–204]. Shim et al. [188] fabricated fibroblast growth factor-2 (FGF-2)-loaded poly (lactide-*co*-glycolide) (PLGA) nanoparticle-coated anodized titanium discs through electrospray deposition. The osteointegration value of this nanostructured implant was 70.1%, considerably higher in comparison to untreated implants (40.1%). As such, the selection of a particular coating technique may alter the surface roughness of the implant as well as the bone-implant interaction. Electrospray deposition of nanoparticles is particularly attractive for maintaining surface topography [196], whereas the dip-coated layer may moderate surface roughness to prohibit bone-implant interaction, ultimately delaying bone growth [197].

Many studies have assessed the potential use of carbon nanostructures as coatings for orthopaedic implants [201,202]. For graphene-coated substrates (*e.g.*, stainless steel, soda lime glass, and silicon wafers), cell adhesion was enhanced and osteoblasts were more uniform than the pristine substrate alone [203]. For the enhancement of cell attachment and proliferation, increases in the area of spread cells was observed after two days from graphene-coated glass substrate, graphene-coated silicon substrate, and graphene-coated stainless steel, *i.e.*, 343 ± 33, 475 ± 70, and 445 ± 59 μm^2, respectively. Ahmed et al. [204] fabricated a chitosan/multi-walled CNTs/$CaCO_3$ nanocomposite-coated Ti6Al4V alloy with enhanced bioactivity and good corrosion resistance (with a corrosion potential of −387 mV and corrosion current density of 0.02 nA/cm^2) in comparison to a multi-walled CNT-coated Ti6Al4V alloy (with respective values of −396 mV and 0.18 nA/cm^2).

4.1.3. Microwave-derived surface modifications

Conventional thermal spray coatings contain defects like higher porosity, oxidation, inadequate adhesive strength, and degradation of the substrate materials (Fig. 8), and microwave is an emerging surface modification technique that can meaningfully address these potential drawbacks [205–208]. In contrast to conventional thermal spray and CVD/PVD coatings, microwave-derived coatings are homogeneous in crystalline structure (Fig. 9) due to the absence of the lamella/columnar structure and the associated splat/grain boundaries [209]. Zhou et al. [210] developed a crack-free coating of strontium-doped apatite over Ti6Al4V-based orthopaedic implants through a microwave-assisted technique. Such microwave-assisted coatings at high temperature (> 500 °C) treatment may have a positive effect on improving implant stability. The splats and associated boundaries are a potential site for the origination and propagation of cracks, which lead to disintegration of coatings [211,212].

In comparison to conventional heating processes, microwave processing requires at least 10% of the amount of time for material

Table 4
Nanomaterials used for coating an orthopaedic implant surface.

Material	Coating-technique	System	Observation(s)	Ref.
SiO_2/PEG nanocomposites-coated Ti implants	Sol gel coating	*In vitro*	More bioactive and biocompatible in comparison to uncoated ones	185
TiO_2/HA reinforced coated 316 L stainless steel	Spin- and dip-coating sol gel processes	*In vitro*	Better biocompatibility of TiO_2/HA composite than TiO_2/HA bilayer and mechanical properties close to bone tissue (such as elastic modulus up to 18 GPa, and hardness up to 0.6 GPa)	186
TiO_2-coated CoCrMo substrate	Atmospheric pressure chemical vapour deposition	*In vitro*	Improved osteogenic differentiation and adhesion of mesenchymal stem cells	187
FGF-2-loaded PLGA nanoparticles-coated anodized Ti discs	Electrospray deposition	*In vitro*	Sustained release of FGF-2 for more than two weeks along with 40% initial burst due to porous native structure of nanoparticles; enhanced bone regeneration	188
Al_2O_3 coated Ti alloy	Oxide magnetron sputtered coating	*In vivo* and *in vitro*	Good biocompatibility due to hydrophilic nature of the coated surface and high corrosion resistance	189
Ta_2O_5 nanotubes-coated tantalum substrate	Anodization processes	*In vivo*	Improved anticorrosion, osteoinduction, and biocompatibility of pure tantalum	190
GMA nanolayer over Ti implant	Chemical vapour deposition	*In vitro*	Improved cellular attachment and good mechanical stability	191
GO/chitosan nanocomposite-coated Ti foil	Electrophoretic deposition	*In vitro*	Highly biocompatible (up to 30 wt% GO)	192
Nanodiamond/alginate-bioactive glass film-coated 316 L stainless steel substrates	Electrophoretic deposition	*In vitro*	Enhanced bioactivity in simulated body fluid and good biocompatibility (MG-63 and L929 cells)	193
Zn-loaded TiO_2 nanotubes-coated over Ti substrates	Anodization and hydrothermal treatment	*In vivo* and *in vitro*	Enhanced osteointegration between bone and implant and inhibited growth of bacteria	194
Fluor-HA-coated Ti substrate	Sol-gel technique	*In vivo*	Uniform coating with low dissolution rates and improved activity and functionality of cells	195
HA-alendronate/BMP-2 nanoparticles embedded into Gel/Chi multilayers on Ti6Al7Nb substrate	Layer by layer assembly	*In vitro*	Enhanced early osseointegration between the implant and the native osteoporotic bone	198
Mesoporous silica nanoparticles/zoledronic loaded-HA composite-coated onto stainless Kirschner wire substrate	Plasma spraying technique	*In vitro*	Improved implant-bone integration and accelerated bone fracture healing	199
Collagen-inserted HA-coated Ti substrate	Langmuir-Blodgett technique	*In vitro*	Enhanced cell proliferation on the modified Ti surfaces and no toxicity	200
Chitosan/MWCNTs/$CaCO_3$-coated Ti6Al4V alloy	Dip-coating technique	–	High long-term stability and good corrosion resistance	204

Fig. 8. Scanning electron micrographs showing the (a) surface and (b) cross-section microstructures of the Ni + 40 wt% Al_2O_3 coating. Reprinted with permission from ref. [208].

synthesis and sintering [155]. Microwave-derived coatings can also help increase strength while providing excellent inter-particle cohesion and adhesion to the substrate with negligible porosity and oxide content. As such, such application is amenable to added tailored properties such as: superior corrosion, wear resistance, mechanical integrity, and biocompatibility. Microwave is highly economical if compared with existing techniques, *e.g.*, laser-based coating [213], which requires high set-up and running costs. Compared to the CVD and PVD techniques, the material deposition rates of the microwave technique are considerably high. Furthermore, such approach can reduce environmental concerns greatly (relative to CVD and PVD), while helping avoid substrate deterioration due to low working temperatures and volumetric heating of the coating powder compared to the conventional conduction heating process (CVD, PVD, and laser); this is because internal heating of the coating powder takes place due to coupling with the microwaves [214]. This fundamental difference in heat generation patterns may enhance the diffusion, while lowering the thermal gradient and heat-effected zones with reduced power consumption and processing time. Earlier use of microwave was restricted to sintering of ceramics, not for metals due to microwave reflections from the metallic surfaces at room temperature. However, Roy et al. [215] pioneered the use of microwave for sintering metallic powders. In recent years, the use of hybrid microwave heating (a combination of conduction and volumetric heating) is advocated to reduce thermal instabilities arising from individual use of either the microwave or conductive heating systems [216].

