REVIEW ARTICLE

Bone cements for percutaneous vertebroplasty and balloon kyphoplasty: Current status and future developments

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Summary   Osteoporotic vertebral compression fractures (OVCFs) have gradually evolved into a serious health care problem globally. In order to reduce the morbidity of OVCF patients and improve their life quality, two minimally invasive surgery procedures, vertebroplasty (VP) and balloon kyphoplasty (BKP), have been developed. Both VP and BKP require the injection of bone cement into the vertebrae of patients to stabilize fractured vertebra. As such, bone cement as the filling material plays an essential role in the effectiveness of these treatments. In this review article, we summarize the bone cements that are currently available in the market and those still under development. Two major categories of bone cements, nondegradable acrylic bone cements (ABCs) and degradable calcium phosphate cements (CPCs), are introduced in detail. We also provide our perspectives on the future development of bone cements for VP and BKP.

Introduction

Ageing has become a global issue as a result of improved living conditions and health care [1]. Due to inadequate calcium and vitamin D intake, as well as reduced daily activities, there is a high incidence of osteoporosis in the elderly. As a result, osteoporosis with subsequent vertebral compression fractures (VCFs) has evolved into a common social and economic burden globally. The annual incidence of osteoporotic fractures exceeds 1.5 million in the US, of

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which more than 50% are VCFs, and this is twice the incidence of hip fractures [2]. About 20% of individuals over 50 years old and 45% of women over 50 experience OVCFs. If left untreated, OVCFs may lead to dramatic physical, functional, and psychological consequences that impair the quality of life of the patient [3]. VCF patients usually suffer from severe back pain. Moreover, restrictive lung diseases may develop when there are multiple thoracic fractures [4]. In the worst cases, female VCF patients have a 23% higher mortality rate compared to those without VCFs [5]. Until recently, conservative treatments have been the only options [6].

In order to reduce the morbidity of patients with acute OVCFs and improve their life quality, vertebroplasty (VP), a minimally invasive surgery (MIS), was developed in the 1980s by Galibert et al [7] (Fig. 1A,B). By using a needle to deliver bone cement to fractured vertebra through the pedicle of the vertebral arch, the VP technique successfully relieved the pain of 75—85% of patients [8]. Compared to conservative treatments, VP is safe, the pain relief after surgery is immediate, and the effect can last for at least 1 year [6]. However, VP does not restore the height of the compressed vertebral body (VB), which may reoccur in the later stage of treatment such that the patients still suffer from kyphosis and chronic low back pain. A variation of VP, kyphoplasty (KP), attempts to restore the height and angle of kyphosis of a fractured VB and to stabilize it using injected bone cement.

BKP, developed in the 1990s by Dr Mark Reiley, is the most commonly used KP technique. BKP involves the use of a balloon to create a cavity within the cancellous bone, followed with bone cement delivery to the cavity to reinforce the VB (Fig. 1A,C). Using this technique, BKP not only relieves the back pain of the patient, but also corrects deformities such as kyphosis. BKP also provides controlled cement filling to make the cement more uniformly distributed within the VB. While the extent of pain relief is similar, BKP results in markedly fewer complications and has a lower risk of mortality than VP [9,10]. However, the survival rates for VCF patients following VP or BKP were all markedly higher than nonoperated patients [10].

