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REVIEW

Advances in biocermets for bone implant applications

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Abstract

As two promising biomaterials for bone implants, biomedical metals have favorable mechanical properties and good machinability but lack of bioactivity; while bioceramics are known for good biocompatibility or even bioactivity but limited by their high brittleness. Biocermets, a kind of composites composing of bioceramics and biomedical metals, have been developed as an effective solution by combining their complementary advantages. This paper focused on the recently studied biocermets for bone implant applications. Concretely, biocermets were divided into ceramic-based biocermets and metal-based biocermets according to the phase percentages. Their characteristics were systematically summarized, and the fabrication methods for biocermets were reviewed and compared. Emphases were put on the interactions between bioceramics and biomedical metals, as well as the performance improvement mechanisms. More importantly, the main methods for the interfacial reinforcing were summarized, and the corresponding interfacial reinforcing mechanisms were discussed. In addition, the in vitro and in vivo biological performances of biocermets were also reviewed. Finally, future research directions were proposed on the advancement in component design, interfacial reinforcing and forming mechanisms for the fabrication of high-performance biocermets.

Keywords Biocermets · Advantageous complementarity · Fabrication methods · Interfacial reinforcing · Bone implants

Introduction

The rapid growth of the global population and aging leads to an increasing demand for implants used for bone tissue defects, which are mainly caused by bone trauma and diseases. Worldwide, bone grafting is performed for over 2.5 million cases annually [1]. It is estimated that more than 500,000 people in USA undergo bone replacement surgery, and the medical costs for bone repair exceed \$2.5 billion every year [2]. In China, the quantity of patients with diseased limb function has reached up to 15 million and the annual growth rate of patients with bone defects is approximately 10%. However, it is reported that most of the bone defects cannot be fully recovered due to the lack of suitable bone implants. As a consequence, it is very important to design and develop bone implants with applicable performance for bone defect repair.

Among the currently studied implant biomaterials, biomedical metals are the most popular materials for bone replacement and fixations in load-bearing applications owing to their significant advantages of mechanical properties, especially high strength and toughness. At present, the mostly used biomedical metals in clinic are non-degradable materials, which might cause long-term complications in the human body or even require a second surgery to remove the implant [3]. In recent years, biodegradable metal materials, mainly include magnesium (Mg), iron (Fe) and zinc (Zn) and their alloys have been widely developed and researched as alternatives for bone implant applications. They not only are the essential trace elements in the human body, but also can corrode gradually in physiological environment until to dissolve completely [4]. However, metal materials also present some limitations in bone implant applications, for instance,

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the incompatible mechanical properties and degradation rate, as well as poor bioactivity and possible cytotoxicity introduced by the high concentrations of metal ions [5–7].

Meanwhile, bioceramics have also been widely studied as potential bone implant materials over recent years due to the good biocompatibility. They are mainly used as bone gap fillers in orthopedics and dentistry. In general, bioceramics mainly include bioinert ceramics and bioactive ceramics depending on the bonding mode with bone tissue. The former has relative high strength and wear property, and the later generally has excellent osteoconductivity and osteogenesis [8]. Nevertheless, some inherent disadvantages of bioceramics limit their wide applications. One of the most important drawbacks of bioceramics is their brittleness characterized by low fracture toughness. Specifically, the complex stress environment in the human body might result in the fast growth of microcracks in bioceramic-bone contact area or even the bioceramic implant itself and as a consequence to the final unpredictable fracture. Moreover, bioceramics usually present poor machinability, which also remains as a vital obstacle for fabricating high-performance bioceramic implants.

Given to the complementary advantages and drawbacks between biomedical metals and bioceramics, biocermets have been proposed as a feasible approach to improve the properties of the individual component. As ceramic-metallic composites, biocermets are regarded as a new generation of biomaterials because they open the possibility of fabricating multifunctional bone implants through the multivariate combinations of biomedical metals and bioceramics (including machinability, fracture toughness, wear property, hardness and damage tolerance and so on). In this paper, a review of recent research and advances in biocermets for bone implant applications is presented. The definition and design principles of biocermets are summarized. And the different types of biocermets as well as the advantages and limitations are systematically reviewed. Emphases of this paper are put on the interactions between biomedical metals and bioceramics, as well as their interfacial bonding (including interfacial microstructure, influencing factors and bonding mechanisms). Moreover, the reinforcing mechanisms of interfacial bonding in biocermets are discussed in depth. In addition, the in vitro and in vivo biological performances of biocermets are also reviewed. In the end, future directions of biocermets are pointed out in the component design and forming mechanisms of biocermets, with highlighting the need to investigate the influence of interfacial bonding on mechanical and biological properties (Fig. 1).

The basic principle of biocermets

Definition and properties of biocermets

Biocermets are a composite composed of a biomedical metal or alloy and one or more bioceramics, arising from the idea to obtain excellent comprehensive properties in the composites by combining the diverse and complementary properties of biomedical metals and bioceramics [11]. Generally, the solubility between the metallic and ceramic phases is quite small at the preparation temperature. And biocermets have the advantages both of metal and ceramics, such as high toughness, good bending resistance and machinability of the former, and the high-temperature resistance, high hardness and good biocompatibility of the latter [12, 13]. The study of biocermets allows the preparation of biomaterials with good comprehensive properties that are not achievable with metals or ceramics alone. As for biomaterials, an ideal biocermets should typically exhibit the following properties (Fig. 2):

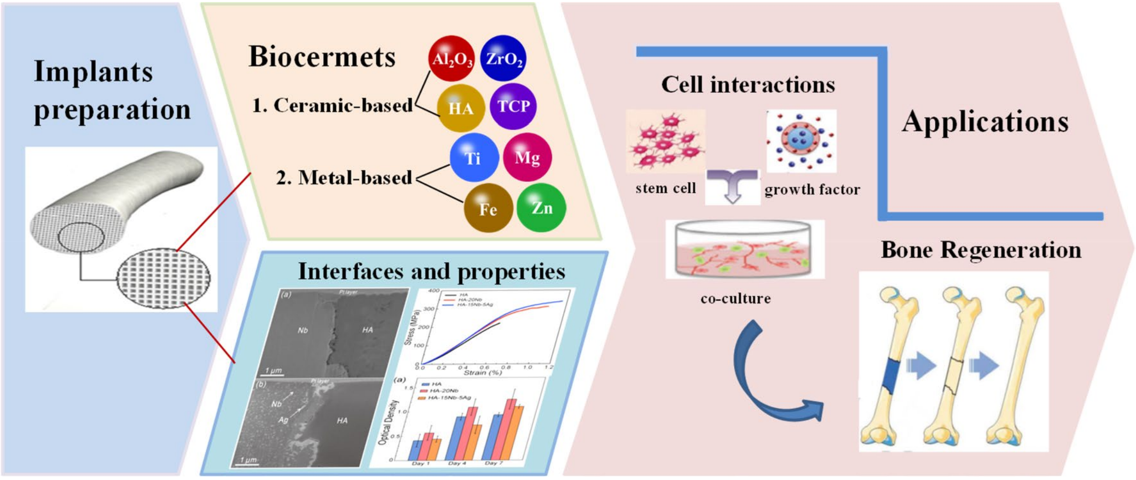
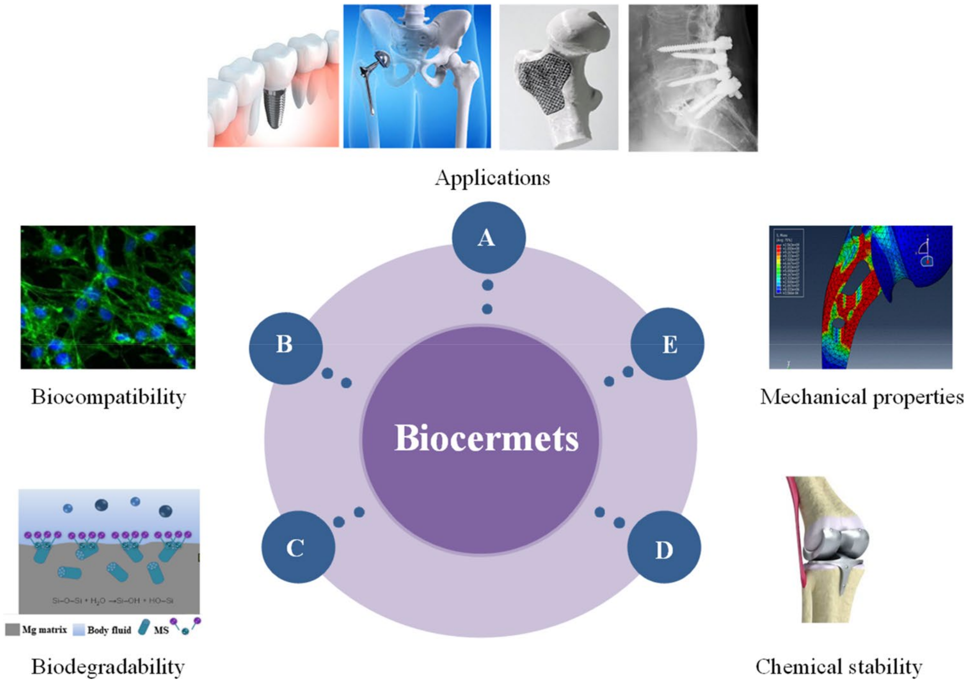


Fig. 1 Research advances in biocermets for bone implant applications [9, 10]

Fig. 2 Properties and applications of biocermets



(1) Biocompatible chemical compositions to avoid adverse cell/tissue reactions.

  - Non-toxicity.
  - Without inflammatory or immune responses.

(2) Appropriate mechanical properties and stability to provide biomechanical support for both the defect site and the newly formed tissue.

  - Suitable modulus matches with that of implant site to avoid stress shielding.
  - High wear resistance to minimize wear debris generation.
  - Desired strength and hardness to sustain cyclic loading at the implanted site.

(3) Suitable biodegradability in the physical environment of the human body.

  - Controllable biodegradation rate for biodegradable materials to match the bone healing rate.
  - Excellent chemical stability for non-degradable materials for long-term services.

In general, the composition and structure of implants should fulfill different demands which vary with the implanted sites, ages, genetic inheritance and living conditions of patients. However, a single kind of biomaterial can hardly fulfill the specific clinical need and biocermets are emerging as a promising alternative to meet the above-mentioned mechanical and biological properties.

Design principle of biocermets

Considering the significant differences in the physicochemical properties of biomedical metals and bioceramics, a well-designed microstructure is essential for the biocermets to effectively combine their individual advantages. The following principles should be considered to obtain the ideal microstructure of biocermets:

(1) A good wettability between the metallic and ceramic phases.

In general, solid and liquid phases co-exist in the forming process of biocermets because of the different melting points of biomedical metals and bioceramics. A preferable wettability is beneficial to the continuous molding of liquid phase, which can minimize the formation of pores and thereby obtain a high density and good interfacial bonding of biocermets [14, 15]. Therefore, the wettability between biomedical metals and bioceramics is closely related to interfacial bonding, which is one of the most important factors affecting the microstructure and performance of biocermets.

(2) A certain solubility and/or interfacial reaction between the metallic and ceramic phases. Solubility and interfacial chemical reactions can improve the wetting effect between the metallic and ceramic phases. However, it is worth noting that the interfacial reactions should be

slight since a violent interfacial reaction might induce detrimental products, such as brittle intermetallic compounds, etc., which would significantly weaken the reinforcing effect in biocermets [16–19].

(3) Minimal difference in the expansion coefficients between the metallic and ceramic phases. Overlarge difference in expansion coefficients would cause a large internal stress and lower the thermal stability, eventually resulting in cracks or even fracture in the biocermets [20, 21].