In conventional thermal spray processes, the elevated process temperatures expose both the coating and substrate materials to rapid

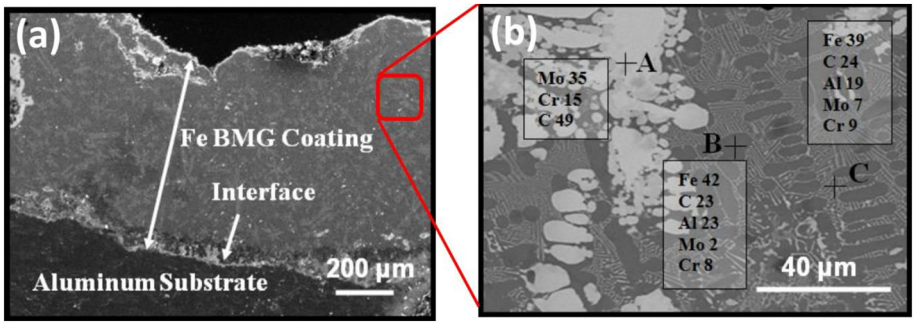

Fig. 9. Scanning electron micrograph showing the microwave-derived Fe-based bulk metallic glass (BMG) coating deposited on an aluminium substrate and (b) magnified micrograph showing the microstructure of the coating consisting of a dendritic structure embedded in a matrix. Reprinted with permission from ref. [209].

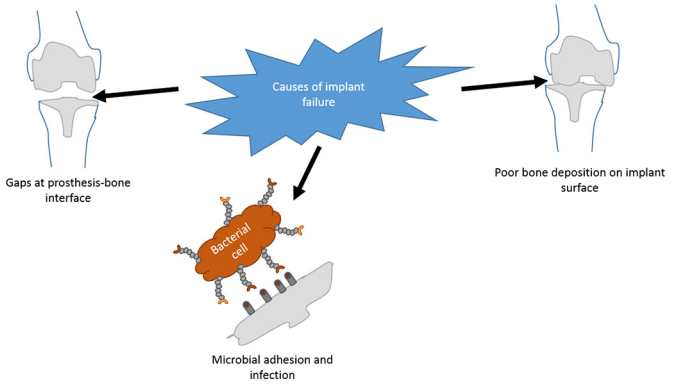

Fig. 10. Several causes of orthopaedic implant failure, such as gaps present at the prosthesis/bone interface, poor bone deposition on the implant surface (leading to poor osseointegration), and infection due to microbial adhesion.

oxidation, metallurgical transformations, and adverse residual stresses [217]. Unlike thermal spray, the microwave technique (MWT) process is capable of producing dense and thick coatings with negligible porosity (< 0.5%), while avoiding oxidation, phase transformations, and adverse residual stresses for a wide selection of metals, cermets, and other material mixtures [218]. The prime benefit of using MWT lies in the flexibility of depositing the coatings with a desired composition. The deposition of high quality nano-composite coatings by thermal spraying is extremely difficult due to the high porosity content and high proportion of unmelted particles present in the suspension for thermal spraying. Both the unmelted properties and porous nature of the particles cause an inhomogeneous coating (in terms of voids and cracks) over the implant surface [219,220]. In contrast, MWT can easily accommodate high quality nano-composite coatings [221]. This is due to the combination of the volumetric and conductive heating approaches used in MWT in contrast to conduction heating in thermal spraying. Guilemany et al. [222] also reported higher abrasive wear resistance for the bi-modular thermal sprayed coatings compared to the nano- and micro-structured coatings due to increased capability of the fine-sized particles to retain the matrix material. However, it should be noted that fine/nano-sized powder particles used were in an agglomerated form (large-sized grain formed by fine power particles) due to difficulty in spraying the fine sized particles. Agglomerated nanostructured powders exhibited low-thermal conductivity in comparison to conventional powders [223], which resulted in unmelted zones and voids [224]. The unmelted regions formed from agglomerated powder tends to lower of the hardness and fracture toughness of the coating. Such agglomerated mixtures of nano- and micro-sized feedstock powder exhibited a reduction in hardness due to an increase in the number of voids and the presence of partially melted zones when non-homogeneous heating was applied to the nanostructured powders [225]. The microwave-derived coatings can help rectify the issue of unmelted zones for nanoparticle-reinforced composite structures as powders with a desired size are directly mixed and applied to the substrate. Further, due to volumetric heating in microwave compared to conductive heating in thermal spraying, the tendency for the formation of unmelted zones and voids is lowered. Therefore, the microwave coating system is more economical (*e.g.*, it does not require a prior agglomeration step), while being convenient for developing nanostructured and multicomponent coatings to be capable of driving the future of surface modification techniques for orthopaedic implants. The microwave-assisted fibrous coating of *Aloe vera* extract over metallocene polyethylene substrates have also been reported to offer several desirable characteristics in order to support and guide the rehabilitation of tissues for multifaceted bioimplant applications [226].

4.1.4. Antibacterial surface treatment strategies

Although the success rate of orthopaedic implants is generally high, there are several device-related issues that can compromise patient outcomes. The major causes of implant failure are: local tissue inflammation (5.3%), aseptic loosening (18%), and infection (20%) [227]. These issues are intimately related and originate from different sources. They can cause wear, impair the function of the bone-implant interface, and promote bacterial adhesion to implant surface, as shown in Fig. 10. Therefore, strong osseointegration and inhibition of infection are essential for a successful implant. The osseointegration of an implant can be improved with appropriate selection of nanophase biomaterials, as discussed in a previous section. Beyond this, infection of an orthopaedic prosthesis can cause a certain decrement in the success rate of an implant. Further, the use of bioimplants is projected to increase the number of related infections.

