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Precision medicine strategies for spinal degenerative diseases: Injectable biomaterials with in situ repair and regeneration

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ABSTRACT

As the population ages, spinal degeneration seriously affects quality of life in middle-aged and elderly patients, and prevention and treatment remain challenging for clinical surgeons. In recent years, biomaterials-based injectable therapeutics have attracted much attention for spinal degeneration treatment due to their minimally invasive features and ability to perform precise repair of irregular defects. However, the precise design and functional control of bioactive injectable biomaterials for efficient spinal degeneration treatment remains a challenge. Although many injectable biomaterials have been reported for the treatment of spinal degeneration, there are few reviews on the advances and effects of injectable biomaterials for spinal degeneration treatment. This work reviews the current status of the design and fabrication of injectable biomaterials, including hydrogels, bone cements and scaffolds, microspheres and nanomaterials, and the current progress in applications for treating spinal degeneration. Additionally, registered clinical trials were also summarized and key challenges and clinical translational prospects for injectable materials for the treatment of spinal degenerative diseases are discussed.

1. Introduction

The developmental stages of humans are divided into growth, maturity and ageing. As the body ages, degenerative changes occur in the spinal system. The most significant of these are intervertebral disc degeneration (IVDD) and vertebral osteoporosis [1,2]. Spinal degeneration is the primary causes of neck, shoulder, lumbar and leg pain in middle-aged and elderly patients and is one of the most common disease in orthopaedic [3]. In an increasingly global ageing society, its incidence is increasing every year. In Western countries, approximately 80% of adults are affected by these diseases [4,5]. Back and neck pain costs the U.S. economy more than $100 billion a year, according to official statistics [6]. Therefore, it is of great importance to effectively treat it [7]. At present, the treatment of spinal degenerative diseases is primarily symptomatic and surgical in nature, and it cannot effectively intervene in the pathophysiological process of intervertebral disc and vertebral body degeneration, resulting in additional complications and higher morbidity [8]. Based on the regenerative and repair functions of injectable biomaterials, they have become a major research focus for proposing new treatment options for spinal degenerative diseases.

2. Spinal degenerative diseases and treatment status

Spinal degenerative diseases refer to the ageing-related diseases caused by comprehensive degeneration and mutual influence of the intervertebral disc, vertebral bone and its accessory structures [9]. The spine consists of 26 vertebrae and the intervertebral discs between them. The vertebral body carries the body's weight, and the disc is made up of the nucleus pulposus, annulus fibrosus, and cartilage end plate, which act as a buffer [10,11]. After IVDD, the spinal load changes, and the blood nutrient supply is insufficient, which leads to a gradual decrease in collagen, proteoglycan and water content and the gradual loss of elastic properties of the intervertebral disc, resulting in the occurrence of related diseases [12]. The nature of vertebral degeneration is osteoporosis, which manifests as decreased calcium deposition in vertebral bone and obvious bone loss, resulting in bone microstructure destruction and a decreased elastic modulus. The weight bearing capacity of the vertebral body is significantly reduced, and spinal compression fracture may occur

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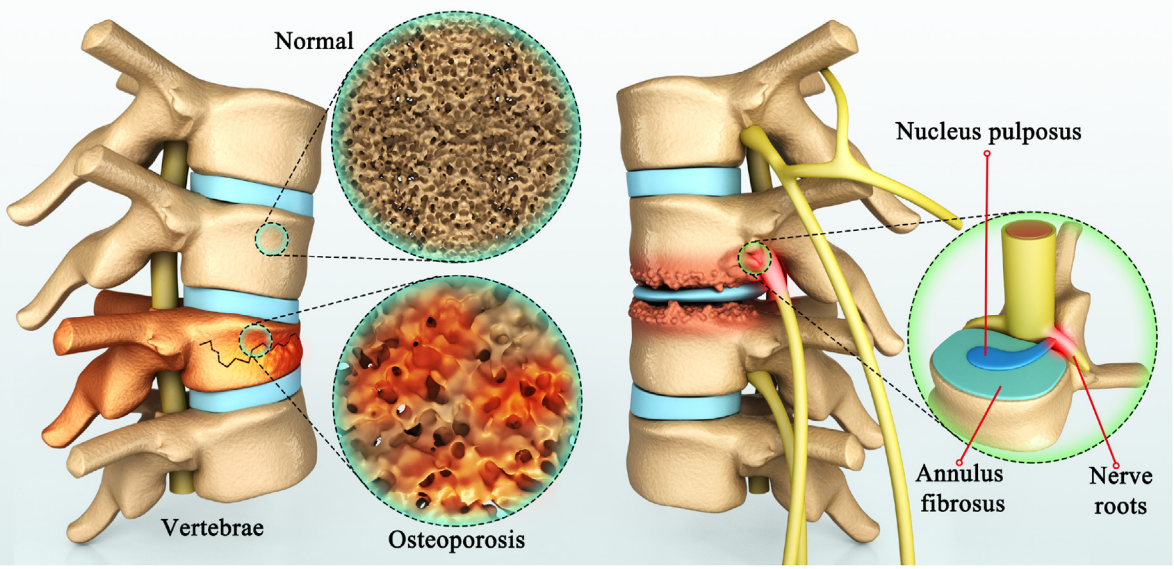

Fig. 1. Schematic diagram of spinal structure and mechanism of degenerative diseases.

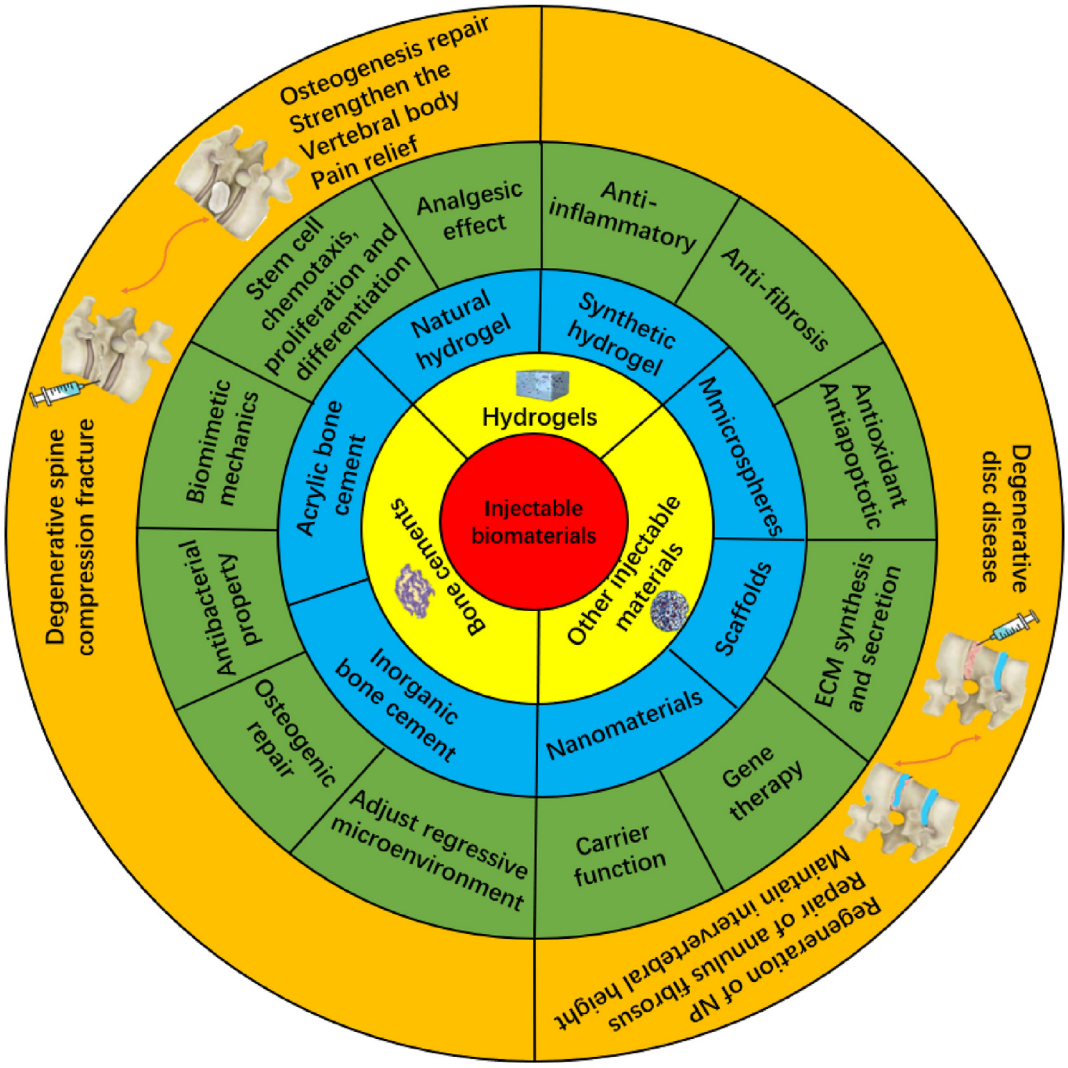

Fig. 2. Schematic diagram of the application of injectable bone repair materials in spinal degenerative diseases.

after even a minor trauma [13]. The composition of the spine and the pathogenesis of degenerative disease are shown in Fig. 1.

Spinal degenerative diseases are one of the most common orthopaedic diseases, including intervertebral disc herniation, intervertebral disc vacuum sign, spinal stenosis, degenerative osteoporotic compression fracture, degenerative lumbar spondylolisthesis, and degenerative scoliosis. At present, the common treatment methods are primarily divided into conservative and surgical modalities. A conservative treatment includes bed rest, drug therapy, physical therapy, etc. The effect and duration are limited, so surgery has become the preferred treatment [14]. The primary surgical treatment measures are discectomy, nerve decompression, and spinal fusion. Although the early curative effect is positive, surgical trauma ultimately destroys the integrity of the spine and its accessory structures, reducing postoperative stability [15]. Therefore, it is urgent to propose a new treatment method to intervene in the process of spinal degeneration without destroying the original structure of the spine.

3. Injectable biomaterials for spinal degenerative diseases

3.1. The significance of injectable biomaterials

Traditional treatments cannot delay or even reverse the progression of spinal degeneration. Based on this, biomaterials that can promote the regeneration and repair of the musculoskeletal system are currently emerging, bringing new hope for the treatment of spinal degenerative diseases. According to the purpose of treatment, biomaterials for spinal degenerative diseases should have the following properties [16]: 1) good mechanical properties and plasticity that restore the vertebral space and height, withstand mechanical load and maintain spinal motion; 2) good biocompatibility with no obvious toxic effects on their own tissues or foreign cells; 3) biodegradability to be metabolized with tissue and that matches the rate of tissue regeneration.