(4) An appropriate choice of toughening metallic phases for ceramic matrix. If the strength of the metallic phase is far higher than that of the ceramic matrix, the toughening effect is likely to occur before the plastic deformation/fracture. As a result, the ceramic matrix would fracture at the phase interfaces, limiting the plastic deformation and thereby toughening effect of the metallic phase.

(5) For orthopedic application, the development of biocermets should also take account of biocompatibility, biodegradability, bioactivity and osteogenesis simultaneously.

Main types of biocermets

In recent years, increasing efforts have been devoted to developing multicomponent biocermets with excellent mechanical performances and biological properties. These biocermets can be mainly divided into two types: ceramic-based biocermets and metal-based biocermets, according to the percentage of each component phase.

Ceramic-based biocermets

Commonly, bioceramics can be categorized into two categories depending on their ability to bond with living tissues after implantation: (1) bioinert ceramics such as aluminum oxide (Al_2O_3) and Zirconia (ZrO_2), etc.; (2) bioactive ceramics, such as calcium phosphate (Ca–P) ceramics, calcium silicon (Ca–Si) ceramics, bioactive glasses, etc. Bioinert ceramics can only form physical combination with the surrounding tissue after implantation and usually have preferable resistance to corrosion and wear, as well as high strength [8]. In contrast, bioactive ceramics can bond directly with living tissues via synostosis, and thus have excellent osteogenic properties and osteoconductivity. The degradation products and released ions of bioactive ceramics can take part in human metabolism, enhance cell activity and accelerate bone repair [22]. Nevertheless, due to the low fracture toughness, bioceramics cannot be widely applied in bone implant. When a load is applied, the bioceramics of inherent brittleness would grow microcracks rapidly, and as a consequence would cause the final unforeseen fracture. This phenomenon is particularly noticeable for implant applications, in view of the complex stress environment in the human body [23, 24]. Biocermets can be an effective approach to enhance the fracture toughness by combining brittle ceramics and ductile metals. Biomedical metals are beneficial to dispersing the energy for propagating cracks in bioceramic matrix in manner of crack bridging and crack deflection, thereby increasing the fracture toughness of the ceramic-based biocermets [25–28]. The types and mechanical properties of bioceramics and ceramic-based biocermets are summarized in Table 1.

Al_2O_3-based biocermets

Al_2O_3 is the earliest bioceramics used in clinical application and induces a series of researches on ceramic biomaterials [29, 30]. In a variety of bioceramics, Al_2O_3 have potential in orthopedic application owing to the high hardness and strength, low friction and excellent wear resistance, etc. In the last decades, Al_2O_3 bioceramic has been widely used in joint replacement, such as hip, knee, elbow, ankle, wrist, phalanges and spine, as well as bone reconstruction [31]. Owing to the excellent thermostability and stable chemical structure, Al_2O_3 hardly release soluble compounds and cause toxic reactions in physiological environment. However, when Al_2O_3 bioceramic is implanted in human, the bioinertness prevents it from forming chemical bonding with bone tissues, avoiding new bone formation in the early stages of bone implantation. Moreover, the inherent brittleness and low fracture toughness of Al_2O_3 bioceramic may easily result in local fine cracks, low structure stability or even secondary fractures at the implanted site [32].

At present, various metals have been introduced into Al_2O_3 bioceramic in many studies, aiming to improve its fracture toughness and/or biological properties. In consideration of the biomedical applications, these metals mainly include titanium (Ti), niobium (Nb), Fe, Zn, silver (Ag), Mg, chrome (Cr), Stannum (Sn), etc. [31, 33–36]. For example, many studies proved that Ti could significantly improve the mechanical properties of Al_2O_3 [37]. Moreover, Guzman et al. [38] fabricated Al_2O_3–Ti biocermets and the results demonstrated that appropriate amounts of Ti in the biocermets contributed to the improvement in roughness and wettability, which thereby enhanced the cytocompatibility and protein adsorption of Al_2O_3. Rahaman et al. [35] developed Al_2O_3–Nb biocermets by hot pressing, and the results indicated that the Al_2O_3-based biocermets possessed significantly enhanced flexural strength (720 ± 40 MPa) compared with Al_2O_3 (460 ± 110 MPa), which could avoid the catastrophic brittle failure of Al_2O_3-based implant in vivo. Park et al. [36] prepared Al_2O_3–Cr biocermets by using mechanical milling followed by pulsed current-activated sintering. It

Table 1 Types and mechanical properties of bioceramics and ceramic-based biocermets

Composition	Preparation methods	Flexural strength (GPa)	Fracture toughness (MPa m$^{1/2}$)	Elastic modulus (GPa)	Vickers hardness (GPa)	Density (%)	References
Al_2O_3	High-energy ball mill and high-frequency induction heated sintering	420 ± 140	–	135 ± 20	12 ± 1_	98	[77]
Al_2O_3–Nb	Hot pressing	720 ± 40	–	80 ± 5	–	98	[77]
Al_2O_3–Nb–SiC	Hot pressing	960 ± 20	–	110 ± 30	–	98	[77]
Al_2O_3–Ti	Hot pressing	329	5.1	–	5.61	96	[78]
Al_2O_3–Ti–Nb	Hot pressing	370.67	16.44	–	6.53	98.5	[78]
Al_2O_3–Cr	High-energy ball milling	–	9.3	–	16.3	99	[36]
Al_2O_3–Mo	High-energy ball mill and high-frequency induction heated sintering	–	7.6	–	14	99.8	[79]
ZrO_2	Spark plasma sintering	1217 ± 10	6 ± 0.3	198 ± 5	13 ± 0.3	99	[80]
ZrO_2–Nb	Hot pressing	908 ± 20	15 ± 1	135	–	–	[11, 51]
ZrO_2(3Y-TZP)-Ta	Spark plasma sintering	970 ± 18	16 ± 0.9	194 ± 7	9 ± 0.7	98	[80]
ZrO_2(2Y-TZP)-Al_2O_3	Spark plasma sintering	1500 ± 30	6.8 ± 0.2	279	14.9 ± 0.3GPa	99	[81]
ZrO_2(2Y-TZP)-Al_2O_3-Ta	Spark plasma sintering	1300 ± 70	16 ± 1	256	10.4 ± 0.4	98	[81]
HA	High-energy ball milling + spark plasma sintering	–	3.32 ± 0.2	64.1 ± 4.9	429.6 ± 13.6 Vickers hardness (HV)	99.7 ± 0.1	[10]
HA-Nb	High-energy ball milling + spark plasma sintering	–	4.17 ± 0.17	72.3 ± 6.1	464.3 ± 23.8 Vickers hardness (HV)	99.2 ± 0.2	[10]
HA-Nb–Ag	High-energy ball milling + spark plasma sintering	–	4.40 ± 0.25	74.4 ± 3.8	456.3 ± 43.7 Vickers hardness (HV)	99.3 ± 0.2	[10]
TCP	Spark plasma sintering	200.4 ± 10.6 Compressive strength (MPa)	0.76 ± 0.05	7.5 ± 0.2	4.0 ± 0.2	–	[74]
TCP-Fe	Spark plasma sintering	637.6 ± 6.12 Compressive strength (MPa)	2.55 ± 0.24	8.1 ± 3.1	2.5 ± 0.3	–	[74]

was found that the Al_2O_3–Cr biocermets possessed improved fracture toughness and hardness compared with Al_2O_3, because the addition of ductile Cr led to a deflective manner of crack propagation in the matrix. In addition, Jastrzebsk et al. [34] and Ma et al. [39] reported that the incorporation of Ag could effectively enhance the antibacterial properties and cell viability of Al_2O_3 bioceramics.

ZrO_2-based biocermets

ZrO_2 bioceramic is also a bioinert ceramic with good corrosion resistance, and its biocompatibility and bonding manner to bone tissue are similar to those of Al_2O_3. In general, ZrO_2 exists in three polymorphic crystalline phases: monoclinic (M) phase, cubic (C) phase and tetragonal (T) phase, depending on temperature (t). M-phase (t <1170 °C) is fragile, while stabilized T-phase (t = 1170–2370 °C) and C-phase (t > 2370 °C) have relatively high toughness, as well as high strength and hardness [40, 41]. This unique feature enables the toughness improvement of ZrO_2 through transformation toughening. Hence, the mechanical properties of ZrO2 can be much higher than those of other bioceramics. For instance, its fracture toughness and flexural strength are about twice those of Al_2O_3 bioceramics [42–44]. Therefore, ZrO_2 bioceramics have been extensively used in orthopedic applications due to the relatively high strength and toughness, as well as appropriate biocompatibility. However, ZrO_2 is likely to undergo low-temperature degradation from T-phase to M-phase spontaneously, which would generate detrimental effects on the mechanical properties of ZrO_2, even leading to the premature failure after implantation [42, 45, 46]. At present, metallic elements are widely used as stabilizers to accomplish the phase transformation of ZrO_2 at room temperature, including Mg, calcium (Ca), yttrium (Y), cerium (Ce), lanthanum (La), etc. [47–49]. For example, Ponnilavan et al. [50] investigated the effect of rare-earth substitutions on the performance of ZrO_2–Al_2O_3 for biomedical applications and found that the combinations of Gd and Dy in ZrO_2–Al_2O_3 displayed better mechanical properties due to the phase transformation.

Additionally, ZrO_2 as a bioinert ceramic material lacks ososteoconduction and osseointegration between new bone and the implant. Bartolomé et al. [51] prepared ZrO_2/Nb biocermet for hard tissue replacement by hot pressing and found that the addition of Nb could effectively improve the mechanical properties of ZrO_2. Furthermore, in vivo and vitro studies [11] showed that the cell proliferation and bone implant interface around ZrO_2/Nb biocermet implants were both higher than those of Nb implants, indicating the advantageous combination of the osteoconductivity and osteointegration ability of Nb and the biocompatibility of ZrO_2. Smirnov et al. [80] introduced Ta to reinforce ZrO_2 and found that the incorporation of Ta could effectively enhance the fracture toughness of ZrO_2. Moreover, the ZrO_2–Ta biocermets exhibited good tribology performance and high resistance to low-temperature degradation. Fernandez-Garcia et al. [52] fabricated ZrO_2–Ti biocermets via spark plasma sintering and found the biocermets exhibited better osteoblast response comparing with ZrO_2 or Ti. Further study reported that the surface bioactivation of ZrO_2–Ti biocermets by incorporating signaling oligopeptides and antimicrobial properties accelerated osseointegration and prevented peri-implant infection, and thereby improved their clinical performance [12].

Hydroxyapatite (HA)-based biocermets

HA-[Ca_{10} $(PO_4)_6$ $(OH)_2$], as one of the most typical Ca–P bioceramics for bone tissue engineering, has similar chemical composition with the main components of natural bone/teeth. HA not only has excellent bioactivity and biocompatibility, but also can form osseointegration with bone tissue in the healing process [53, 54]. After implantation, it can promote new bone growth and form chemical bonding with autogenous bone tissue, and thereby obtain higher bonding strength than that of bioinert ceramics [55]. Furthermore, HA have great osteoinductivity, and its hydroxyl group's boasts via hydrogen bonding an ideal affinity for amino acids, proteins and organic acids. Moreover, HA's degradation products and released ions can be part of human metabolism, creating an alkaline environment to boost cell activity and speed up bone repair. A key issue that hampers the extensive clinical application of HA is their brittleness and low strength. Besides, HA enjoys a relatively high crystallinity and stability, making it hard to degrade in vivo.