For instance, the most common implant materials (*i.e.*, titanium and its alloys) offer enhanced biocompatibility; however, imperfections can arise at implant surface due to inhomogeneity of microstructures including impurities, grain boundaries, and second phase particles. Under external loading, these imperfections led to the creation of weak sites for the expression of the immune system. Even bacteria with a low level of virulence could lead to catastrophic consequences [228]. Once bacteria adhere to the implant surface, they start to proliferate, leading to the formation of a biofilm. The biofilm plays a role in protecting the bacterial colony by offering resistance to antibiotics and other infection-defence mechanisms [229]. Thus, it is crucial to address pathogenic bacteria in its early stages to minimize biofilm formation. Infections lead to osteolysis, and there are several treatments to avoid osteolysis such as immunomodulatory treatments [230] and anti-inflammation treatments [231]. There are several strategies to prevent bacterial attachment on the implant surface or kill bacteria upon contact, as shown in Fig. 11 [232,233]. Ultraviolet (UV) functionalization of Ti and Ti6Al4V implants enabled the recovery of osteoconductivity and bioactivity along with antimicrobial properties; however, the effect of UV treatment on the antimicrobial properties of Ti persists only for a short duration; for instance, bacterial growth can be seen after seven

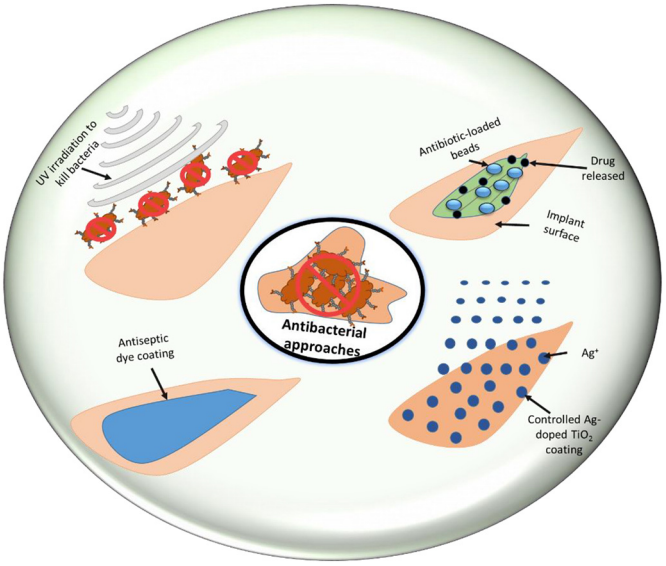

Fig. 11. Schematic representation of antibacterial approaches for orthopaedic implants.

days of UV treatment [234]. A fast re-absorbable antibacterial-loaded hydrogel coating was effective at preventing the bacterial colonization and formation of a biofilm along with a retrievable efficiency of 80% on the implant surface after press-fit insertion [235]. Inzana et al. [236] demonstrated the local delivery of rifampin and vancomycin-laden three-dimensional (3D) printed CaP scaffolds (implanted in a mouse model) to overcome bone infection. The 3D-printed CaP scaffolds offer regeneration of a bone defect, avoiding the revision of further surgery. However, the existing antibiotic treatments were suspected to be ineffective at eliminating infections entirely, creating another issue of an increased number of drug-resistant bacteria [237]. Some of these treatments are too fleeting and costly, and are highly susceptible to mechanical abrasion and delamination that ultimately lead to implant removal and debridement [238].

Advanced antiadhesive and antimicrobial coatings are also promising to prevent early-phase bacterial colonization and biofilm formation [239–241]. The nanomaterials can exhibit significant antimicrobial activities [242–244], *e.g.*, Ag nanoparticles (cell membrane disruption, and electron transport) [245], TiO_2 nanoparticles (cell membrane damage) [246,247], chitosan (rupture of membrane, and increased permeability) [248], CNTs (destruction of cell membrane, and oxidation of cell membrane lipids and proteins) [249,250], and nanoemulsions (membrane disruption) [251]. The antimicrobial properties of nanomaterials are effective for their use as antibacterial and antifungal agents in surface coatings of implants [252,253]. Table 5 summarizes the antimicrobial activities of different materials. Silver and its compounds are good alternatives to antibiotics due to their broad spectrum of antimicrobial activities against various microbes, *e.g.*, antibiotic-resistant bacteria, yeasts, viruses, and fungal species [254–256].

Improvements in antibacterial coatings can be achieved by coating thin nanostructured films (*e.g.*, chitosan-deposited Ag nanoparticles carried by Ti nanowires) [257]. The chitosan nanofilms help reduce the toxic effect of Ag-doped Ti nanowires to improve the antibacterial activity. The local delivery coating technique may provide protection to implants from infectious pathogens and promote faster bone healing [258]. Yazici et al. [259] engineered *in vitro* chimeric peptides with biofunctionality (*e.g.*, antimicrobial properties) through a robust solid-surface coating. Zhu et al. [260] described an atomic layer deposition of one-dimensional (1D) ZnO nanostructures on chitosan-modified CNTs; after that modified CNTs were coated onto the implant substrate. This hybrid coating endowed the implants with high self-antibacterial efficacy against *Staphylococcus aureus* (*S. aureus*) by 98% and *Escherichia coli* (*E. coli*) by 73%. Li et al. [261] developed an *N*-halamine-immobilized silica-coated polystyrene-acrylic acid (PSA)-ZnO nanoparticle coating on Ti implants with promising self-antibacterial activity (without antibiotics: *e.g.*, against *Pseudomonas aeruginosa* (*P. aeruginosa*), *E. coli*, and *S. aureus*).

Silver-based coatings on titanium and Ti6Al4V have *in vitro* antimicrobial efficacy against *E. coli*, *P. aeruginosa*, *S. aureus*, and *Staphylococcus epidermidis* (*S. epidermidis*) with well-maintained biocompatibility [262]. Silver cations bind to the negatively charged membrane, leading to its perforation and leakage of cellular compounds, ultimately resulting in cell death. Silver ions also bind with phosphoryl and sulfhydryl groups of proteins; these bindings cause aggregations of different groups of protein while reducing their activity to almost inactive [263,264]. Further, DNA molecules also get condensed and lose their replication abilities due to the denaturation effects of silver ions [265]. The complicated production and diffusion of silver ions make the device less efficacious [266]. However, it is possible to passively diffuse the silver ions from the implant surface to the surrounding biological environment [267]. The antibacterial mechanism of silver nanoparticle-coated Ti can be improved by plasma immersion ion implantation through generation of reactive oxygen species that can burst both bacteria cells and the culture medium [268]. Thereby, reactive oxygen species lead to bacteria death through intracellular oxidation, variation in membrane potential, and release of cellular contents.

