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Review

Functional Macromolecular Adhesives for Bone Fracture Healing

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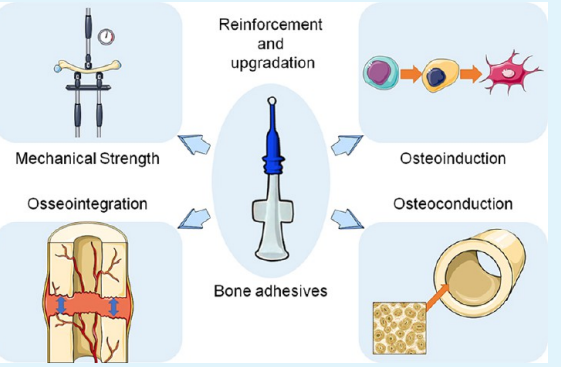
ABSTRACT: Compared with traditional internal fixation devices, bone adhesives are expected to exhibit remarkable advantages, such as improved fixation of comminuted fractures and maintained spatial location of fractured scattered bone pieces in treating bone injuries. In this review, different bone adhesives are summarized from the aspects of bone tissue engineering, and the applications of bone adhesives are emphasized. The concepts of "liquid scaffold" and "liquid plate" are proposed to summarize two different research directions of bone adhesives. Furthermore, significant advances of bone adhesives in recent years in mechanical strength, osseointegration, osteoconductivity, and osteoinductivity are discussed. We conclude this topic by providing perspectives on the state-of-the-art research progress and future development trends of bone adhesives. We hope this review will provide a comprehensive summary of bone adhesives and inspire more extensive and in-depth research on this subject.



KEYWORDS: *biomaterial, bone adhesive, bone fixation, bone regeneration, bone tissue engineering*

1. INTRODUCTION

Every year, the number of hospitalizations due to bone fractures is increasing worldwide. Femoral shaft, humeral, and tibial fractures account for 3%, 14%, and 24%, respectively, of working-age adults' fractures in the United States.[1,2] These bone fractures are often comminuted because of high violence. Orthopedic surgeons who operate on comminuted fractures feel the need to stick comminuted fracture sheets together to hold them in place. The idea of a bone adhesive was proposed as early as 1890 by Gluck *et al.*[3,4] Unfortunately, the designed adhesives were initially not practical because of their biological toxicity, but the concept opened a new avenue for orthopedic surgeons worldwide.

Currently, the treatments of bone fractures mainly include both surgical and conservative ones. Other than for a few fractures suitable for functional reduction, most bone fractures still need surgical treatment. Strong internal fixation with steel plates or nails has always been the gold standard of surgical treatment. However, the following issues remain to be addressed for managing bone fractures: (i) Most comminuted periarticular fractures require anatomic reduction to meet the athletic needs and prevent the occurrence of osteoarthritis. It is difficult to accurately fix the broken joint fragments together by internal fixation devices, especially when these fractures are comminuted.[5] (ii) Osteoporotic bones cannot hold the screws firmly.[6] (iii) Internal fixators are prone to cause implant infection of bone tissue and need removal after bone healing.[7] Moreover, studies have confirmed that metal surfaces tend to form a pseudomembrane in the body that encourages bacterial growth.[8,9] Therefore, bone adhesives have been developed to treat bone fractures and make the treatment more convenient, faster, and safer than traditional internal fixation devices.

A bone adhesive is believed to bind fractures around the joint and shaft fractures that do not require immediate load-bearing after treatment. From this perspective, a suitable bone adhesive should provide quick and robust adhesion and be biodegradable and bioactive to promote gradual bone regeneration. Kandalam *et al.* reported that when bone fractures were fixed with resorbable plates and adhesives, the shear bonding strength of *N*-butyl cyanoacrylate in the adhesives was significantly higher than when fractures were fixed with resorbable plates and screws.[10] However, the cytotoxicity and bone-healing-promoting performance of *N*-butyl cyanoacrylate were not confirmed in their research. In recent years, many researchers have attempted to develop bone adhesives with excellent properties to meet the biological

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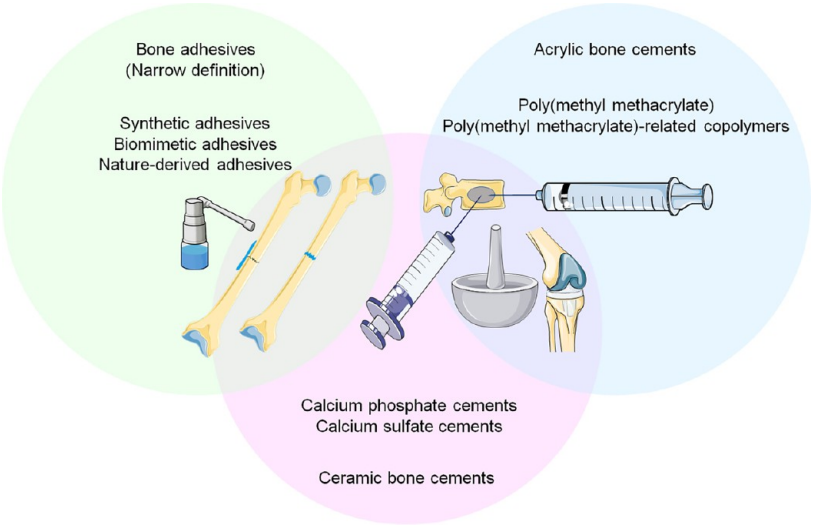
Scheme 1. Bone Adhesives and Bone Cements



needs for improved adhesive strength. Linderman *et al.* showed that adhesives with relatively high strength and low stiffness could increase the strength of the tendon to the bone by >10 times, which also provides a theoretical basis for the treatment of fixed avulsion fracture and tendon−bone junction fracture by using adhesives.[11] Yuan *et al.* developed a kind of composite adhesive based on citrate to accelerate bone-to-tendon healing.[12]

Both bone adhesive and bone glue are the correct expressions to describe the materials used to bind fracture pieces, owing to their adhesive properties. However, "bone adhesive" used hereafter in this review has become the preferred terminology over "bone glue" in recent publications.

It should be noted that the concept of bone adhesive is often confused with bone cement. Commonly being used as a medical material to fix vertebral fractures or fix metal parts in prosthesis replacement surgery, bone cement is a family of materials comprising a powder phase and a liquid phase, which can form a gel paste that solidifies after mixing.[13] Because the appearance and performance of bone cement after curing is very similar to that of the white cement used in architecture and decoration, it is named "bone cement".

Acrylic bone cements and calcium phosphate (CaP) cements for bone repair and implant fixation are the two most commonly used categories of bone cements.[14] Acrylic bone cements, such as poly(methyl methacrylate) (PMMA), lack chemical interaction with tissue and therefore have negligible or no intrinsic adhesion to the bone.[15] Moreover, the polymerization processes of acrylic bone cements are always exothermic and lead to volume shrinkage. They are also non-biodegradable and toxic, limiting their application in fracture treatment.[16] CaP cements can be used to treat tibial plateau, calcaneus, and proximal humerus fractures because they can replace the cancellous bone to support the articular surfaces and prevent the screw from pulling out.[17−20] However, CaP cements are inorganic and have weak adhesion strength. Therefore, they cannot be used by themselves to bond bone fracture pieces and promote bone regeneration. Krticka *et al.* proposed a modified protocol for CaP cement based on dopamine and sodium iodinate to treat comminuted fractures *via* minimally invasive injection.[21] Gelinsky *et al.* improved CaP cement to treat bone defects by adding a fibrin gel or growth factor.[22,23] Engqvist *et al.* developed a method for treating skull defects by mesh enriched with CaP to improve bone conductivity, and they also improved the bond strength and mechanical performance of CaP cement by adding phosphoserine or citric acid.[24−27] Therefore, the bone adhesives discussed in this review will only include those of a narrow sense and phosphate cement (Scheme 1).

When it comes to bone adhesive, the concept of tissue adhesive cannot be circumvented. Tissue adhesives are made of materials that can close soft tissues, such as muscle and skin, and keep wounded tissues from separating through their adhesive force.[28−30] In a broad sense, adhesives for medical applications can be categorized as hemostatic agents, sealants, and adhesives.[29,31,32] So far, only a few commercially available tissue adhesives with registered trademarks and manufacturers are recognized. The most commonly used one is fibrin glue (trade names: Tisseel, Evicel, Cryoseal, *etc.*).[33] Cyanoacrylate adhesive, which evoluted from the industrial adhesive named Super Glue, are also widely used as a tissue adhesive with trade names as SurgiSeal, Dermabond, Histoacryl, and Epiglu.[33] But they are toxic and can generate formaldehyde after decomposition. Thus, they are generally limited in external soft tissue wound closure rather than hard tissue fracture adhesion. Polyurethane-based tissue adhesive (trade name: TissuGlu), protein-based adhesive with a trade name as BioGlue composed with bovine serum albumin and glutaraldehyde, and poly(ethylene glycol) (PEG)-based DuraSeal and CoSeal are other representative commercially available tissue adhesives.[33] When a tissue adhesive is used to treat bone fractures, we often focus on whether the material meets the strong adhesive strength requirements for bone fracture fixation.[34] However, the sole consideration of a tissue adhesive's strength is insufficient, as more attention should be given to whether the used adhesive is conducive to fracture healing. Compared with other tissue adhesives, the most important properties that bone adhesives need are adequate adhesion strength to fractured bone fragments, suitable cohesion strength, and the ability to maintain the spatial locations of fractured fragments. In addition, bone adhesives should also have tunable biodegradability to match bone growth rate, good biocompatibility, and the ability to promote osteogenesis. Moreover, in the application process, bone

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ACS Appl. Mater. Interfaces XXXX, XXX, XXX−XXX

Table 1. Different Categories of Traditional Bone Adhesives in Research

category	main component	trade name	ref
natural materials-derived adhesive	chitosan and dextran bone adhesive		35
	chitosan, HA, and $CaCO_3$ combination		36
	fibrin glue		37
synthetic adhesive	tris[2(3-mercaptopropionyloxy)ethyl] isocyanurate (TEMPIC) and 1,3,5-triallyl-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione (TATATO)		38
	nano-bioactive glass fillers and hydroxyethyl methacrylate (HEMA)		39
	poly(ethylene glycol) dimethacrylate matrix and isocyanate		40
biomimetic adhesive	tetracalcium phosphate and phosphoserine	Tetranite	41
	mussel-inspired adhesives (elastic proteins)		42, 43
	sandcastle-inspired adhesives (polyacrylate glue protein analogs)		44, 45
	frog-inspired adhesives		46

adhesives should enable rapid bonding and fixation of fractured fragments at room temperature.

