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Orthopedic implants and devices for bone fractures and defects: Past, present and perspective

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ABSTRACT

Bone is a unique tissue that is capable of repairing itself after damage. However, there are certain instances of fractures and defects that require clinical intervention for proper alignment and healing. As with any implant, careful consideration of the material used to create the implants to treat these problems is needed. If the incorrect material is chosen, the implants themselves can lead to bone fractures or defects, or bone healing may not take place at all. All three classes of biomaterials–metals, ceramics, and polymers–have been used in the treatment of both bone fractures and bone defects, and each has its own unique benefits and limitations for its applications. Furthermore, composites of these different materials have also been created to try to take advantage of all the different benefits offered by each different material. This review highlights different materials that have been used for the development of internal fixators and bone graft substitutes to treat fracture and bone defects as well as their limitations and needed future research.

1. Bone healing and bone implants

Bone is a dynamic tissue, undergoing constant remodeling, and in the case of an injury, bone has the potential to regenerate with restorations of its biological and mechanical properties prior to damage [1–3]. However, certain diseases, disorders, and trauma afflicting the skeletal system result in damage to the skeletal system. The resulting fractures and defects in the skeletal system can lead to an increase in mortality, with the extent of the mortality link being different for different bones [4–6]. The precise reason is unknown, but it is likely due to the associated comorbidities of the fractures or defects. Fractures and defects can be themselves the event leading to the need for an implant, or they can also be caused by the presence of an implant. Furthermore, bone is the most transplanted tissue in the human body, after blood [7,8]. Therefore, careful consideration in the design of orthopedic devices to properly treat trauma in the skeletal system while not harming the patient is important.

Orthopedic implants become necessary with severe fractures–that are in need of realignment and fixation for proper healing–or in cases when bone altogether fails to regenerate, producing bone defects. The design of these implants requires consideration of the material's biocompatibility, mechanical properties, and surface properties as well as its chemical properties and failure properties so that the implant closely parallels the biomechanical properties of bone and integrates with the native tissue while maintaining its integrity for the requisite duration. The cardinal requirements of bone tissue engineering can be summarized with the diamond concept, which provides four basic factors that are needed for successful bone healing with bone tissue engineering (Fig. **1A**): a healthy population of osteogenic cells to permit bone regrowth, growth factors to effectuate cellular events to promote healing, an osteoconductive scaffold conducive to bone growth, and a good mechanical environment to provide sufficient stability for healing while still mirroring the native tissue's mechanical properties [1]. Additionally, the patient and their history need to be taken into consideration, as the patient's history can consist of risk factors that increase their chances of fractures, fracture nonunions, or bone defects [9]. For example, a patient's age can have great connotations related to the skeletal system, as aging is related to higher fracture rates and reduced fracture healing and is also associated with conditions such as osteoporosis and osteoarthritis [10].

Another important consideration is the natural healing process of bone (Fig. **1B**) [11]. Implants should aim to take advantage of or, at the least, provide no impediments to the natural physiology of bone regeneration. Bone healing can occur either via indirect or direct healing. Indirect, or secondary, fracture healing is the natural healing process of bone and contains three phases that overlap temporally. It starts with an inflammatory, destructive phase lasting about a week that clears up the fracture site and gives rise to hematoma formation [2,3,12–14]. This is

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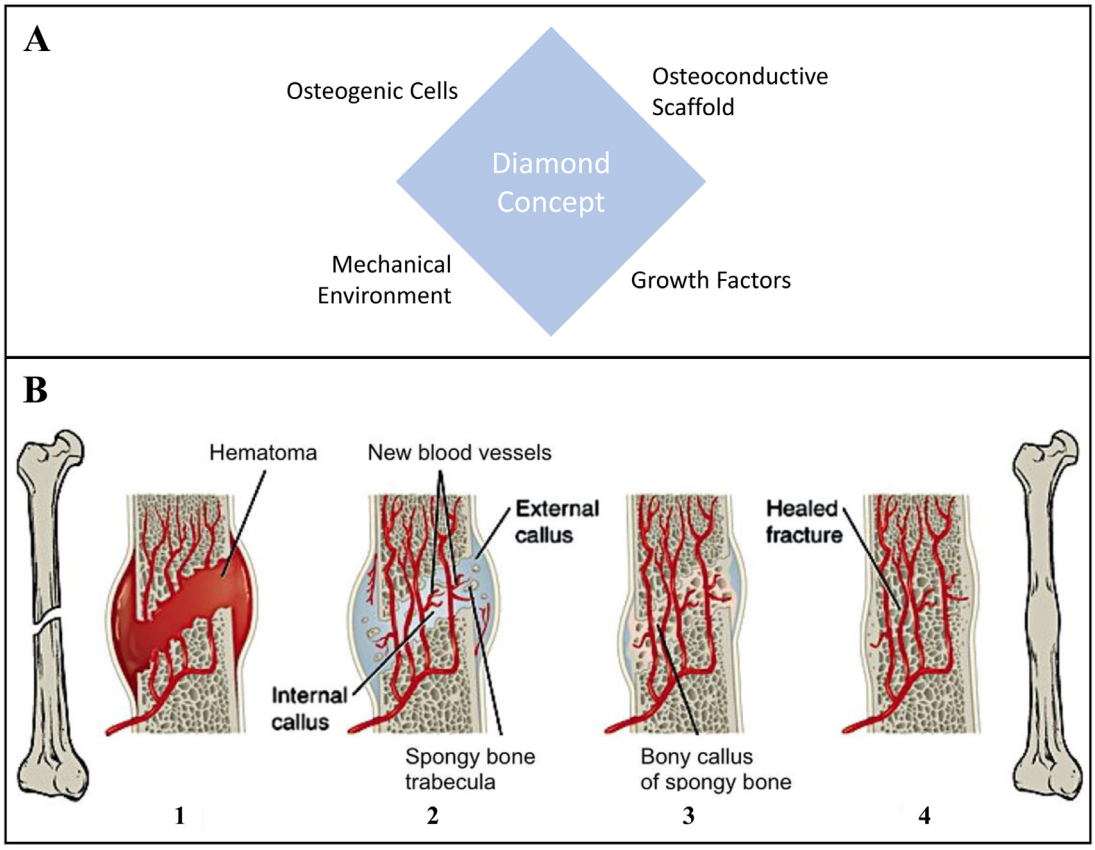


Fig. 1. (a) Diamond concept of bone healing [1]. (b) Natural healing process of bone: (1) hematoma formation, (2) soft callus formation, (3) hard callus formation, and (4) remodeling [11].

followed by a reparative phase starting about a week after and lasting until around the fourth week after the fracture in which a soft callus of cartilage is formed and subsequently replaced with a hard callus of bone formed either via intramembranous ossification or endochondral ossification, depending on the type of bone [2,3,14]. The final phase is the remodeling phase and can start as early as the third week after the fracture and can take years to complete, and this length of time is influenced by factors such as the type of fracture, the age of the patient, and other existent disease conditions [14]. The remodeling phase reestablishes the anatomy and physiology of the bone to the state it was prior to the fracture [2,3,15]. Direct, or primary, healing only occurs when the fragments of the vascular bone surfaces are in contact and therefore only occurs as a result of rigid fixation [15]. It follows the same process as indirect bone healing but bypasses the formation of the callus, since the vascular bone surfaces are already in contact [14,16].