As the concept of minimally invasive surgery is widely accepted in the clinic, injectable biomaterials have been widely used [17]: 1) Minimally invasive surgery, which can be injected into the lesion site; 2) In-situ curing to fill irregular areas in the body; 3) Carrier function, which can carry cells, drugs, genes, factors, etc. Currently, the injectable biomaterials commonly used in clinical and experimental studies for spinal system diseases are primarily divided into hydrogel materials (natural and synthetic hydrogel), bone cement materials (including acrylate, calcium phosphate, calcium sulphate, bioactive glass and calcium silicate) and other injectable materials. Fig. 2 summarizes the injectable biomaterials currently commonly used for degenerative spinal diseases, including injectable hydrogel and bone cement *etc*. Fig. 3 summarizes the main chemical structures of currently commonly used injectable biomaterials, including natural polymers (chitosan, collagen, gelatin, hyaluronic acid, alginate, silk fibroin) and synthetic polymers (polyethylene glycol, polyvinyl alcohol, polymethyl methacrylate) and inorganic biomaterials (calcium phosphate, calcium sulphate, bioactive glass, calcium silicate). The following section reviews the research status of injectable biomaterials in the two most common clinical spinal degenerative diseases by systematically evaluating the composition, advantages and disadvantages of the materials as well as the primary modification measures.

3.2. Injectable hydrogel

Among a wide variety of injectable biomaterials, organic hydrogels are polymer materials with a three-dimensional network structure formed by the cross-linking of hydrophilic macromolecular chains, which is a hot spot in the research of spinal degenerative disease. According to the origin of polymer hydrogels, they can be divided into natural and synthetic categories. Natural hydrogels contain natural components of biological structure with biochemical similarities to natural tissues, so they have great advantages in biocompatibility with low cytotoxicity. However, they also have some issues, such as a lack of mechanical strength, limited source, and large differences between different production batches [18]. Synthetic hydrogels have the advantages of strong controllability, easy design and convenient synthesis, and their mechanical properties have been improved compared to those of traditional natural hydrogels. However, due to the need to add an initiator, cross-linking agent and other toxic ingredients during the preparation process and to their shortcomings of slow degradation and insufficient biological

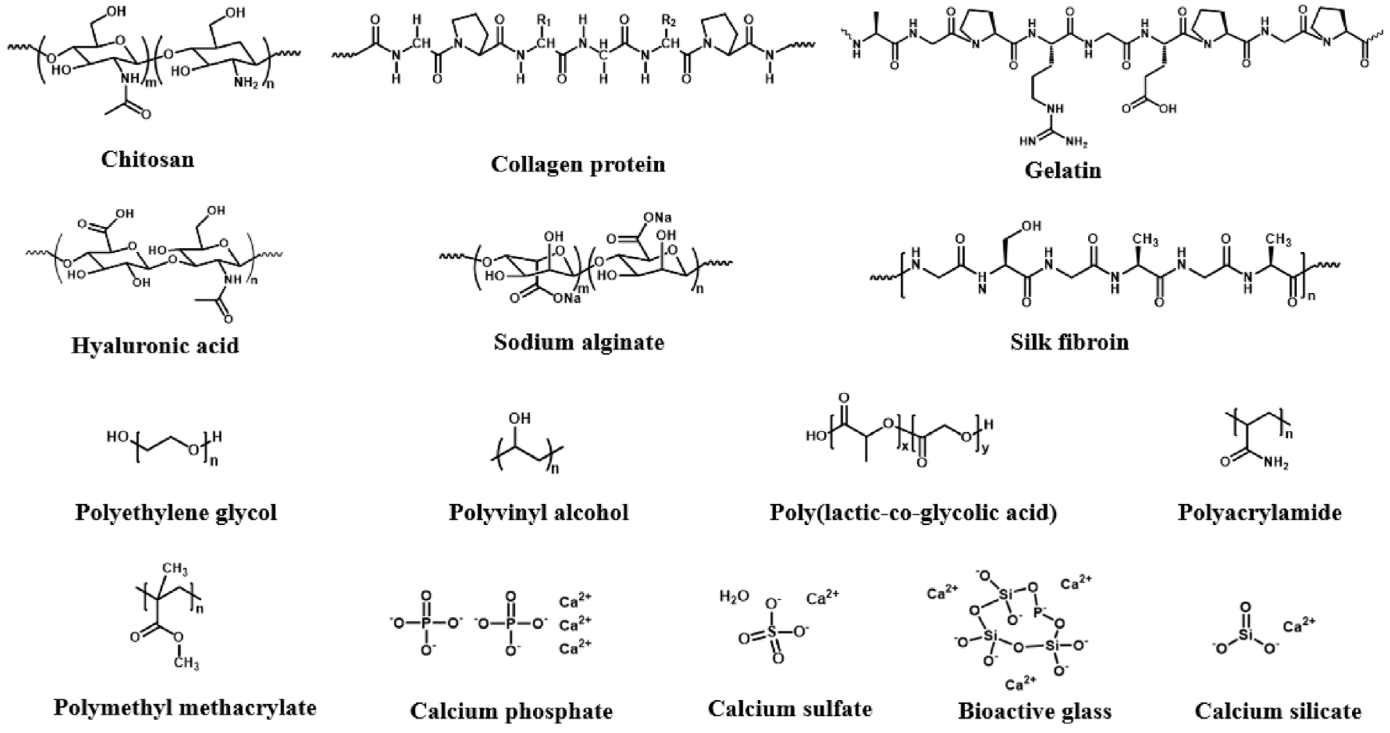

Fig. 3. Basic chemical structure of common injectable biomaterials.

Table 1
Injectable natural hydrogels and properties.

Category	Components	Biofunctions	Physicochemical properties	Ref
Chitosan	chitosan/chondroitin sulphate/type II collagen/fibrin	Promote cell adhesion, migration and proliferation	Temperature sensitive, hydrophilic, structural mimicry, viscoelastic	[21]
	ethylene glycol chitosan/acetyl anhydride	Promote cell adhesion, proliferation	*In vivo* stability, temperature sensitivity, biomimetic mechanics	[22]
	chitosan/fibre/nanocrystalline/ calcium phosphate	Osteoinduction	Controllable ion release, good mechanical properties and stability	[23]
	chitosan/fibroblast growth factor/ TGF-β1/BMSC	Promote the differentiation of stem cells into NP cells, Promotes ECM secretion	Good encapsulation, slow release	[24]
Collagen/ Gelatin	collagen/ADSC	Intervertebral disc tissue repair	Good encapsulation	[26]
	collagen/HA/PEG	Promote NP cell adhesion, proliferation and phenotypic maintenance	Resistance to enzymatic hydrolysis, slow degradation, good mechanical properties	[27]
	gelatine/chondroitin sulphate	Promotes cell proliferation	Self-healing, Ph response, tissue and organ adhesion, biomimetic mechanical properties	[29]
	gelatine/hydroxyapatite/zirconia/ chitosan/stem cells	Promote stem cells osteogenic differentiation, good osteoinduction	Degradability and good mechanical stability	[30]
Hyaluronic acid	HA/N-isopropylacrylamide/NP cells	Promote phenotypic maintenance of NP cells, Promotes ECM production	Encapsulation, interpenetrating network, good mechanical properties, cohesion	[32]
	HA/chitosan/KGN	Promote NP cell proliferation and differentiation, promote ECM secretion	Thermal sensitivity, high water content, sustained release, biomimetic mechanical properties, biodegradation	[34]
	HA oxide/oxalic acid acyl	Promotes cell proliferation, Promotes ECM secretion	Temperature sensitivity, slow degradation, stability	[35]
	high molecular weight HA	Anti - inflammation, anti - apoptosis, promote ECM secretion		[36]
Sodium alginate	sodium alginate hydrogel	Anti-inflammatory, analgesic, promote ECM secretion, inhibit postoperative IVDD	Bioabsorbable, rapid gelation	[38]
	sodium alginate/BMSC/mRNA	Gene therapy, promote stem cell proliferation and differentiation, promote ECM secretion		[39]
	sodium alginate/calcium carbonate/ glucose acid - delta lactone	Promote cell proliferation and cell distribution	Controllable gelation rate, high water retention, excellent mechanical properties and stability	[40]
Fibrin	fibrin hydrogel	Repair annulus fibrosus defect	Good biomechanical properties, good sealing	[42]
	fibrin/HA	Promote cell differentiation to NP cells , promote tissue repair	Good mechanical properties and internal stability	[43]
	fibrin/collagen granules	Promote proliferation and phenotypic maintenance of NP and annulus fibrosus cells, promote ECM secretion		[44]
	fibrinogen/hyaluronan/thrombin/ FGF-18	Promote ECM secretion	Good encapsulation	[45]
Silk fibroin	SF/tussah silk protein	Promote the proliferation of NP cells	Self-assembly, rapid gelation, good swelling and slow degradation, biomimetic mechanical properties	[47]
	SF/polyurethane	Good histocompatibility	Fatigue resistance, stronger axial compression stiffness, slow degradation, *in vivo* stability	[48]
	SF/platelet derivative	Promote cell proliferation and differentiation, anti-apoptosis	antioxidant	[49]

Table 2
Injectable synthetic hydrogels.