A promising strategy is to reinforce HA with ductile biomedical metals, combining their mechanical strength and toughness with HA osteoconductivity. So far, the mechanical properties or biological functions of HA have been ameliorated by incorporating Ti, Fe, Ag, Zn, Mg, Nb, etc. [10, 56–63]. Wei et al. [10] prepared HA-Nb and HA-Nb–Ag biocermets via spark plasma sintering. In contrast with HA, these biocermets exhibited higher compressive strength and fracture toughness, as well as high interface strength. And the incorporation of Nb could also stimulate cell response of osteoblasts and enhance the osteointegration ability of HA, while the addition of Ag could significantly enhance the antibacterial activity of HA. Nordin et al. [58] used Fe to improve the mechanical property of HA by using mechanosynthesis method and found that HA-Fe nanocomposite showed higher hardness and Young's modulus than that of HA due to the high crystallinity of Fe powders. Moreover, the hydroxyl site, phosphate site or calcium site of HA can tolerate the incorporation of a certain amount of metallic ions, thereby modifying the properties. Recently, a crowd of metallic ion substitutions have been reported, including Mg, Zn, La, Y, In, Bi, Y, etc., and co-doped metallic ions such as Cu–Zn, Sr–Mg, Sr–Cu, Zn–F, Co–Mg to stimulate osteoblast responses [64, 65].

Tricalcium phosphate (TCP)-based biocermets

TCP is another popular Ca–P bioceramics and has the ability to form a strong chemical bonding with bone tissue after implantation. In general, TCP exists in three different allotropic polymorphs, and β-TCP stands out as the most popular form for implant applications as its preferable mechanical strength and chemical stability. The main mechanism of TCP bioactivity is the partial dissolution and release of Ca ion and phosphate products in vitro and in vivo, thus producing biological apatite precipitations on implant surface to induce bone regeneration. Moreover, the TCP's inherent brittleness and low bending strength make it unfit to be used in load-bearing sites. In addition, TCP can actively participate in the metabolic processes, and then gradually degrade in vivo [66]. Some researchers illustrated that the degradation rate of β-TCP was too fast compared with the growth rate of new bone tissue [67]. As a consequence, it is difficult to maintain a stable bonding interface between β-TCP implants and bone, which limit their clinical applications. Moreover, the inherent intrinsic brittleness and low bending strength of TCP make it unsuitable for to be used in load-bearing sites.

To overcome these limitations, biomedical metals have been incorporated into TCP to obtain TCP-based biocermets with good mechanical performance and implant stability. For instance, incorporating Fe [68–70], Mg [71] and Zn [72, 73], etc., can improve the toughness of TCP, and at the same time ameliorate the densification and crystallinity of TCP. Tkachenko et al. [74] produced TCP-Fe biocermet, and the results showed a dramatic substantial improvement in both strength and ductility in comparison with TCP. The toughening mechanism of TCP-Fe biocermet both in tension and compression was attributed to crack bridging caused by the plastic deformation of Fe reinforcement. Furthermore, Montufar et al. [75] incorporated 25 vol% Fe into β-TCP ceramic matrix to prepare β-TCP-Fe biocermet, which presented high mechanical strength and degradation rate, as well as good biocompatibility to osteoblast cells. It was found that there are no significant differences in the tensile strength of the β-TCP-Fe biocermet during 8 weeks' degradation, but a slight decrease after 16 weeks. Swain et al. [76] introduced Ag into β-TCP-Fe biocermet and the result showed that partial substitution of Fe with Ag improved mechanical performances of β-TCP. Moreover, they prepared β-TCP-Fe–Mg biocermet and found remarkably enhanced compressive and bending strength owing to the toughening effect of lath-shape ductile Fe. The biocermet also performed positively in terms of osteoblast attachment and proliferation (Fig. 3) [71]. Li et al. [73] fabricated TCP-Zn biocermet by means of immersion curing. The results presented that the addition of Zn not only increased the hardness of pure TCP, but also enhanced the cell viability of osteoblasts, and thereby preferably stimulated bone formation.

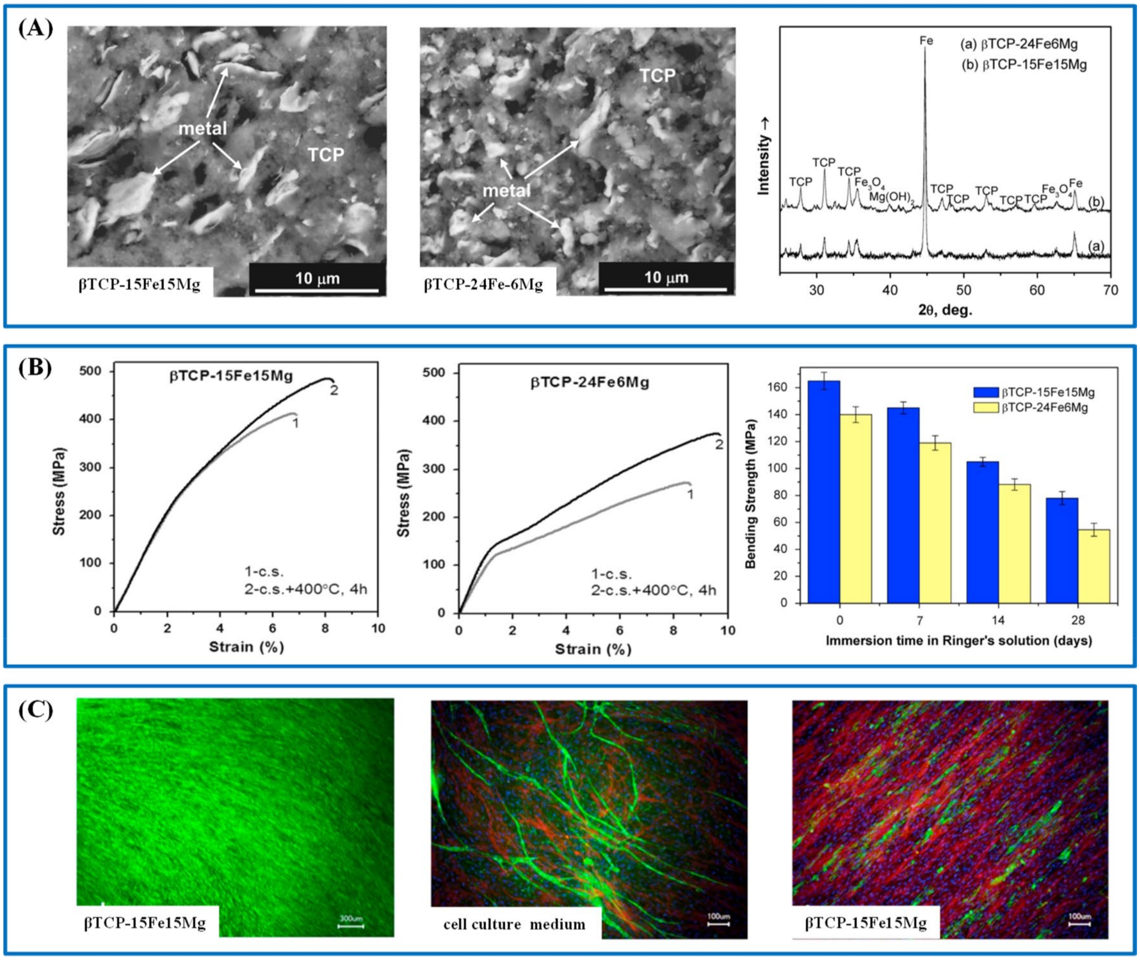


Fig. 3 **a** Fracture surface morphology and X-ray diffraction (XRD) patterns of βTCP-Fe–Mg biocermets; **b** Compressive stress–strain and bending strengths of βTCP-15Fe15Mg and βTCP-24Fe6Mg biocermets after different immersion periods in Ringer's solution; **c** Fluorescent images of primary human osteoblasts cultured on βTCP-15Fe15Mg, and immunofluorescent images of primary human endothelial and osteoblast cells co-cultured with cell culture medium and βTCP-15Fe15Mg after 2 weeks, respectively [71]

Metal-based biocermets

Ti-based biocermets

Ti and its alloys have been used to fabricate orthopedic implants for long time in clinic due to good mechanical strength, acceptable biocompatibility and corrosion-resistant properties. However, the surfaces of Ti-based biomaterials are bioinert, which results in limited osseointegration between the implants and bone tissues, even leading to the failure of implantation [82]. And the elastic modulus of Ti is incompatible with that of natural bone, which may easily cause stress shielding and further bone loss, bone relaxation and osteoporosis [83]. Moreover, with the increase in human lifetime, second surgery becomes necessary because of tribocorrosion and inflammations caused by wear particles of the Ti-based biomaterials [84]. For this reason, improving the osseointegration and prolonging the service life of Ti-based implants have attracted much attention in recent years. Until now, alloying has been a common approach to develop Ti-based biomaterials, but there still remains some issues such as comparatively poor wear resistance.

To improve this aspect, hard ceramics have been viewed as an effective reinforcement to enhance the wear resistance of Ti-based biomaterials. The most commonly used reinforcements for Ti are titanium carbide (TiC), titanium boride (TiB) and titanium nitride (TiN), etc. [85, 86]. For example, Georgiou et al. [87] prepared nanostructured Ti-TiC cermets by using supersonic spraying, and the result showed that the nanostructured Ti-TiC cermets enjoyed an ameliorative wear property and relatively low friction owing to the second-phase strengthening and dislocation pinning. Besides, bioceramics are also frequently incorporated into Ti matrix to improve the bioactive and osseointegration properties of Ti-based biomaterials. Among Ti-based biocermets, Ti-HA biocermet is one of the earliest studied biocermets aiming to combine the bioactivity of HA with the mechanical stability of Ti [88]. Bovand et al. [89] fabricated the Ti-HA biocermets by using mechanical alloying and powder metallurgy, and the result showed enhanced surface hardness and roughness compared with Ti. In addition, Li et al. [90] prepared porous Ti-HA-chitosan scaffold and found that the scaffold not only exhibited appropriate mechanical properties matching with nature bone, but also had positive influence in adhesion and proliferation of osteoblasts.

Fe-based biocermets

Recently, biodegradable metals have been proposed as potential candidates for orthopedic applications to avoid the negative effects related to non-degradable metal implants. Among of them, Fe and its alloys have better mechanical properties such as strength and plasticity, and thus are appropriate for bone implant applications which require strong mechanical support during the bone healing process. In physiological fluids, Fe can transform into Fe ion by oxygen absorption corrosion and then form degradation products such as $Fe(OH)_2$, $Fe(OH)_3$ and Fe_3O_4 [4]. Although concerns over the potential cytotoxicity due to the excessive intake of Fe element have been raised, numerous in vitro and in vivo studies on Fe-based implants have illustrated their good biocompatibility and biosafety for orthopedic applications. However, the degradation rate of Fe is way slower than the growth rate of new bone [91].

In light of this, more and more efforts have been devoted toward increasing the degradation rate of Fe for bone implant applications. Reindl et al. [92] introduced β-TCP bioactive ceramic into degradable Fe via powder injection molding and found that Fe-β-TCP biocermets possessed significantly enhanced degradation rates in comparison with pure Fe, which was attributed to the bioactivity of the β-TCP ceramic. Moreover, the compressive yield strength of the Fe-β-TCP biocermets gradually decreased during the degradation process and decreased slower with higher content of β-TCP. Ulum et al. [93] developed a series of Fe-based biocermets by incorporating HA, TCP and HA-TCP mixtures, respectively. It was found that the degradation rates of these Fe-based biocermets were slightly enhanced compared with Fe, because the incorporation of HA, TCP or HA-TCP had a favorable effect on the corrosion potential and impedance of these Fe-based biocermets. And in vivo evaluation in their following study confirmed that the bioactivity of these Fe-based biocermets was higher than that of Fe, as indicated by the promoted proliferation of rat smooth muscle cells. Heiden et al. [94] produced Fe–Mn-HA biocermet by means of salt-leaching for bone implant applications and found that the biocermet not only exhibited higher degradation rates than pure Fe and Fe–Mn alloys, but also had positive effects on cell response. Wang et al. [95] incorporated calcium silicate (CS) bioceramic into Fe via powder metallurgy, and the result showed that the Fe-CS composites can accelerate the degradation rates of Fe. Meanwhile, the addition of CS could enhance the deposition of CaP and stimulate the proliferation of human bone marrow stromal cells on Fe. Montufar et al. [96] prepared Fe-CNT-TCP biocermets for orthopedic applications via spark plasma sintering, and the result showed that the addition of CNT resulted in a hypoeutectoid steel microstructure, and the TCP was beneficial to the attachment of osteoblasts.