2. DIFFERENT CATEGORIES OF BONE ADHESIVES

On the basis of the sources of their main components, bone adhesives can be categorized into nature-derived adhesives, synthetic adhesives, and biomimetic adhesives (Table 1).[47] The regeneration of bone tissue is more challenging than that of soft tissue because bone tissue comprises 60−65 wt % inorganic phase, *e.g.*, hydroxyapatite (HA) embedded in an organic collagen matrix.[48] Pure nature-derived adhesives, such as chitosan-based adhesives[35,36] and fibrin glue[37] derived from proteins composed of concentrated fibrinogen, thrombin, and calcium chloride ($CaCl_2$), thus duplicating the last stage of biological coagulation cascade, possess poor adhesion strength to biological tissues. Hence, they cannot be used as suitable bone adhesives. Synthetic bone adhesives usually have a single component, and it is challenging to have favorable osteoconductivity and osteoinductivity simultaneously, which is not conducive to fracture healing.[38−40]

As bone is a mixture of organic and inorganic materials, the design of bone adhesives should incorporate both types of materials.[49] If only inorganic materials are used to fill the fracture space, a secondary fracture may occur due to its fragility.[50] Ideally, the organic components are responsible for providing adhesion. By contrast, the inorganic ingredients are accountable for enhancing the cohesive strength of adhesives, simulating the typical shapes of bones and promoting fracture healing. Therefore, novel bone adhesives should be designed to be biomimetic, multicomponent adhesives containing organic and inorganic materials.

A multicomponent bone adhesive, sandcastle worm glue, with a composite structure similar to that of natural bone, is excellent in treating fractured bone.[41,44,45] Inspired by mussel elastin, the research and development of adhesive with high resilience, large strains, and low stiffness have never stopped.[42,43] Similarly, another multicomponent adhesive inspired by the frog has been used to repair rotator-cuff tissue, a group of tendon complexes around the humeral head, in a cadaveric laboratory model.[46] Furthermore, conventional bone adhesives only provide mechanical stability to bind the fractured bone pieces together. In contrast, an advanced bone adhesive with preferable biocompatibility and porous structure could serve as a bridge to accelerate the in-growth of bone cells and promote orthopedic regeneration and is therefore in high demand.

These bone adhesives possess some fundamental properties, such as adhesion, cohesion, biocompatibility, and biodegradability, and have been reviewed in previous reports on bone adhesives (Table 2).[4,31,34,51] First, the adhesion and cohesion

Table 2. Typical Properties of Bone Adhesives

property	detailed requirement
adhesion	strong adhesion to bone surface under clinically relevant situations
cohesion	maintaining integrity of adhesive in treatment of fractures
biocompatibility	no acute and chronic toxicity
	biocompatibility toward surrounding tissues
	allow for fracture healing and bone regeneration
biodegradability	tunable degradation rate
	nontoxic and bioresorbable degradation products
	controllable mechanical strength over time

provide a stable and reliable mechanical environment for fracture healing. Second, bone adhesives with good histocompatibility have few side effects on cells, tissues, and organs. Finally, biodegradability ensures that the bone adhesive will gradually disappear along with the fracture healing, making room for the in-growth of new bone tissue.

From the point of view of bone tissue engineering, the bone adhesive applied in the fracture gap to adhere the two fractured bone fragments together and serve as a scaffold in-between after curing is similar to a liquid scaffold. Thus, if the bone adhesive is used as a liquid scaffold to treat fractures, adhesive and cohesive force that holds the fracture fragments together before and after curing, respectively, is essential. Additionally, the bone adhesive often has special functions to promote bone fracture healing and enhance new bone remodeling after curing (Scheme 2). The most significant difference between a bone adhesive acting as a liquid scaffold and the conventional bone adhesive lies in promoting fracture healing after curing. In this review, recent progress on bone adhesives for fracture treatment is considered from the following aspects: enhancement of mechanical strength, osseointegration, osteoconduction, and osteoinduction. Therefore, the liquid scaffold proposed in this review is essentially a reinforced and upgraded bone adhesive.

In addition to liquid scaffold bone adhesives, another type of adhesive is used for adhering to the cortical bone surface at both ends of the fracture instead of filling the fracture gap. This type usually needs primers to pretreat the cortical bone surface and light initiation to solidify the bone adhesive to fix the fracture.[38,52] Although this fixation is more like plate fixation

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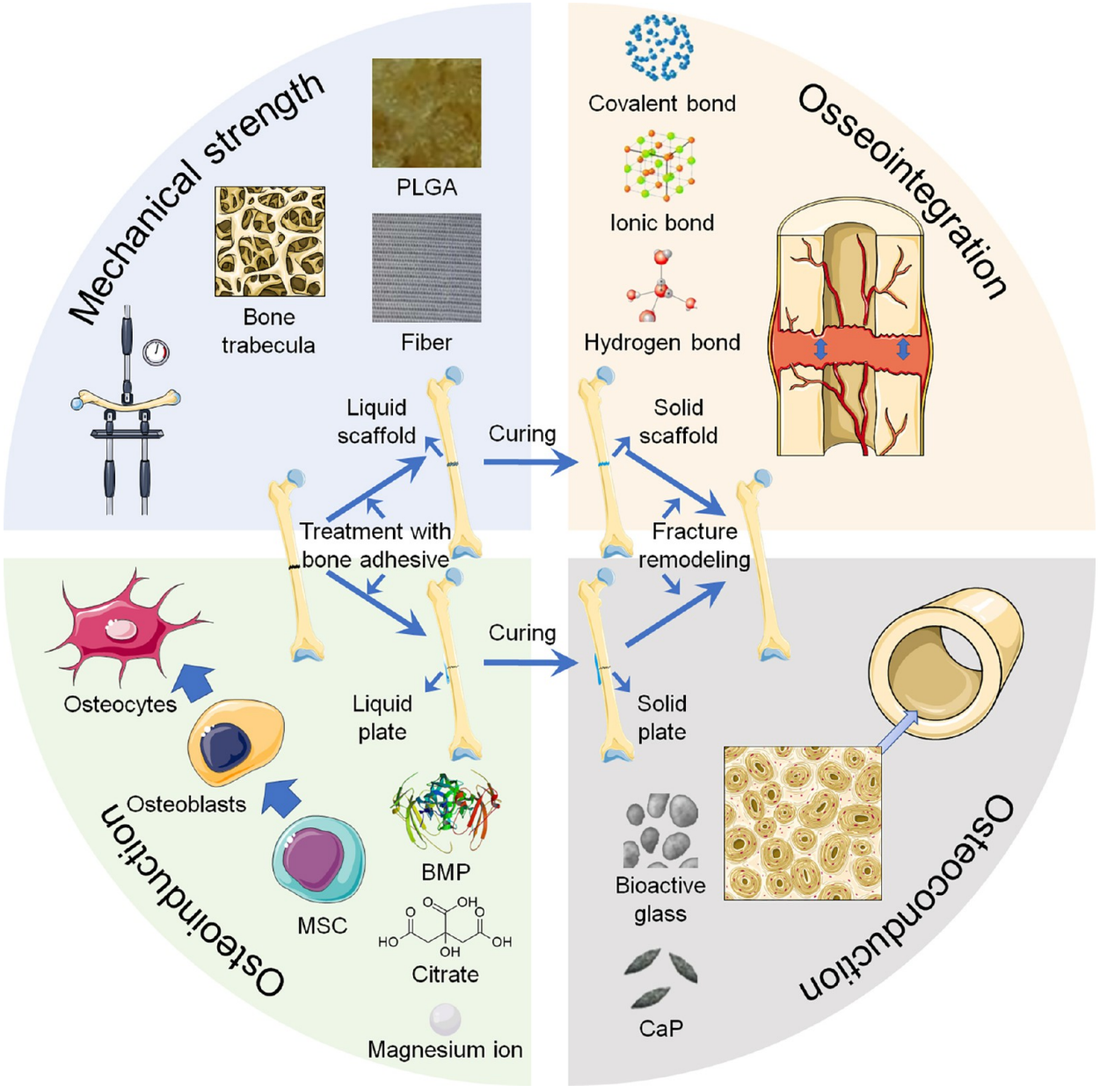
Scheme 2. Bone Adhesives for Bone Fracture Treatment



for the fracture, there are no holes at the fracture ends to install screws. Therefore, such types of bone adhesives that adhere to the two fractured bone fragments from outside and serve as an outside fixer after curing are termed "liquid plate". Compared with the steel plate currently used in clinical practice, the liquid plate can be perfectly shaped before coagulation. It adheres to the surface of bone cortex and does not need punched holes that destroy the original bone structure. This type of adhesion cannot directly accelerate fracture healing by changing the components. Still, it can indirectly promote fracture healing by improving the adhesion strength and ensuring a solid fracture fixation.

Summarizing the results in recent years, it can be concluded that liquid scaffold and liquid plate are two methods, and they are also two technical routes to improve the effectiveness of bone adhesives in fracture treatment.

3. REINFORCED AND UPGRADED BONE ADHESIVES

We reviewed the trend of research on bone adhesives in recent years. We found that bone adhesives were developed from a single component versus multicomponent and from only possessing a bonding function to having multiple parts to promote fracture healing. Among these enhanced and upgraded functions, the improved mechanical strength makes it possible to treat long-bone fractures of the extremities, and osseointegration provides a stable microenvironment for fracture healing,[53,54] osteoconduction provides space for bone cell migration and proliferation,[53,55] and osteoinduction promotes the differentiation of undifferentiated cells into osteoblasts.[53,55] These functions speed up the fracture healing process and make it possible to treat fractures with bone adhesives.