The mechanism for bone healing with an implant is similar to that of bone healing without an implant. The bone formed around the implant acts as stabilization for the implant, and this bone formation is highly dependent on the surface chemistry and topography of the implant [17]. Upon implantation, the bone formation surrounding the implant increases greatly [18–20]. When implants are placed in the body, blood is among one of the first tissue to come in contact with them, leading to the arrival and activation of platelets on the implant surface as well as a concurrent inflammatory response produced by neutrophils and macrophages that ultimately leads to hematoma formation [17]. Together, these platelets and leukocytes create an environment that ultimately result in the recruitment of mesenchymal stem cells (MSCs) to the surface of the implant, and in a process known as contact osteogenesis, the mesenchymal stem cells differentiate into osteoblasts and begin to lay down new bone in the direction of the bone edges [17,21]. Bone growth also occurs in the opposite direction, from the edges of the bone towards the implant, in a process known as distance osteogenesis [17]. Contact osteogenesis and distance osteogenesis both result in the formation of immature woven bone, filling the gaps between the bone and implant [17,21]. Remodeling of the peri-implant bone replaces the immature bone with mature bone, enhancing the bonding between the bone and the implant [17]. As remodeling constantly takes place, the connections between the bone and the implant would ideally remain secure; however, in instances when the peri-implant bone does not sufficiently get stimulated, such as from disuse of the bone or stress shielding by the implant, the peri-implant bone can degrade and lead to implant failure.

This review will discuss the biomaterials used, the properties of, and the limitations of the most common types of orthopedic devices used for the treatment of fractures and bone defects as well as the perspectives on future development of innovative bone implants and devices.

2. Fracture fixation materials and devices

The goals in the treatment of fractures is the reduction of the fracture–or an alignment of the fractured fragments–and the preservation of the reduction through immobilization [2]. The reduction can be achieved surgically or with outward manipulations of the bone, and the immobilization is achieved with fixation, either external or internal. Depending on the nature of the treatment, the healing process of the fracture differs. Treatments that fix fractures so that there are still minor movements of the bone undergo indirect or secondary fracture healing while treatments that rigidly fix fractures and result in direct contact of the vascular bone surfaces undergo direct or primary healing [15].

External fixation is used to stabilize a bone or joint by orthopedic surgeons during reconstruction, with pins or wires placed percutaneously

Table 1
Different internal fixators used for different fracture sites and types [27].

Fracture Site		Internal Fixators
Head	Skull Fracture	Wires, pins, and plates
	Craniofacial Fracture	Wires, screws, and plates
Trunk	Clavicle Fracture	Intramedullary nails and plates
	Scapular Fracture	Screws and plates
	Pelvic Fracture	Screws, plates, and external fixators
	Spinal Fracture	Fixation device consists of rods, pedicle screws, and plates
Upper Limb Fracture	Humeral Fracture	Open reduction with plate and screws
	Radius, Ulnar Fracture	Close reduction with intramedullary nail
	Metacarpal and Phalangeal Fracture	Open reduction with plate and screws
		Close reduction with intramedullary nail
		Open reduction with intramedullary nail, screws and plates
		Close reduction with external fixators
Lower Limb Fracture	Femoral Fracture	Open reduction with plate and screws
	Tibial and Fibular Fracture	Close reduction with intramedullary nail
	Metatarsus Fracture	Open reduction with plate and screws and intramedullary nails
	Calcaneal Fracture	Open reduction with plate and screws and intramedullary nails
		Close reduction with screws or wires

[22,23]. Compared to internal fixation, external fixation offers minimal soft tissue damage and invasiveness, which can be especially beneficial for instances of acute trauma, and the placement of external fixators can easily be adjusted after fixation whereas the same cannot be done with internal fixators. However, external fixators have limitations to their use, such as a restriction in limb movement. Additionally, external fixation treatments of fractures results in higher rates of malunions and nonunions and comparatively poorer outcomes than internal fixation [24,25]. Therefore, external fixators are only used as temporary treatments in patients who are not yet able or are unable to undergo surgery.

Internal fixation is accomplished with surgical implantation of fixtures to hold together the fracture fragments. These include plates, screws, nails, rods, wires, and pins, and different methods and internal fixators are used depending on the fracture site and type (**Table 1**) [26,27]. Bone plates are the most common internal fixation implants used for fixating fractures [28]. They are attached to bone fragments with screws and function to reduce the fracture and prevent any movement, while also shielding the fracture site from stress to allow healing. Screws can also be inserted into bone fragments independently to reduce the fracture and fixate the fracture fragments. Bone plates and screws are conventionally composed of bioinert materials, such as stainless steel and titanium, rather than bioactive materials, as bonding of the bone with the plate is undesirable in the case of plate removal or corrective surgeries [29]. Bone is normally exposed to cyclic loading conditions; therefore, bone plates should have a sufficiently high fatigue resistance in addition to having a high stiffness to shield the fracture site from stress. Bone healing with plates takes about one to two years; thereafter, they can be removed or left in the body.

Biomaterials used for internal fracture fixation are confined to those that are able to withstand cyclic loads, allowing for the intrinsic functionality of the skeletal system. Metals, polymers, and ceramics have all been used as orthopedic biomaterials, but metals supply the most desirable properties that are needed [30]. Furthermore, metals are the most common class of biomaterials used for fracture fixation, owing to their mechanical properties that lend to the stabilization required; although, polymers and ceramics have also been used to fixate fractures. The three most common metals used as biomaterials are titanium alloys, cobalt-chromium alloys, and stainless steel [30]. Of these, titanium alloys and electropolished stainless steel are most commonly used for fracture fixation, as the cobalt-chromium alloys are more difficult to fabricate and have a high production cost [31,32].

2.1. Metals

Both titanium and its alloys and stainless steel can be manufactured under different conditions to produce different mechanical properties for different orthopedic applications [32]. Despite these tunable qualities, stainless steel is stiffer, denser, and more ductile and has a greater elastic modulus and yield strength than titanium [32]. Meanwhile, titanium has a greater maximum torque and greater fatigue resistance [32]. Additionally, the intrinsically microrough structure of titanium provides a surface allowing for osseointegration whereas electropolished stainless steel does not [32]. The magnetism of stainless steel produces distortions in imaging while titanium does not. Titanium has a thicker oxide layer and regenerates its oxide layer faster than stainless steel, which altogether means titanium implants are better protected from corrosion by the body. Additionally, the metal ions that are released with corrosion from stainless steel have been seen to have greater negative health effects than titanium alloys [32–34]. The thickness and regeneration rate of the protective oxide layer coupled with the corrosion products of the metals indicate that titanium alloy implants are better at minimizing metal debris toxicity.

The high axial stiffness of metals can produce an excessive stress-shielding effect on the unfractured segments of the long bone, leading to overall bone resorption [29]. This outcome is seen to a lesser extent with titanium because it is less stiff than stainless steel. Hypothetically, the stress shielding could be reduced by decreasing the thickness of the bone plates, which would decrease the axial stiffness of the plates, but this would also decrease the stiffness of the plates in other directions as well as decreasing the fatigue resistance. Therefore, Ramakrishna et al. proposed a stiffness-graded plate with the greatest elastic modulus at the center of the plate, in line with the fracture, and a linear decrease in elastic modulus towards both ends of the plate [35]. Similarly, Ganesh et al. proposed the use of stiffness-graded plates with the elastic modulus varied along either the axial axis or the transverse axis of the plate [29]. These stiffness-graded plates showed promise in addressing the issues of stress shielding with bone plates; however, the manufacture of plates that have a graded elastic modulus along their lengths would not be easily achieved. A solution to this was suggested by Fice & Chandrashekar by creating a gradation in the geometry of the plate along the length of the plates to introduce a gradation in the stiffness of the plates [36].