Mg-based biocermets

Mg and its alloys, as well-researched biodegradable metals, have attracted the most attention owing to the compatible elastic modulus with that of natural bone, which can effectively prevent the stress shielding [97]. In addition, Mg, as an important microelement in human body, can improve the activity of various enzymes related to metabolism [98]. After implanted in human body, Mg-based biomaterials can not only offer support mechanically at the first stage but also degrade into Mg ions as new bone tissue grows, then this biomaterials can be absorbed by surrounding tissues or discharged through excretion [99]. However, Mg is chemically active with a low standard corrosion potential (− 2.37 V), and porous surface oxide film developed in corrosive medium. Both factors lead Mg and its alloys to degrade rapidly, especially in an environment with high Cl ion concentration [100, 101]. For one thing, the degradation of Mg implant is so rapid in human body that its mechanical integrity and stability may soon disappear [102]. For another, such a fast degradation releases rapidly a mass of hydrogen, which after aggregating around the implant forms bubbles that inescapably injure the physiology of the surrounding tissue and the regeneration of the defect site [103].

Current studies have shown that many bioceramics can be used to improve the biodegradable properties of Mg-based biomaterials [104–106]. Witte et al. [107] introduced HA into Mg alloys (AZ61) by using spark plasma sintering, and the result showed that the addition of HA can slow down the corrosion by enhancing the corrosion resistance of AZ61, and the mechanical properties of the AZ61-HA biocermets can also be adjusted by different particle size and distribution of HA. Khalajabadi et al. [108] prepared Mg-HA-MgO by means of powder metallurgy, and the results showed increased corrosion resistance from 0.25 of Mg-HA to 1.23 kU cm^2 of Mg-HA-MgO, which was attributed to the promoted formation of denser corrosion product by MgO (Fig. 4). Cui et al. [109] incorporated nano-HA into Mg–Zn alloy and found that the degradation rate of Mg–Zn-HA biocermets was decreased by 49% compared with that of Mg–Zn alloy, attributing to the protection of more uniform Ca–P layer. The Mg–Zn-HA biocermets also possessed enhanced compressive yield strength and bending strength, as well as preferable cytocompatibility to mouse fibroblast cells. Ghasali et al. [110] fabricated Mg-Al_2O_3 and Mg-Si_3N_4 biocermets by means of microwave sintering. The electrochemical experiment revealed that Al_2O_3 and Si_3N_4 reinforcements enhanced the polarization resistance of Mg, and thereby retarded the rapid degradation of Mg. Furthermore, the incorporation of Al_2O_3 and Si_3N_4 can promote the formation of bone-like calcium phosphate layer on Mg. Shao et al. [111] prepared Mg-TCP-wollastonite biocermets via extrusion-based 3D printing and found that the

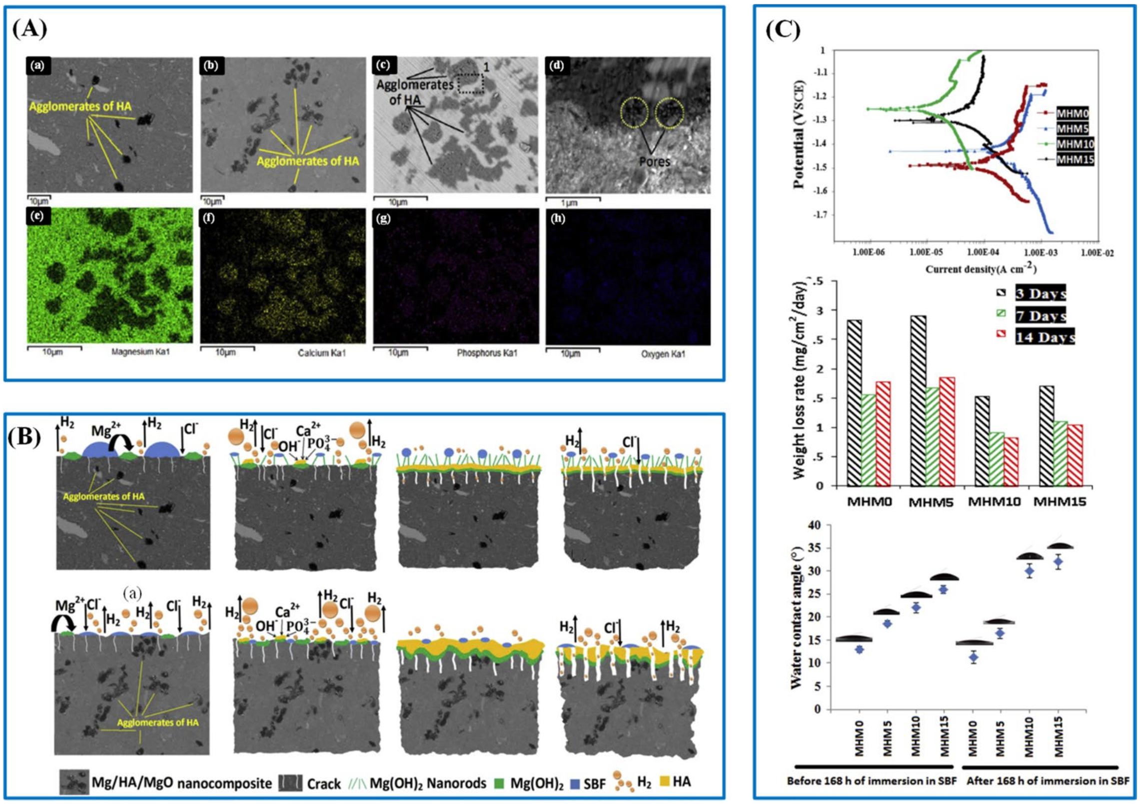


Fig. 4 **A** SEM images of the Mg-HA-MgO (a) and Mg-HA (b, c) biocermets, as well as a high magnification image (d) and corresponding X-ray map (e–h) of area 1 in (c); **B** the degradation mechanism of Mg–HA–MgO biocermets in SBF solution; **C** potentiodynamic polarization curves and corrosion rate of the Mg–HA–MgO biocermets in SBF solution, as well as the water contact angles before and after immersion in SBF solution [108]

biocermet scaffolds exhibited high compressive strength and adjustable degradation rates. After degradation, the biocermet scaffolds showed a gradual loss of compressive strength but still appropriate mechanical flexibility.

Zn-based biocermets

In recent years, Zn-based biomaterials have drawn more and more attention as biodegradable metals owing to their relatively ideal degradation behavior. In comparison with Mg and Fe, Zn has relatively suitable degradation rate as bone implants due to the middle electrode potential between Fe and Mg. Moreover, Zn is known to play a crucial role in the functions of over 300 enzymes, and it is essential to a lot of human metabolism [112]. More importantly, Zn can promote osteoblast differentiation and mineralized tissue formation. It is also has positive effect on inhibiting osteoplastic bone resorption and preserving the bone mass in the human body. Both in vitro and in vivo studies had revealed that Zn implants exhibited good biocompatibility, as well as preferable degradation behavior than Mg and Fe [113–115]. Nevertheless, the strength and ductility of Zn are lower than that of nature bone, which cannot meet the clinical requirements for bone implants applications. Besides, many studies reported that the degradation rate of pure Zn (0.06–0.08 mm/year) was slower than the requirement of an ideal bone implant (0.2–0.5 mm/year) [116, 117], which also have to be further improved.

With the above limitations in mind, metal-ceramic composites was proposed as promising approach to improve the mechanical performance or degradation rate of Zn. Karimzadeh et al. [118] induced Al_2O_3 to strengthen Zn, and the result presented that Al_2O_3 bioceramics boosted the hardness and wear property of Zn. Yang et al. [119] prepared Zn-based biocermet-reinforced by HA via spark plasma sintering, and the result showed that HA could adjust the degradation rate with different amount and also improve the biocompatibility of Zn, but immolated the compressive strength. Our recent study used SiC nanoparticles as a reinforcement to prepare Zn–SiC biocermet by using laser melting [120]. The result indicated that the incorporation of SiC ceramics significantly enhanced the mechanical strength and hardness of pure Zn owing to grain-refinement strengthening and dispersion strengthening. Moreover, the degradation was also accelerated due to intergranular corrosion.

Preparation process for biocermets

Hot pressing

Hot pressing is a traditional process in which the densification process is accelerated after applying during sintering pressure to the powder, so as to bring down the sintering time and temperature [9]. Sintering is driven by not only the surface free energy of composite powder but also powder rearrangement under pressure, concentration gradient and accelerated diffusion of vacancies caused by grain-boundary sliding.

Smirnov et al. [121] reported the hot pressing preparation of ZrO_2-Ta biocermets by sintering at 1400 °C for 1 h under Ar atmosphere. It was found that the Ta reinforcement uniformly distributed in the matrix without the formation of pores, and the fracture toughness increased from 8 ± 0.5 for ZrO_2 to 16 ± 0.6 MPa $m^{1/2}$ for ZrO_2-Ta biocermets due to the plastic deformation of Ta reinforcement. Shi et al. [78] fabricated Al_2O_3-Ti biocermets by using hot pressing at 1350–1500 °C for 1.5 h under a pressure of 30 MPa, and the results indicated that the bending strength of the Al_2O_3–Ti biocermets increased to 527 MPa, which was 1.5 times than that of Al_2O_3. In addition, the fracture toughness increased twice that of Al_2O_3 (Fig. 5). In addition, Chu et al. [122] also used hot pressing in the fabrication of Ti-reinforced HA biocermets at 1100 °C for 30 min in nitrogen atmosphere under a pressure of 20 MPa. Before hot pressing sintering, HA-Ti mixture powders were producted by ball milling for 12 h to avoid the agglomeration of HA, followed by pre-compacting at 200 MPa. It was found that the addition of Ti could promote the conversion of HA to more stable phases (α-Ca_3 $(PO_4)_2$ and Ca_4 O $(PO_4)_2$) at high temperatures and effectively toughen the brittle HA matrix owing to crack deflection on the ductile metal Ti. Consequently, the HA-40 vol%Ti biocermet showed remarkably enhanced fracture toughness (2.692 MPa $m^{1/2}$), bending strength (92.1 MPa) and work of fracture (91.2 J/m^2) in comparison with that of pure HA. Moreover, further in vivo study [123] illustrated that the HA-Ti biocermets possessed appropriate histocompatibility and osteogenesis. Dezfuli et al. [124] prepared Mg-bredigite biocermets by sintering at 150–350 °C for 1–4 h under a pressure of 500 MPa and found that the biocermets had lower degradation rates and better mechanical properties than Mg. During degradation, the mechanical properties of the biocermets gradually decreased, but the ultimate compressive strength was still comparable with that of cortical bone after 12 days' degradation.