Others have focused on developing nanotechnology that can be built directly on the implant surface using battery-activated devices [269]. The idea behind the use of battery-activated devices is to improve antimicrobial efficacy of silver coatings by electrically activating the microscopic germ killers. Antibiotic-resistant bacteria such as methicillin-resistant *Staphylococcus epidermidis* (MRSE) and methicillin-resistant staphylococcus aureus (MRSA) are of particular concern. Spadaro et al. [270] demonstrated *in vitro* antimicrobial efficacy of silver ions that are generated with the application of low intensity direct current (LIDC) in the range of 0.02–20 μA. The LIDC-generated silver ions have 10–100 times lower inhibitory and antimicrobial concentrations than those of silver sulfadiazine. The antimicrobial efficacy of silver has been evaluated *in vitro* and *in vivo* for use in orthopaedic implants [271]. Tan et al. [272] demonstrated the *in vitro* antibacterial efficacy and cytotoxicity of LIDC-activated silver/titanium implant. The implants without LIDC activation were not able to suppress the bacterial growth. In contrast, in case of LIDC activation (6 μA), the bacterial concentration was lower than that of without activation; the bacterial concentration was lower by two orders of magnitude after 24 h and by one order of magnitude after 48 h. The current intensity and the anode surface area are the most dominant system parameters that impact the antimicrobial efficacy as well as the formation of anodic oxide films. The chitosan-Ag/HA composite coating was fabricated over the titanium substrate through electrochemical deposition [273]. The coating exhibited excellent antibacterial activity due to the synergistic effect of chitosan and silver with a non-toxic nature to MC3T3-E1 cells. Sathishkumar et al. [274] fabricated a samarium/gadolinium-substituted HA coating on borate-passivated AISI 316 L stainless steel through electrodeposition techniques to yield a uniformly covered granular texture with good anticorrosion ability. The samarium/gadolinium-substituted HA coating also exhibited antibacterial activity while promoting cell viability and proliferation of MC3T3-E1 cells. Amin Yavari et al. [275] fabricated 3D-printed porous Ti scaffolds coated with Ag-loaded TiO_2 nanotubes to achieve the desired biofunctionality. Such a biomaterial was found to be very effective at killing planktonic bacteria with the prevention of a biofilm formation at early stages (*e.g.*, up to one day). However, it should also be noted that increases in Ag concentrations can adversely affect cell viability.

Table 5
Strategies to prevent infections by enhancing antimicrobial properties of implants.

Material	System	Organism(s)	Primary findings	Ref.
A. UV treatment				
Ti and Ti6Al4V disks	*In vivo*	*S. aureus*	Significant reduction in bacterial colonies; maintained antimicrobial activity for seven days after UV treatment	234
B. Antibiotics-loaded coatings				
Different antibiotics-loaded hydrogel over titanium disks	*In vitro*	*S. aureus*, and *S. epidermidis*	Reduced bacterial colonization and inhibited biofilm formation	235
Antibiotics-loaded 3D printed CaP scaffolds	*In vivo*	*S. aureus*	Significant reduction in bacterial burden and osteolytic bone loss	236
C. Nanomaterial coatings				
Se-coating over polymeric substrates	*In vitro*	*S. aureus*	Significantly inhibited growth of *S. aureus*	240
ZnO + HA coating	*In vivo*	*Streptococcus* spp., anaerobic, and aerobic colony	Effective osteoconductive and antimicrobial functionalities to prevent implant failure	252
Ag-loaded HA/lignin coatings	*In vitro*	*P. aeruginosa*, *S. aureus*, osteoblasts	Diminish the growth of bacteria strain (98.17% cell reduction after ih)	256
Chitosan-deposited Ag nanoparticles carried by Ti nanowires	*In vitro*	*E. coli*, and *S. aureus*	Enhanced antibacterial activity and biocompatibility of Ti implants	257
Ag-loaded chitosan coated-porous CaP microspheres	*In vivo*	*S. aureus*, and *Porphyromonas gingivalis*	Reduction in incidence of infection; 90% reduction in bacterial viability	258
Chimeric peptides	*In vitro*	*S. mutans*, *S. epidermidis*, and *E. coli*	Development of infection-free surfaces; reduced bacterial colonization onto Ti surfaces below detectable limit	259
1D ZnO/chitosan-modified CNTs hybrid coating	*In vivo*	*E. coli* and *S. aureus*	Self-antibacterial efficacy; regulated proliferation and osteogenic differentiation of osteoblasts	260
PSA-ZnO-SiO_2-DMH (5,5-dimethylhydantoin) −Cl coated Ti implants	*In vitro*	*P. aeruginosa*, *E. coli*, and *S. aureus*	Self–antibacterial ability of PSA-ZnO-SiO_2-DMH-Cl-coated Ti implant with good biocompatibility toward the MC3T3-E1 preosteoblast	261
Ag loaded-Ti implant activated by 30 μA direct current	*In vitro and in vivo*	*S. aureus*	Effective in inhibiting bacterial growth; more pronounced reduction in bacterial colonization	271
Chitosan-Ag/HA composite-coated TiO_2 nanotubes	*In vitro*	*S. aureus* and *E. coli*	Antibacterial efficiency of 99.1% (against *S. aureus*) and 99.3% (against *E. coli*)	273
Samarium/gadolinium-substituted HA-coating on borate-passivated AISI 316 L stainless steel	*In vitro*	*S. aureus* and *E. coli*	High anticorrosion performance in Ringer's solution; good antibacterial activity, cell viability, and proliferation of the MC3T3-E1 cells	274
Ag-loaded TiO_2 nanotube coating	*In vitro*	*S. aureus*	Extremely effective at preventing biofilm formation; decreased planktonic bacteria	275

Table 6
Surface treatment strategies for orthopaedic biomaterials.