Category	Components	Biofunctions	Physicochemical properties	Ref
Polyethylene glycol	four arm -PEG/silver ions	Gene therapy, promote NP ECM synthesis	Self-healing, high water retention, antibacterial, degradable	[51]
	PEG/PLGA/HGF	Anti – fibrosis, promote NP cell proliferation and differentiation	Sustained release, heat sensitive, degradable	[52]
	polyethylene glycol acrylate/laminin	Cell adhesion, promote the maintenance of NP cell phenotype	Optical cohesion, dynamic adjustment of shear modulus	[53]
	polyethylene glycol fumaric acid ester/ carbon nanotubes Tube/black P	Osteogenesis repair, osteointegration	Biomimetic mechanical properties, electrical conductivity, ion release	[54]
Polyvinyl alcohol	PVA/polyvinylpyrrolidone	Injectable artificial nucleus pulposus, promote cell adhesion and proliferation	Bionic viscoelasticity, expansion and pressure performance	[56]
	PVA/chitosan/starch/sodium tetraborate	Promote cell proliferation and differentiation		[57]
	PVA/formaldehyde	Good cell compatibility, promote cell proliferation	High elongation at break, fatigue resistance, low friction coefficient	[58]
Polylactic acid/ polyglycolic acid	PLGA/ADSC/TGF-β3	Promote ECM secretion , promote stem cell differentiation into NP cells	Sustained release and degradability	[60]
	PLGA/PEG/TGF-β6	Promote ECM secretion , promote the differentiation of stem cell into NP cells	Controlled release, effective encapsulation	[61]
	PLGA/HA	Cell chemotaxis and tissue integration	Excellent hydrophilicity	[62]
Polyacrylamide	polyacrylamide hydrogel	Anti-apoptosis of nucleus pulposus cells, Regulate cell adhesion and chemotactic morphology	Adjustable mechanical strength	[63]
	PEG/POLY (n-isopropylacrylyl)/haem oxygenase gene	Good gene carrier, anti-inflammatory, promote NP ECM secretion, promote nucleus pulposus repair regeneration	Temperature sensitivity, anti - nuclease degradation, anti - protein adsorption	[64]
	Poly n-isopropylacrylamide/hyaluronic acid/gefitinib	Promote autophagy, promote the maintenance of NP cell phenotype, regulate ECM metabolism	Thermal sensitivity, controlled release	[65]

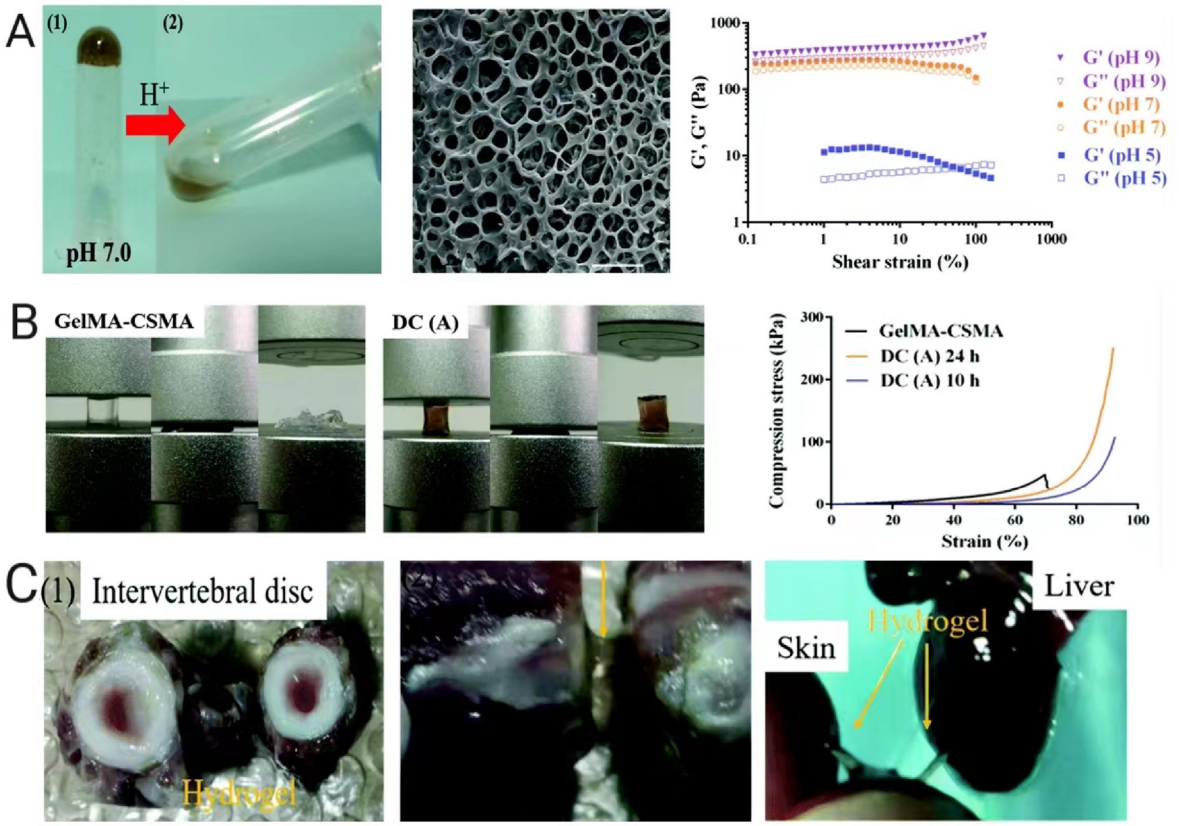

Fig. 4. Double crosslinked hydrogels improve mechanical properties. A) Viscoelastic properties of the pH response of composite hydrogel and SEM image of gel cross section (scale bar, 50 μm). B) Compressive properties and stress–strain curves of double crosslinked hydrogels. C) Good tissue adhesion of composite hydrogel in liver, skin and intervertebral disc [29].

activity, the application of synthetic hydrogels in the field of tissue engineering needs improvement [19]. The application of several common injectable hydrogel materials (natural and synthetic) and other special injectable hydrogels (microspheres, scaffolds, nanocomposites) in spinal degenerative diseases is described below (Tables 1 and 2).

3.2.1. Chitosan

Chitosan is the product of the deacetylation of chitin and is a naturally derived amino polysaccharide. Due to its low cytotoxicity, good biocompatibility, *in vivo* biodegradation, and antibacterial properties, it has been widely used in tissue engineering research. Chitosan is a double-responsive hydrogel, and its temperature responsiveness and pH responsiveness makes it very suitable as an injectable material [20]. However, the crosslinking mode of chitosan hydrogels is hydrogen bond, so the elastic modulus and compressive strength are significantly lower than those of the spine structure. Ghorbani et al. added chondroitin sulphate, type II collagen, gelatine and fibrin to chitosan to enhance its mechanical strength and optimize the proportion of each component to achieve the best energy storage modulus [21]. The molecular structure of chitosan has a large number of active groups, such as amino and hydroxyl groups that easily form covalent bonds due to chemical reactions. Li et al. synthesized a new chitosan hydrogel using ethylene glycol chitosan and hexanoyl anhydride by a simple N-hexanoylation reaction. N-hexanoyl glycol chitosan (HGC) hydrogels exhibit thermally reversible sol-gel transformations at low concentrations (3–7 wt%), and the long-term stability and good therapeutic effect were confirmed in rats [22]. Modified chitosan hydrogel is also used in the treatment of compression fracture. Soheila et al. added calcium phosphate into cellulose nanocrystals/chitosan hydrogels as ionic crosslinking agents, endowing it with excellent time-dependent and concentration-dependent osteogenic induction, and the addition of calcium phosphate also improved the compressive strength of the hydrogel [23]. In addition, studies use chitosan hydrogels as carriers, such as BMSCs, fibroblast growth factor, diclofenac, *etc* to increase its versatility, such as anti-inflammatory, antioxidant, anti-fibrosis, which will enhance the basic therapeutic effect of the treatment of spinal degeneration [24].

3.2.2. Collagen/gelatin

Collagen, which is primarily derived from connective tissues such as bone, cartilage tendon and disc, is a bioabsorbable protein composed of RGD sequences that is rich in arginine, glycine, aspartate sequences with anti-tensile and anti-shear functions [25]. Andrea et al. constructed ADSC-loaded injectable collagen scaffolds for the treatment of IVDD in goats. After 6 and 12 months, CT and tissue sectioning revealed that the height of the intervertebral disc and the histological score were significantly higher than those of the degenerative group [26]. Collagen also plays an important role in cell differentiation, adhesion and cell chemotaxis in tissue engineering due to its surface activity. Estelle et al. synthesized a new hydrogel using hyaluronic acid, polyethylene glycol (PEG) and type II collagen, which promoted the proliferation of stem cells and maintained the phenotype of NP cells *in vitro* [27].

Gelatin is a large water-soluble protein obtained from the irreversible degradation of collagen, composed of a variety of amino acids. Gelatins have excellent water absorption and expansibility and can be crosslinked in a variety of ways, including physical (thermal crosslinking, ultraviolet, C-ray crosslinking) and chemical (acyl azide, polyepoxy). However, due to the high-temperature treatment during the preparation process, the three-strand helical structure of collagen is destroyed, making the mechanical strength of gelatin significantly lower than that of collagen [28]. Han et al. prepared a bionic double-network hydrogel using chondroitin sulphate, PEG and gelatin. It exhibited adjustable stiffness and good elasticity that changed with the pH value and displayed excellent tissue