Isostatic pressing

Isostatic pressing technology is a manufacturing process to achieve isotropy of both microstructure and mechanical properties by exerting isotropic pressure on the composite during the sintering process. Generally, isostatic pressing technology can be divided into cold isostatic pressing and hot isostatic pressing based on the forming and consolidation temperature. At present, these two methods have been widely used in the medical industry to improve the

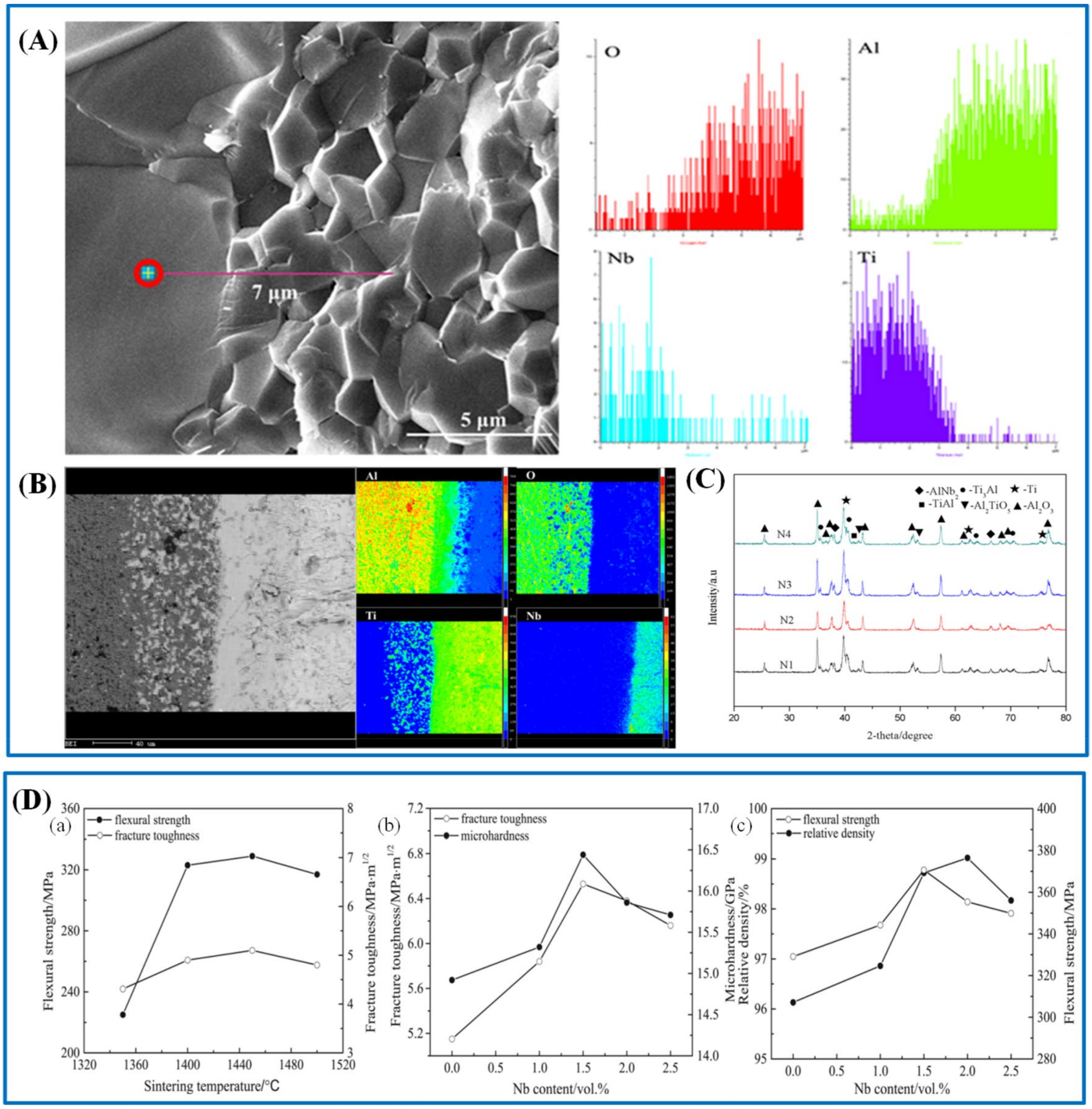


Fig. 5 Preparation and mechanical properties of Al_2O_3–Ti and Al_2O_3–Ti–Nb biocermets prepared by hot pressing. SEM images and EDS scanning analysis of the **A** surface and **B** interface of Al_2O_3–Ti–Nb biocermets; **C** XRD patterns of Al_2O_3–Ti–Nb biocermets; **D** flexural strength and fracture toughness (a) Al_2O_3–Ti biocermets at different sintering temperatures; microhardness and fracture toughness (b) of Al_2O_3–Ti–Nb biocermets with different Nb content; relative density and flexural strength (c) of Al_2O_3–Ti–Nb biocermets with different Nb contents [78]

mechanical performances by control the forming process (such as densification and crystallinity) of metals, ceramics and cermets [125–127].

He et al. [128] reported β-TCP-Fe biocermet prepared via cold isostatic pressing at room temperature under a pressure of 200 MPa with a holding time of 2 min, followed by high heat sintering. The X-ray diffraction pattern and corresponding calculated lattice parameters demonstrated that atomic diffusion occurred between the Fe and β-TCP matrix during the sintering process, which could form a strong bonding to benefit the interface between β-TCP and Fe. Consequently, the β-TCP-Fe biocermet attained significantly improved fracture toughness and compressive strength compared to that of the β-TCP (Fig. 6). Swain et al. [76] fabricated β-TCP-Fe–Ag ceramic-based biocermets by using high-pressure cold sintering at 2.5 GPa. Before sintering, the FeAg metallic compound was prepared via high-energy attrition milling under argon for 4 h. In contrast with the β-TCP-Fe biocermet, the β-TCP-Fe–Ag biocermets not only possessed increased strength and ductility due to partial substitution of Fe with Ag, but also displayed accelerated degradation owing to the galvanic corrosion between Ag and Fe. It was worth noting that the bending strength of the β-TCP-Fe–Ag biocermets decreased with degradation, but was still significantly higher than that of the β-TCP-Fe biocermets. In addition, Dercz et al. [129] prepared Ti/ZrO_2 and Ti/Al_2O_3 biocermets by mean of high-energy ball milling, followed by cold isostatic pressing under 1000 MPa and then sintering at 900 °C for 12 h. The results illustrated that the Ti/ZrO_2 and Ti/Al_2O_3 biocermets possessed improved microstructure and mechanical properties under suitable process parameters during isotactic pressing, and the incorporation of Ti was helpful for the mechanical stability of m-ZrO_2.

Spark plasma sintering

Spark plasma sintering, as a new sintering technique, employs electric current to produce discharge plasma among powder particles for sintering; at the same time, it facilitates the densification process by imposing pressure on both ends of the powder. Compared with traditional sintering, this method enjoys fast heating rate, low sintering temperature and short holding time [130]. Therefore, it is believed to have great potential to be applied in biocermets fabrication and has earned increasingly more attention over past few years. Many studies applied the spark plasma sintering to develop a series of ceramic-based biocermets (such as ZrO_2–Ti [52], Al_2O_3–Ti [38], and TCP-Fe [74], etc.) by incorporating metal reinforcements into bioceramics, in order to combine excellent mechanical properties with biological functions.

Smirnov et al. [81] prepared ZrO_2-Al_2O_3-Ta biocermets with high fracture toughness and elastic modulus by using spark plasma sintering at 1400 °C under a vacuum pressure of 80 MPa. Before sintering, the ZrO_2 and Al_2O_3 nanoparticles were produced by CO_2 laser co-vaporization and then mixed with Ta particles by means of wet milling. Wei et al. [10] prepared HA-Nb/HA-Nb–Ag biocermets by spark plasma sintering combined with ball millling. As presented in Fig. 7, the incorporation of Nb or Nb–Ag

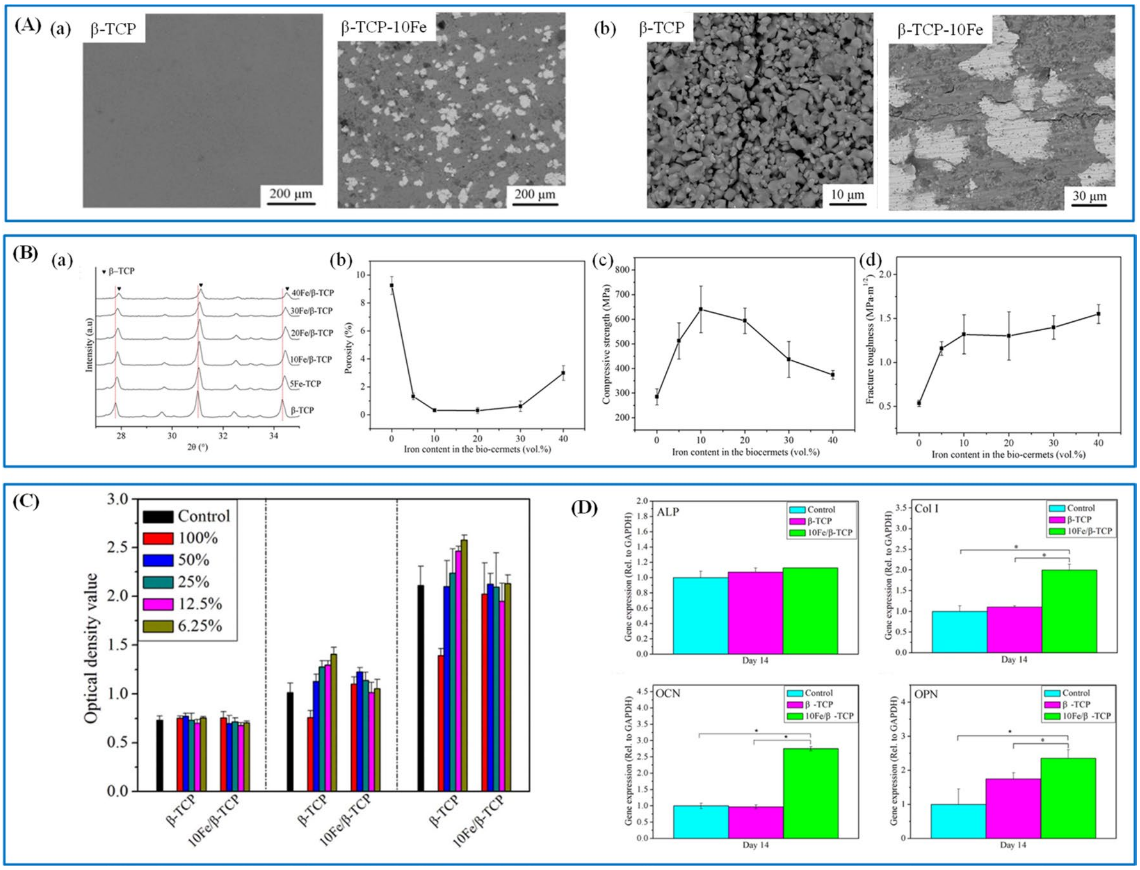


Fig. 6 Characteristics of β-TCP-Fe biocermets for load-bearing area prepared by cold isostatic pressing. **A** SEM images of surface (a) and indentation crack paths (b) of β-TCP bioceramic and β-TCP-Fe biocermets; **B** XRD patterns (a), porosity (b), compressive strength (c) and fracture toughness (d) of β-TCP bioceramic and β-TCP-Fe biocermets; **C** cell proliferation (a) of mBMSCs incubated in the extracts of β-TCP bioceramic and β-TCP-Fe biocermets with different concentrations; **D** bone-related gene expression: alkaline phosphatase (ALP), collagen type I (Col I), osteocalcin (OCN) and osteopontin (OPN)) of mBMSCs cultured in the extracts of β-TCP bioceramic and β-TCP-Fe biocermets for 14 days [128]

could effectively enhance the mechanical strength and fracture toughness to pure HA. The in vitro and in vivo results revealed that the incorporation of Nb could promote osteoblast proliferation, as well as osteogenic differentiation and osteointegration ability of the biocermets. And the addition of Ag could remarkably increase the antibacterial activity of HA-Nb-Ag biocermets compared to HA. Besides, Ulum et al. [93] incorporated bioactive ceramics (HA, TCP or HA-TCP) into Fe by spark plasma sintering to ameliorate the degradation and enhance the biological performance of Fe. Similarly, Guo et al. [131] reported Mg-based biocermets with improved degradation and bioactivity. Moreover, Prakash et al. [132] fabricated Mg–Zn–Mn-HA by using mechanical alloying and spark plasma sintering. The XRD pattern analysis confirmed the formation of MgCaO, β-TCP, Mn–CaO and Ca–Mg–Zn phases, which reduced the degradation rate from 1.98 for Mg alloy to 0.97 mm/year for Mg–Zn–Mn-HA. Moreover, the addition of HA also refined the grains and improved porosity of the Mg-based biocermets, which favored osseointegration.