Material	Objective	Observation(s)	Ref.
Acid-etched Ti and sandblast chromium-cobalt alloy	To study the effect of titanium aging and **UV treatment** on osteoblast proliferation	Time-dependent biological degradation of Ti and Cr−Co alloy and enabled restoration	277
Zirconia	To examine the effect of **UV treatment** on *in vitro* osteoconductive capacity of zirconia surfaces	Enhanced osteoconductivity, augmented amount of bone formation, and a rapid bone-implant integration	284
Nanostructured TiO_2	To study the influence of **oxygen plasma treatment** on *in vitro* biological response with osteoblast-like cells	Enhanced osteoblast-like cell response	285
Pure titanium	To yield nanostructures through **reactive ion etching** for enhancing bactericidal efficiency of implants without compromising their cytocompatibility	Good cell attachment and proliferation; excellent antibacterial activity (98% ± 2% against *P. aeruginosa*, and 95% ± 2% against *E. coli*)	286
PEEK	To study the effect of **oxygen and plasma etching** on differentiation of human mesenchymal stem cells	Extensive cell adhesion, proliferation, and differentiation in comparison to original PEEK	287
Pure titanium	To examine the influence of chemically modified surfaces of Ti by **acid etching or acid etching with alkaline treatment** on gene expression of human osteoblastic cells	More pronounced effect of acid etching with alkaline treatment on surface morphology, roughness, wettability, and osteoconductive behaviour	289
Porous titanium alloy implants	To investigate the effect of alkali-acid heat treatment (AlAcH), and acid-alkali treatment (AcAl) on static and fatigue properties of highly porous titanium alloy	AcAl treatment offered significantly less static and fatigue properties for porous titanium with high porosity in comparison to AlAcH treatment	291

4.1.5. Others

The biocompatibility of materials can be improved beyond the nanocrystalline grain surface through alteration of surface chemical composition and surface roughness. Several attempts have been made to obtain an orthopaedic application-oriented biological response by influencing the morphologies of the nanostructured surface through surface treatment, *e.g.*, ion bombardment [276], UV light [277,278], plasma modifications [279], and chemical treatments (using alkalis, acids, and hydrogen peroxide) [280]. These treatments led to significant changes in nanostructure, protein adhesion, contact angle, and electrochemical properties in a treatment-dependent way. Different cell types showed different reactivity to nanotopography features, which were significantly useful in promoting the adhesion and proliferation for one cell type to another [281]. The application of UV treatment to an acid-etched Ti surface increased osseointegration strength during the early stage of healing in a rat model (Table 6) [282]. The UV irradiation facilitated the reversal of biological aging due to photofunctionalization effects. UV treatment has the capability to convert the titanium surface from hydrophobic to super-hydrophilic by removing hydrocarbons from the surface [283]. In the case of zirconia, UV treatment enhanced the osteoconductivity of the materials and accelerated the integration of bone-zirconia along with enhanced strength of the bone-implant interface [284]. Oxygen plasma treated-TiO_2 nanotubes (15–100 nm in diameter) offered the appropriate support necessary to obtain the optimal growth and proliferation of osteoblast-like cells in implants [285].

To nanostructure a titanium surface, a chlorine-based reactive-ion etching process was introduced [286]. The etching process rendered the titanium surface into anisotropic nanostructures, appearing 'black' in colour (similar to that of black silicon). The black titanium exhibited multi-biofunctional properties such as good attachment, high antibacterial activity (98% ± 2% against *P. aeruginosa* and 95% ± 2% against *E. coli*), and proliferation of human mesenchymal stem cells. The activation of PEEK surfaces through oxygen and plasma etching (10 and 50 W, respectively, 5 min exposure) resulted in extensive adhesion and proliferation of adipose tissue-derived mesenchymal stem cells in comparison to original PEEK implants [287].

Further, the presence of chemical groups over the implant surface can have a significant impact on bone growth and regeneration [288,289]. For instance, hydroxylation of the titanium surface is efficient and supports high wettability and cell viability (note that a higher hydroxyl fraction leads to the formation of a thicker amine layer) [290]. The more pronounced impact of surface treatments (*e.g.*, alkali-acid heat or acid alkali treatment) can be seen in porous materials in terms of substantial mass loss, and significant loss of corrosion-fatigue properties [291]. These treatments can lead to the formation of micro- or nanostructures over biomaterials without affecting their biocompatibility, especially for metal implants.

5. New trends in orthopaedic biomaterials

The development of stimulus-responsive biomaterials along with easy-to-tailor properties is the most vital aim of the research in tissue engineering and orthopaedic implant applications. Traditional biomaterials (having single components) suffer from several limitations in terms of poor control over biochemical and biophysical characteristics that tended to hamper their utility in biomedical applications. In recent years, significant progress has been reported with new trends such as engineered biomaterials from natural sources [292], porous structures [293], smart biomaterials [294], and 3D implants [295]. The ideas for new biomaterials have been driven by blending synthetic polymers with natural polymers as well as combining the properties of the different forms of polymers such as natural polymers with high biocompatibility (*e.g.*, silk, elastin, chitosan, collagen, and keratin) and synthetic polymers with good mechanical properties (*e.g.*, polyethylene, polyester, epoxy, and teflon) [296,297]. These biomaterials can be designed to efficiently mimic living tissues for tissue engineering, cell-based transplantation, and gene therapy. Along with the introduction of new natural biomaterials, remarkable progress in fabrication technologies has empowered a new generation of intelligent nanomaterials such as nanoporous anodized alumina (NAA) [298]. Nanopores are highly attractive due to (i) a large surface area to promote high surface loading and (ii) nano-confined volumes to modulate protein dissolution rates [299]. The large surface area of nanopores should efficiently facilitate the linking of bio-active molecules to implants, avoiding the role of intermediate linkers such as oxyilanes [300] and phosphonates [301]. The nanopores have a great impact on protein adsorption and cell adhesion and also promote their usage as bioactive coatings on diverse biomaterial substrates [302]. Porous metals with structures feasible for orthopaedic applications have been reported to replace damaged bones with ones having similar properties as that of bone [303,304]. In this respect, the potential role of smart biomaterials and 3D implants is described in detail here.