3.1. Bone Adhesives with Enhanced Mechanical Strength. Depending on the application locations, bone adhesives need to bear different stresses during fracture

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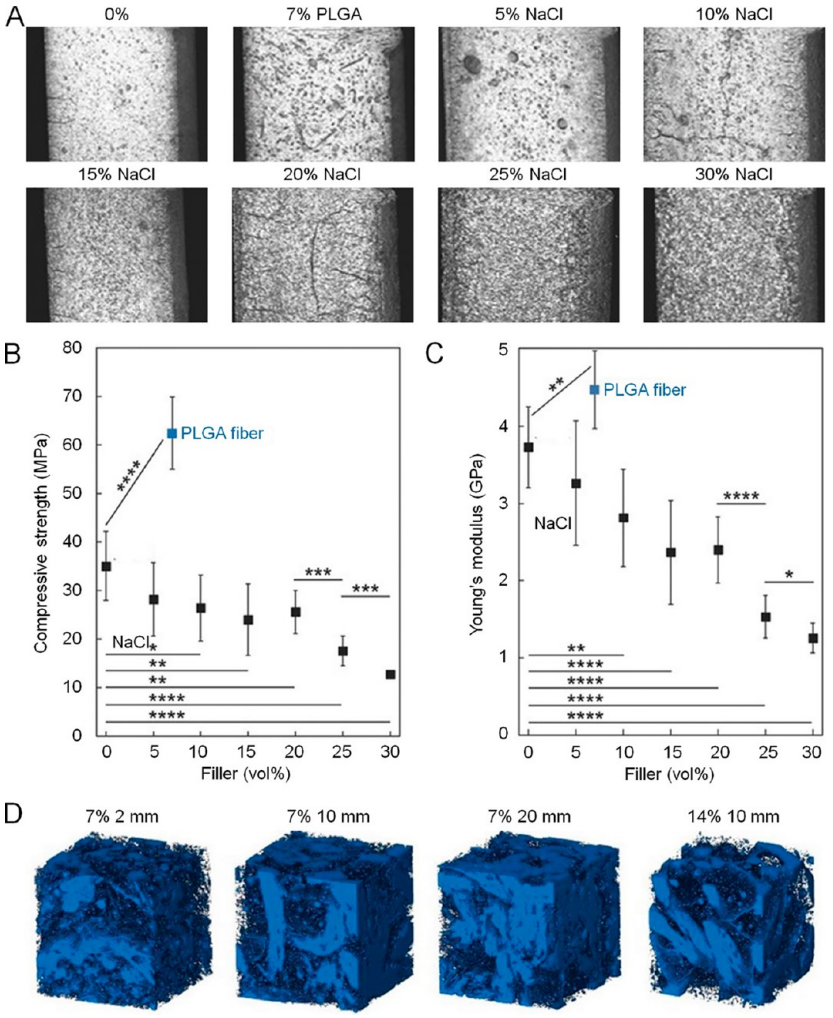

Figure 1. Characterizations and compression testing of bone adhesive with fillers. (A) Representative micro-CT images (axial cross-sections) of tetranite cylinders with different filler (PLGA fiber or NaCl) volume fractions. (B) Compressive strengths and (C) Young's moduli of samples depending on filler volume fraction (n = 10; data depict mean ± SD; compared with control with 0% fillers and with the next filler percentage (0% with 5%, 5% with 10%, and so forth) by one-way analysis of variance (ANOVA); α = 5%; asterisks (*) depict statistically significant difference: *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001). (D) Representative micro-CT images of bone adhesive samples reinforced with vicryl PLGA sutures, where cube sides are 4 mm. Panels A−C reproduced with permission from ref 41. Copyright 2018 John Wiley & Sons. Panel D reproduced with permission from ref 66. Copyright 2020 John Wiley & Sons.

treatment. The mechanical strength generally varies in one direction between the proportions of static loads (shear force, compression, tensile force, and torsional force) and dynamic loads (vibration and impact loads). In general, bone adhesives should withstand peak loads, although the mechanical performances of healthy bones are not an essential guideline for the suitability of bone adhesives. At present, there is no uniform standard for the mechanical strength of a bone adhesive. However, some studies consider that the elastic modulus of a bone adhesive for the treatment of fractures should be higher than 50 kPa.[56,57] When sufficient mechanical strength cannot be satisfied with bone adhesives alone, other substances need to be combined to enhance the mechanical strength.[38,41]

3.1.1. Bone Adhesives Containing Organic/Inorganic Filler. Biodegradable and bioresorbable synthetic polymer scaffolds comprising poly(α-hydroxy esters) and their copolymers, including poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-*co*-glycolic acid) (PLGA), and poly(ε-caprolactone) (PCL), have been widely used in various tissue engineering and shown to exhibit enhanced bone regeneration.[58−60] The U.S. Food and Drug Administration-approved PLA, PLGA, and PCL are most widely used.[61,62] Many studies on the treatment of bone defects have proven that PLGA is an unmatched scaffold material with good mechanical strength.[63] In addition, some absorbable plates used clinically to treat fractures are also made of PLGA, further indicating its excellent mechanical strength and biocompatibility.[64,65]

Inspired by the sandcastle worm, which can create a layer of protective tubular shell around its body, Kirillova *et al.* developed a novel bone adhesive based on tetracalcium phosphate and phosphoserine.[41,66] It cures in several minutes in a moisture-rich microenvironment and provides high bone-to-bone adhesion strength. Different fillers were added to this new type of bone adhesive, and mechanical tests were carried out to investigate the effect of the inclusion of polymer fillers on the mechanical strength (Figure 1). The micro-CT images of the solidified bone adhesives with different fillers are shown in Figure 1A. According to the results of mechanical tests, the group with 7% PLGA filler achieved the highest compressive

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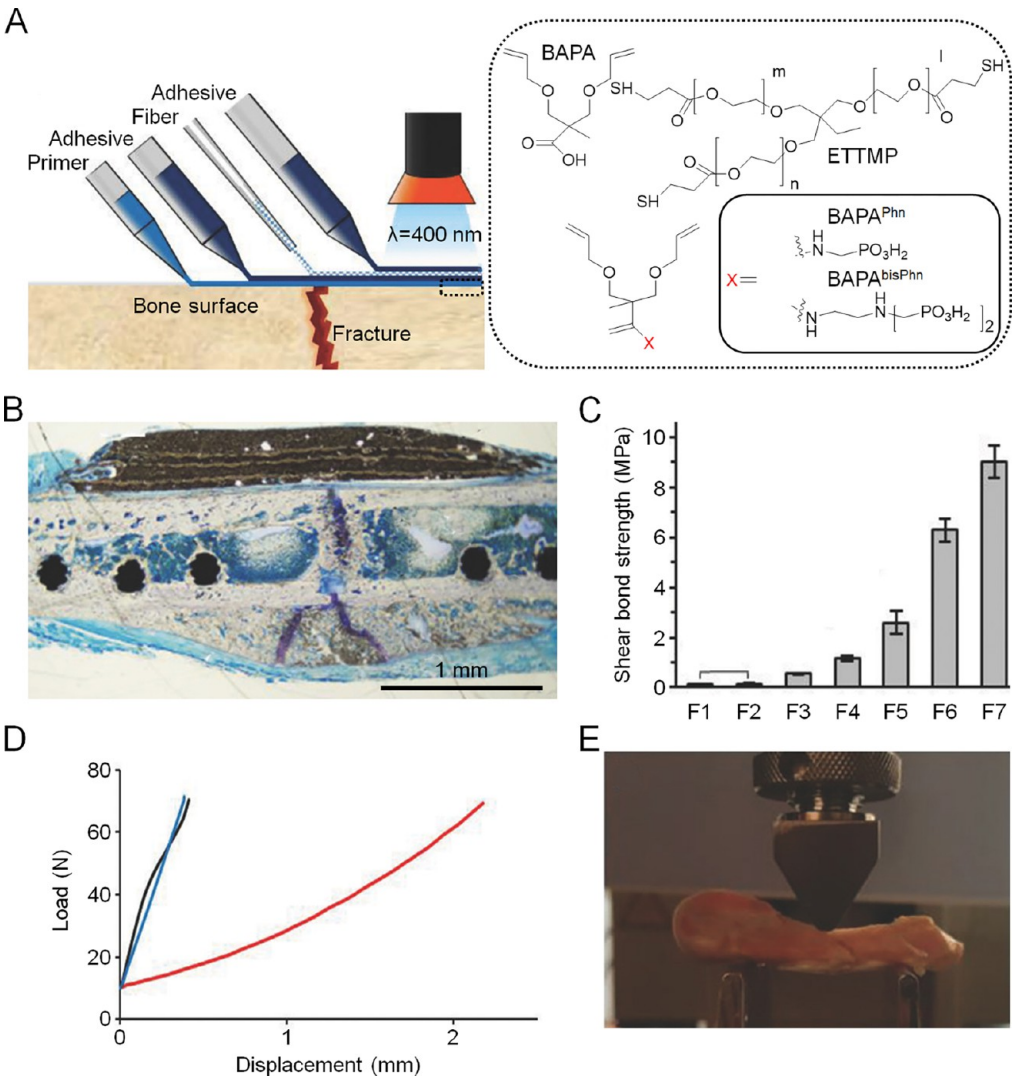

Figure 2. Characterizations of FRAP and cyclic three-point bending test of bone adhesive with fiber compared with internal fixations. (A) Schematic overview of FRAP build-up. (B) Overview of healed femur bone fracture. FRAP with four layers of adhesive and three layers of fiber on surface of femur. (C) Different shear bond strength obtained by diverse primer combinations. (D) Load and displacement curve of first load increase of cyclic three-point bending test of K-wire (red), Compact Hand 1.5 (black), and TEC FRAP (blue) fixation of a transverse fracture. (E) Images of dislocation at maximum load of 70 N (TEC FRAP with transverse fracture). Reproduced with permission from ref 38. Copyright 2018 John Wiley & Sons.

strength (Figure 1B) and Young's modulus (Figure 1C). Furthermore, the PLGA filler improved the fatigue resistance of bone adhesives.[66] Kirillova *et al.* introduced a new idea to develop bone adhesives. Supposing the mechanical strength of bone adhesives is not enough to maintain the regular load demand of bone tissue before fracture healing, polymer materials, such as PLGA, can be added to increase the mechanical strength of the bone adhesive.[66] This idea also makes it possible to treat load-bearing bone fractures with bone adhesives.

Kirillova *et al.* also studied three different lengths (2, 10, and 20 mm) of the PLGA fibers and two different volume fractions (7 and 14 vol %) and their effects on the compressive properties of adhesive material. The micro-CT analysis of different suture-reinforced formulations is shown in Figure 1D.[66] As PLGA suture and fiber have the same chemical composition, more continuous structure, larger diameter, and aspect ratio, they are used for comparison. The above series of studies have proven that the use of organic fillers is feasible to enhance the mechanical properties of bone adhesives.