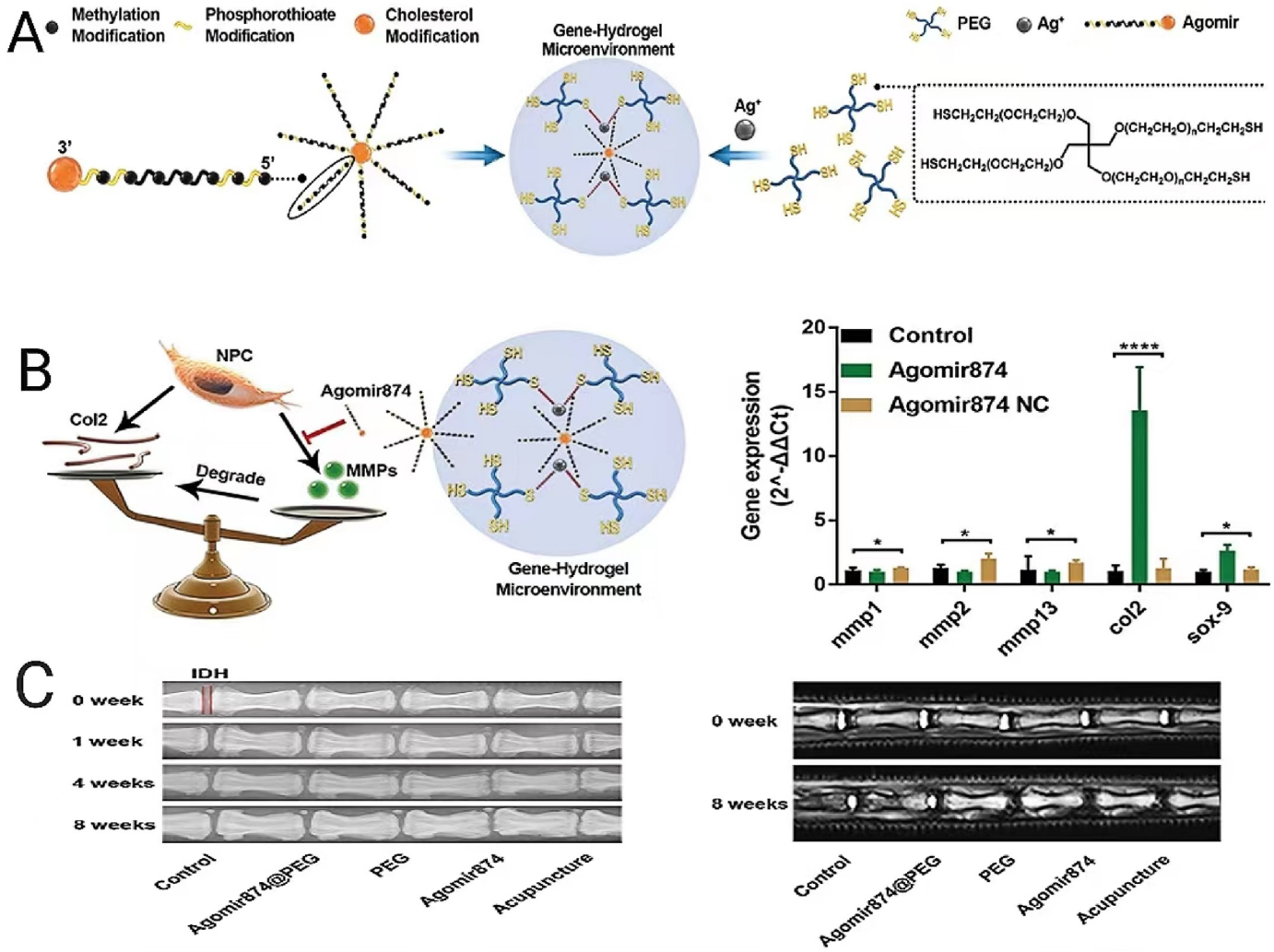

Fig. 5. Gene-hydrogel microenvironment for regeneration of IVDD. A) The construction of gene-hydrogel microenvironment. B) The effects of Agomir874@PEG on regulating the synthesis/catabolism balance of NPCs *in vitro* of the rat IVDD. C) The X-ray and MRI imaging data of rat coccygeal vertebrae after treatment [51].

adhesion in intervertebral discs [29](Fig. 4). Shao et al. constructed a composite hydrogel composed of hydroxyapatite, zirconia, gelatin and chitosan, which can promote the expression of type I collagen, osteocalcin and osteopontin in *vitro*. Meanwhile, the biomechanical strength of gross specimens was much better than that of other implant materials, and it exerts a similar effect to autologous bone grafts, which have good application prospects in vertebral compression fractures [30].

3.2.3. Hyaluronic acid

Hyaluronic acid (HA) is a water-soluble polysaccharide composed of D-glucuronic acid and N-acetylglucosamine that is widely found in the epithelium and connective tissue of animals and is the primary component of human extracellular matrix (ECM) [31]. It also interacts well with the cell matrix and cell surface receptors, so it plays an important role in wound healing, cell movement, angiogenesis and ECM formation. Natural HA contains a variety of active groups, such as hydroxyl, carboxyl, and amino groups, which can be cross-linked with a variety of hydrazide compounds and double ring oxides. In addition, injectable hydrogels can be prepared by carbodiimide crosslinking, protein crosslinking, photocrosslinking and other covalent crosslinking or modification of functional groups. Guo et al. prepared a mixed interpenetrating network hydrogel by establishing noncovalent crosslinking between HA and poly(N-isopropylacrylamide), with good cohesion and rheological properties similar to those of natural NP. At the same time, the hydrogel promoted the encapsulated NP cells to maintain their phenotype and secrete ECM for 4 weeks, which demonstrated the potential for regenerative treatment in IVDD [32]. Poor mechanical strength of linear HA limits its applicability in the tissue engineering of load-bearing structures [33]. Zhu et al. designed a KGN-coupled chitosan-glycerophosphorate-HA hydrogel, enabling the composite hydrogel to achieve a Young's modulus similar to that in the intervertebral disc. Meanwhile, the hydrogel continuously released the KGN, promoting the proliferation of adipose-derived stem cells and their differentiation into NP cells [34]. However, HA degrades rapidly under high temperature and *in vivo* hyaluronidase. SU et al. prepared injectable hydrogels by chemically cross-linking oxidized HA with dihydrazine adipate under physiological conditions. Morphological stability was maintained in continuous culture for 35 d in PBS at 37 °C, with a degradation rate of 40% [35]. HA also has good anti-inflammatory and antioxidant properties. High molecular weight HA synthesized by Zepur *et al* exerted this effect through the classical IFN-α signaling pathway, which was beneficial to disc degeneration accompanied by local inflammatory responses [36].

3.2.4. Sodium alginate

Alginate is a natural polymer extracted from the cytoplasm and cell walls of algae. In recent years, the immunogenicity of sodium alginate has decreased significantly due to the optimization of extraction technology. Due to its good biocompatibility, biodegradability, low toxicity,

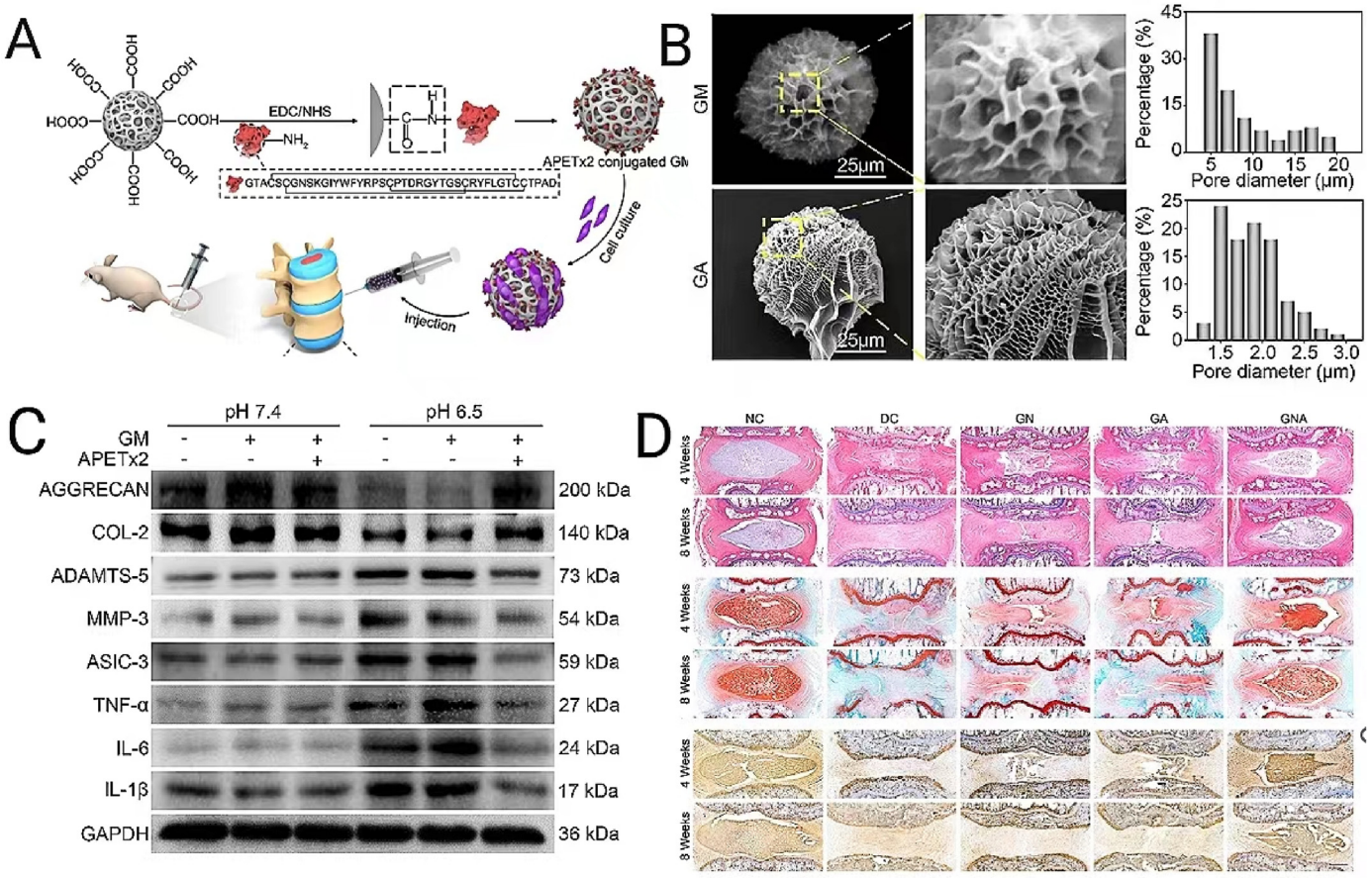

Fig. 6. Injectable "peptide – cell – hydrogel" microspheres that regulate inflammation to treat IVDD. A) The injectable process of APETx2-GelMA microspheres with cell-laden GA in the IVD degeneration rat model. B) SEM image of GelMA microspheres before and after grafting APETx2. C) Protein expression level of nucleus pulposus cells based on western blot in different pH microenvironment in 7 days. D) Histological evaluation of animal experiment (H&E、Safranin O-Fast Green and Immunohistochemistry staining) [67].

low cost and wide source, it has been widely used in tissue engineering research [37]. Sodium alginate is a kind of anionic polysaccharide polymer containing a large number of carboxyl groups. It exhibits polycation behaviour in aqueous solution and can rapidly form hydrogels with multivalent cations (e.g., Ca^{2+}, Ba^{2+}, Mg^{2+}) under relatively mild conditions, so it is widely used as an injectable hydrogel matrix material. Katsuro et al. implanted the ultra-purified sodium alginate hydrogel into the intervertebral disc, and found it reduced the inflammatory stimulation of pain-sensing nerves by inhibiting the production of TNF-α and IL-6 [38]. Due to the mild gelatinization conditions, alginate brine gel avoids the inactivation of sensitive drugs, proteins, cells and enzymes. Bucher et al. transfected GDF-5 mRNA into BMSCs using alginate hydrogel as the carrier, which upregulated the expression of proteoglycan, SOX-9 and keratin 19, promoting ECM synthesis. In addition, the compound hydrogel was injected into the papain-induced bovine IVD degeneration organ model *in vitro*, and the secretion of ECM partially recovered 7 days later, which indicates that hydrogels play an auxiliary role in gene therapy for IVDD [39]. The mechanical strength of simple sodium alginate gel is low due to difficulty in controlling the cross-linking time and inadequate degree of cross-linking. Emily et al. synthesized a calcium carbonate and gluconate-δ-lactone-sodium alginate hydrogel. By controlling the concentration of different components, the crosslinking time of the hydrogel was prolonged, and an alginate hydrogel with stronger water retention, higher mechanical strength and long-term stability was created [40].