5.1. Smart orthopaedic biomaterials

The development of smart biomaterials has been the focus of intensive research interest. Here the term 'smart' corresponds to the nature of the interactions in between a biomaterial and its surrounding biological environment (including cells and tissues). The smart biomaterials differ from traditional biomaterials in terms of their instructive/inductive (or triggering/stimulating) effects to the surrounding cells and tissues. Besides making a direct contact with host

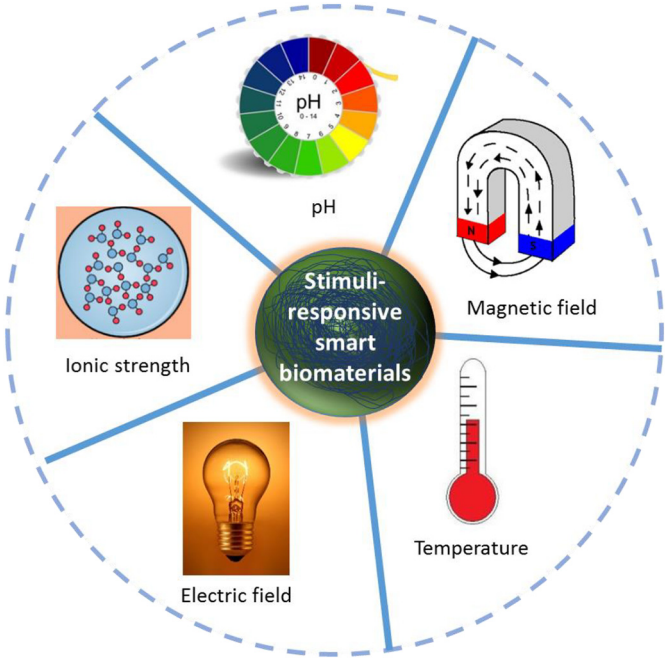

Fig. 12. Stimuli-responsive behaviour of smart orthopaedic biomaterials.

cells, smart biomaterials can be intimately associated with host constituents for prolonged periods to provide several physical and chemical prompts to the host cells [305]. The key challenge in smart biomaterial design is to attain a degree of complexity required to replicate the extracellular matrix of natural tissues for the proper stimulation of cellular attachment and proliferation.

Recent research efforts have focused on the development of composite biomaterials with smart properties (such as mimicking native tissues in terms of physical and chemical properties, their inductive/instructive effects to cells, their stimuli-responsive delivery (*e.g.*, pH, temperature, *etc.*; Fig. 12), and sustainable/controlled delivery of biofactors) for diverse applications ranging from hard tissues (involving bone and teeth) to soft tissues [306]. A smart biomaterial-based implant can actively participate in the restoration of damaged tissues to respond effectively to stimuli from its biological environment. In smart composite biomaterials, peptides or synthetic hybrid block polymers have been the most common choice as the basic building unit [307,308]. The conventional bone reconstruction approaches (*e.g.*, autografts and allografts) suffer from limited availability, donor site morbidity, and risk of infection [309]. To address these shortcomings, recent research activities have been directed toward scaffold-based bone implants using different biomaterials involving mainly aliphatic polyesters and ceramics to offer favourable stability as well as allow the tailored structure of implants (Table 7) [310]. Comesaña et al. [311] fabricated customized bone implants, consisting of a CaP-modified inner core (with moderate degradation rate) and a bioactive glass outer layer (with higher degradability) through a laser-assisted fabrication technique. Such implants exhibit gradual resorbability and usually are employed for low load-bearing bone restoration along with sufficient potential to integrate specific properties such as angiogenic, antibacterial, or antiresorptive activity. Das et al. [312] fabricated magneto-thermo-responsive sunflower oil-modified hyperbranched polyurethane (HBPU)/Fe_3O_4 nanocomposites *via* an *in situ* polymerization technique. The incorporation of Fe_3O_4 into the polymer matrix offered enhanced thermomechanical properties, biocompatibility, biodegradability, and antibacterial activity in comparison to their pristine system. The smart magnetically-controlled behaviour of bio-based polymeric nanocomposites makes them particularly attractive and promising for implant applications.

To date, smart hydrogels, microgels, and nanogels are some of the fastest stimuli-responsive materials in terms of pH, ionic strength, magnetic field, electric field, or temperature [313]. The biocompatible and biodegradable nature of those materials make them more promising for use in orthopaedic implants as smart biomaterials [314]. Note that, in one study, poly(tannic acid) particles were prepared using two epoxy-based crosslinkers such as trimethylolpropane triglycidyl ether (TMPGDE) and glycerol diglycidyl ether (GDE) [315]. Poly(tannic acid) particles showed more biocompatibility against L929 fibroblast cells (~84% cell viability) as compared to linear tannic acid particles (~53% cell viability). Furthermore, functional nanogels have been preferably applied to bioactive coatings over implants due to their antibacterial activity against oral pathogens and adhesive properties [316].

A gelatine methacryloyl (GelMA) scaffold grafted over a titanium implant surface helped in triggering mineral deposition of both MG63 osteoblasts and normal human osteoblasts without exogenous osteogenic factors (*e.g.*, calcium mineral deposition) in cells grown over GelMA hydrogel films [317]. The incorporation of nanomaterials (including ceramic nanoparticles, clay-based platelets, CNTs, and graphene) within hydrogels can generate multifunctional scaffolds that exhibit compatibility with electroactive and load-bearing tissues [318–321]. However, there is a need of further improvements in matrix-directed regulation of the cell function to resolve cellular interaction with the biomaterials and their own matrices.

5.2. 3D orthopaedic implants

3D implants are one of the most promising future trends over monolithic structures to acquire target material properties in desired structures. Recent advances in 3D bioprinting techniques make it possible to generate complex organs (involving bone, skin, cartilage, and vascular tissues) and scaffolds for stem cell differentiation with successful *in situ* transplantation of cartilage tissues in humans [322–324]. In 3D implants, the selection of the biomaterial (*e.g.*, polyphosphate, HA, and tricalcium phosphate with SrO and Mgo doping) and shape specificity are leading factors that must be accounted in order to ensure proper biomolecule attachment for cell adhesion, proliferation, and differentiation [325–327]. Many opportunities are available to further develop bioimplants possessing finer structures with better resolution for processing. 3D printing technology holds immense potential to create the customized coatings (such as 3D-printed trabecular titanium) that are intended to modify the osseointegration of bioimplants [328]. There are different 3D printing technologies in terms of applications in biomaterials such as 3D plotting/direct ink writing [329], laser-assisted bio-printing [330], stereolithography [331], selective laser sintering [332], fused deposition modeling [333], and robotic assisted deposition/robocasting [334] (Fig. 13). However, all of the technologies have both advantages and drawbacks. For instance, 3D plotting/direct ink writing supports easy incorporation of both drugs and biomolecules (*e.g.*, protein and living cells), although it suffers from complicated processing along with a certain range of viscosities [335]. Similarly, stereolithography involves layer-by-layer fabrication of simple and complex designs, but it is applicable only for photopolymers. For metallic materials, electron beam- or laser-based 3D printings are the most common techniques that have been optimized for industrial applications [336]. Some reported 3D printable nanocomposites-based orthopaedic implants are given in Table 7. Nasiri et al. [337] prepared 3D nanocrystalline HA morphology with high porosity and a micro-nano-structural hierarchy in order to modify the osseointegration of metallic implants. The coating of a porous nanoparticle network of crystalline HA over titania implants may offer improved osteoconduction and osseointegration for the bone-implant interface [337].