Selective laser sintering/melting

Additive manufacturing (AM), also known as three-dimensional printing, has appeared recently as an environment-friendly manufacturing technology which churns out enormous benefits, including energy saving, less material consumption and efficient production [133]. As representative AM technologies, selective laser sintering (SLS) and selective laser melting (SLM) have been extensively explored in the fabrication of biomaterials with complex geometric structures over decades [134]. These processes integrate laser, computer, numerical control, protective atmosphere and powder materials, etc., achieving layer-by-layer manufacturing by deposition methods. The main difference between SLM and SLS is the bonding process between powder particles. SLM boasts complete melting and solidification of powder, while SLS sinters powder particles by surface fusing or requires a binder to bond the particles [135]. On the one hand, SLM and SLS can fabricate personalized implants similar to nature bone in the defect site, according to the predefined external shape and internal

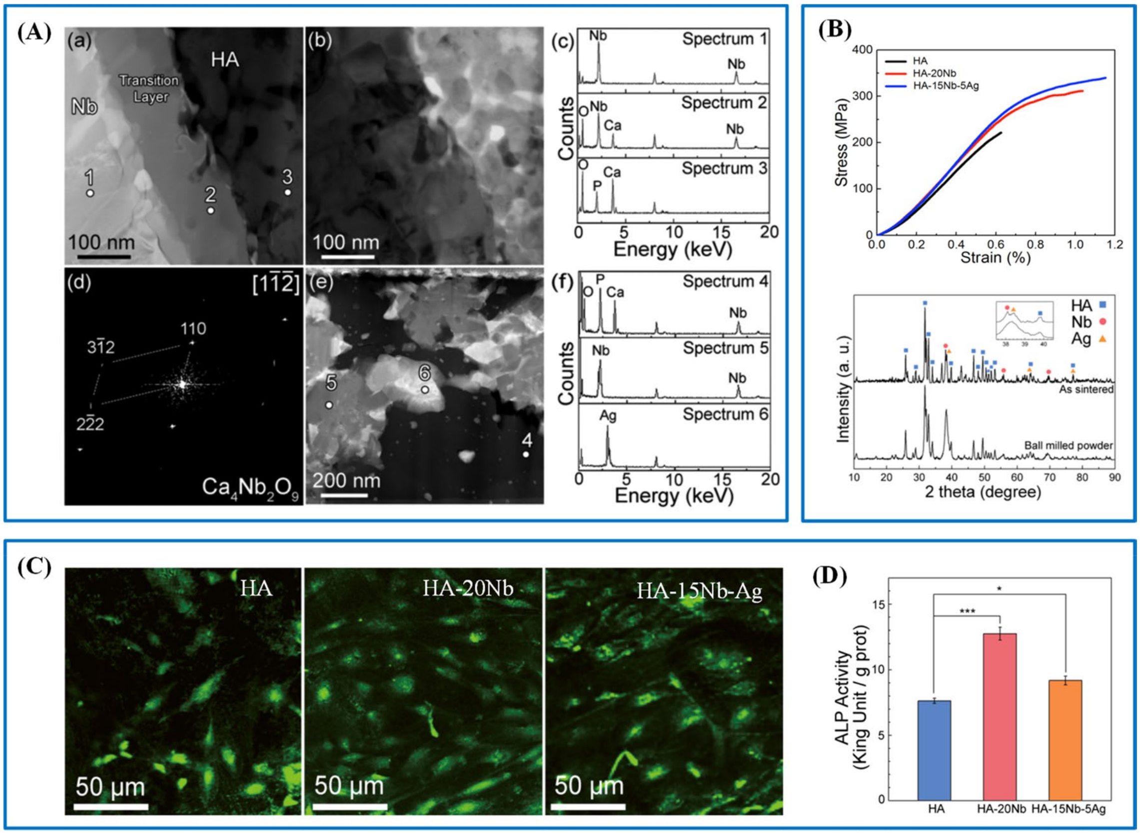


Fig. 7 Microstructure and performance of HA–Nb and HA–Nb–Ag biocermets fabricated by spark plasma sintering. **A** Transmission electron microscopy (TEM) images (a, b) and selected area electron diffraction (SAED) patterns (d) of the interface in HA–Nb biocermet, EDX spectra (c) corresponding to (a), TEM image (e) of HA–Nb–Ag biocermet and corresponding energy-dispersive X-ray (EDX) elementa spectra (f); **B** Compressive stress–strain (a) and XRD patterns of HA, HA–Nb and HA–Nb–Ag; **C** Fluorescent images and **D** ALP activity of osteoblastic MC3T3-E1 cells cultured on HA, HA–Nb and HA–Nb–Ag, respectively [10]

architecture. The interconnected porous structure can provide space for the in-growth of new bone, hence accelerating the osseointegration process [136]. On the other hand, the high energy laser makes an extremely high heating rate and a short holding time, which can further shorten the processing time [137]. This feature is able to reduce the structural change of ceramic phases at high temperature. In addition, the rapid melting and solidification process can improve the microstructural and mechanical properties of metals [102]. Hence, SLS and SLM have great advantages and potential in combining metals with ceramics to fabricate biocermets.

Our recent studies focus on the use of SLS or SLM to fabricate biocermets for orthopedic applications, such as Mg-mesoporous silica (MS) [138], Mg-β-TCP [139], Mg–Zn-HA [140], Zn–SiC [120], Fe–Mg_2Si [138] and so on. Concretely, we introduced MS into Mg alloy by using SLM to improve the degradation behavior. It was observed that the reinforcement (MS) was evenly distributed in the matrix with ideal interface bonding. MS was chemical inert against Mg and shifted the corrosion potential positively, thus enhancing the corrosion resistance of Mg [125]. Moreover, MS promoted the biocompatibility and the deposition of apatite on the biocermets. In addition, we fabricated Fe–Pd-bredigite ($Ca_7MgSi_4O_{16}$) biocermet via SLM to ameliorate the degradability r and bioactivity of Fe (Fig. 8) [141]. It was observed that a fine microstructure was obtained within the biocermet with a nearly continuous Pd-rich intermetallic phases and bredigite phase homogeneously distributed at the grain boundaries of Fe matrix, which could be ascribed to the rapid melting/solidification of SLM. As a result, the degradation of Fe was significantly accelerated due to the efficient micro-galvanic corrosion between Pd-rich intermetallic phases and Fe matrix, as well as the facilitated penetration of corrosion medium via bredigite dissolution. Moreover, the developed Fe–Pd-bredigite biocermet also featured improved bioactivity, cytocompatibility and suitable mechanical properties as the native bone.

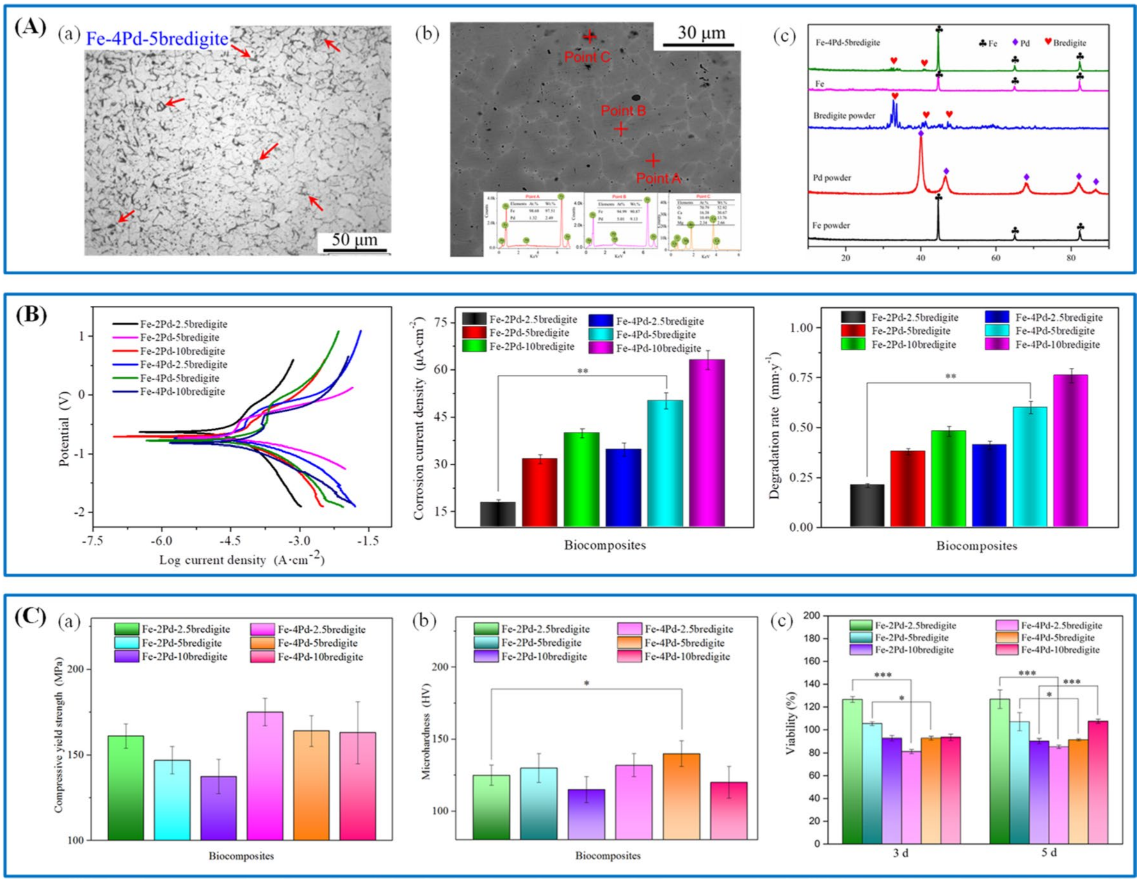


Fig. 8 Microstructure and properties of Fe–Pd-bredigite biocermets prepared by selective laser melting. **A** Optical micrograph (a), SEM image (b) and XRD patterns (c) of Fe–Pd-bredigite biocermets; **B** Potentiodynamic polarization curves, corrosion current densities and degradation rates of Fe–Pd-bredigite biocermets by electrochemical measurements; **C** Compressive yield strength (a) and microhardness (b) of Fe–Pd-bredigite biocermets, as well as cell viability (c) of MG-63 cells cultured in the extracts of Fe–Pd-bredigite biocermets [141]

Methods and mechanisms for interfacial reinforcement

The interface of biocermets is a "bridge" between the matrix and the reinforcements. When a load is applied to biocermets, the interface transfers the load from the matrix to the reinforcements. Hence, interface characteristics is crucial to the mechanical properties of biocermets, and a good interface is conducive to the strengthening effect of reinforcing phase [53]. Therefore, it is of great significance to reveal the bonding mechanism and influencing factors of the phase interfaces, thereby controlling the interface structure, and improving the properties and stability of biocermets.