3.2.5. *Fibrin and silk fibroin*

As one of the components of blood, fibrin gel avoids the problem of immunogenicity. It has the advantages of simple materials, convenient preparation, and satisfactory toughness and has promising application prospects in intervertebral disc tissue engineering [41]. Fibrin gel is similar to the NP, with proper viscoelasticity. Torkian et al. combined fibrin blockers with discectomy endoscopic surgery to treat disc herniation, which reduced early postoperative pain and postoperative recurrence rates, exhibiting good clinical application potential [42]. Since fibrin gels alone lack mechanical strength, Park et al. designed a fibrin/HA hydrogel as a substitute for the NP component in the disc tissue engineering scaffold. The enclosed porcine annulus fibroblasts and chondrocytes displayed good compatibility in the material. In *in vivo* experiments, the material stably existed for two weeks [43]. Du et al. synthesized a fibrin glue composed of porcine plasma fibrin with a coagulation factor of III and thrombin, with the function of antibacterial, repairing degeneration and accelerating healing [44]. Sojia et al. cross-linked fibrinogen and HA to form a composite hydrogel and loaded Fibroblast growth factor-18 (FGF-18), which could increase the expression of type II collagen and carbonic anhydride XII genes and promote to promote the secretion of glycosaminoglycan [45].

Silk fibroin (SF) is a natural high molecular fibre protein extracted from silk that contains the same 18 amino acids as the human body [46]. Bibhas et al. extracted two different kinds of silk (Bombyx mori and Tussah silkworm) to construct a new SF hydrogel with the characteristics of rapid gelation through hydrophilic and hydrophobic action for the treatment of IVDD [47]. SF hydrogels exhibit significantly improved mechanical properties, which is related to the β-folding structure in the crystallization area of the protein. Hu et al. constructs a high-strength hydrogel with excellent fatigue resistance through liquid SF and liquid

polyurethane. The hydrogel exhibited excellent fatigue resistance, could withstand millions of fatigue cycles, and was confirmed to provide stronger axial compression stiffness in constrained compression experiments, which has significant application value in the spine where frequent deformation is required [48]. Elia et al. prepared a mixed microglue of silk protein, regenerated platelet lysate and platelet-poor plasma. The composite hydrogel has good antioxidant activity, which can clear the reactive oxygen species in the intervertebral disc, playing an anti-apoptotic role by regulating the oxidative stress process and attenuating inflammation in the intervertebral disc [49].

3.2.7. Polyethylene glycol

Polyethylene glycol is a synthetic polyether, which is made from polyethylene and ethylene oxide by polymerization. By changing the ratio of chemical reactants, the length range of the molecular chain of PEG can be effectively controlled to obtain a more uniform molecular weight distribution [50]. Due to its good biocompatibility, nontoxicity, low immunogenicity, good degradation and excretion through the kidney, PEG is often used as a carrier in spinal degenerative diseases. Gene therapy regulates gene expression levels by delivering synthetic micribonucleic acids (miRNAs), providing an ideal potential treatment for IVDD. Chen et al. synthesized a PEG hydrogel by Ag–S coordination of four-arm PEG-SH and silver ion solution, loaded with thio-phosphorylated miRNA (Agomir). The hydrogel was self-healing, antibacterial and degradable, which regulated the catabolism of ECM, and improved the microenvironment of nucleus pulposa tissue [51] (Fig. 5). Zou et al. loaded hepatocyte growth factor (HGF) into a PLGA-PEG-PLGA hydrogel, which promoted the expression levels of type II collagen and BMP-2 and significantly enhanced the magnetic resonance T2 signal intensity [52]. Due to the end-group active group (hydroxyl), various specific bioactive groups can be introduced through chemical reaction modification to make the material multifunctional. Francisco et al. synthesized a functional PEG hydrogel by photopolymerization of modified PEG diacrylate and laminin. They found that flexible hydrogels promoted the maintenance of phenotype and the expression of cadherin, cytokeratin 8 and integrin α3, which facilitates the differentiation of immature cells into NP cells [53]. Liu et al. synthesized an injectable carbon nanotube-black phosphorous hydrogel

Table 3
Injectable bone cement.

Category	Components	Biofunctions	Physicochemical properties	Ref
Polymethyl methacrylate cement	clinical PMMA (PCD)	Spinal curvature correction, pain relief, strengthening intervertebral disc	Stable mechanical properties	[77]
	clinical PMMA (percutaneous enhanced pedicle screw)	Spinal curvature correction, nerve decompression, recovery of intervertebral height	Reinforced screw stability	[78]
	PMMA/castor oil		Prolonged curing time, reduced heat release, matching mechanical strength	[80]
	PMMA/organic monomer NMP		Low heat release, low elastic modulus	[81]
	PMMA/normal saline		Low bending strength, low compression strength, long curing time, low heat release, good radiation visibility	[82]
	PMMA/styrene		Hydrophilic, excellent expansion rate	[83]
	PMMA/Mg–Al LDH	Osteoinductivity	Prolonged curing time, Reduced elastic modulus	[84]
	PMMA/Magnesium microspheres	Osteogenic properties	Excellent degradation, good mechanical properties, surface roughness	[85]
	PMMA/collagen minerals	Promote cell adhesion, proliferation, osteogenic differentiation	Matching mechanical strength	[86]
Calcium phosphate cement	CPC/PEG poly decyl diacid glyceride	Promote cell adhesion, proliferation and osteogenesis	High compressive strength, high elongation at break	[90]
	CPC/graphene/active carbon nanotubes	Osteogenic properties	Shortened curing time, high bending resistance and compressive strength	[91]
	CPC/metal ion	osteogenic properties	Good mechanical properties and degradability	[92]
	CPC/starch/BaSO4	Osteoconduction, osteoinductivity	Improve the screw pulling strength and maximum torque, good degradation	[93]
	CPC/type I collagen	Promote cell adhesion, proliferation, osteogenesis, promote intervertebral bone fusion	Enhanced mechanical properties, internal anti - scouring effect	[94]
Calcium sulphate bone cement	clinical CSC(PVP)	Relatively poor bioactivity	Fast degradation rate and long curing time	[97]
	CSC/chitosan/silk fibroin	Osteogenic properties and osteointegration promotion	Slow degradation rate, excellent mechanical properties	[98]
	CSC/hydroxyapatite	Excellent clinical efficacy, minimally invasive operation	Degradability	[99]
	CSC/nano porous lithium/ magnesium silicate	Promote vascularization and promote osteogenic differentiation	Improve the tissue microenvironment after degradation	[100]
	CSC/Tio2/gentamicin	Promote osteogenic differentiation	Better injection, antibacterial property, excellent compression resistance, *in vitro* mineralization performance	[101]
Bioactive glass cement	BAG/PMMA	Promote osteoblast adhesion, proliferation, migration, osteogenic differentiation, osteointegration	Prolonged curing time, reduced heat release, matching mechanical strength	[105]
	BAG/Sr	Promote the proliferation of stem cells, Osteogenic differentiation, mineralization, osteoinductivity	Extended curing time, Reduced rate of degradation	[106]
	BAG/vancomycin	Osteogenic properties	Degradability, antibacterial property	[107]
	calcium phosphate bioglass/ Cu	Osteogenic properties	Antibacterial property	[108]
Calcium silicate cement	calcium silicate/calcium phosphate/zinc	Osteoinductivity	Good compressive strength	[111]
	calcium silicate/SR	Promote osteoblast adhesion, proliferation, migration, osteogenic differentiation	Prolonged curing time, reduced heat release, excellent degradation, ion release performance, *in vitro* mineralization performance	[112]
	calcium silicate/curcumin	Anti-inflammatory and osteogenic properties	In vitro mineralizability performance and good operability	[113]
	calcium silicate/chitosan	Osteoinductivity	Long solidification time, good mechanical properties, *in vitro* mineralization, antibacterial property	[114]