3.1.2. Bone Adhesives Combined with Organic or Inorganic Fibers. Adding fillers has been a method frequently used to reinforce the strength of various materials.[67] However, polymer materials, such as PLGA, may affect the viscosity of adhesives. Can we use some other substances together to enhance the mechanical strength? The material and bone adhesive are packed separately, and the specially designed application sequence ensures that the viscosity of the adhesive will not be reduced. After the bone adhesive acts as a patch to bridge the ends of the fracture like a steel plate, the fibers on both ends can protect the adhesive from breaking and offer stable fixation simultaneously. Adding a fiber layer aims to form a hard shell on bone adhesive like a liquid plate mentioned in previous sections. The liquid plate may require light-induced reaction and sufficient contact area to fix the fracture, making it possible to add a reinforcement layer.

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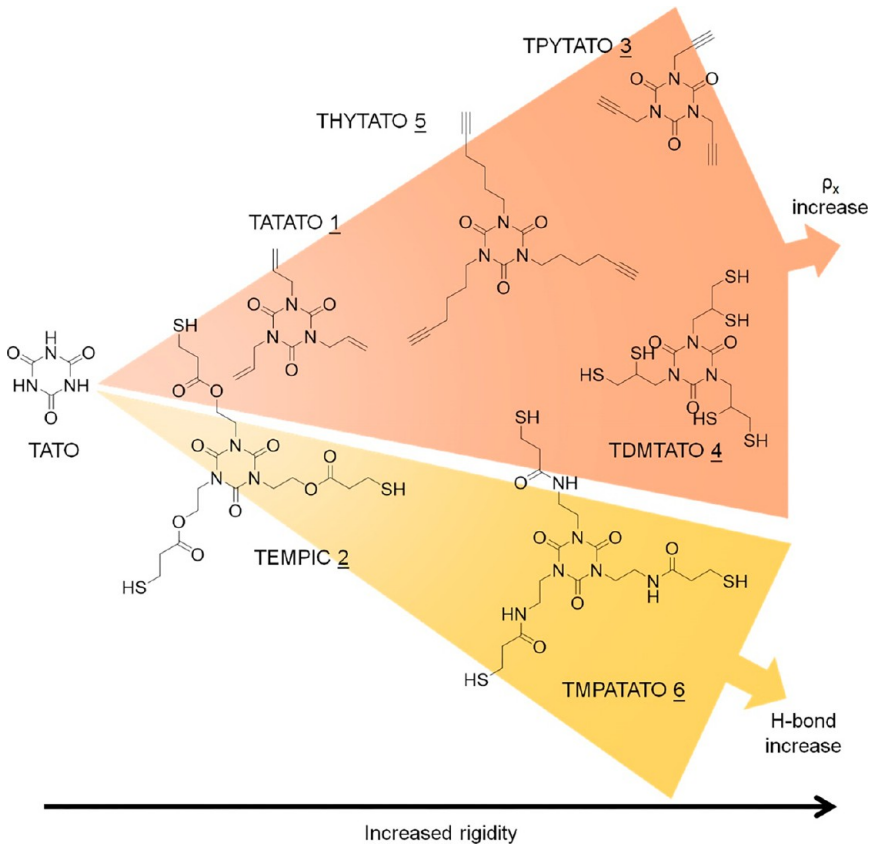

Figure 3. Structural variations of monomers evaluated as a means to increase mechanical rigidity with increased cross-linking density and hydrogen bonding. Reproduced with permission from ref 69. Copyright 2018 John Wiley & Sons.

Nordberg *et al.* introduced a kind of fiber-reinforced adhesive patch.[68] The maximum shear strength could reach 3.4 MPa by pretreatment of the bone surface with dopamine and poly(*p*-hydroxystyrene). It is worth mentioning that the reinforcing fiber material is electric glass (E-glass), a kind of inorganic material.

Granskog *et al.* presented a surgically achievable adhesive system using a thiol−ene coupling (TEC) chemistry system initiated by visible light.[38] The adhesive is designed and formulated as a new class of chemically influenced dental resin composites and self-etching primers (Figure 2). The bonding strength was verified on wet bone substrates by a fiber-reinforced adhesive patch (FRAP) (Figure 2A). In this system, the reinforced fiber is made of poly(ethylene terephthalate) (PET). The chemical formula in the box represents the different compositions of primers, and different primer combinations will affect the shear bond strength. In Figure 2B, the callus and three layers of fibers (the white band in the black matter on the surface below the bone is the fiber layer) can be observed after treatment by FRAP. In Figure 2C, the seventh group (F7) achieved a shear bond strength of 9 MPa. In the primer combinations of the seventh group, the adhesion enhancing molecule is a phosphonate-containing monomer called BAPA^{bisPhn}, and its chemical structure is shown in the right panel of Figure 2A, where the solvent is water and ethanol.

The authors showed that the load and displacement curves of the first load increase of the cyclic three-point bending tests of K-wire (red), Compact Hand 1.5 (black), and TEC FRAP (blue) fixation of a transverse fracture (Figure 2D,E). Compared with K-wire, TEC FRAP achieved excellent mechanical strength in the treating fracture like Compact Hand 1.5, one kind of plate. This means that if the adhesion strength is not adequate to satisfy the needs of fracture rehabilitation, another layer of fibers can be considered to increase the strength of reconstructed bone. The degradation of TEC FRAP itself is prolonged and not conducive to fracture healing. However, it is of great referential significance to apply a high-strength fiber layer (E-glass or PET) to two sides of the fracture gap to improve the mechanical strength after fracture repair.

In another study by Granskog *et al.* the researchers introduced a series of substances to improve the strength and stiffness of thermosetting materials (Figure 3).[69] Inspired by the rigid triazine-trione (TATO) ring, they used a click reaction between 1,3,5-triallyl-1,3,5-triazine-2,4,6-trione (TATATO) with the vinyl group and tris[2-mercaptopropionyloxy)ethyl]isocyanurate (TEMPIC) with the mercaptan (thiol) group to obtain the adhesive layer in FRAP. The introduction of alkyne group and the increase in the number of thiol group can increase the cross-linking density (ρ_x) of the product, which can be proved by 1,3,5-tri(prop-2-yn-1-yl)-1,3,5-triazinane-2,4,6-trione (TPYTATO) and 1,3,5-tris(2,3-dimercaptopropyl)-1,3,5-triazinane-2,4,6-trione (TDMTATO). In the reaction, 1,3,5-tri(hex-5-yn-1-yl)-1,3,5-triazinane-2,4,6-trione (THYTATO) can replace TPYTATO to improve the fluidity of the product. Compared with TEMPIC, *N*,*N*′,*N*″-((2,4,6-trioxo-1,3,5-triazinane-1,3,5-triyl)-tris(ethane-2,1-diyl))tris(3-mercaptopropanamide) (TMPATATO) contains a mercaptan group and possesses amide bond, which resulted in the generation of strong hydrogen

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ACS Appl. Mater. Interfaces XXXX, XXX, XXX−XXX

Table 3. Chemical and Physical Bonding of Bone Adhesives

bone adhesive	chemical bonding	physical bonding	reaction site	ref
polyurethane	covalent bond	hydrogen bonds	carbamate group of adhesive system and amine presented in bone collagen matrix	74
cyanoacrylate	covalent bond		acrylate group of adhesive system and amine presented in bone collagen matrix	33
fibrin adhesive	covalent bond		amino group of fibrin/fibronectin of adhesive system and carboxylic acid group presented in bone collagen matrix	37
polysaccharide-based adhesive	covalent bond		aldehyde of oxidized adhesive system and amine presented in bone collagen matrix	35
mussel-inspired adhesive	ionic bond		catecholic hydroxyl/carboxylic acid groups of adhesive system and calcium ion (Ca^{2+}) presented on surface of bone	42, 43
sandcastle-inspired adhesive	covalent bond	ionic interaction	amine group of adhesive system and carboxylic acid presented in bone collagen matrix; phosphate anions/catecholic hydroxyl of adhesive system presented on surface of bone	44, 45
frog-inspired adhesive	covalent bond		carboxylic acid of adhesive system and amine presented in bone collagen matrix	46

bonds in click reaction products. Both methods will increase the rigidity of final fixation.

3.2. Bone Adhesives with Osseointegration. The concept of "osseointegration" was first proposed by Branemark *et al.* and is defined as the direct connection between the bone and surface of an implant.[70] With the development of scientific research, another biomechanically oriented definition of osseointegration has been proposed: "A process whereby clinically asymptomatic rigid fixation of alloplastic materials is achieved, and maintained, in bone during functional loading".[53,54] In fracture treatment, osseointegration is considered to achieve and maintain clinical asymptomatic fracture healing. Norton *et al.* believe that bone adhesives can provide primary stability of bone through their adhesive properties and prevent early failure of fixation, which is also a new interpretation of osseointegration.[71]

It is often needed to improve the fatigue resistance of hydrogels to repair soft tissue,[72] but bone adhesives often need to enhance the rigidity of materials and ensure the absolute stability of bone tissue. Hence, it is necessary to provide a stable alignment for the fracture, whether it is fixed using internal fixation devices or with bone adhesives during the operation on the bone fracture, thereby facilitating fracture healing. A minimum distance of 150 μm of the implant interface movement will inevitably lead to soft tissue rather than bone formation.[73] The internal fixation devices can firmly fix the bone on both sides of the fracture ends. However, orthopedic surgeons cannot guarantee that there are no local deformities and other complications after a fracture treatment, solely by ensuring that the fracture is appropriately fixed.

In fact, after fracture fixation with internal fixation devices, uncontrollable fretting often occurs. Therefore, bone adhesives that can provide instant adhesion to fix bone fractures may be a better choice than internal fixation devices. If orthopedic surgeons want to fix the fractures firmly and promote fracture healing with bone adhesives, osseointegration is indispensable. The osseointegration is often achieved by chemical and physical bonding of bone adhesives, as listed in Table 3.[49] Polyurethane-based bone adhesives, for example, mainly rely on hydrogen bonds to hold fracture fragments together.[74] Both chemical and physical bonding form the basis for the successful treatment of fractures by bone adhesives. Chen *et al.* improved the strength of hydrogen bonds and protein aggregation density.[75] By adding guar gum, the zero-shear viscosity of soybean protein isolate adhesive was increased. Liu and Scherman developed a supramolecular hydrogel network as a dynamic adhesive for all kinds of nonporous materials, such as glass, stainless steel, aluminum, copper, and titanium, and porous matrices, such as wood and bone.[76] This adhesive provides a stable connection for fracture healing by providing supramolecular noncovalent interaction.