2.2. Polymers

Polymer based composite materials have a greater fatigue resistance than other materials, in addition to having a high strength and low stiffness [37,38]. Clinical trials with unidirectional laminate composites of carbon fiber reinforced epoxy resin showed that polymeric composites are potentially viable options for fracture fixation [39–41]. Saidpour performed a finite element analysis of a composite bone plate composed of short carbon fibre reinforced plastic and found that it would be able

to lessen the influence of stress shielding effects [42]. A potential issue with the smaller elastic modulus offered by composite materials is it results in the need of a greater thickness for the desirable stiffness. In order to address this, Fujihara et al. created composite bone plates composed of biocompatible thermoplastic polyether ether ketone (PEEK) and carbon fibers as reinforcement that were braided together to form a single layer, and these layers were placed on top of each other and pressed together to create the plates [43]. This braided plate allowed for a thinner plate with greater stiffness than other composite plates, such as unidirectional laminates or discontinuous short fibers [44].

A few studies have also considered hybrid composites bone plates that offer advantages, such as more balanced mechanical and thermal properties and improved fatigue resistance, over conventional composites [45]. Therefore, Bagheri et al. designed a hybrid composite with a flax/epoxy composite sandwiched between carbon fiber/epoxy composites, which was further optimized by Samiezadeh et al. [46–49]. Similarly, Manteghi et al. investigated a hybrid composite composed of a flax/epoxy composite sandwiched between glass/epoxy composites [50]. The sandwich structure provided a more flexible core surrounded by stiffer sheets that created more ideal conditions for fixating bone fractures. These studies have only looked at the mechanical properties, and they have not looked at the overall biomechanical environment that the implants would be placed in. Therefore, though they show some promise, more studies in vivo need to be done to truly assess their potential.

2.3. Bioceramics

Bioceramics are a good material for bone tissue engineering because the mineral phase of the extracellular matrix (ECM) of bone is itself composed of hydroxyapatite, but bioceramics on their own are not widely used as internal fixation devices. Work has been done to potentially use pure ceramics for fixating anterior cruciate ligament (ACL) injuries [51–53]. Although they have properties that made them possible candidates, their brittle nature and high elastic modulus make them non-ideal for bone fracture fixation [54]. Composites composed of polymer and bioceramics have been developed for interference screws, which are mainly used for ACL fixation but can also be used for fracture fixations [55,56]. Dos Santos et al. has also proposed a composite biodegradable bone plate composed of PLGA microinjected with a calcium phosphate to improve the osseointegration of the bone and make up for the long degradation time of the PLGA plate, but this incorporation also influenced the thermal properties and reduced the maximum strength [57]. In general, bioceramics do not seem like an optimal material for bone fixation purposes.

2.4. Biodegradable materials

An ideal internal fixation device would be one that is biodegradable or, in other words, one that decreases in stiffness over time as the fracture heals and does not require a second surgery for removal. There are currently many commercially available biodegradable polymers used in fixation in craniofacial and maxillofacial applications [58]. For example, Inion CPS® implants are biodegradable polymers used for the fixation of craniofacial fractures that are composed of a combination of trimethylene carbonate, L-lactide, D, L-lactide, and polyglycolide, and they have a comparable performance to titanium (Fig. **2A**) [59,60]. Additionally, their degradation rate makes them acceptable for use [61]. Other examples of biodegradable internal fixators include the Synthes Rapidsorb® fixation implants and Zimmer Biomet LactoSorb®, both of which are composed of poly(lactic-co-glycolic acid) (PLGA) (Fig. **2B**) [62,63]. However, there are concerns over the insufficient mechanical properties for the load-bearing conditions they could be exposed to in other limbs, which would lead to the need for much thicker plates [64]. Altan et al. showed that biodegradable screws, both Inion and Rapidsorb, had a much lower elastic modulus and hardness than titanium screws (Fig. **2C**) [65]. In order to address this issue, Gaball et al. designed a biodegradable plate composed of poly(L-lactide-co-D,L-lactide) (P[L/DL]LA) using finite element modeling to optimize the geometry of the commercially available degradable polymer plate to produce mechanical properties comparable to titanium plates [64]. More research needs to be done before polymeric biodegradable fixators can be used to stabilize fractures in other parts of the body.

Magnesium is a biodegradable metal with good mechanical properties and is also the fourth most abundant element in the human body, mostly found in skeletal tissue and skeletal muscle tissue [27]. Furthermore, magnesium degradation has been shown to induce bone formation via a neuropeptide, Calcitonin Gene-Related Peptide (CGRP), released from the periosteum [66]. However, magnesium cannot be combined for use with other metals because it causes very fast degradation via electrolytic corrosion [67]. Additionally, it is not strong enough to fixate fractures on its own, and it degrades too rapidly. The rapid degradation rate is typically the result of its low purity and can be somewhat addressed with purifying, alloying, or surface modifications [27]. Magnesium alloy screws are approved for use in Germany and Korea but only for non-load-bearing applications [68,69]. However, Chaya et al. showed that pure magnesium plates and screws have potential for bone healing in load-bearing applications (Fig. **3A**) [70].

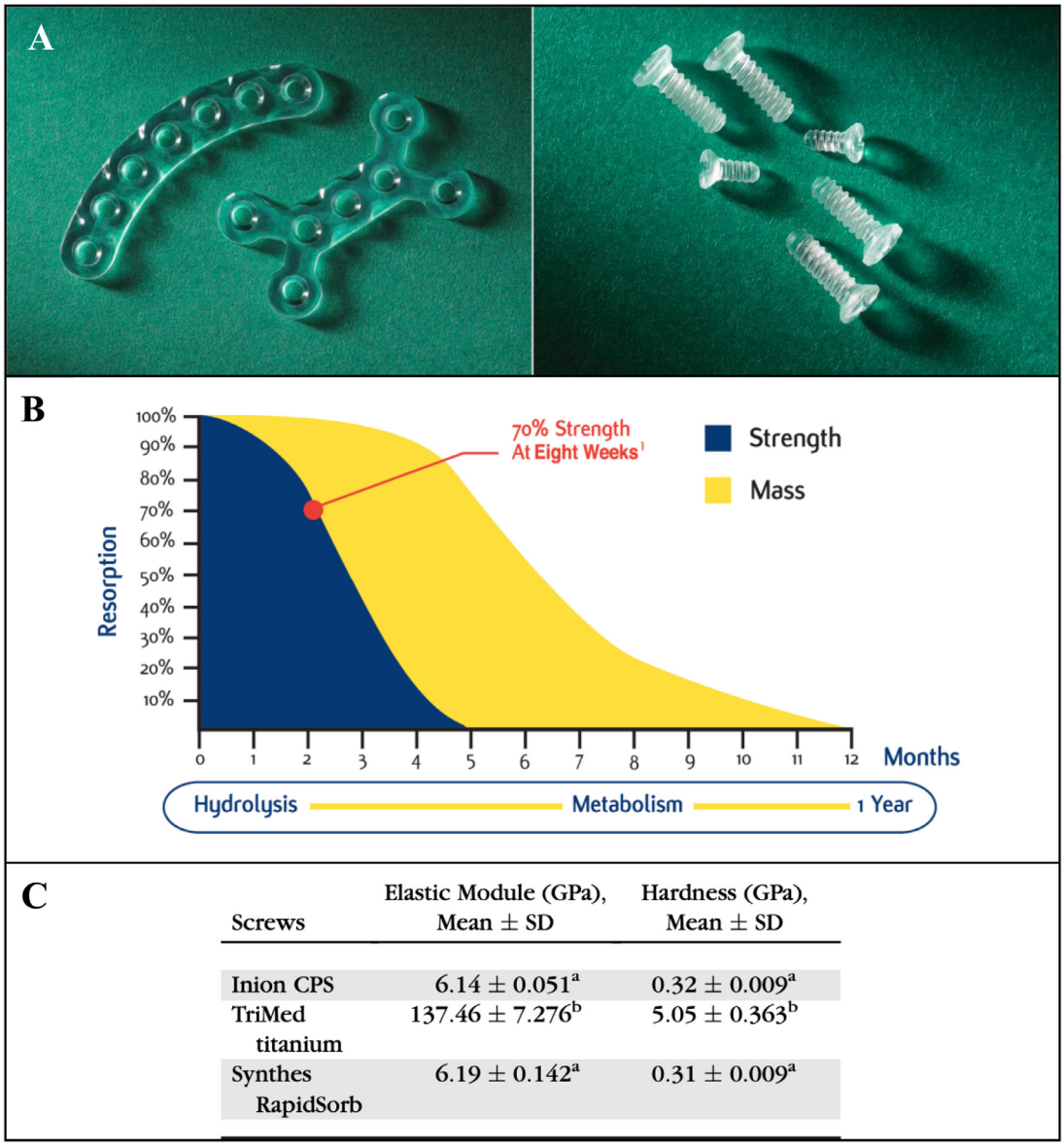
Magnesium has been incorporated in systems with other materials to make use of their degradability. For example, Tian et al. designed a hybrid metal system with magnesium and titanium, controlling the electrolytic corrosion with a polymeric coating on the surface of the magnesium, and the finite element model showed desirable results [27]. The fracture would be supported well with the titanium and initially by the magnesium, and the gradual degradation of the magnesium would help promote fracture healing (Fig. **3B**) [27]. Implant removal would still be needed with this design, but the chances of refracture and the effects of stress shielding would be lower.