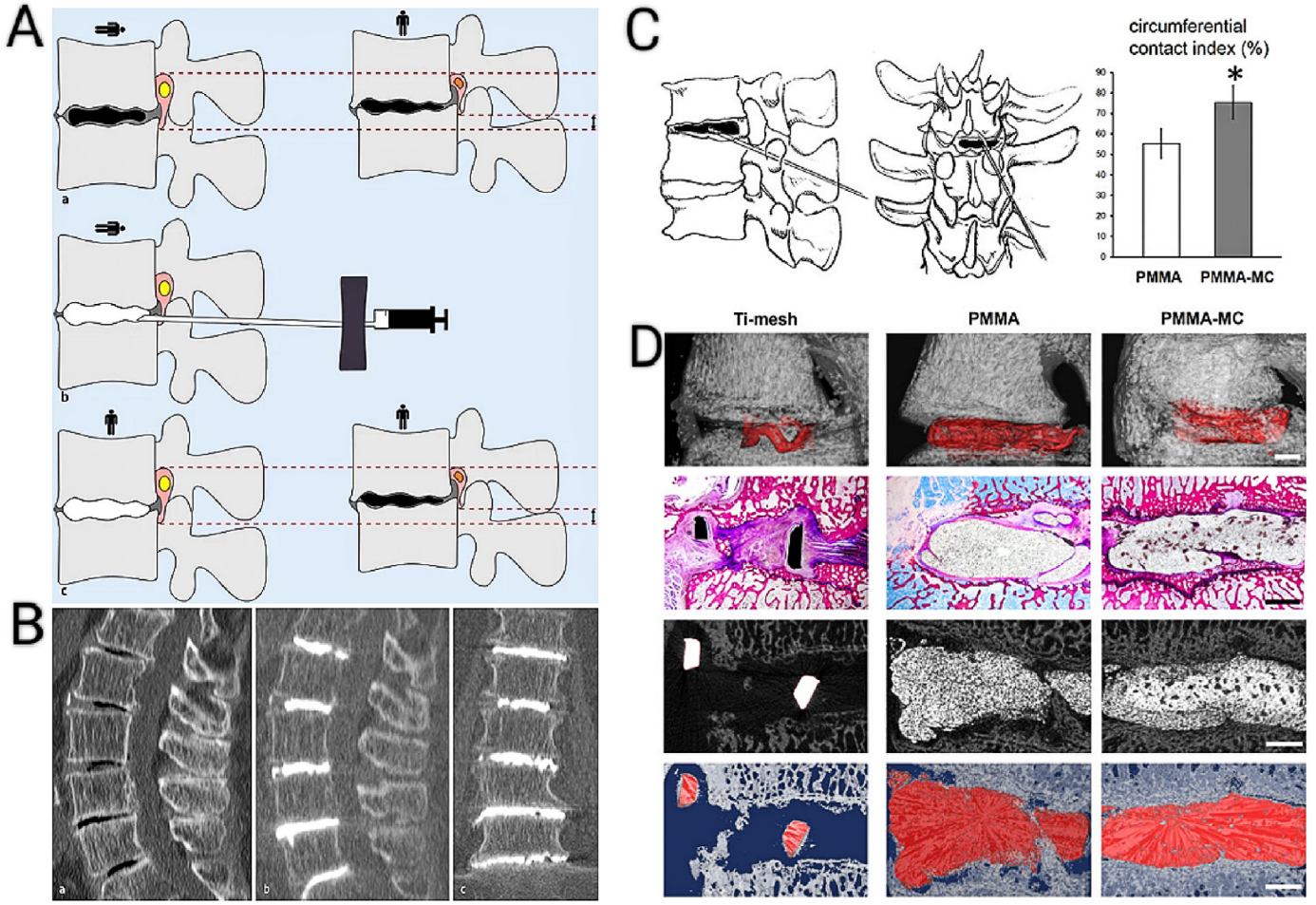

Fig. 7. Clinical and basic application of percutaneous bone cement discplasty in degenerative disc diseases. A) Schematic diagram of the therapeutic mechanism of percutaneous bone cement discplasty. B) Clinical complications of PCD. C) Schematic diagram of the clinical operation of the PCD technique and peripheral bone contact index in the sheep cervical spinal degeneration model. D) Radiographic reconstruction and histological evaluation in animal studies (methylene blue-basic fuchsin staining) [86].

using a low-poly(ethylene glycol) fumarate polymer as a crosslinking matrix. It exhibited excellent mechanical strength, electrical conductivity, and suitable degradation. Meanwhile, phosphate ions released during its degradation also exhibited osseointegration performance in posterior lateral spinal fusion [54].

3.2.8. *Polyvinyl alcohol*

Polyvinyl alcohol (PVA) is a long-chain water-soluble polymer synthesized from vinyl acetate, which is obtained through polymerization and hydrolysis. PVA has the advantages of water solubility, histocompatibility, safety, nontoxicity, lack of irritation to the skin and so on. PVA hydrogels are very similar to human intervertebral disc tissue and have been used in injectable artificial intervertebral disc replacement [55]. To develop a 3D network of *in vivo* formation that maintains injectability, Gemma et al. mixed PVA and polyvinylpyrrolidone, which displayed good viscoelastic behavior under dynamic shear and compression conditions. Due to its thixotropy, the composite hydrogel maintained good injectivity [56]. PVA hydrogels have good application prospects for the targeted delivery of drugs for spinal diseases. Using sodium tetrborate and PVA chitosan/starch as raw materials, Yener et al. designed a new hydrogel scaffold loaded with insulin-like growth factor 1 (IGF-1) and bone morphogenetic protein (BMP)-2. The results showed that the controlled release of growth factor in hydrogel significantly promoted proliferation and ECM secretion in annulus fibrosus cells and NP cells culture and were good carriers for intervertebral disc administration [57]. Although PVA hydrogels have high water content and adequate mechanical properties, they still have issues such as poor elongation at break, poor fatigue resistance and a high friction coefficient. Li et al. prepared a new type of high-performance hydrogel using a physical-chemical double cross-linking method with formaldehyde as a crosslinking agent, whose elongation was more than 600%, modulus loss after the fatigue test was reduced by 42%, and the average coefficient during friction was reduced to 0.048, satisfying the clinical application of meniscus, cartilage and intervertebral disc [58].

3.2.9. *Polylactic acid/polyglycolic acid*

Poly(lactic acid) and poly(glycolic acid) are synthetic temperature-sensitive aromatic polyesters with good biocompatibility. Their intermediate metabolites in the body are lactic acid and glycolic acid, which participate in metabolic processes of the human body and can be easily discharged from the body through the tricarboxylic acid cycle. Although the ester groups on the long chains of pure poly(lactic acid) and poly(-glycolic acid) are liable to hydrolyse and lead to the degradation of the entire polymerization chain, they can be further polymerized to obtain the more stable physical and chemical properties of poly(lactic acid)-poly(glycolic acid) copolymer (PLGA), and the mechanical properties and degradation rate of the material can be adjusted by polymerization into a distribution ratio to meet the performance requirements of different tissue engineering needs [59]. Its good carrier performance can be used to load cells, small molecules, drugs, etc. In a study by Liang et al., PLGA hydrogel microspheres were constructed and loaded with ADSCs and TGF-β3 to repair IVDD. Compared to the control group, more

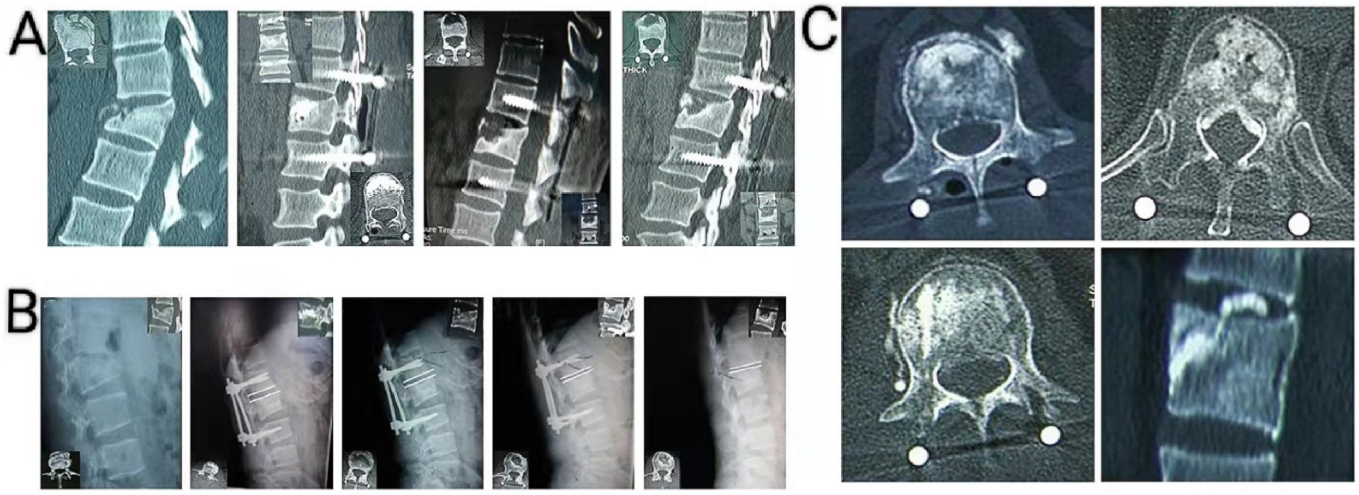

Fig. 8. Complications in the clinical application of calcium sulphate cement in percutaneous vertebroplasty. A) Nonunion of the fracture site. B) Collapse of the upper endplate and screw fracture. C) Cement leakage [97].

cartilage matrix was secreted, and intervertebral disc height was correspondingly increased [60]. Huang et al. constructed a PEG-PLGA-PEG injectable nanosphere hydrogel loaded with TGF-β6 and the potential of promoting the differentiation of stem cells into NP cells was verified at the genetic and histological levels, providing a good regeneration strategy for IVDD [61]. As Poly(lactic acid) and its copolymer have hydrophobic chain segments, resulting in poor hydrophilicity, Endres et al. combined HA with PLGA copolymer to repair degenerative disc annulus fibrosa, and cell migration was observed after implantation of this composite hydrogel [62].

3.2.10. Polyacrylamide

Polyacrylamide is a homopolymer and copolymer of acrylamide and its derivatives. It is prepared by the reaction of acrylamide and ammonia at low temperature. Polyacrylamide hydrogels are prepared using polyacrylamide or acrylamide monomers through chemical or physical crosslinking. It is a homogeneous colourless transparent colloidal material with elasticity, heat resistance, hydrophilicity, acid and alkali resistance and nonirritant that was initially widely used in tissue engineering as a soft tissue filler material. Because polyacrylamide contains a large number of amide groups and easily forms hydrogen bonds, and its mechanical strength can be adjusted by controlling the proportion of internal cross-linking. Yu et al. prepared polyacrylamide gels with different elastic moduli, and confirmed that mechanical signals played an important role in regulating the biological behavior of cells. The results showed that hydrogels with a higher elastic modulus had a significant effect on the diffusion morphology of NP cells and promoted the apoptosis of NP cells through the PI3K/AKT signaling pathway [63]. Traditional hydrogels are limited in many applications due to a lack of active functional groups, poor temperature resistance, poor environmental responsiveness and relatively single overall function. Feng et al. previously used PEG and poly n-isopropylacrylamide to prepare thermally reactive multiphase coronal polyion micelle hydrogels. The system delivers the haem oxygenase gene, which regulated the interleukin-induced inflammatory response and can be used as a safe and efficient nonviral vector for gene therapy of IVDD [64]. Pan et al. synthesized a thermosensitive hydrogel using the copolymerization reaction of poly n-isopropylacrylamide and HA, and the controlled release of gefitinib reduced the expression of MMP-13 and promoted the production of ECM of NP [65].