Regardless of the kind of bone adhesive developed, including synthetic, biomimetic, and natural-derived adhesives, our purpose is to enhance the strength of chemical or physical bonding between bone adhesive and bone and improve the bone integration of bone adhesive. In this way, an optimal microenvironment can be provided to promote bone healing.

3.3. Bone Adhesives with Upgraded Osteoconductivity. Osteoconduction refers to the growth of osteoblasts on the bone surface.[53] A conductive bone surface is a surface that allows the bone to grow on its surface or penetrate the pores, channels, or ducts. Wilson-Hench *et al.* proposed that osteoconduction was a process wherein bone was guided to conform to the surface of material.[77] In Scheme 2, we emphasize that novel bone adhesives provide osteoconduction using a liquid scaffold to promote fracture healing. The liquid scaffold uses adhesive and cohesive force to hold the fracture fragments together before and after curing. After curing, the liquid scaffold changes into a solid one. Scaffolds with excellent osteoconductivity are significantly superior to scaffolds with poor osteoconductivity in treating fractures and bone defects. However, since the osteoconduction of conventional bone adhesives is generally unsatisfactory, combining bone adhesives with osteoconductive materials, such as bioactive glasses (BGs) and CaPs, could promote bone tissue regeneration efficacy during bone fracture treatment.

3.3.1. Bone Adhesives Containing Bioactive Glasses. It has been proven that BG composited with Ca and silicon has excellent osteoconductivity.[79−81] Recently, Xu *et al.* developed a class of BG-containing bioactive pore-forming adhesives (Figure 4A).[78] The inclusion of BG and water-soluble PEG created macropores facilitating cell penetration, thus promoting new bone formation and fracture healing. The bone adhesive comprises 10% PSC BG (PSC is composed of 10.8% P_2O_5, 54.2% SiO_2, and 35.0% CaO), 40% PEG, and 50% 2-octyl cyanoacrylate (OCA). This type of bone adhesive exhibited higher mechanical strength than other components (Figure 4B,C), and BG also exhibited superior bioactivity in promoting fracture healing. Nevertheless, the toxicity of formaldehyde that originated in OCA against cells limited the further improvement of bioactivity.

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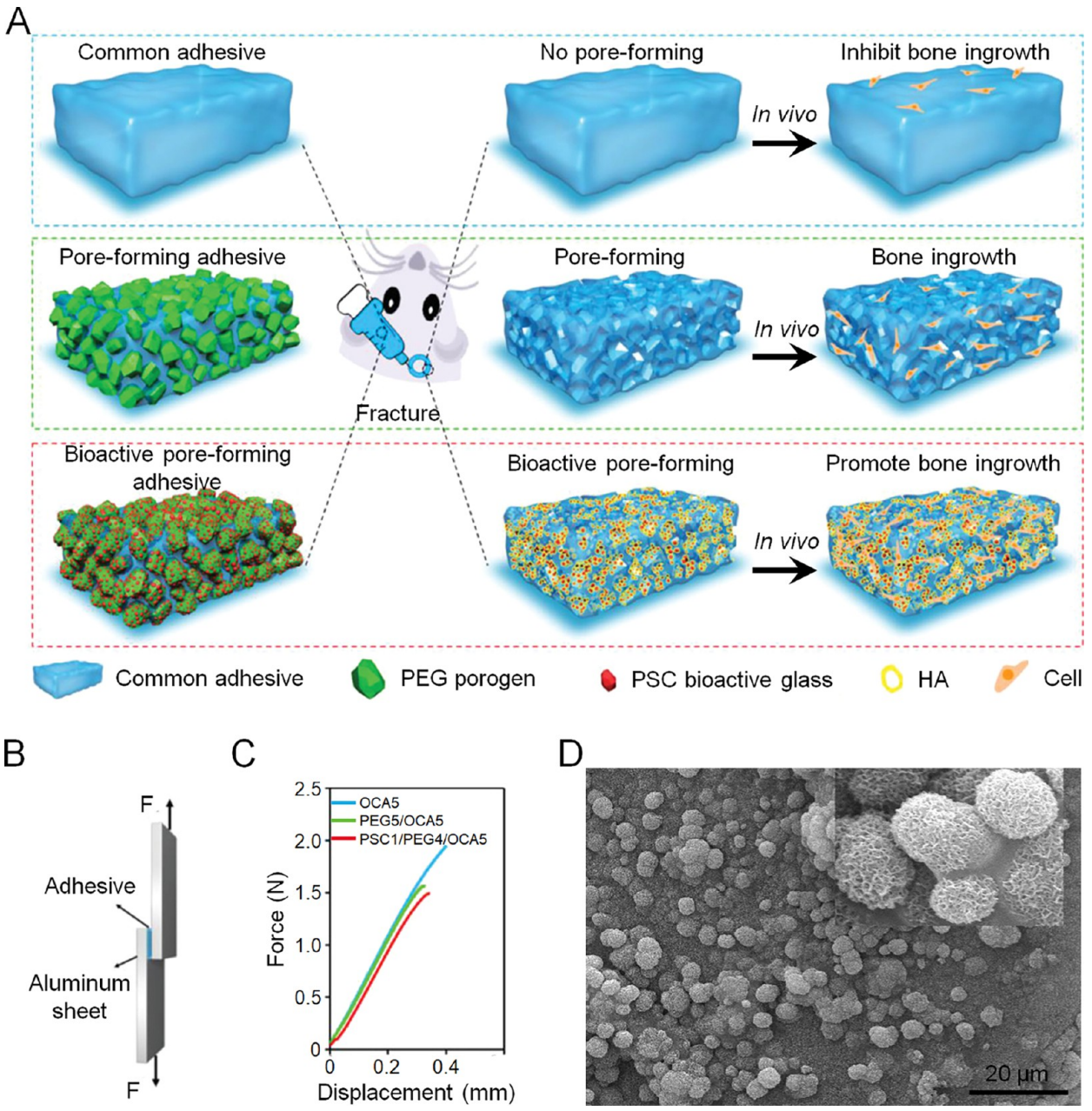

Figure 4. Schematic overview and bonding strength of bioactive pore-forming adhesive and osteoconduction of bone adhesive containing NBG. (A) Design of bioactive pore-forming adhesives. First type of adhesive: common cyanoacrylates-based adhesive (blue) with no pores, thus inhibiting cell migration and bone healing. Second type of adhesive: preliminary design of pore-forming adhesives with encapsulated PEG microparticles (green). Formation of pores by PEG dissolution enables cell replacement and growth. Third type of adhesive: bioactive pore-forming adhesives incorporating PSC/PEG composite porogen. Red particles are prewrapped PSC bioactive glass. These adhesives can create pores with a bioactive HA layer (yellow) to further promote bone regeneration. (B) Schematic illustration of lap-shear adhesion test. (C) Adhesion force versus displacement measured by lap-shear adhesion test for OCA, PEG_5/OCA_5-M, and $PSC_1/PEG_4/OCA_5$-M adhesives after curing for 24 h. (D) SEM images from cross-linked PPF/HEMA matrix containing 20% NBG after two weeks immersion in SBF. Panels A–C reproduced with permission from ref 78. Copyright 2020 John Wiley & Sons. Panel D reproduced with permission of ref 39. Copyright 2016 Elsevier.

Shahbazi *et al.* developed a type of poly(propyl fumarate) (PPF)-based adhesive containing nano-bioactive glass (NBG) as a reinforcer and hydroxyethyl methacrylate (HEMA) as a cross-linking agent.[39] The bioactivity, biodegradability, biocompatibility, and bone adhesion of the adhesive were thoroughly investigated. PPF/HEMA/NBG enhanced the adhesion of adhesive to the wet bone surface. The joint tensile and shear resistance between the two wet bone surfaces was measured to be in the range of 9–59 MPa. Composite adhesive exhibited excellent biomineralization capability in simulated body fluid (SBF) (Figure 4D). The inclusion of NBG confers excellent osteoconductivity on the bone adhesive.

3.3.2. Bone Adhesives with CaPs. To mimic biomimetic inorganic bone composition, many kinds of CaPs, including HA and tricalcium phosphate (TCP), have been widely used in bone tissue engineering.[82,83] It has been proven that the HA scaffold with appropriate porosity has sufficient mechanical strength and exhibits excellent osteoconductivity.[84–86] Granskog *et al.* introduced HA into the bone adhesive to ensure