A problem facing magnesium degradation in vivo is H_2 gas evolution, which is a byproduct of magnesium degradation, because there is a potential for emphysema, especially if the rate of degradation surpasses the absorption capacity of the surrounding tissue [71,72]. Schaller et al. addressed this by coating magnesium alloy bone plates with plasma electrolytic coating, which was able to lessen bursts of gas evolution [73]. This shows that this obstacle, like others faced by magnesium, can be addressed with surface modifications.

Zinc is another biodegradable metal that has potential applications in bone fixation. It is an essential trace element, and the byproducts of its degradation can stimulate osteoblasts for bone formation through the regulation of alkaline phosphatase (ALP) [74–76]. Pure zinc does not have sufficient mechanical strength for orthopedic applications, but this is easily remedied with alloying. Zinc alloys have good mechanical properties close to that of titanium and have the benefit of a more optimal degradation rate than magnesium [77,78]. Zinc has been studied to a much lesser extent than magnesium; thus, more studies need to be done overall concerning zinc for orthopedic fixation applications.

2.5. Smart materials

Smart materials are materials that have properties that respond to external stimuli, such as pH, temperature, and light. They are beneficial for use in bone fixation as they would make the implant easier to handle by the orthopedic surgeon and would be able to conform to the fracture requirements. For example, Eshghinejad et al. designed a pedicle screw used in spinal fusion surgery containing the shape memory alloy, nitinol, to expand and retract with temperature changes to allow an easy insertion and removal of the screw [79]. Similarly, Liu et al. developed a self-fastening and self-reinforcement screw composed of a triple-shape memory polymer, poly(lactic acid)-b-poly(lactide-co-



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Screws	Elastic Module (GPa), Mean ± SD	Hardness (GPa), Mean ± SD
Inion CPS	6.14 ± 0.051[a]	0.32 ± 0.009[a]
TriMed titanium	137.46 ± 7.276[b]	5.05 ± 0.363[b]
Synthes RapidSorb	6.19 ± 0.142[a]	0.31 ± 0.009[a]

Fig. 2. (a) Inion CPS® biodegradable plates and screws [60]. (b) Percent strength and mass remaining of LactoSorb® plating over the course of a year [62]. (c) Elastic modulus and hardness of biodegradable screws, Inion CPS and Synthes RapidSorb, are significantly lower than TriMed titanium and may not meet the needed clinical demands [65].

caprolactone) (PLA-b-PLCL), that had sufficient mechanical strength to meet the demands of bone fixation (Fig. 4) [80].

Smart fixation systems, which are to be distinguished from implants composed of smart materials, allow for the monitoring of fracture healing, which is limited by conventional bioimaging techniques to the later stages of healing [81]. For example, Lin et al. designed external fixators and bone plates that contained electrodes, which allowed for monitoring of fracture healing with electrical impedance spectroscopy [82].

Despite proper fixation, there are still cases of fracture delayed unions, malunions, or nonunions, which are when healing takes longer than normal, the fracture heals in a poor position, or the fracture does not heal at all [2]. Depending on the location, fracture malunions may not need to be treated. However, some cases will require osteotomy and re-fixation to properly align the fracture. Fracture nonunions can be treated with nonsurgical stimulation, such as ultrasound, but there are some cases when a bone graft will be needed, which will be discussed in the next section.

3. Bone grafts and substitutes

Bone defects can be the result of a variety of different circumstances, such as high energy trauma, tumor resections, and infection requiring resections. The defect can be classified by location–diaphyseal, metaphyseal, or articular–and by the extent of the missing bone (Fig. 5) [83,84]. Though there is no set definition of critical size defects, they are generally considered defects that do not spontaneously heal without intervention and are generally considered those that result in a bone loss of greater than 50% of the circumference of the bone and at least 1-2 cm in length [83,85–87]. Additionally, the bone with the defect, the soft tissue environment of the defect, and the patient history all play a role. Critical size defects–and some cases of fracture nonunions–need to be treated with a bone graft [86,87]. The gold standard for bone grafts is the autologous iliac crest bone graft [85–87]. Other sources for bone grafts include allografts, xenografts, and synthetic biomaterials. In certain cases, the best treatment for the bone defect may be amputation.