Main factors for interface bonding

The important factors for interface bonding mainly include the wettability, thermal expansion difference and chemical compatibility of each component in biocermets. [142–144]. As mentioned above, liquid-phase sintering is a preferable process for the preparation of biocermets owing to its superiority in the densification process and the resulting density [145]. In the process of liquid-phase sintering, the morphology and characteristics of phase interface are closely related to the surface properties of the solid and liquid phases. When the solid and liquid phases are in equilibrium, it conforms to the following formula [146–148]:

$$R_{SS} = 2R_{SL} \cdot \cos \varphi/2$$

where φ wetting angle between the solid and liquid phases, R_{SS} the solid–solid interface energy, R_{SL} the solid–liquid interface energy.

Therefore, the ratio of solid–solid interface energy to solid–liquid interface energy determines the wetting angle (φ), i.e., the distribution of liquid phase at the interface. It is widely accepted that the φ should be $< 90°$ to achieve persistent liquid-phase sintering. In this condition, the liquid phase could partially or completely wet the solid phase and penetrate into the micropores and cracks of matrix, even at grain boundary. Moreover, the liquid phase may distribute in different states when the φ changes. It would be very beneficial for the densification of biocermets if the liquid phase evenly wets the solid phase and capillary pressure is formed during sintering. If $\varphi > 90°$, the components with low melting point would turn into liquid phase immediately at the beginning of sintering and exude the sintering zone rapidly, resulting in the loss of the liquid phase and thereby poor densification process [149–154]. Therefore, the surface wettability of liquid phase on solid phase is one of the key factors for the densification, microstructure and performances of biocermets. In a biocermet, the wettability between metal phase and ceramic phase is usually poor, which may lead to the limited addition and reinforcing of reinforcements in the matrix.

In addition, there are always large differences in the thermal expansion coefficients between metal phase and ceramic phase, which also easily leads to a poor bonding at the phase interfaces during the heating and cooling process [154–157]. For example, Lu et al. [158] observed holes in the two-phase interface of sintered $A1_2O_3$/nickel (Ni) cermet due to the different thermal expansion coefficients of Ni and $A1_2O_3$, which could reduce the interface bonding force and adversely affected the mechanical properties of the cermet. Moreover, chemical reactions are easy to occur in the interface of solid and liquid phases during the preparation process. Thus, the chemical compatibility of metal phase and ceramic phase should be considered in the design and preparation of biocermets, which plays a vital role in the interface bonding strength to ensure the effectively reinforcing and toughening of biocermets.

Considering these important factors, the main methods for improving interface bonding include surface modification, interface phase introduction and in situ reaction, etc.

Surface modification

Surface modification refers to changing the surface properties of metals or ceramics through physical methods or chemical methods, thereby improving the interface interaction in biocermets. These surface properties include surface energy, surface charge, wettability, surface chemistry and surface topography, etc. [159, 160].

Li et al. [161] investigated the influence of pre-oxidization treatment of SiC on the interfacial bonding and mechanical properties of Mg-SiC cermet. It was found that the surface oxide layer of SiC could improve the wettability between SiC and Mg alloy matrix. Moreover, a profitable $MgAl_2O_4$ layer was generated at the interface with appropriate pre-oxidation parameters, leading to strong interface bonding by chemical bonding. As a consequence, the yield strength and ultimate tensile strength were increased by 24.4% and 8.0%, respectively, compared with those of without pre-oxidization treatment. Besides, surface metallization of ceramics has also gained lots of interests due to it able to improve wettability by altering the surface properties. Ru et al. [162, 163] prepared Al_2O_3–ZrO_2 with Ni–Cr coatings by using electroless plating and then induced into high-Mn steel. It was found that the surface metallization of Al_2O_3–ZrO_2 can improve the wettability between the ceramics reinforcement and metal matrix. Thus, the interfacial bonding strength significantly enhanced due to the diffusion of metal elements between ZrO_2-Al_2O_3 ceramic composite and metal matrix as well as the formation of interface layer. Zhang et al. [164] reported that the surface metallization of ceramic with

Ni–Cu coating not only improved the wettability between ceramic and metal phases, but also endowed the interface with the unique corrosion and wear resistance of Ni–Cu.

In situ reaction

In situ reaction refers to a series of chemical reactions taking place at the interface between reinforcement and matrix during the preparation process. Generally, the degree of interface reaction and the formation of interface products have a great influence on the microstructure and properties of the biocermets. Appropriate interface products can improve the wettability and form a strong chemical bonding between the reinforcement and matrix [165].

Recently, many efforts were devoted to enhance interface bonding of biocermets by in situ reaction. Wei et al. [10] fabricated Nb-reinforced HA biocermets. It was observed that when Nb was incorporated into HA, a strong interface bonding could be developed between the matrix and Nb since a nanothick $Ca_4Nb_2O_9$ interface layer is formed. As the in situ reaction boosted interface bonding strength, the HA-Nb biocermets registered higher compressive strength and fracture toughness than that of HA (Fig. 7). Ghasalia et al. [110] reported that the incorporation of Al_2O_3 or Si_3N_4 could adjust the biodegradability and bioactivity of Mg. For Mg–Al_2O_3 biocermets, the interface product (MgO) distributed at the grain boundary with strong interfacial bonding and acted as a protective layer to hinder the corrosion of Mg matrix in body fluid. For Mg-Si_3N_4 biocermets, the interface products (Mg_2Si, Si and Mg_3N_2) could promote the formation of apatite phase on the surface of Mg matrix, thereby enhancing the bioactivity of Mg. Haiyan et al. [166] incorporated Ti_3AlC_2 into Zn alloy (ZA27) to enhance its mechanical properties. It was found that in situ reaction occurred at the interface between Ti_3AlC_2 and ZA27 due to the decomposition of Ti_3AlC_2, forming a strong interface bonding between the ceramic reinforcement and the metal matrix. Therefore, the tensile strength increased from 203 of ZA27 to 310 MPa of ZA27-Ti_3AlC_2 biocermets, and the bending strength of ZA27-Ti_3AlC_2 biocermets increased by 55% than Ti_3AlC_2. Similarly, our recently study reported Zn-based biocermet with strong interface bonding ascribed to the in situ reaction between the Zn alloys and Ti_2AlN [167]. Qia et al. [168] fabricated Ti_3SiC_2 and TiC reinforced Al_2O_3-based cermets by the in situ reaction between ceramics reinforcement and Ti matrix. The results revealed that the incorporation of SiC not only limited the generation of brittle Ti/Al intermetallic compounds, but also generated new ceramic reinforcements including Ti_3SiC_2, Ti_5Si_3 and TiC which were beneficial for the interface bonding. As a result, the Al_2O_3–Ti_3SiC_2–TiC biocermet had the optimal combination of density, microhardness, flexural strength and fracture toughness, etc. Specially, the fracture mode of the biocermet changed from the intergranular fracture to a mixed intergranular and transgranular fracture due to the toughening effect of Ti_3SiC_2. Shi et al. [78] prepared Ti-reinforced Al_2O_3 biocermet and observed some brittle intermetallic compounds (such as TiAl and $TiAl_3$) due to the interfacial reactions between Al_2O_3 and Ti at high sintering temperature, which decreased the mechanical properties of Al_2O_3–Ti biocermets. Thus, further study to optimize the interfacial structure was conducted by introducing Nb into Al_2O_3–Ti, and the results revealed that the formation of $AlNb_3$ prevented effectively the interfacial reaction between Al and Ti. The Al_2O_3–Ti–Nb biocermets exhibited higher bending strength and fracture toughness than those of Al_2O_3–Ti biocermet due to the ameliorative interfacial microstructure (Fig. 5).

Biological properties of biocermets

In addition to the mechanical properties, biological performances of the biocermets should be taking into account for their applications in bone implants. At present, there are mainly two methods for evaluating the biological performances of biomaterials. One is in vitro cell culture, in which biomaterials or their extracts are cultured with various cells to study the effects of biomaterials on cell growth, adhesion, proliferation and metabolism [169–171]. The other is in vivo experiment, in which biomaterial is implanted into an animal body, such as rabbit or mouse, and the implant and the surrounding tissue are taken out in stages to perform histological examination.

In vitro biological properties mainly include cytocompatibility, bioactivity, biodegradability, antibacterial activity and so on. Presently, many studies have proved that the incorporation of bioceramics into biomedical metals had a positive effect on cell behavior [172, 173]. For example, Guzman et al. [38] fabricated Al_2O_3–Ti biocermets and analyzed the response of pre-osteoblast cells to the biocermets, as shown in Fig. 9. They found that the proliferation and early-differentiation stages of pre-osteoblasts cells were considerably improved after the addition of Ti, which thereby improved the cytocompatibility of Al_2O_3. He et al. [128] evaluated cell activity of β-TCP-Fe biocermet by using mouse bone mesenchymal stem cells (mBMSCs), the result of showed that the biocermet was cytocompatible and bone-related gene expression of mBMSCs was up-regulated by the released Fe ions. In addition, Swain et al. [71] introduced Fe–Mg into β-TCP-based biocermets and evaluated the in vitro biological performances using osteoblast and endothelial cells. The results illustrated that β-TCP-Fe–Mg biocermets were biocompatible and demonstrated characteristic markers for bone formation and angiogenesis. The results illustrated that β-TCP-Fe–Mg biocermets were biocompatible