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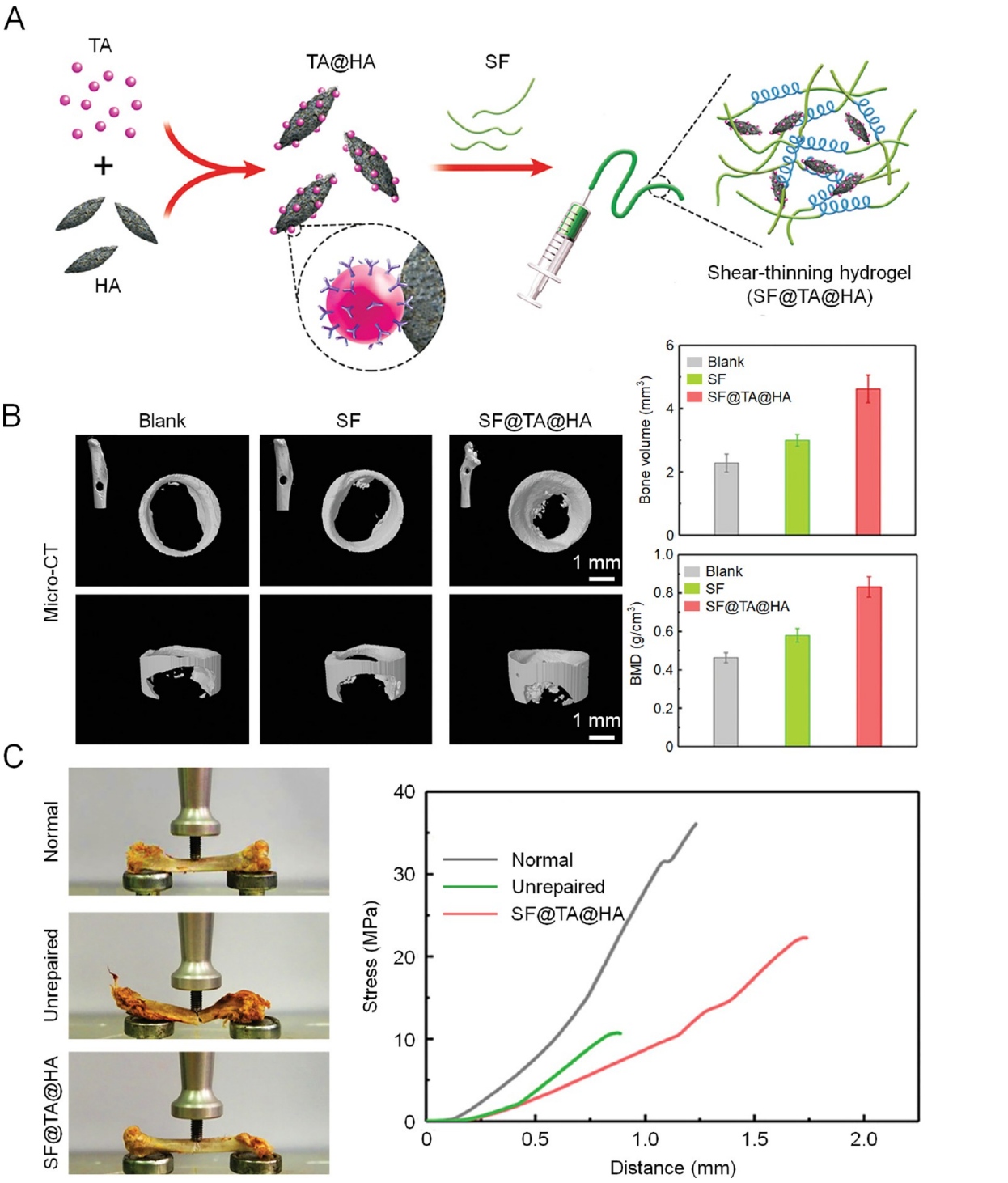

Figure 5. Schematic illustration of SF@TA@HA fabrication and comparison of osteoconduction between bone adhesive containing HA and bone adhesive alone. (A) Schematical illustration of SF@TA@HA fabrication. (B) *In vivo* assessment of bone regeneration in rat femoral defect model. Micro-CT images included the analysis of axial and radial bone distribution in the defect sites after eight week implantation. Bone volume and bone mineral density (BMD) were determined by micro-CT. (C) Images of rat femurs under three-point bending test and load versus distance curves of normal, unrepaired, and SF@TA@HA groups in three-point bending test. Normal group, normal rat femur. Unrepaired group, cracked rat femur without fixation treatment. SF@TA@HA group, broken rat femur treated with SF@TA@HA. Reproduced with permission from ref 89. Copyright 2019 John Wiley & Sons.

high filling volume, stiffness, and elastic modulus to improve the osteoconduction of bone adhesive.[38] Serrano *et al.* introduced HA to a chitosan-based adhesive, and the tensile strength of adhesive in physiological conditions was improved. Calcium carbonate ($CaCO_3$) and hyaluronic acid covalently cross-linked hydrogels showed good biocompatibility *in vitro*.[87] Schreader *et al.* developed a unique kind of polyurethane-based foam-like adhesive reinforced with nanosized HA particle and carried out a series of experiments for bone-to-bone bonding application in terms of mechanical adhesion and biocompat-

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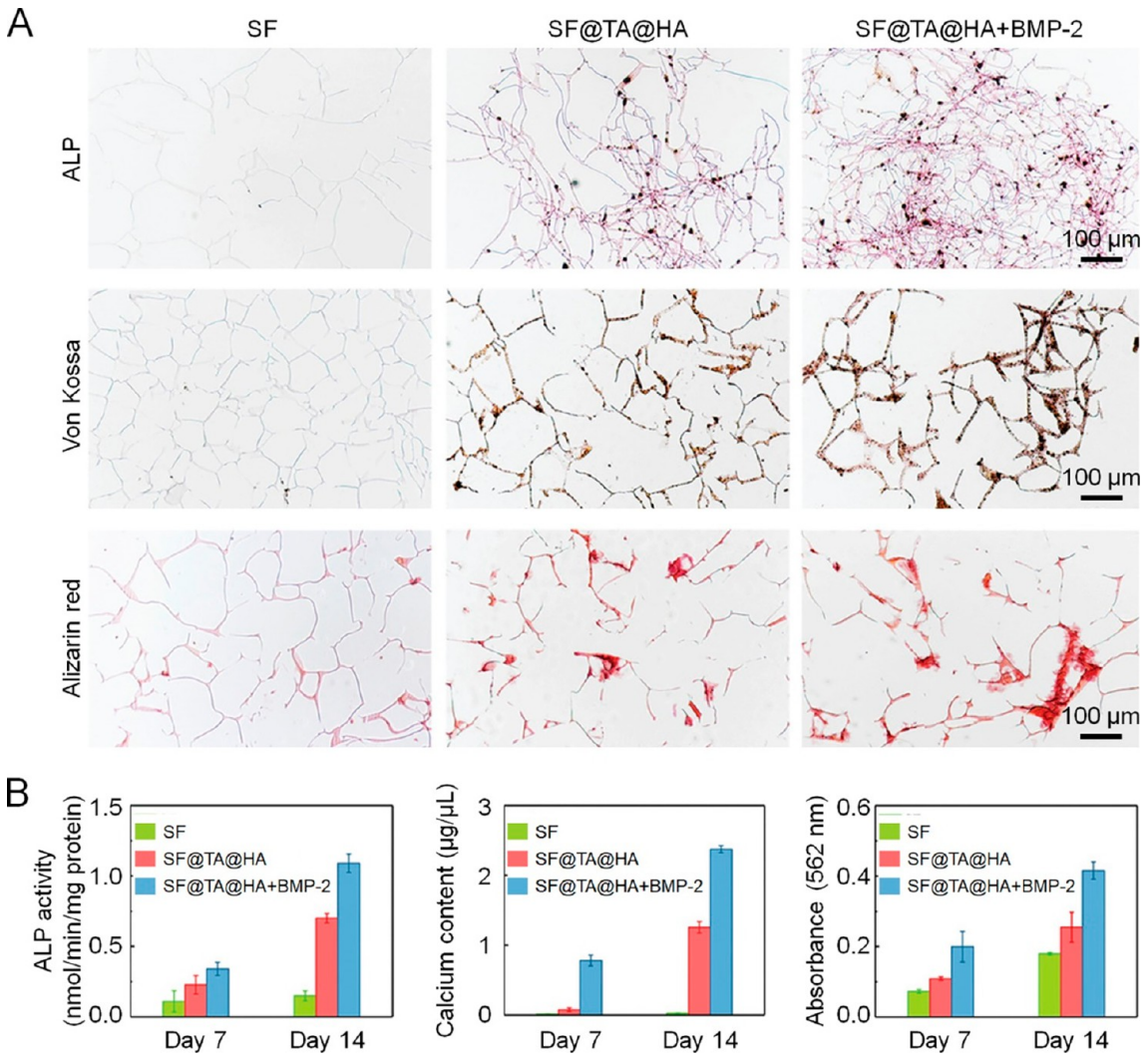

Figure 6. Comparison of bone regeneration capacity among SF, SF@TA@HA, and SF@TA@HA containing BMP-2. (A) *In vitro* osteogenic differentiation of rat bone, MSCs seeded on SF@TA@HA with or without BMP-2. ALP, von Kossa, and ARS staining used to characterize the osteogenic differentiation of MSCs. (B) ALP activity, contents of Ca deposition, and absorbance (562 nm) also measured. Reproduced with permission from ref 89. Copyright 2019 John Wiley & Sons.

ibility.[88] Similarly, Bai *et al.* developed a mineral−organic bone adhesive with strong water-resistant fixation and enticed bone tissue regeneration.[89] The system leveraged tannic acid (TA) as a phenolic glue molecule to spontaneously co-assemble with silk fibroin (SF) and HA to fabricate the inorganic−organic hybrid hydrogel (SF@TA@HA). HA conferred excellent osteoconduction for the adhesive named SF@TA@HA (Figure 5A). Compared with the blank and SF groups, SF@TA@HA exhibited the best bone regeneration effect in bone defect *in vivo* (Figure 5B). After treating an animal femoral fracture, a three-point stress test on the healed fracture model confirmed that SF@TA@HA exhibited an excellent therapeutic effect (Figure 5C).

In addition to HA, TCP can also improve the osteoconductivity of bone adhesives. Erken *et al.* developed a new bone adhesive containing β-TCP ceramics.[90] The MG63 human osteosarcoma cell line was used to test the bioactivity of material *in vitro*, and bovine ribs were used to test the mechanical strength of material. All materials showed high porosity (>90%) and uniform ceramic particle distribution. The compressive strength of polyurethane scaffold containing 40 wt % 1−2 mm of β-TCP was 1.34 ± 0.10 MPa. Furthermore, owing to the excellent osteoconductivity of β-TCP ceramics, a polyurethane-based bone adhesive containing β-TCP showed great potential to be transformed into a final product. A series of *in vitro* and *in vivo* experiments conducted by Lei *et al.* proved that the addition of β-TCP to the porous polyurethane adhesives enhanced the mechanical strength and improved the osteoconductivity of adhesive and was more conducive to fracture healing.[91]

3.4. Bone Adhesives with Upgraded Osteoinductivity. Osteogenic induction implies that primitive, undifferentiated, and pluripotent cells are stimulated to develop into an osteoblastic lineage. Osteoinduction is the process by which osteogenesis is induced.[77] In the recent surgery for non-union of fracture, using osteoinductive material is an effective treatment. The conventional bone adhesive does not always possess excellent osteoinductivity. Osteoinductive materials, such as bone morphogenetic protein (BMP) and citrate, were included to enhance the osteoinductivity of bone adhesive.