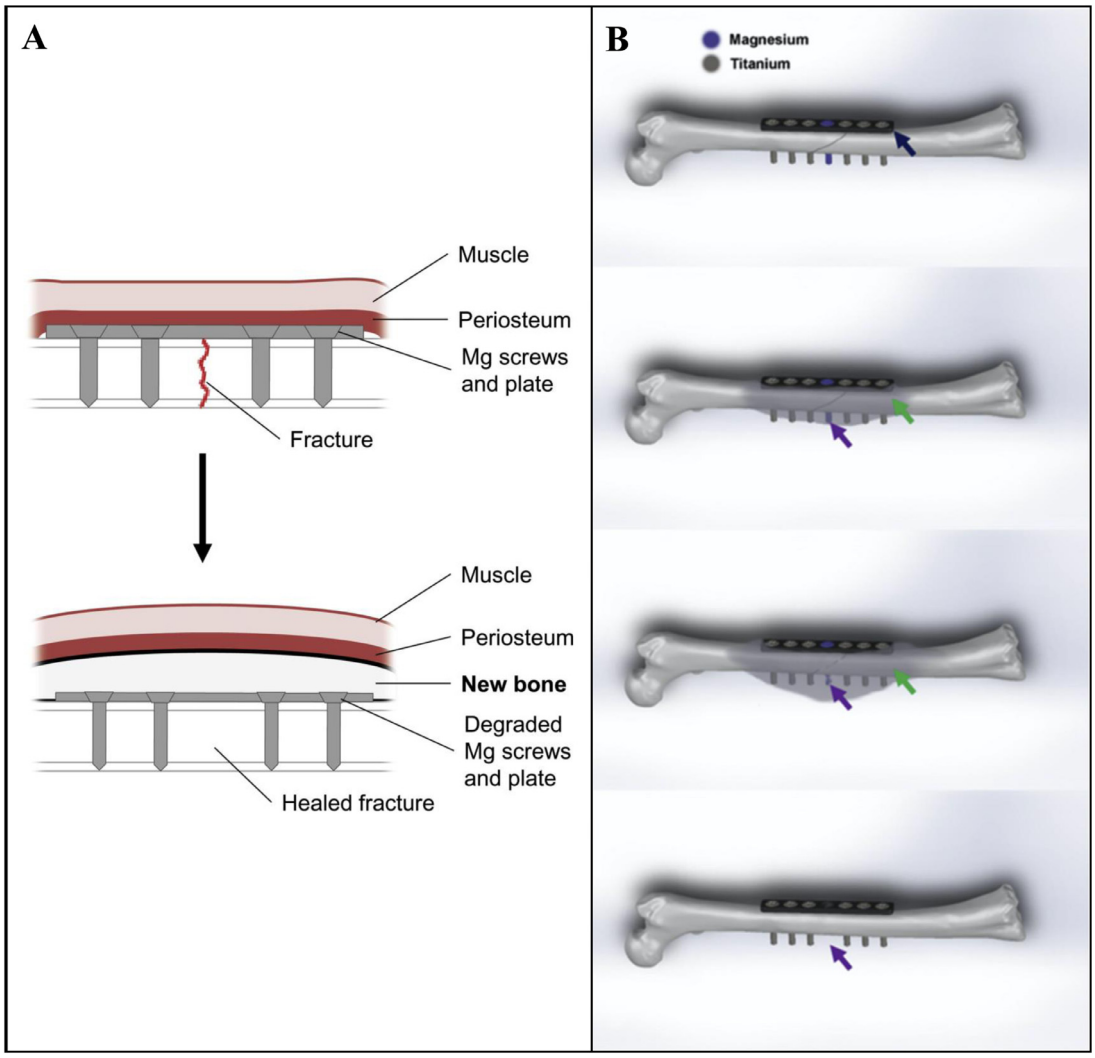

Fig. 3. (a) Proposed mechanism of bone healing with a pure magnesium plate and screw [70]. (b) Hypothesized workings of hybrid magnesium titanium system (blue arrow: titanium plate, purple arrow: magnesium screw with polymeric coating, green arrow: fracture callus) [27].

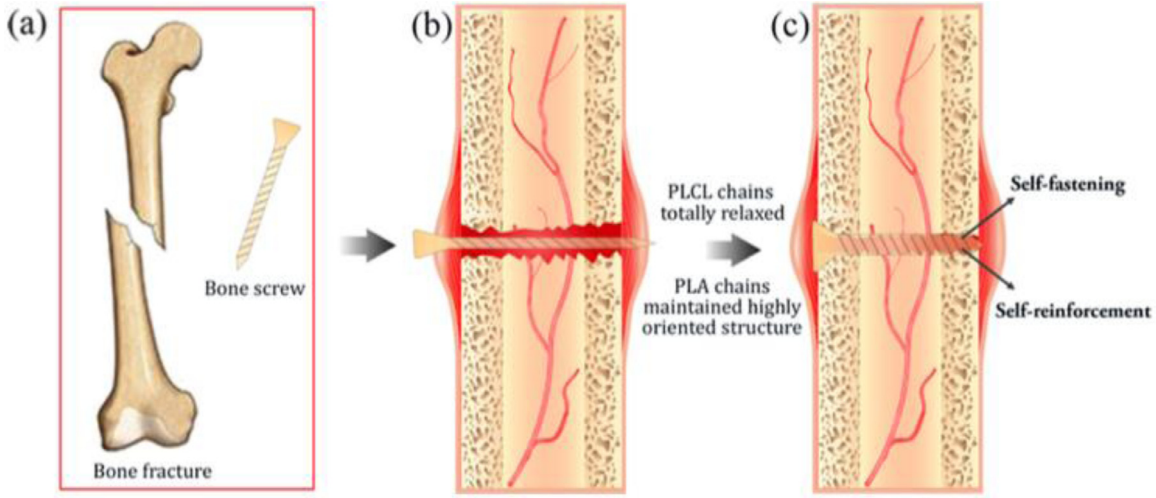

Fig. 4. Triple-shape memory polymer PLA-b-PLCL shows potential use as a self-fastening, self-reinforcement screw with sufficient mechanical properties. (b) The polymer is inserted into the fracture at a high temperature in its temporary state, and (c) as it cools to body temperature, it returns to its permanent shape [80].

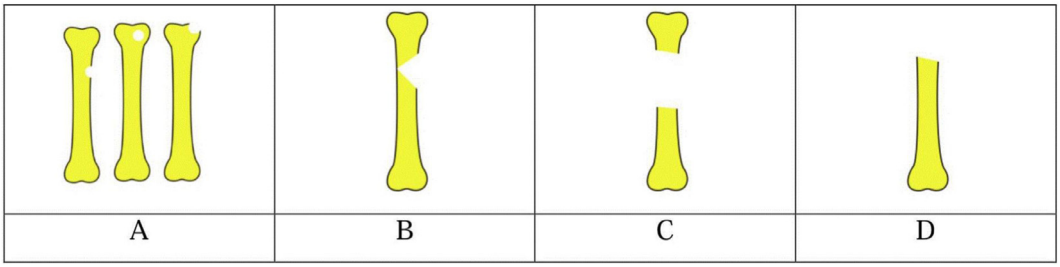

Fig. 5. Classifications of bone defects: (A) limited defects (<20%), (B) bone fragments still have contact, (C) segmental bone defects in which bone does not have contact, and (D) complete articular defect [84].

3.1. Natural bone grafts

Autologous bone grafts have the benefit of preserving the intrinsic properties of living bone. As these grafts are taken from the patient, they have no risk of graft versus host disease and disease transmission. Large amounts of cancellous bone can be obtained from the iliac crest that offer a good scaffold for bone regeneration in bone defects [88]. Additionally, cortical bone grafts or bone marrow aspirates can be taken from the iliac crest or from sites local to the site of implantation [88,89]. However, autografts have limitations because there is a limited availability for the grafts and can result in donor site pain, which results in an associated high donor site morbidity [88]. Furthermore, if the bone graft is taken from the iliac crest, there is an increase in the time of the operation simply to obtain the graft, but bone grafts can also be taken locally to the site of implantation, which would decrease the time of operation [88]. However, this local autograft collection is more limited in quantity than the iliac crest. Additionally, if the patient has an underlying condition that leaves a poor bone quality, autografts may not be an option at all.

Allografts are often obtained from cadavers, which provides a more abundant source than autografts and allows for the graft to come in a greater variety of states, which includes demineralized bone matrix [88]. Demineralized bone matrices are obtained from allografts by chemical treatments that leaves behind an osteoconductive scaffold consisting of proteins [89]. Using allografts also means there is no donor site pain or any associated morbidities. However, with allografts, there is the chance of graft versus host disease as well as the chance of disease transmission [88]. Additionally, the mechanisms of sterilization and storage affects the overall osteoconductive nature of the grafts, and the grafts obtained can be vastly different from one another [89].

Bovine-based xenografts are also used in orthopedic surgery for bone defect repair [90]. Their main advantage is their relative abundance and long shelf life, compared to autografts and allografts. However, they have a greater antigenicity than autografts and allografts and require much more substantial sterilization before use, which can also influence the osteoinductive properties of the graft [90]. In general, autografts and allografts appear to lead to better clinical outcomes than xenografts [90].