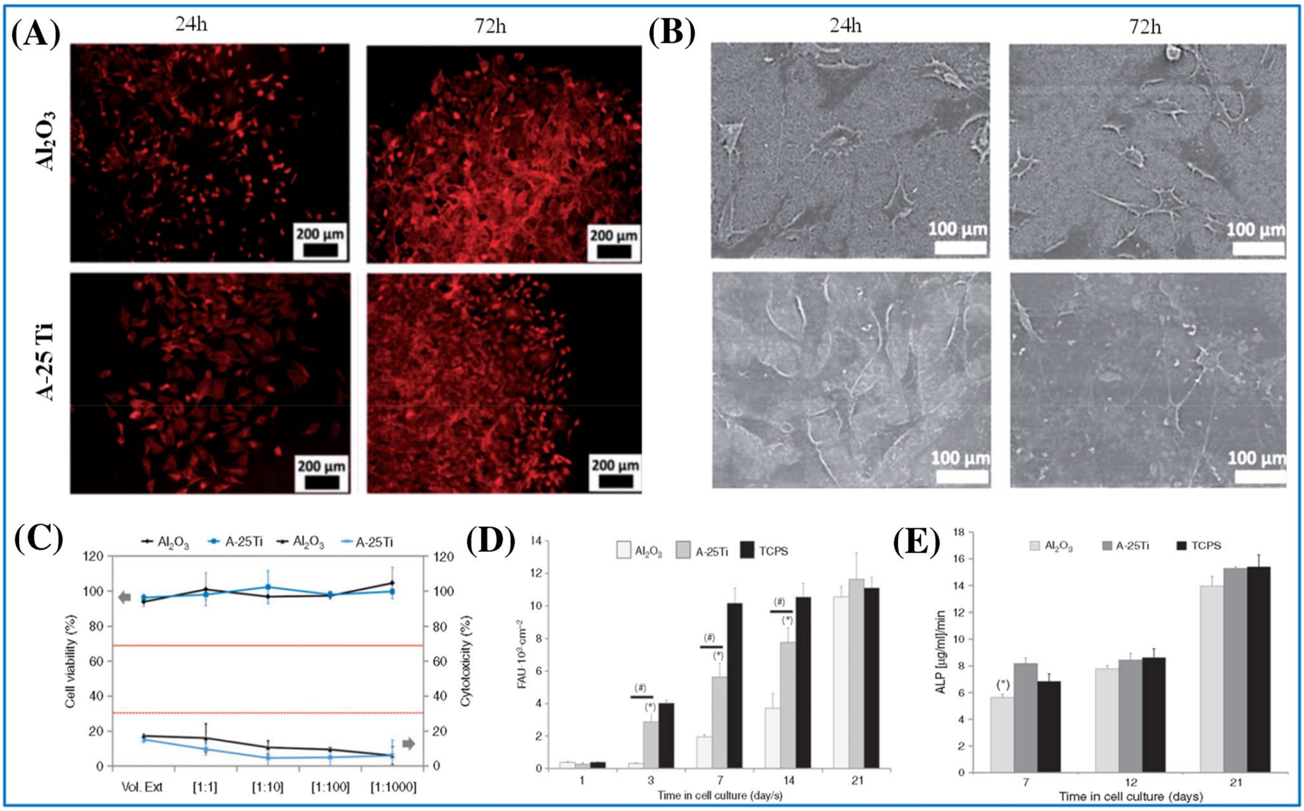


Fig. 9 In vitro biocompatibility assessment of Al_2O_3 bioceramic and Al_2O_3–Ti biocermets. Cell adhesion: **A** F-actin fluorescence images and **B** SEM images of mouse pre-osteoblast cells (MC-3T3) on Al_2O_3 bioceramic and Al_2O_3-25 vol% Ti (A-25Ti) biocermets; **C** Cell viability and cytotoxicity of MC-3T3 cells on Al_2O_3 bioceramic and A-25Ti biocermets; **D** Cell proliferation and **E** osteoblastic differentiation: ALP activity of MC-3T3 cells after cultivation on Al_2O_3, TCPS and A-25Ti biocermets for 7, 12, and 21 days [38]

and demonstrated characteristic markers for bone formation and angiogenesis. During the biodegradation, the bending strength of the β-TCP-Fe–Mg ceramic-based biocermets decreased which was ascribed to the increase in porosity. Furthermore, the biocermets presented a moderate loss (15%) in strength as compared with the significant drop (> 50%) in the polymer reinforced β-TCP. Moreover, Ulum et al. [93] prepared Fe-based biocermets (Fe-HA, Fe-TCP and Fe-HA-TCP) by mechanical mixing and sintering process and evaluated the biological performances in vitro by using rat smooth muscle cells. The result showed that the Fe-based biocermets had higher cell viability and cell proliferation than pure Fe. Besides, bioceramics lowered the corrosion potential and then accelerated the degradation of the Fe-based biocermets compared with pure Fe. Similarly, Wang et al. [95] prepared Fe-CS biocermets and demonstrated that incorporating bioactive bioceramics could improve the in vitro biodegradation rate and bioactivity of pure Fe.

In vivo biological properties mainly include histocompatibility, bioactivity and bone regeneration capacity, etc. The most commonly used methods include radiography, microcomputed tomography and histological staining, etc. [169]. Bartolomé et al. [11] reported that the ZrO_2–Nb biocermets had improved in vivo biocompatibility and osteoconductivity in the tibiae of rabbits after 24 weeks. Moreover, the histological analysis showed that the ZrO_2–Nb biocermets could directly contact with newborn bone tissues to achieve full osseointegration, which might be attributed to the improved bioactivity of the ZrO_2–Nb biocermets via the generation of Nb-OH groups at the interfaces. Chu et al. [174] studied the in vivo biological properties of HA-based biocermets with 20–40 vol% Ti by implantation in rabbit skull. From histological analysis, the biocermets not only showed good biocompatibility, but also bonded directly with new bone tissues at 4 weeks and fully osseointegrated at 8 weeks, demonstrating better osteointegration ability than Ti due to the bioactivity of HA. Consequently, the bonding strength between the biocermets and bone tissues increased with the implanted time. After 12 weeks' degradation in vivo, the fracture surface morphology of the HA-Ti biocermets showed shear fracture occurred in newborn bone tissues zones, implying the bonding strength between the biocermets and newborn bone tissues might be higher than the shear strength of the newborn bone tissues. Li et al. [73] prepared TCP-Zn biocermets and evaluated the biological performances in rabbit's femur at 4-week post-surgery by histologic measurements. The results illustrated an increased amount of new bone formation and active osteoblasts of TCP-Zn biocermets compared to pure TCP, because the released Zn ions had positive effects on bone formation. However, it was worth noting that a high amount of Zn caused an inflammatory tissue response. Ulum et al. [175] implanted Fe-HA, Fe-TCP and Fe-HA-TCP biocermets into the leg defect sites of sheep to investigate their in vivo biological properties, and the results showed that these Fe-based biocermets possessed better bioactivity and biodegradation behavior than Fe. Besides, they found that the density of these Fe-based biocermets decreased with increasing implantation period because of gradual degradation [60], which might influence the mechanical stability of the biocermets. A recent study by Yang et al. [119] reported that Zn-HA biocermets exhibited improved in vivo biocompatibility and adjustable degradation rates in the rat femur condyle defect site after 4–8 weeks (Fig. 10). As evidenced by the computer radiographs, degradation products analysis and histological analysis, the Zn-HA biocermets not only showed a better osteogenesis performance at 8 week compared to pure Zn owing to the combined promotion effects of Zn and HA, but also accelerated degradation and localized corrosion by introducing HA. Furthermore, the element of Zn can stimulate osteoblast proliferation and differentiation and promote bone formation and mineralization. To date, in vivo studies mainly focused on the biological properties and degradation behavior of biocermets. However, as for biodegradable implants, it should be noted that the structural integrity of the biocermets might alter due to the dynamic degradation under complex in vivo microenvironment, thereby leading to a variation of the mechanical performance. Therefore, more in vivo research is needed to explore the degradation behavior of biocermets and the resulting effects on the mechanical properties to ensure their feasibility for bone implant applications.

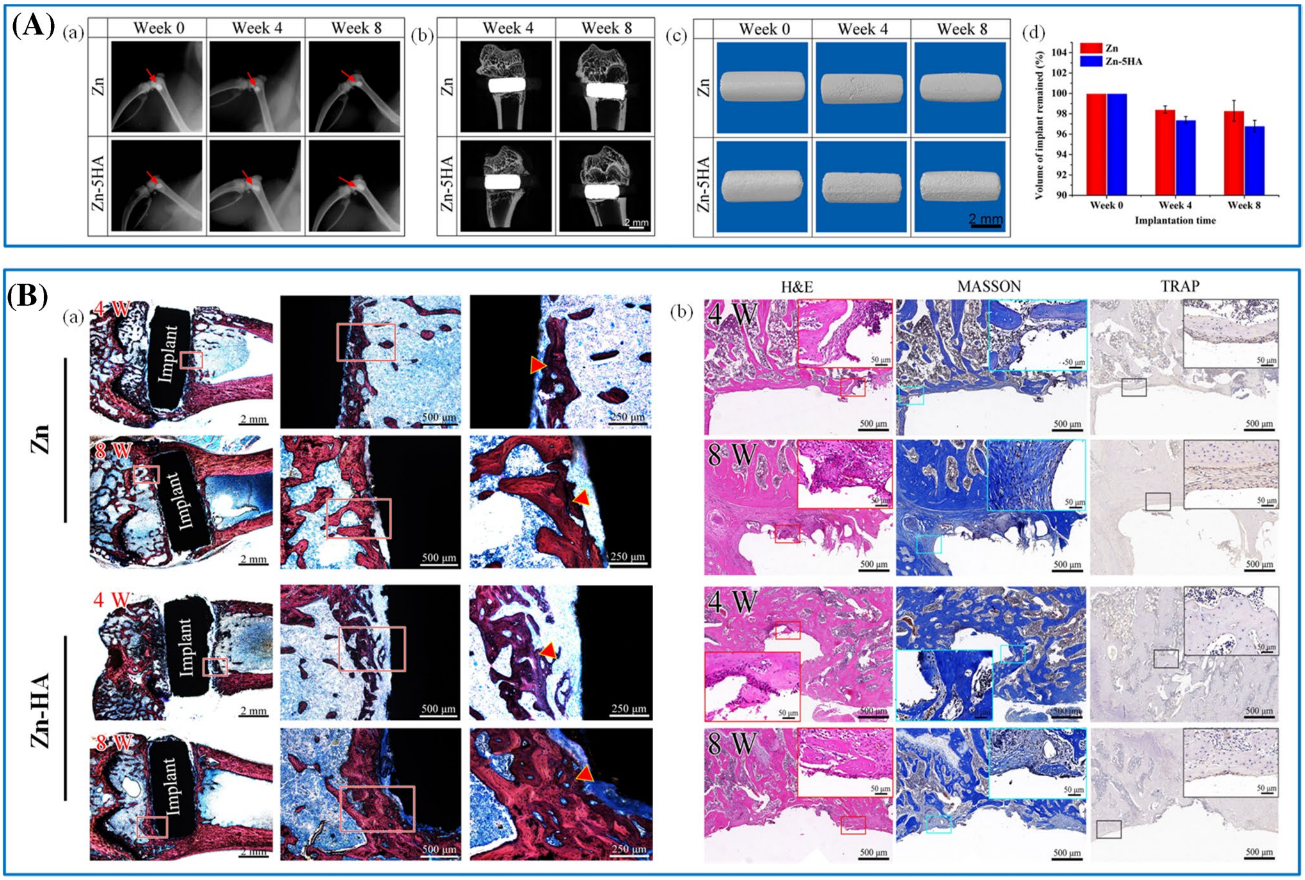


Fig. 10 In vivo biological properties of Zn and Zn-HA biocermets implant. **A** Micro-CT analysis of femoral condyle containing Zn and Zn-HA implants: Radiographs (a), micro-CT reconstruction images (b), 3D reconstruction models (c) and volume change of metallic part of implants (d); **B** Histological characterization of hard tissue sections at implant sites: Van Gieson staining (a), Hematoxylin & eosin (H&E), Masson's trichrome and Tartrate-resistant acid phosphatase (TRAP) staining (b) of Zn and Zn-HA biocermets after 4 and 8 weeks' implantation [119]

Conclusions

In recent years, biocomposites have been extensively studied to develop multifunctional biomaterials for orthopedic applications. Biocermets can be an promising way to combine the advantages of bioceramics and biomedical metals. Although the current researches have shown that biocermets can improve the mechanical properties and/or biological performance of the single-component bioceramics and biomedical metals, some challenges still lay ahead to be solved in future study:

(1) Multiple combinations of biomedical metals and bioceramics to develop new multifunctional biocermets for bone implant applications.
(2) Adjustable mechanical properties and/or biological performance by controlling the proportion of each component in biocermets. At the same time, it is necessary to minimize the damage to the original properties of matrix when combining the complementary advantages of the biomedical metals and bioceramics.
(3) The interface characteristics of biocermets, including the interface microstructure, combination mechanism and influencing factors, as well as corresponding influences on the final properties, need to be further studied to achieve excellent comprehensive performance.
(4) Although numerous novel biocermets have been developed, less concern is placed on the forming mechanism and microstructure evolution. And the relationship between the preparation technology and the performance of biocermets should also be studied in-depth.
(5) More in vivo studies should be conducted to comprehensively evaluate the biological performance and dynamic mechanical properties of biocermets for the clinic applications in bone repair.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval This study does not contain any studies with human or animal subjects performed by any of the authors.

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