3.4.1. Bone Adhesives Containing Bone Morphogenetic Proteins. BMP-2 has been widely used in the treatment of bone non-union and bone defects. It has been proven that BMP-2 is a potent inducer of bone remodeling that can

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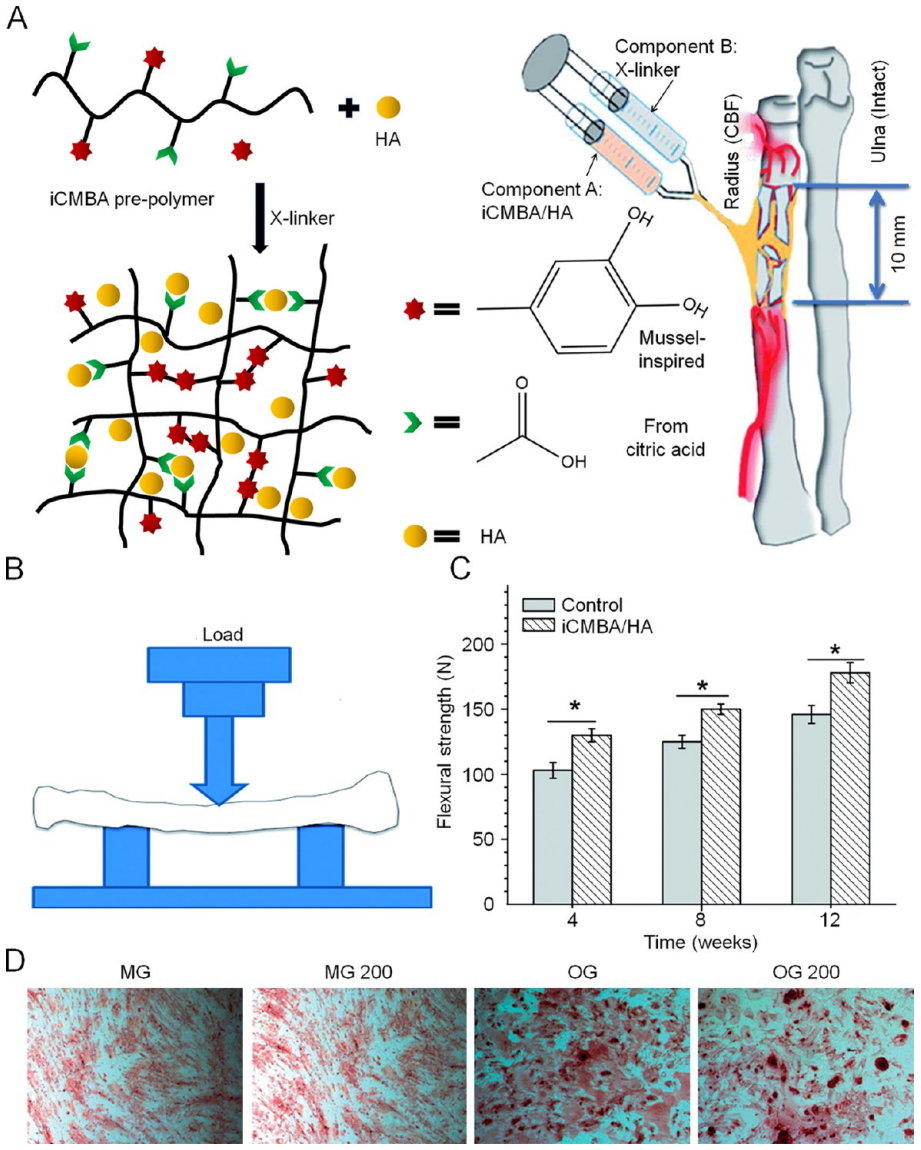

Figure 7. Schematic overview and bonding strength of bone adhesive called iCMBA/HA and evidence of ability of citric acid to promote differentiation of MSCs. (A) Schematic representation for iCMBA/HA cross-linking process and iCMBA/HA injection procedure to treat a comminuted bone fracture. (B) Three-point bending test performed for the comminuted fracture area of the radius bone. (C) Maximal flexural strength, recording a significant difference ($P < 0.05$). (D) ARS staining for Ca deposit in MSC cultures treated with growth media (MG), growth media with 200 μM citrate supplement (MG 200), osteogenic media (OG), osteogenic media with 200 μM citrate supplement (OG 200) at the 21st day. Citrate in markedly enhanced Ca deposit formation of osteogenic differentiated MSCs (ARS staining, 40×). Reproduced with permission from ref 101. Copyright 2015 Royal Society of Chemistry.

directly regulate osteoblast differentiation and osteoclast activity.[92] The inclusion of BMP-2 in the bone adhesive to treat bone fractures is a promising clinical attempt.

Bai *et al.* introduced BMP-2 into the SF@TA@HA bone adhesive and studied its bone regenerative capacity.[89] The addition of BMP-2 conferred excellent osteoinductivity on the bone adhesive (Figure 6). Von Kossa and Alizarin Red S (ARS) staining of the hydrogel histological sections showed that SF@TA@HA-containing BMP-2 promoted osteoinductivity. The staining images provided clear evidence of cell-mediated Ca mineral deposition and demonstrated that mesenchymal stem cells (MSCs) were inclined to differentiate into osteoblasts (Figure 6A).

After adding BMP-2, the Ca deposit of the cells treated by SF@TA@HA was the highest, suggesting that SF@TA@HA containing BMP-2 may improve early bone formation *in vitro* (Figure 6B). Osteogenic differentiation of MSCs *in vitro* was characterized by the expression of alkaline phosphatase (ALP), an early indicator for evaluating the metabolic activity of osteoblasts.[93] Compared to the pure SF as a control group, the ALP activity was significantly enhanced in the SF@TA@HA group after 14 days of culture, suggesting that SF@TA@HA upregulated the level of ALP. In particular, the combination of BMP-2 and SF@TA@HA showed the highest expression of ALP in osteogenic MSCs. Additionally, the new bone tissue also enhanced the biomechanical strength of fixed bone in the early stage of fracture treatment, further accelerating the healing process of fracture.

3.4.2. Bone Adhesives Containing Citrate. Citrate is an intermediate product of the Krebs cycle, which is highly conserved in native bone. Over 90% of the body's total citrate content is located in the skeletal system and is closely related

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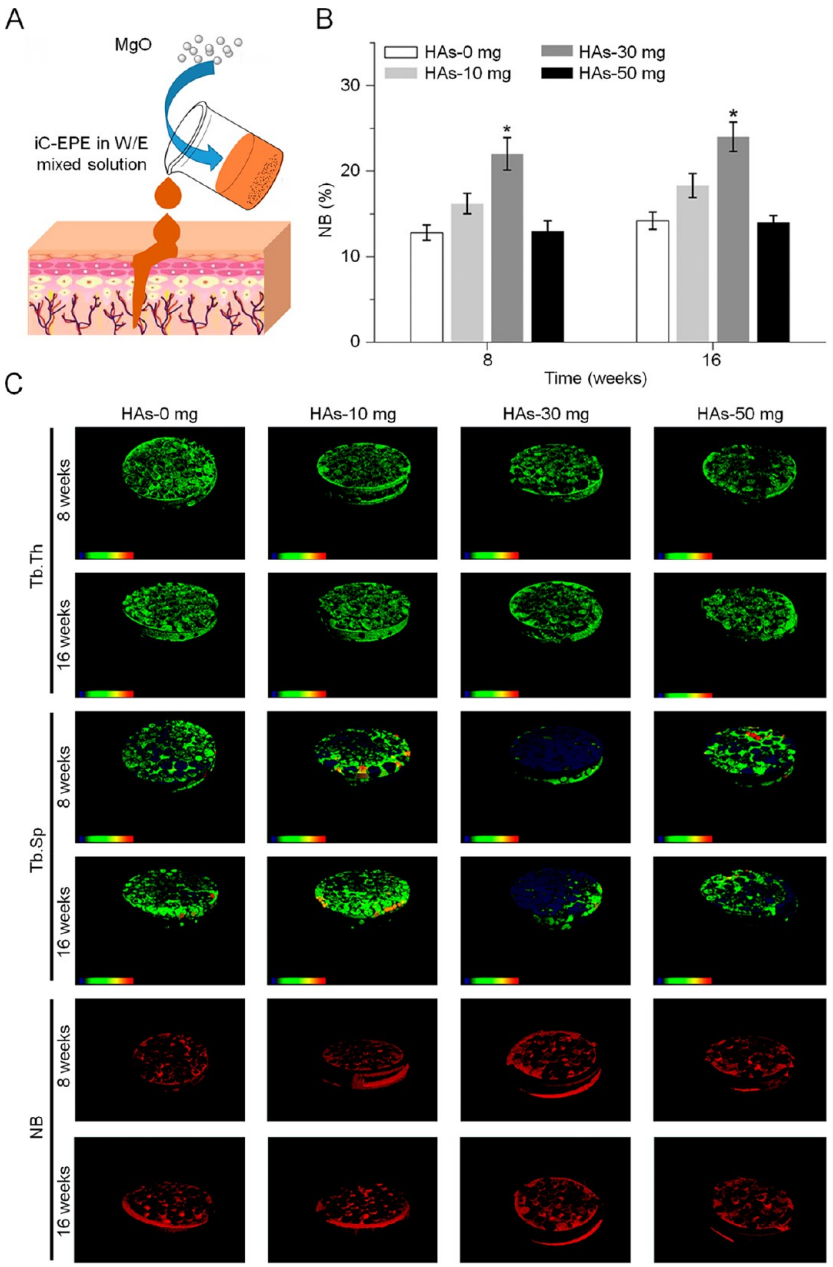

Figure 8. Schematic overview about cross-linking effect of MgO in tissue adhesive and osteoinduction of Mg^{2+} in bone tissue engineering. (A) MgO serving both as a cross-linker and a composite filler to enable a wide tunability on cross-linking time and adhesion strength of resultant iC-EPE/MgO hydrogel that holds great potential for a myriad of surgical applications, such as wound closure and healing. (B) Percentage of new bone areas in scaffolds with Mg particle 8 and 16 weeks after implantation in dorsal muscles. *P < 0.05. (C) Micro-CT images depicting formation of new bone in scaffolds and histomorphometric parameters. Panels A and B reproduced with permission from ref 105. Copyright 2019 Elsevier. Panel C reproduced with permissin from ref 102. Copyright 2019 Royal Society of Chemistry.

to bone formation metabolism.[94−97] Hu *et al.* quantified the citrate content in primary bone and discussed the indispensable role of citrate in regulating bone apatite nanocrystalline structure.[50] Costello *et al.* stated that "osteoblast citration" plays a critical role in the osteogenic differentiation and subsequent mineralization of MSCs.[98] Tran *et al.* first demonstrated that citrate-based degradable polymers significantly increased the expression of *ALP* and *osterix* genes in C2C12 cells.[99] Recently, as a metabolic factor, citrate was found to elevate cell energy status during osteodifferentiation through a metabonegenic regulation process, thus promoting osteodifferentiation.[94] Therefore, citrate has been used as a building block for hydrogels or adhesive development.[100]

Inspired by the adhesive strategy of mussels,[42,43] Xie *et al.* proposed a new injectable citrate-based mussel-inspired bioadhesive HA (iCMBA/HA) bone substitute for comminuted bone fracture treatment (Figure 7A).[101] iCMBA/HA can cross-link in less than 5 min and fix the fracture fragments. The as-prepared iCMBA/HA possessed a low swelling ratio, complete degradation within 30 days, excellent biocompatibility, osteoinductivity, and flexural strength (Figure 7B−D). The polymers containing citrate provide different solutions for the development and application of bone adhesives and improve the bioactivity of the materials to a certain extent.