3.2. Bone graft substitutes

3.2.1. Ceramics

The limitations of the autologous, allogeneic, and xenogeneic bone grafts have led to the development of bone graft substitutes. Common clinical materials are generally biodegradable ceramics that can come in different forms, including cements, pellets, injectable fluids, blocks, granules, etc. [88,89]. Calcium sulfates have a crystalline structure that allows for growth of vasculature and new bone tissue, and it is easily prepared and is an inexpensive material [76,91]. They resorb in about 1-3 months, which is faster than the rate of new bone growth [76,89,91]. Calcium phosphates include compounds like β-tricalcium phosphate (β-TCP), hydroxyapatite (HA), and biphasic calcium phosphate (BCP), which is a mix of β-tricalcium phosphate and hydroxyapatite [76]. Their degradation rate and mechanical properties can be tuned with the ratio of calcium to phosphate; for example, HA has a greater ratio of calcium to phosphate, degrades slower, and has better mechanical properties than β-TCP [30,91]. Being a mix of HA and β-TCP, BCP has an intermediate degradation rate and intermediate mechanical properties. Calcium phosphate cements are composed of calcium phosphates and an aqueous curing agent to create a moldable material [76,91]. Finally, bioglasses are bioactive silicate-based ceramics that strongly binds with bone and has tunable bioactivity and degradation correlated to the ratios of the constituents ratios [76,91]. These bone graft substitutes are biodegradable, osteoconductive, nonimmunogenic, sterilizable, easily stored, and in good supply. Despite these benefits, these grafts lack the osteoinductive qualities that make autologous bone grafts so advantageous, but this issue is somewhat addressed with the incorporation of biological factors [76,88,89]. Additionally, these ceramics alone do not have the mechanical properties that are needed for the load-bearing conditions of the skeletal system.

Bioinert ceramics, such as alumina and zirconia, provide superior mechanical properties and corrosion resistance to other biodegradable and bioactive ceramics and are thus used in load-bearing arthroplasties [30]. However, they have limited applications as bone graft substitutes because they lack the biodegradable and osteoinductive qualities offered by other ceramics. In order to overcome this limitation, scaffolds composed of the bioinert ceramic with biodegradable or bioactive ceramics have been created and shown to have potential for bone graft substitutes in bone defect repair [92–95].

Mesoporous silica are silica networks with tunable porosities and hydrophilic-hydrophobic properties as well as a similar chemical surface to bioactive glasses–meaning that in physiological settings it forms bonds with the surrounding bone [96,97]. Furthermore, silicon plays an essential role in bone formation, and thus, mesoporous silica is likely beneficial in promoting bone healing [98]. Rather than being used alone as a bone graft substitute, mesoporous silica nanoparticles (MSNs) have been used as reinforcing agents in polymer materials and have been seen to have benefits over other traditional reinforcers, such as carbon nanotubes [97]. MSNs are also good drug carriers and have been incorporated into synthetic bone graft scaffolds to help promote bone regeneration or have been injected on their own to treat bone conditions [97–99]. For example, He et al. generated PLGA microspheres containing MSNs and nanohydroxyapatite that improved the osteoinductivity and bone healing in a bone defect model over lone PLGA microspheres [100]. Similarly, Wang et al. created polycaprolactone (PCL)/gelatin nanofibrous scaffolds that were electrospun with mesoporous silica nanoparticles, loaded with alendronate, to promote bone regeneration [101]. Zhou et al. created a composite of vancomycin loaded MSNs and gelatin as a bone graft substitute that would prevent infections during bone defect repair [102].

3.2.2. Metals

Metals, as discussed earlier, are widely used in orthopedic applications to aid in fracture fixation, among other applications. Porous

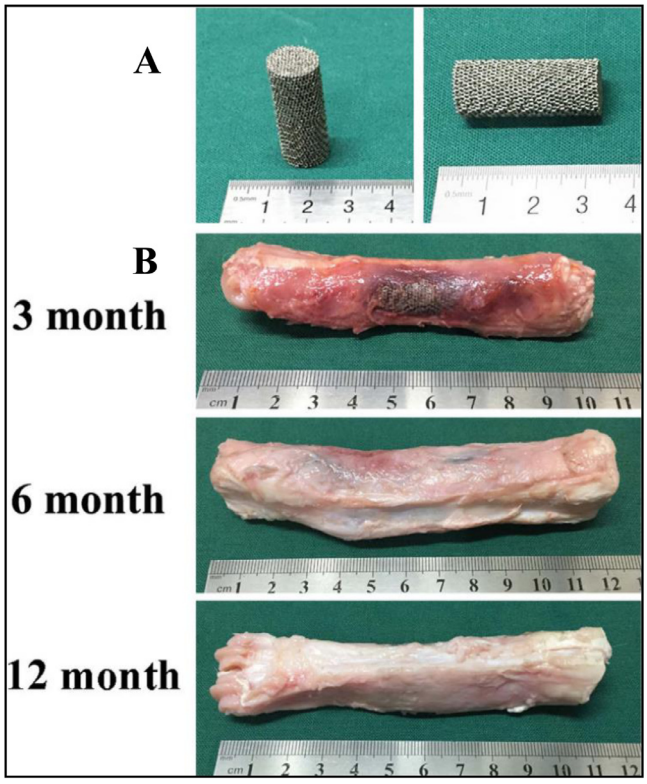

Fig. 6. (a) 10 mm diameter and 30 mm height Ti6Al4V scaffold with pore size in the 300–400 μm range and a diamond lattice structure, and (b) bone regeneration with Ti6Al4V scaffold in goat metatarsus bone defect model (bottom) [106]

metal scaffolds provide the mechanical properties that are lacking in biodegradable ceramics while the porosity also allows cell ingrowth. Metals that have been employed for the development of bone scaffolds include titanium alloys, tantalum, and magnesium [103–105]. The osseointegrative property of titanium along with its widespread clinical use in orthopedic applications makes it a nice option for applications in bone defect repair as a scaffold. Li et al. used additive manufacturing methods to produce a porous Ti6Al4V scaffold with a diamond lattice shape that allowed for bone ingrowth and was stable in load bearing bone defect model (Fig. 6**A**) [106]. Similarly, both Tamaddon et al. and Pobloth et al. developed porous titanium scaffolds with additive manufacturing methods that integrated with bone [107,108]. Nitinol, a nickel-titanium alloy, is a shape memory alloy with a lower elastic modulus and a greater elasticity than other titanium options that is able to support osseointegration to a similar extent as standard titanium [109]. Additionally, the shape memory property of nitinol means that it has the potential to be used to apply mechanical stimuli for improved bone regeneration or it can be used to provide a better fit into bone defects. However, a major concern with nitinol is the toxicity of nickel and potential carcinogenicity [103].

As a bioactive metal, tantalum offers a unique set of qualities absent in titanium, and it has been used in load-bearing orthopedic applications, such as hip and knee arthroplasties and spine surgery [110]. Ren et al. demonstrated the potential for porous tantalum implants in bone defect repair with a firearm injury bone defect model [111]. Furthermore, the bioactivity offered by tantalum means that it likely allows for better osseointegration and bone bonding than other metals: Guo et al. used additive manufacturing methods to produce a porous Ti6Al4V scaffold and a porous tantalum scaffold to compare the two scaffolds and demonstrated that the tantalum scaffold appears to be better suited for bone defect repair than the titanium alloy scaffold [112].