3.2.11. Other injectable hydrogels

In addition to the common hydrogels mentioned above, the forms of injectable hydrogels include microspheres, scaffolds and nanocomposites, but they are rarely used in the study of spinal degenerative diseases, which are summarized in this section. Microspheres could be dispersed or adsorbed in the polymer matrix and display good injectable properties and targeting properties *in vivo*. Chang et al. constructed the injectable circRNA silencing gel microspheres by binding cationic liposomes loaded with the circSTC2 silencing gene to hyaluronic acid methacrylate (HAMA) microspheres through amide bonding to improve the metabolic balance of ECM under IVDD [66]. By covalently coupling APETx2, Bian et al. constructed a novel injectable "peptide--cell-hydrogel" microsphere, which provided an effective way for tissue regeneration under overactive inflammatory reaction [67] (Fig. 6). The injectable MgO and $MgCO_3$-encapsulated PLGA microspheres could promote mineral deposition under osteoporosis [68].

Tissue engineering scaffolds are usually the porous biomaterials that can be combined with living tissue cells and implanted into different tissues of organisms to replace the functions of tissues and promote tissue regeneration. The injectable scaffolds are the focus of bone and cartilage tissue engineering in the future. An increasing number of references are paying attention to injection therapy for intervertebral disc repair. Recently, Adoungotchodo et al. developed a new biomimetic viscoelastic injectable scaffold composed of chitosan-gelatin-link N natural peptide [69]. Rebecca et al. constructed acellular scaffold of NP to restore disc height [70].

Due to the special size and properties, the nanoscale biomaterials play important roles as injectable drug carriers for tissue repair and tissue engineering. Zhang et al. prepared albumin/heparin nanoparticles as an injectable vector of stromal cell-derived factor-1α (SDF-1α), which was a powerful chemical attractant for homing BMSCs and induced improved regeneration of the AF and NP [71]. Xiao et al. combined the C60 nanoparticle with cFlFlF peptide to form a composite nanoparticle, FT-C60, which has analgesic and anti-inflammatory effects on spinal degenerative diseases [72]. Sravisht Iyer et al. loaded simvastatin onto PLGA nanoparticles [73], to explore its application in spinal fusion, and found it could induce an increase in mineralization as well as an increase in markers of bone formation.

3.3. Injectable bone cement

In recent years, injectable bone cement materials with self-curing properties and good operation characteristics have been widely used in various clinical fields, mainly including acrylic bone cement and inorganic bone cement. Compared to those of injectable hydrogels, bone cement materials exhibit excellent mechanical properties, which can fill

Table 4
Clinical trials of injectable biomaterials in spinal degeneration.

Clinical trial number	Injectable biomaterials	Therapeutic purpose	Study location
NCT0233 8271	HA + ADSCs	Disc repair	South Korea
NCT05001893	S53P4 Bioactive Glass cement	Spinal fusion	Finland
NCT0164 0457	Albumin + Chondroitin Sulphate + HA + Autologous chondrocytes	Disc repair	Germany
NCT02466048	SurgiFill High Purity Collagen Hydrogel + Autologous Bone	Spinal fusion	South Korea
NCT0177 1471	Fibrin gel + Juvenile chondrocytes	Disc repair	America
NCT04605120	Supercritical CO_2 virus inactivation bone cement	Spinal fusion	France
NCT0129 0367	HA + Mesenchymal precursor cells	Disc repair	America
NCT05329129	Calcium Phosphate Cement	Spinal fusion	America
NCT0241 2735	BMSCs + HA	Disc repair	America
NCT01751841	Silicate (Si–CaP) bone cement	Spinal fusion	America
NCT0319 7415	Autologous platelet rich plasma gel	Disc repair	China
NCT00931333	Calcium phosphate cement	Fracture repair	France
NCT04727385	Double cross-linked microgels	Disc repair	France
NCT02763956	Gelstix (Polyacrylonitrile) hydrogel	Disc repair	Netherlands Switzerland
NCT01494441	Recombinant BMP-2/ Biphasic calcium phosphate bone cement	Spinal fusion	N/A
NCT01335243	Mineralized collagen/ Hydroxyapatite/Tricalcium phosphate cement scaffold	Spinal fusion	France
NCT04102761	Bone Marrow Concentrate + Platelet Rich Plasma Gel	Disc repair	America
NCT01513694	Injectable hydroxyapatite/ Calcium phosphate cement scaffold + Mesenchymal stem cells	Spinal fusion	Spain
NCT02343484	Ethanol-Fibrotic Developable Hydrogels	Disc repair	Greece
NCT04615260	Silicone gel + Nano-hydroxyapatite	Spinal fusion	America
NCT04849429	Platelet rich plasma gel + Exosomes	Disc repair	India
NCT03331159	Silicone gel + nano-hydroxyapatite	Spinal fusion	Germany
NCT01011816	Fibrin gel sealant	Disc repair	America

the vacancy of human tissues and are one of the most commonly used materials for bone enhancement and bone reconstruction in clinical load-bearing parts. In addition, currently modified injectable bone cements have many important properties, such as good biocompatibility, bioactivity, bone conductivity, high radioactivity, low curing temperature, appropriate cohesion, large porosity allowing fluid flow and cell penetration, and appropriate degradation depending on the site of application [74]. The research status of injectable bone cement materials commonly used in spinal degeneration is summarized in Table 3.

3.3.1. Polymethyl methacrylate

As the first generation of bone cement, polymethyl methacrylate (PMMA) bone cement was first used by doctors as a dental material in the 1930s and was later used for femoral head replacement in 1953 and hip replacement in 1964 [75]. In 1987, Chamley et al. first injected PMMA into the vertebral destruction caused by haemangioma [76]. PMMA bone cement is composed of solid (PMMA powder, initiator BPO and developer BaSO4) and liquid materials (MMA monomer, promoter DMPT and inhibitor hydroquinone). The material has good plasticity and mechanical performance, widely used in the clinical treatment of spinal degeneration. Gaston et al. performed PCD in 180 IVDD patients with low back pain [77]. Gazzeri et al. performed bone cement-based porous pedicle screw internal fixation for 20 patients with spinal degeneration [78]. Both of the two emerging minimally invasive spine surgeries have good clinical outcomes.

Defects in PMMA cement are also apparent, such as high polymeric heat release, mismatched elastic modulus, low bioactivity and non-degradability [79]. Current research is also focused on improving PMMA bone cement to develop more suitable bone cement materials for clinical needs. Given the short-term high temperature rise of PMMA, Tai et al. used castor oil as an additive [80], and Boger et al. selected N-Methyl--pyrrolidone (NMP), an organic monomer that can be embedded in PMMA segments, to partially replace MMA [81], which can effectively alleviate the thermal effect of bone cement. Due to the excessive stiffness of PMMA, the risk of adjacent vertebrae fracture is correspondingly increased. Increasing the porosity in polymerized bone cement and reducing the polymerization of MMA monomers are major modification measures. Christian et al. mixed isotonic saline into bone cement system [82], Yang et al. prepared a hydrophilic and expansive bioactive bone cement using PMMA and styrene in a free radical polymerization method [83], both of which significantly reduced their elastic modulus and compressive strength. PMMA bone cement has poor degradability, Zhai et al. added magnesium microspheres into PMMA, which can gradually degrade and generate bioactive magnesium ions, which is conducive to the growth of bone tissue. At the same time, interconnected macroporous structures are formed in the degraded cement matrix, which is conducive to the growth of bone tissue [84]. Aiming at the aseptic loosening caused by the bioinert PMMA, the reasonable and effective scheme is to modify it with biological activity. Wang et al. added the active metal component Mg–Al layered double hydroxide (LDH) into PMMA. The micro-CT 3D reconstruction showed that after 2 months surgery the volume of new bone was 2.17- and 18.34-fold greater than that of the PMMA&Collagen-I and PMMA groups, respectively, and its role in inducing bone regeneration was further confirmed by assessing key osteogenic pathways [85]. Yang et al. developed a composite bioactive bone cement by adding MC into PMMA, which could hinder the proliferation and fusion of macrophages, promote osseointegration, and reduce fibrous tissue formation. It is a good substitute for PCD filler materials [86] (Fig. 7).

3.3.2. Calcium phosphate

Calcium phosphate cement (CPC) was first reported by Brown et al., in 1983 [87]. Its physical and chemical properties are similar to those of hydroxyapatite with good bone integration. The FDA began to approve CPC for clinical use in 1991, and it has been widely used in bone defects, fracture repair and oral and maxillofacial surgery. CPC consists of solid (calcium phosphate salts) and liquid phases (water or phosphate solution). Compared to PMMA, its polymerization heat release is lower. Its degradation products, such as calcium and phosphorus, are also essential elements for bone matrix metabolis [88]. CPC takes longer to solidify, which may cause dispersion at the injection site and result in inadequate local filling, poor cohesion and anti-scouring performance [89]. Meanwhile, its mechanical strength cannot meet the requirements of clinical load-bearing parts. Ma et al. modified CPC scaffolds by synthesizing hydrophilic elastomer PEG and using simple osmotic and thermal crosslinking processes, and its strength and toughness were significantly improved, providing 3.82 MPa compressive strength and 13.2% elongation at break [90]. Wang et al. investigated the solidification process of reduced graphene (RGO)/carbon nanotube (CNT)-reinforced CPC in a microwave environment, with half the final setting time. At the same time, the mechanical strength was also improved, and the bending strength and compressive strength increased by 19.86% and 21.68% [91]. To improve bioactivity, the addition of metal ions, such as magnesium, zinc, manganese, or active polymers, such as chitosan, to CPC significantly improved its osteogenic activity, mechanical strength, and degradability [92]. Bone cement, a strengthening material for pedicle screws, carries risks of postoperative prolapse. Sun et al. mixed CPCs with gelatinized starch and BaSO4 powder to develop a novel calcium phosphate-based nanocomposite material for pedicle screw fixation,

which significantly improved the screw removal strength and maximum torque [93]. Hu et al. dispersed type I collagen into CPC, which exhibited better anti-scour ability *in vivo*. In a rat posterolateral lumbar fusion model, it significantly improved the alkaline phosphatase activity and promoted the formation of new bone [94].