3.4.3. Other Bone Adhesives with Enhanced Osteoinductivity. There are many other substances with osteoinductivity,

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ACS Appl. Mater. Interfaces XXXX, XXX, XXX−XXX

such as magnesium (Mg^{2+}) and zinc ions (Zn^{2+}). Many studies have reported the induction of Mg^{2+} in bone tissue engineering.[102−104]

Lu *et al.* found that magnesium oxide (MgO) can cross-link iC-EPE (injectable citrate-based mussel-inspired bioadhesive (iCMBA, iC) made with PEG−PPG-PEG (EPE) diol) through facile, simple mixing, having great potential to be used as a bone adhesive (Figure 8A).[105] Although this work does not verify the potential of this Mg-containing adhesive in fracture treatment, we found that Mg is beneficial in inducing osteoblast differentiation and promoting fracture healing (Figure 8B,C), based on the results of Xu's group on Mg-containing scaffolds.[102] In this study, HAs-0Mg, HAs-10Mg, HAs-30Mg, and HAs-50Mg represent the Mg contents of different HA scaffolds, namely 0, 10, 30, and 50%, respectively. After 8 and 16 weeks, micro-CT scanning was performed on bone tissue samples implanted with different scaffolds to compare their trabecular thickness (Tb.Th), trabecular separation (Tb.Sp), and new bone (NB).

Magnesium phosphate ($Mg_3(PO_4)_2$) cement was also used as bone cement to treat fractures, but it may not be practical for clinical use given its poor degradability.[106] Many clinical drugs with osteoinductivity properties, such as simvastatin, have also been used to study pseudobone thermogel for fracture treatment *in vitro* and have shown practical therapy effects.[107] Liu *et al.* modified multifunctional bone-adhesive hydrogel with framework-8 nanoparticle that upregulated the production and secretion of ALP, collagen I, and osteocalcin, promoting osteogenic differentiation MSCs.[108]

4. CONCLUSION AND PERSPECTIVES

In recent years, there has been considerable research progress in bioactive scaffold implantation and other bone tissue engineering methods to treat bone defects and non-union. Research pioneers have been attempting to use these methods to improve the performances of liquid scaffolds or liquid plates to treat fractures. However, some of the examples discussed above usually only improve one or, at the most, two aspects of bone adhesives. Identification or discovery of adhesives that can simultaneously possess the four characteristics of mechanical strength, osseointegration, osteoconductivity, and osteoinductivity will be considered a milestone in fracture treatment with bone adhesives.

The development of bone adhesives should focus on mechanical strength, including bonding strength. The biggest challenge for the clinical application of bone adhesive is the uncertainty of clinicians to determine whether it could provide stable adhesion strength to the fracture site. Moreover, the application methods of bone adhesive need to be constantly optimized. A more convenient and effective large-scale preparation method of bone adhesives is also beneficial for their large-scale clinical application. In the future, researchers can perhaps start with the reaction kinetics and chemical compositions of bone adhesives to improve the bonding strength. However, it is not easy to make a significant breakthrough in the short term. According to the examples discussed earlier, organic and inorganic fibers can enhance the cohesive and adhesive strength of bone adhesives. To ensure the mechanical strength of fixed bones, we should improve the osseointegration, osteoconductivity, and osteoinductivity of bone adhesives to make the fractured bone heal as soon as possible after adhesion.

Researchers are expected to optimize bone adhesives through the perspective of bone tissue engineering to become an adequate substitute for the internal fixation of metal devices, such as steel plates and nails, in the process of fracture treatment. However, for the time being, at least, there is no advantage in using a bone adhesive over steel plates or nails in terms of strength. Some researchers have proposed that the best bonding strength that a bone adhesive can achieve at present is 9.0 MPa by way of liquid plate bonding.[38,47] Recent research has reported that the best adhesion strength to be adhered to the bone by hydrogel detected *in vitro* is 0.05 MPa by way of liquid scaffold bonding.[109] These *in vitro* instant bond strength tests are not necessarily meaningful. Because bonding bone tissue is different from bonding other materials, bone is considered to be regenerative tissue. Once the fracture has healed, mechanical testing of the whole bone becomes meaningful. The elastic modulus of a titanium alloy steel plate is similar to that of cortical bone (20 GPa). It is an ideal material for fracture fixation at present, and it also has advantages under periodic load.[110]

Nevertheless, by adding or changing the compositions of bone adhesives, it is possible to make fracture healing faster and better and recover bone function earlier than was possible before. This is the most significant advantages of bone adhesives over steel plates. Moreover, another challenge is adding other components to provide bone adhesives anti-inflammatory or antibacterial functions to meet various applications.

Some adhesives, such as chitosan-based ones, were usually used in dry conditions. Although they have excellent mechanical and biological properties, they cannot be used to repair fractures. Because of this, Villanueva *et al.* pointed out that the water sensitivity of this adhesive can be reduced by adding a cross-linking agent so that it can be used to adhere to tissues and even bone fractures.[111] In addition, Morsali *et al.* pointed out that the future development direction of bone adhesives can be studied at a microlevel to determine ways to improve the ability to withstand large nonlinear degeneration.[112]

At present, orthopedic doctors often consider the possibility of occasionally using bone adhesives when dealing with bone fragments of periarticular fractures. However, orthopedic doctors usually do not expect to use bone adhesives to treat long bone fractures. Compared with traditional metal internal fixation, bone adhesives cannot provide stable fixation and help patients exercise early after surgery. This limitation goes against the Arbeitsgemeinschafts fur osteosynthesefragen (AO) principle of fracture treatment.[113]

The AO principle is the gold standard guideline for orthopedic doctors worldwide. However, in recent years, the principle of fracture treatment is also changing from the AO principle to the Biological Osteosynthesis (BO) principle.[114,115] Compared with the former, the BO principle prefers to regard bone as an organism and argues that fracture healing and reduction need to meet the requirements of alignment, further considering that the blood supply to the bone should not be affected to ensure rapid fracture healing. The bone adhesive does not need to expose both ends of the fracture in an extensive range when it is used. Thus, it will not damage the blood supply around the fracture like steel plates or nails do, which is more in line with the BO principle and hence, easy to operate.

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ACS Appl. Mater. Interfaces XXXX, XXX, XXX−XXX

Orthopedic surgeons would naturally prefer such a perfect type of bone adhesives with simultaneous enhanced mechanical strength, excellent osseointegration, osteoconduction, and osteoinduction. This bone adhesive will show strong adhesion when placed at the fracture ends and integrate the fractured pieces. After bone adhesive curing, it also needs to show superior mechanical strength to ensure the safety of early functional recovery of the fractured bones. More importantly, substances in the bone adhesives are required to exhibit excellent osteoconduction and osteoinduction so that new bones can form rapidly, repair the fractures, and remodel the whole bones. In the best-case scenario, the new bone adhesives can make the fractures heal quickly and ensure biomechanical strength comparable to traditional metal internal fixation. In Scheme 2, we summarize two research ideas of bone adhesives, including liquid scaffold and plate. Perhaps the two-component adhesive is a bold and practical attempt. Component 1 is responsible for the function of the liquid plate, which is attached to the bone surface to fix both ends of the fractures and provides continuous mechanical strength. Component 2 is responsible for the function of the liquid scaffold, which exists in the fracture gap and still offers excellent osseointegration, osteoconduction, and osteoinduction after curing.

Bone adhesives are still not widely used in the clinical treatment of limb-bearing bone and jaw fractures and are only at the stages of *in vitro* or *in vivo* experiments.[39,40] However, fixation using well-established bone adhesives, such as medical aural and encephalic glue, for the second stage of reimplantation after skull fracture or cranial flap decompression has been reported.[116,117] This method of fixation not only has minor side effects but also has more apparent therapeutic efficacy.

The enormous potential applications for bone adhesives are summed up according to the demands of the clinical medical market (Table 4). From this table, we can infer that mature bone adhesive is not only needed during orthopedic trauma-related surgery[118] but also general joint surgery,[119,120] thoracic surgery,[121] oral surgery,[49] and neurosurgery.[122]

Table 4. Application Prospects for Bone Adhesives

clinical scenario	anatomical site	purpose	required mechanical strength	ref
neurosurgery	skull	adhesive fixation of skull	weak	122
oral surgery	jaw	adhesive fixation of jaw	medium	49
thoracic surgery	sternum and rib	closure of sternum	strong	121
		fixation of rib		
joint surgery	meniscus and cartilage	repair of meniscus	medium	119, 120
		transplantation and fixation of cartilage		
trauma department of orthopedics	extremities and pelvis	fixation of systemic bone fracture	extremely strong	118

Thus, far, there is no perfect solution for the mature design of bone adhesives. There are few *in vivo* studies on bone adhesives because it is not easy to establish the standard models of animal fractures. In addition, most of the bone adhesives that have been used or will be used still show inadequate adhesion and mechanical performances. However, the development and progress of bone tissue engineering technology are continually increasing. Although most of the existing studies on bone adhesives mainly focuses on improving their adhesive strength, future bone adhesives should enhance their fracture healing performances. Furthermore, establishing a standard animal model for *in vivo* testing of bone adhesives also requires attention. We believe that improved strategies will help overcome existing challenges and open new avenues for the use of bone adhesives in fracture treatment.

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Notes

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ACS Appl. Mater. Interfaces XXXX, XXX, XXX−XXX

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ACS Appl. Mater. Interfaces XXXX, XXX, XXX−XXX

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