The biodegradable metal, magnesium, has many beneficial qualities for applications in orthopedic applications, as discussed earlier. Its rapid degradation and associated loss of mechanical properties limits its use in load-bearing conditions, which makes their application in bone graft substitutes more promising than in internal fixation [113,114]. However, the rapid degradation along with the H_2 gas evolution during degradation still limit the potential of magnesium scaffolds for bone defect repair [115]. Furthermore, the porous designs often used for bone graft substitutes further increases the degradation rate. Similar to in internal fixation applications, these disadvantages of magnesium in bone defect repair applications can be addressed with coatings or alloying. For example, Yazdimamaghani et al. added a biodegradable composite coating of PCL and bioactive glass to a porous magnesium scaffold, which significantly improved the mechanical stability by reducing the degradation rate [116]. Although this coating did significantly improve the mechanical stability compared to the uncoated scaffold, the mechanical properties still decreased rapidly (Fig. 7). Another way that the benefits of osteoinductive benefits of magnesium have been harnessed for bone defect repair is through the incorporation of magnesium as a component of bone scaffolds composed of other materials, including ceramics and polymers [117,118]. For example, Kim et al. incorporated magnesium ions into a porous scaffold composed of PCL, which promoted bone ingrowth through stimulation of osteoblast motility [117]. Similarly, Wong et al. incorporate magnesium microparticles into a porous PCL scaffold to improve the mechanical properties and bioactivity [119]. Ghițulică et al. substituted some calcium ions with magnesium ions in hydroxyapatite resulting in an increased osteoblast proliferation [120]. Both Kim et al. and Ghițulică et al. did not test the mechanical properties of their scaffolds, so their potential in load-bearing conditions is unknown. Lai et al. incorporated magnesium powder into a porous scaffold composed of PLGA and TCP, which conferred the osteoinductive properties of magnesium while also improving the mechanical strength [118]. Similarly, Go et al. incorporated magnesium hydroxide into a scaffold of PLGA and TCP that enhanced bone repair in a bone defect model [121].

Magnesium-based ceramics have also been developed and applied to bone defects with good outcomes [122]. These ceramics offer higher mechanical strength than calcium-based ceramics and can also be used in a variety of different forms, such as cements and scaffolds [122]. The incorporation of magnesium in these ceramics eliminates the H_2 byproduct of magnesium degradation while still providing the magnesium ion byproduct to help promote bone growth [122]. However, studies of magnesium-based ceramics are still in their earliest stages, and these ceramics remain much less studied than traditional ceramics. More studies need to be done regarding their potential for load-bearing conditions as well as general characterizations of their properties.

3.2.3. *Polymers*

Synthetic polymers are promising materials for bone graft substitutes as they are generally biocompatible and are easily tuned to have desirable degradative and mechanical properties. Saturated poly(α-hydroxy esters), including poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and PLGA, are among the most common biodegradable synthetic polymers used for scaffolds in tissue engineering with monomers that can be removed by natural pathways [123]. PGA is not typically used on its own for bone scaffolds owing to its fast degradation whereas the more hydrophobic PLA has been used as a bone graft substitute for bone defect repair [123–126]. The mechanical properties and degradation rate of PLGA are easily tuned with changes in the ratios of the composing monomers. These polymers lack an optimal mechanical strength and osteoconductivity, limiting their solitary use. Consequently, they are often paired with other materials. For example, Toosi et al. used combined PGA with a collagen sponge, the major protein in bone, to create a scaffold for bone defect repair [127]. The osteoconduction of collagen made up for the lack thereof in PGA, and the addition of PGA to the collagen sponge improved the attachement, proliferation, and differentiation of

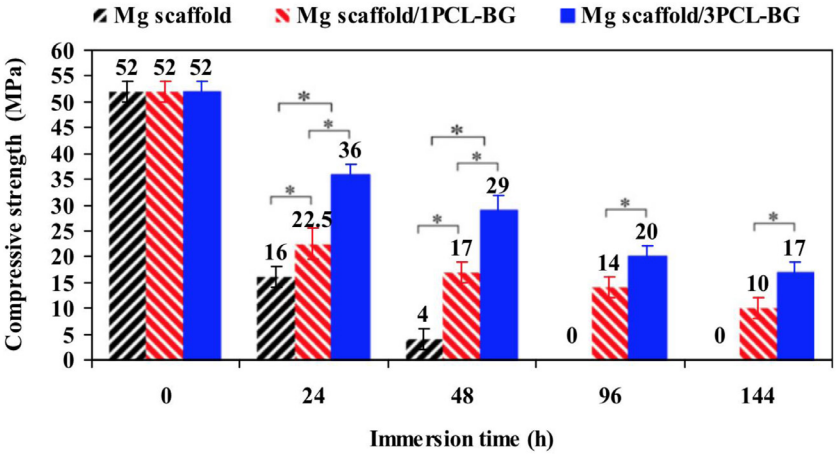

Fig. 7. Compressive strength of uncoated porous magnesium scaffold, porous magnesium scaffold coated with 1 layer of PCL and bioglass composite, and porous magnesium scaffold coated with 3 layers of PCL and bioglass composite *p < 0.05 [116].

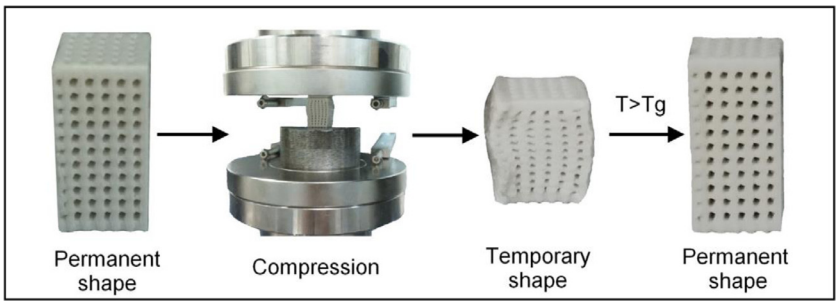

Fig. 8. Shape-memory HA and PLA composite [129].

bone MSCs [127,128]. This study did not show evidence of improvements in mechanical strength, so its potential for load-bearing applications is unclear. Senatov et al. created a composite of HA and PLA with shape memory properties that could be deformed then reshaped with heat to create a tight fit when placed in bone defects (Fig. **8**) [129]. Ma et al. created a Janus membrane with HA and PLA that was able to maintain the unique properties of each material–osteoinductivity and hydrophobicity, respectively–to induce bone regeneration in the bone defect while preventing soft tissue ingrowth into the defect [130]. Chen et al. added nanoscale HA powder to PLA to create a composite with better osteoconduction and mechanical properties than PLA on its own [131]. Zhou et al. incorporated both collagen and HA into a scaffold with PLA that improved the osteoinduction of the scaffold [132]. This scaffold, however, exhibited lower tensile strength than PLA alone, and the compressive properties were not tested, so it may not be an option for load-bearing applications. Similar to PGA and PLA, PLGA has been paired with HA and collagen to improve the integration with bone tissue and the mechanical properties [133–136]. PLGA was also combined with HA and TCP in bilayer membranes that improved the biodegradation and mechanical properties, making it more suitable for bone defect repair [137]. Furthermore, PLGA has been combined with graphene, which helped to improve bone growth, as well as with other ceramics and magnesium, as described earlier [138,139].

Polycaprolactone is another biodegradable polyester commonly used as bone scaffolds [140]. It has a slower rate of degradation than PGA, PLA, and PLGA, which may make it more beneficial for the reparation of bone defects [141]. PCL also may be better than traditional ceramics, such as HA and TCP, used as bone graft substitutes [142,143]. Nevertheless, PCL on its own lacks optimal mechanical and osteoconductive properties and can be improved by combining it with other materials [140]. Domalik-Pyzik et al. combined PCL with PLA to create a scaffold with superior mechanical properties [144]. Like the aforementioned polyesters, PCL has been paired with HA to improve the osteoconduction [141,145,146]. Ma et al. incorporated HA and polyvinyl acetate (PVA) with PCL to successfully improve the bioactivity of the scaffold as well as increase the degradative rate [147]. Additionally, like PLGA, PCL has been paired with magnesium to improve the bioactivity and, in some cases, the mechanical properties, as described earlier.

Other polymers have been studied for bone regeneration including PVA, poly(propylene fumarate) (PPF), and polyurethane (PU) [105]. Additionally, a new biodegradable hyper-crosslinked carbohydrate polymer was FDA-approved for non-load-bearing bone defect repair [148,149]. Natural polymers have also been applied as bone graft substitutes and have the benefit of being biocompatible, biodegradable, and osteoconductive [150]. They include collagen, hyaluronic acid, chitosan, alginate, silk, and gelatin [105,126].