Complex tissues present several challenges for bioprinting that must be resolved for clinical use such as stresses of the bioprinting, potential for proliferation, and proper functionality [338]. It was demonstrated

Table 7
Reported smart and 3D printed orthopaedic biomaterials.

Biomaterial	System	Observation(s)	Ref.
Nano-sized HA-reinforced poly(-propylene fumarate)-*co*-poly(caprolactone)	*In vitro*	Good attachment, proliferation, and maturation of pre-osteoblasts	310
CaP inner core with bioceramic glass outer layer	*In vitro*	Supports implants with gradual resorbability to match bone growth rates	311
Thermo-responsive sunflower oil-modified HBPU/Fe_3O_4 nanocomposites	*In vitro*	Promoting antibacterial activity of biomaterials for biomedical devices and implant applications	312
GelMA scaffold-grafted titanium implant	*In vitro*	Triggering mineral deposition of both human primary osteoblasts and MG63 osteoblasts without any exogenous osteogenic factors; as osteogenic coatings over implant surface	317
Nanosilicate-reinforced collagen-based hydrogels	*In vitro*	Promoting bone regeneration of non-union defects with increased network stiffness and porosity	319
GelMA/HA hybrid hydrogel	*In vivo*	Enhanced mechanical properties and cell functional expression of GelMA hydrogels for osteon biofabrication (human osteoblast-like cells and human umbilical vascular endothelial cells)	320
MeTro/GO	*In vivo*	A Biocompatible and stretchable hydrogel with tunable electro-mechanical and biological properties	321
3D-Printed porous titanium implant	*In vivo*	High fixation ability of P600 implants (with average pore size of 632 μm) after two weeks of implant	336
3D-Interconnected macro porous TCP	*In vivo*	Good compressive strength of 10.95 ± 1.28 MPa	340
3D-Printed bioactive glass-ceramic (strontium-doped hardystonite-gahnite) porous scaffolds	*In vivo* and *in vitro*	High fatigue resistance and 150 times greater compressive strength than those reported for polymeric and composite scaffolds; good choice for load bearing bone applications	341
3D alginate-PVA-HA hydrogel scaffolds	*In vitro*	Biocompatible scaffolds with 95.6% cells viability	345
3D-Printed porous scaffolds based on a hydroxyl-functionalized polyester (PHMGCL)	*In vivo* and *in vitro*	Enhanced hydrophilicity, improved cell-material interaction, and increased biodegradation rate as compared to poly(ε-caprolactone)	346
Graphene reinforced-3D scaffolds	*In vivo*	Excellent cell viability comparable to the commercial titanium and good biocompatibility and stability	347

that 3D bioprinted tissues composed of multiple cell types should have the potential to develop vascularisation, survive, and proliferate [339]. Tarafder et al. [340] fabricated 3D interconnected macro-pores tri-calcium phosphate (TCP) scaffolds using microwave sintering. These 3D scaffolds have significant potential for tissue repair and regeneration. In comparison to conventional sintering, microwave sintering is advantageous in that it can offer uniform heating of a sample over a shorter time period; it can provide enhanced mechanical properties (i.e., 6.62 ± 0.67 MPa and 10.95 ± 1.28 MPa compressive strength for scaffolds provided with 500 μm pores sintered in conventional and microwave furnaces, respectively), well-ordered grain growth, and higher densification without any crack development. Highly porous 3D bioactive glass-ceramic (strontium-doped hardystonite-gahnite) scaffolds have been fabricated by direct ink writing techniques that resulted with high compressive and flexural strength (i.e., 110 MPa and 30 MPa, respectively) comparable to cortical bone [341]. In addition to ceramic materials, natural biopolymer hydrogels (such as alginate and chitosan) have been used for 3D bioprinting due to their novel characteristics such as high water content, inherent biocompatibility, and similarity in molecular structure as that of the natural extracellular matrix [342,343].

The biological properties (in terms of mechanical strength, controlled bioactivity, and biodegradability) of implants can be enhanced through the addition of appropriate fillers into matrix powder [344]. Bendtsen et al. [345] developed a novel *in vitro* alginate-poly (vinyl alcohol) (PVA)-HA hydrogel formulation for 3D bioprinting of mouse calvaria 3 T3-E1 cells into scaffolds. This 3D scaffold with high shape fidelity offered optimal rheological properties (i.e., 600–1200 Pa of storage modulus), good osteoconductivity, biodegradability, and good cell viability (i.e., 95.6%). 3D-printed porous scaffolds made of a hydroxyl-functionalized polyester (poly(hydroxymethylglycolide-co-ε-caprolactone), PHMGCL) offered a high biodegradation rate in comparison to PCL; PHMGCL 3D scaffolds showed > 60% weight loss after 3 months of implantation in comparison to PCL with the same weight (no change before or after implantation) [346]. Chakravarty et al. [347] were able to produce graphene sheets-incorporated 3D scaffolds *via* a spark plasma sintering technique for biological applications. The 3D porous graphene scaffolds showed extreme cell viability, high porosity (i.e., 35–50%), good mechanical properties, thermal stability, and biocompatibility that made graphene a more promising material for implants. Recent research tends to focus on 3D-printed scaffolds that possess structural similarities to bone tissue through the utilization of biomimetic plywood design. This plywood designing can help improve the mechanical performance of 3D scaffolds while help reduce some of