3.3.3. Calcium sulphate

Calcium sulphate, an artificial bone replacement material, has been studied and applied for more than one hundred years. In 1892, Dreesman reported for the first time that calcium sulphate could be used as a filler for bone defects caused by bone tuberculosis [95]. In 1961, Pehier's team expanded the use of calcium sulphate to treat bone cysts and osteomyelitis [96]. Commonly used calcium sulphate cement (CSC) is composed of powdered hemihydrate calcium sulphate ($CaSO_4{\cdot}0.5H_2O$) and liquid water. CSC has good degradation performance and bone conductivity. While, defects of CSC have been found in clinical application. Bu et al. performed PVP treatment on 28 patients with thoracolumbar compression fracture with CSC. The results showed that some cases presented with poor vertebral height, angle correction and bone nonunion during follow-up, which was considered to be largely related to the rapid degradation and poor biological activity of CSC [97] (Fig. 8). Aiming at the defects of CSC, Wang et al. constructed chitosan microspheres (SLCMs), SF and CSC composite scaffold to improve the mechanical properties and enhance osteoinductive [98]. Salvatore et al. synthesized calcium sulphate-hydroxyapatite composite bone cement. The 79% patients were found to experience significant improvement in symptoms and no surgical complications compared to the control group, confirming that this absorbable CSC was an effective minimally invasive treatment option for patients with low back pain [99]. To further improve the biological activity of CSC and reduce the adverse effects of degradation products, Cao et al. introduced nanoporous lithium-doped magnesium silicate into hemihydrate calcium sulphate to prepare composite CSC. The introduction of modified ingredients neutralized the acidic degradation products of CSC. Meanwhile, in animal experiments, it was found that the positive expression of vascular endothelial growth factor and type I collagen was higher than that of traditional CSCs, which exerted obvious vasogenic and bone-promoting effects [100]. Multifunctional antibacterial bone cement is also a future research direction. Luo et al. added gentamicin-loaded porous titanium dioxide microspheres into CSCs, effectively avoiding infection of bone implants while improving mechanical strength [101].

3.3.4. Bioactive glass

Bioactive glass (BAG), originally developed by professor Hench in the early 1970s, is a silicate-based biomaterial composed of SiO_2, Na_2O, CaO and P_2O_5 [102]. When BAG is implanted into the body, it reacts with the humoral microenvironment and mineralizes on its surface to form a hydroxyapatite layer. The interface binding force of HA can reach three to four times that of bone tissue, to achieve bone integration [103]. Due to the different forms of bone defects caused by osteoporosis, trauma and infection in clinical practice, it is sometimes difficult to achieve satisfactory filling of bioglass-based particles and scaffolds. Therefore, BAG bone cement has emerged as required. Although BAG cement products have been applied in clinical tissue repair with definite effects, they still have the following limitations [104]: 1) poor mechanical properties. 2) Slow degradation rate, which does not match the rate of new bone synthesis. 3) Single functional component and limited bone regeneration effect. Cui et al. prepared composite bone cement with PMMA and BAG. Compared to that of PMMA, the heat release temperature of the composite bone cement was significantly reduced, and an appropriate setting time and high mechanical strength were maintained. In addition, BAG-PMMA promoted the adhesion, proliferation, migration and collagen secretion of MC3T3-E1 cells [105]. To further enhance biological activity, Pan et al. mixed strontium into BAG cement, which regulates the proliferation, differentiation and mineralization of hBMSCs [106]. Cui et al. mixed vancomycin powder into BAG bone cement to treat chronic osteomyelitis. After bone cement was implanted into a rabbit model, satisfactory anti-infection and bone repair effects were observed [107]. Teresa et al. added Cu-TCP composite particles into the calcium phosphate BAG-PMMA bone cement, which also achieved antibacterial activity against various bacteria, such as Virescent, Aureus aureus and Escherichia coli [108].

3.3.5. Silicates

Silicon is an important trace element in the human body and widely exists in serum, liver, kidney, lung, muscle, cartilage and hard bone tissue. Silicon is a component of collagen and have important effects on osteoblasts and osteoclasts. Silicon participates in the calcification process of bone tissue, affecting bone formation and development [109]. In 1960, Hench developed silicate as the primary component of bone repair materials and then introduced it into the field of oral implants for the treatment of intra-articular fractures [110]. Due to its good biocompatibility, excellent mechanical behavior and good osteogenesis *in vivo*, silicate bioceramic materials ($CaSiO_3$,Ca_3SiO_5) have become a hot spot in the research of modified bone cement. Metal ions are closely to cell metabolism. Paul et al. introduced Zn into the new phosphor-calcium silicate composite bone cement, which displays both *in vitro* and *in vivo* biological activities, stimulating the proliferation of bone cells and further improving its bone regeneration effect. Meanwhile, it significantly improved the compressive strength because it leads to the appearance of Si in the form of amorphous SiO_2 [111]. Although calcium silicate cement has good bioactivity and osteogenesis, its primary disadvantage is its slow degradation rate, which may limit the efficiency of bone regeneration. Huang et al. added strontium into cement and synthesized degradable strontium-calcium silicate cement through solid sintering [112]. Researchers have also added curcumin and chitosan to develop multifunctional calcium silicate bone cement with anti-inflammatory and antibacterial effects [113,114].

4. Summary of ongoing clinical trials

Substantial progress has been made in recent years in the field of cell therapy and tissue engineering in the development of injectable biomaterials for degenerative diseases of the spine due to the extensive exploration of biologic therapies for restoring spinal anatomical structure and mechanical properties. Injectable biomaterials can not only alleviate early discomfort but also delay or even reverse the progression of degenerative spinal disease from the perspective of repair and regeneration. Moreover, injectable biomaterials are a potential new tool for achieving minimally invasive surgery, which is a desirable clinical treatment resulting in minimal trauma. Although injectable biomaterials have various advantages, they are still in the *in vitro* modification, cell and animal experiment stage, and their translation into a clinical treatment has yet to be achieved due to the uncertain clinical effects that need to be verified in long-term clinical trials. Table 4 shows the ongoing clinical trials on the injectable biomaterials.

At present, only a small number of related clinical studies are underway. We found 23 clinical studies evaluating the application of new injectable biomaterials for degenerative spinal diseases on the ClinicalTrials official website (www.clinicaltrials.gov). The trials evaluating fifteen biotherapies based on hydrogels and 8 based on bone cements were found, of which 6 are related to the cell implantation (including mesenchymal stem cells, stromal cells and precursor chondrocytes). Trials evaluating twelve therapies for IVDD repair (mainly hydrogels) and 10 for spinal interbody fusion (mainly modified bone cement) were found. Only one modified bone cement for spinal compression fracture is currently being evaluated. PMMA is currently the most common bone cement used in clinical research (Table 4).

5. Conclusion and future perspectives

The development of injectable biomaterials has recently progressed

rapidly. The specific physical and chemical properties and excellent biological functions of such materials endow them with the ability to specifically repair tissue in the human body. Progress in this field has played an important role in regenerating the intervertebral NP, annulus fibrosus and vertebral body.

Although injectable bioactive materials provide a new direction for the treatment of spinal degeneration, their development and clinical application are still at the cell and animal experimentation stage. There remain major challenges that need to be overcome in the future: 1) High-performance hydrogels should be explored for lesions in the load-bearing parts of the spine as these hydrogels possess the required mechanical characteristics, are easy to inject, have no adverse impact on the survival rate of encapsulated cells and can be used to release drugs and other factors. 2) The addition of modified materials will alter the structure and function of injectable materials; however, increasing the type and content of added materials may cause the original performance level to decrease, and the toxicity levels of the composite materials may also increase. Thus, the selection of modified materials and the effects of incorporating such materials needs to be further explored. 3) The tissue microenvironment in the degenerating spine is different from that of normal tissue and includes hypoxia, acidity and abnormal stresses. Future research will lead to the construction of stimulus-responsive injectable biomaterials for these adverse microenvironments. 4) Finally, animal models more consistent with the physiological degeneration process should be established to further explore the pathogenesis of spinal degeneration and the reparative mechanisms of biomaterials.

Further efforts are also required to produce injectable biomaterials more suitable for clinical needs: 1) At present, surgery is the main treatment strategy for spinal degeneration, and it is challenging to obtain long-term stable effects with injectable biomaterials. The development of injectable materials for surgical defects and their use as a supplementary treatment combined with minimally invasive spine surgery may yield a more positive therapeutic effect. 2) Clinically, patients with spinal degeneration often have coexisting conditions such as inflammation, tumours and tuberculosis. It is important to develop injectable materials with various biological functions, such as anti-inflammatory, antioxidant, antibacterial, antitumour (photothermal and magnetothermal effects) and *in vivo* biological imaging functions. 3) The diagnosis of spinal degeneration mainly relies on imaging (MRI, CT, X-ray), but there are often no obvious positive signs in the early stage of the disease. Therefore, injectable biological materials with biochemical analysis functions are highly desirable; for example, materials allowing the analysis of the microenvironment components of spinal degeneration without damaging the disc structure, facilitating early diagnostics and treatment. 4) Some patients have no obvious pathological spinal structure changes, and their clinical symptoms are mainly pain. Therefore, it is relevant to construct disk-derived and fracture-derived pain models, establish good evaluation indicators and better combine tissue engineering repair strategies with clinical symptom relief. 5) The development of personalized injectable biomaterials for patients with spinal degeneration at different clinical stages can achieve corresponding therapeutic effects for patients with different disease severities.

Although much work is required before injectable materials can be applied clinically, prospective clinical trials should be carried out to determine safety standards, and problems should be approached from the perspective.

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.

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Abbreviations

IVDD	intervertebral disc degeneration
HA	hyaluronic acid
FGF18	fibroblast growth factor-18
HGC	n-hexanoyl glycol chitosan
PEG	polyethylene glycol
HGF	hepatocyte growth factor
PVA	polyvinyl alcohol
IGF-1	growth factor 1
BMP	bone morphogenetic protein
PLGA	poly(lactic acid)-poly(glycolic acid) copolymer
PCD	percutaneous cement discplasty
PMMA	polymethyl methacrylate
PVP	percutaneous cementplasty
NMP	n-methyl-pyrrolidone
MC	mineralized collagen
LDH	lamellar dihydroxide
CPC	Calcium phosphate cement
RGO	reduced graphene
BMSC	bone marrow mesenchymal stem cells
CNT	carbon nanotube
CSC	calcium sulphate cement
SLCMs	chitosan microspheres
SF	silk fibroin
BAG	bioactive glass
SR-BBG	strontium borate BAG particles
TNF-α:	tumour necrosis factor-α
IL-1	interleukin-1
ECM	extracellular matrix
HAMA	hyaluronic acid methacrylate
DBM	demineralized bone matrix
SDF-1α	stromal cell-derived factor-1α
FPR-1	formyl peptide receptor-1

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