3.2.4. *Hydrogels*

Hydrogels are water-swollen, polymer scaffolds that have also been applied to bone defect repair. They are more favorable than plain polymer scaffolds as they can be designed to mimic the natural ECM [151]. Biodegradable, injectable hydrogels are particularly beneficial because they can fill in the irregular shapes of the bone defects easily with minimally invasive procedures, reducing operation and recovery time [151]. These hydrogels have been widely applied for cell and drug delivery, and bioactive, osteoinductive components or cells can easily be incorporated to create an optimal bone graft substitute [151,152]. Hydrogels can also have natural or synthetic origins.

Alginate is an anionic, biodegradable, injectable hydrogel that is inexpensive and has a large abundance, and it is one of the most widely used and studied natural polymers for hydrogels in bone tissue engineering [153,154]. Alginate has osteoinductive properties that make it suitable for bone regeneration purposes [155]. Alginate on its own is mechanically insufficient for load-bearing and require fixation, which

eliminates the benefits of its injectable qualities [156]. Therefore, alginate have been combined with other materials to create composites, which have been studied and shown to improve the mechanical properties of alginate as well as potentially improving the osteoinductivity [153,156]. These materials include natural polymers, such as chitosan, collagen, and gelatin, synthetic polymers, and bioactive and biodegradable ceramics [153,157–160]. A limitation of alginate is that the human body lacks alginase and is thus unable to degrade alginate, but if steps are taken in its preparation, such as making the gel ionically cross-linked or partially oxidizing the alginate, this is not a major issue [156].

Chitosan is a biodegradable, natural polymer widely studied for bone regeneration that can also be made into a cationic, injectable hydrogel [154,161–164]. Like alginate hydrogels, chitosan hydrogels lack mechanical strength and bioactivity and are thus often combined with other materials, like those that have been combined with alginate, to overcome these limitations [154,164–168]. Other materials have also been incorporated with chitosan hydrogels, such as TiO_2 nanoparticles to improve the mechanical strength and bioactivity [169].

Other natural hydrogels that could be applied to bone defect repair include hyaluronic acid, collagen, and gelatin [170,171]. Synthetic, injectable hydrogels have more controllable properties and have also been studied for bone defect repair [154]. Some polymers used for these hydrogels include PEG, PPF, and PCL [170,172,173]. There is overlap with the natural and synthetic polymers that can be used just as non-hydrogel scaffolds as well as turned into hydrogel scaffolds. The major differences between the two states lie in the mechanical properties and the fact that hydrogels more closely mirror the natural ECM.

4. Perspectives and future directions

4.1. Innovative materials

Degradable materials are the optimal material for fracture fixation devices as they remove the need for implant removal and avoid the complications associated with surgeries for implant removal. There are currently degradable polymer fixation devices on the market, but they are only applied to non-load-bearing, craniofacial applications. Furthermore, these degradable polymeric fixation devices are not great options for load-bearing fixation, as they would need to be made much thicker to have the needed strength.

Degradable ceramic materials are the most common biomaterial used as bone graft substitutes for bone defect repair. The beneficial quality of ceramics is they closely mimic the mineral phase of the bone ECM, but they generally lack sufficient strength. Therefore, future directions for bone graft substitutes need stronger materials to be able to bear loads. Metals, including titanium alloys and tantalum, have been suggested for these purposes. These metals are a good option because they are FDA approved materials and have osseointegrative or bioactive properties. However, the ideal materials for bone graft substitutes, like fracture fixation devices, are degradable materials, as they allow for the replacement of the implant with natural tissue.

Degradable metals, such as magnesium and zinc, have a great potential for fracture fixation and bone graft substitutes, and they address the issues of mechanical strength faced by other degradable materials. Magnesium screws have been approved for use in Korea and Germany in non-load-bearing applications, and some studies have suggested that magnesium is capable of being applied to load-bearing applications. The main hindrance to magnesium use is its quick degradation and the associated H_2 evolution, but magnesium can be combined with other metals, alloyed, or coated to overcome their quick degradation rate. Additionally, the degradation products of magnesium stimulate bone regeneration. Similarly, the degradative byproducts of zinc induce bone regeneration. Zinc has been studied to lesser extent than magnesium and therefore requires more studies. In sum, more studies are needed to characterize magnesium and zinc and to optimize their degradation rates and mechanical strength before they can be applied clinically.

4.2. Advanced manufacturing

Computer aided design (CAD) or computer aided manufacturing (CAM) systems allows for the design of implants that fit the unique anatomic features of a patient and the injury. Computed tomography or magnetic resonance imaging scans of the bone can be employed to create a model of the fracture or bone defect and used to create a suitable fracture fixation device or implant for bone defect repair via CAD or CAM. Early CAD/CAM systems used subtractive manufacturing, typically using computer numerical control (CNC) manufacturing, which cut away material from a block to get the desired shape [174,175]. However, subtractive manufacturing has a limited resolution and limited geometries by the tool used to cut, and there is an associated waste of material.

Additive manufacturing, on the other hand, is a newer method of employing CAD or CAM designs and is a great way to create patient-specific devices. It works by layering material, allowing for more precise shapes, and does not waste material like subtractive manufacturing. Many materials can be printed with additive manufacturing to suit the patient-specific conditions for fractures and bone defects [176–179]. The most common fabrication techniques used for tissue engineering that have been used to generate bone implants are laser based printing, such as stereolithography (SLA) and selective laser sintering (SLS), extrusion based printing, such as fused deposition modeling (FDM), and inkjet printing, such as three dimensional printing (3DP) [180,181]. SLA has been used with polymers and some bioceramics and works by using a laser to cure photosensitive liquid resin [181]. SLA has a high resolution, but it requires post-processing steps to remove any excess resin. SLS is a technology that can be categorized as a powder bed fusion (PBF) method that uses a laser to fuse powders of any material–except natural polymers–together, and it has been used for the successful development of porous titanium implants for clinical applications [181,182]. Selective laser sintering and PBF methods are beneficial because they allow very precise prints but have limited sizes. Additionally, the high temperatures generated by the laser in SLS prevent the incorporation of bioactive agents during the manufacturing. As the name suggests, extrusion printing extrudes material and can be used with ceramics and polymers, and its accuracy depends on the rate of extrusion and hardening of the molten material [181]. Inkjet printing dispenses a binder solution to bind material within a powder bed and is largely used with bioceramics, which had been applied clinically to non-load-bearing applications, and with some polymers [181].

For metal implants in particular, PBF or direct energy deposition (DED) have widely been used [182]. They both involve the use of lasers either to melt and shape the metal powder or to sinter and bond the metal powder together to generate the construct. PBF includes methods such as selective laser sintering (SLS) and electron beam melting (EBM), and DED includes methods such as direct metal deposition (DMD). These additive manufacturing methods have been successful with titanium constructs and have been used in clinical settings, allowing the generation of quicker implants that fit better and improved patient recovery [182,183].

5. Conclusion

There is an overlap in the materials used and the desired properties of orthopedic implants used to treat fractures and bone defects. This paper described these different materials used for the different applications, their benefits, and their limitations. Additions, such as growth factors, to the fixators and scaffolds, which were not discussed in this paper, can further improve the efficacy of these different materials. However, despite this, there is still no ideal biomaterial for either fracture fixation or bone defect repair.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Tiffany Kim: Conceptualization, Writing - original draft. **Carmine Wang See:** Writing - review & editing. **Xiaochun Li:** Writing - review & editing. **Donghui Zhu:** Conceptualization, Supervision, Writing - review & editing.

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