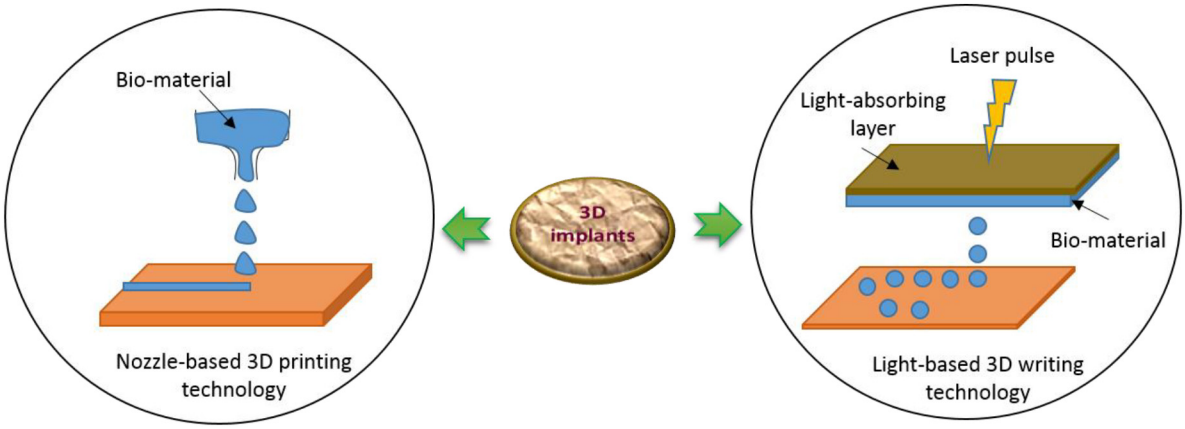

Fig. 13. Common 3D printing technologies, *i.e.*, (i) nozzle-based 3D printing technologies with inkjet printing and layer-by-layer 3D printing of biomaterials, and (ii) light-based 3D writing technologies with laser-assisted bioprinting and stereolithography.

their defects like asymmetric buckling, fracture propagation, and plastic deformation [348].

The major concerns with widespread use of 3D-printed bioimplants are regulatory issues such as requirement of accomplishment of preferred material properties with desired architecture, sterile environment desirable for part fabrication, and drug/drug and drug/materials interactions during 3D printing. These are the crucial topics and must be resolved through significant process optimization before clinical use.

6. Commercial challenges

Before commercialization of any new innovation in the biomedical field, there is a need to keep in mind their effects from a value-consciousness point of view. These effects can be classified into: (i) the impact on treatment quality in comparison to the pre-existing treatment options, *e.g.*, reduction of morbidity, increase in implant life, and pain relief; (ii) the effect on value of treatment (relating to quality of treatment); and (iii) the effect on treatment costs in relation to already existing treatment options [349]. In the market, there are several companies that are particularly involved in the development and commercialization of nanomaterials for bioimplant applications such as tissue engineering and orthopaedics (Table 8) [350–357].

There are several issues that hinder the market growth of bioimplants, *e.g.*, high cost and lack of favourable reimbursements. Nanostructures have unique physical, chemical, and biological properties that modify the functionality and reliability of implants. However, the challenge is how to properly mimic living bone tissue. There are three key parameters that significantly contribute to the development of improved orthopaedic implants: surface topography (*i.e.*, nanoscale surface structuring for better optimization of osteoblast functions), surface chemistry (to control chemical surface properties of bioimplants), and wettability (*i.e.*, better cell adhesion on hydrophilic surfaces) [358–360]. The major challenge for coating techniques is to produce coatings with dissolving capabilities at a similar rate in comparison to bone apposition, which would help in getting a direct bone contact on implant nanosurface. Beyond these limitations, detailed case studies are required for nanomaterial-based orthopaedic implants. Overall, significant research has elucidated the importance of nanophase materials for implant applications to improve the bonding of the implant with its surrounding bones [361,362]. The exposure of engineered nanomaterials to the air and water is still unclear. Upon exposure to a nanomaterial-contaminated environment, their impact on humans and animals needs to be accurately assessed for any negative consequences [363–366]. In order to determine the potential health risks of nanomaterial-based bioimplants, considerable attention must be paid during production, implantation, and wear patterns of these implants before approval for clinical use.

7. Conclusion and future perspectives

Nanotechnology is advantageous in controlling the topography and chemistry of bioimplant surfaces that would help (i) understand the biological interactions and (ii) develop novel implant nanosurface with predictable tissue or organ interactive properties. The nanophase biomaterials can offer favourable properties to osteoblast functions, regeneration of tissues, and bone ingrowth which promotes their role in orthopaedic implants. The nanomaterials in implants can be utilized in different ways either through nanostructured surface or functional nanocoatings over the implant surface. The future of nanophase biomaterials relies on the development of enhanced design methodologies that are capable of combining the benefits of nanomaterials and advanced fabrication technologies. Undoubtedly, the nanomaterials are driving the future of orthopaedics through resolving several unanswered questions in terms of enhanced osteointegration and effective healing of bone defects with bioactive scaffolds, however, before clinical/commercial use of nanotechnology-driven orthopaedic implants, it

Table 8
Commercialization of nanomaterials for tissue engineering and orthopaedics.

Company name	Major area of activity	Technology	Manufacturing	Ref.
3DM (USA)	Nanoscale scaffolds	PuraMatrix® scaffolds for cell culture, accelerated cartilage and bone growth, soft tissue regeneration, anti-adhesion, drug delivery, neurosurgical, and cardiac muscle	F-MOC solid-phase peptide synthesis methodology with appropriate processing modifications	350
Anteo Diagnostics (Australia)	Surface coatings	Nanoglue for medical devices, life science, and *in vitro* diagnostics	Coordination chemistry for gentle and secure multipoint binding of biomolecules to the synthetic surfaces	351
AparnaBio (USA)	Biomedical nanoparticle technology-based on biodegradable macromolecular carriers	NanoElectroPlex™, a proprietary tissue selective nanoparticle technology for research and treatment of human disease	Polymer-based nanoparticles	352
Biomet 3i (USA)	Implants with nanoscale coatings	Contemporary hybrid surface, seal integrity, and integrated platform switching through tissue preservation	–	353
Celsense (USA)	Fluorochemical nanoparticles	Real-time MRI detection of inflammation and cellular therapeutics	–	354
Debiotech (Switzerland)	Pumps, coatings, and micro-needle arrays	Innovative drug delivery systems and medical devices	–	355
Foster (USA)	Nanocomposite materials	Engineered polymeric solutions for medical device technologies	Expert formulation, development, and production of polymer enhancements including custom colours, radiopaque fillers, and other specialty additives	356
Innovative Bioceramics (Canada)	Amorphous nano-hydroxyapatite powder	Nano-structured HA for bone tissue engineering, and binding numerous biological networks	–	357

is significantly important to examine the potential health risks of cell-nanophase biomaterials interactions. Overall, in the realm of medicine, nanotechnology holds great promise for providing exciting orthopaedic implants to society in near future.

Declaration of competing interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

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