Apparently, the filling material, i.e., the bone cement, plays a critical role in the effectiveness of VP or BKP treatments. Bone cements for VP or BKP are self-curing compounds that are applied in a flowable state and become fully cured in the body to provide adequate support to the fractured VB. They must have considerable mechanical strength and toughness in order to achieve long-term sustainability. They should have adequate viscosity and be injectable for facilitating VP or BKP surgeries. In addition, they should have appropriate working and setting times to match the general progress of surgeries. They should also be radiopaque and present clear contrast under fluoroscopy. These fundamental requirements make VP and BKP bone cements a special
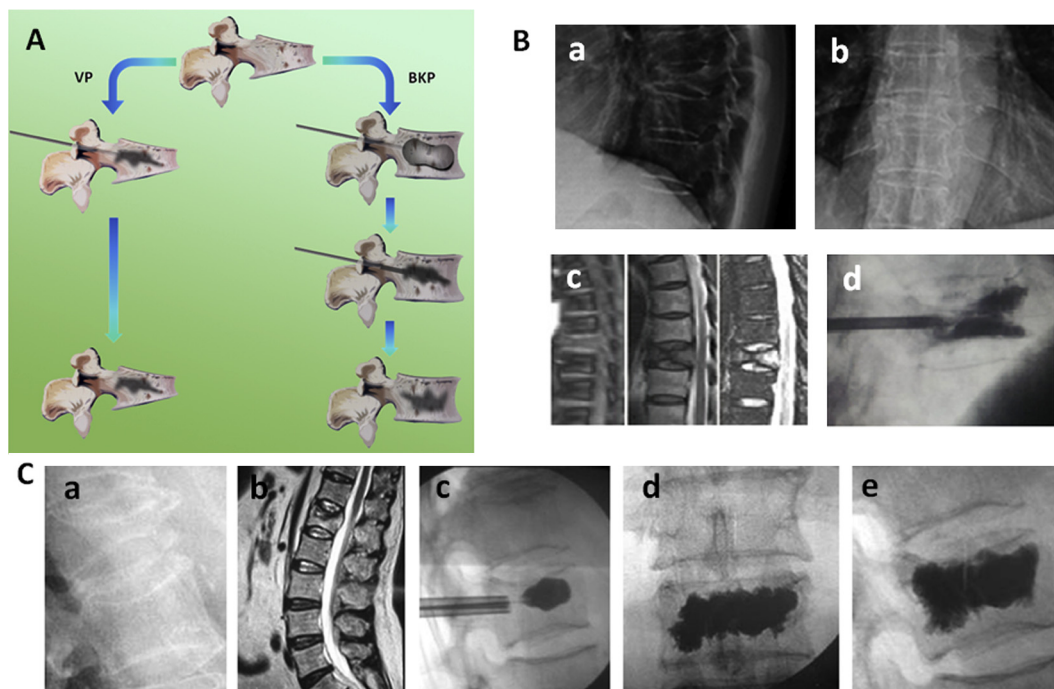

Figure 1 (A) A schematic illustration of VP and BKP procedures. (B) VP for a patient with severe vertebral compression: (a—c) lateral, anteroposterior X-ray radiographs and sagittal MR image showing severe H-shaped VCF at the T9 VB; (d) postoperational lateral radiograph showing the VB filling with cement. (C) BKP for a patient with L1 vertebral compression: (a—b) X-ray radiograph and MR image showing a compression fracture at the L1 VB; (c) fluoroscopy image showing the filling of bone cement in a cavity created by a balloon; (d,e) anteroposterior and sagittal fluoroscopy images showing complete filling of bone cement and restoration of vertebral height after BKP BKP = balloon kyphoplasty; MR = magnetic resonance; VB = vertebral body; VCF = vertebral compression fracture; VP = vertebroplasty. *Note*. Figure 1B is from "Unilateral versus bilateral vertebroplasty for severe osteoporotic vertebral compression fractures," by C. Chen et al, 2014, *J Spinal Disord Tech* 2014;27:E301—E304 [73]. Reproduced with permission.

category, which largely differs from the cements for other purposes such as total hip arthroplasty (THA) or total knee arthroplasty (TKA).

To date, the most popular bone cement is poly(methyl methacrylate) (PMMA)-based acrylic bone cement (ABC). However, several drawbacks of PMMA, including non-biodegradability, monomer toxicity, heat generation during exothermic polymerization, and leakage of monomer, limit its applications. To overcome these disadvantages, biodegradable calcium phosphate cements (CPCs) and other types of cements that generate no or little heat upon curing have been developed and their applications in VP and BKP have been recently explored. In this article, we summarize the bone cements that are currently available in the market and have been clinically used. We also provide our perspectives on the future development of bone cements for VP and BKP.

ABCs

In 1958, Dr John Charnley [11] first started to use self-curing PMMA cement in total hip replacement (THR) and succeeded in anchoring femoral head prostheses in the femur. Since this major breakthrough, use of PMMA-based bone cements has prevailed in various orthopaedic applications. In 1987, Galibert et al [7] first used PMMA bone cement to treat cervical vertebral haemangioma in patients. Since then, this technique has been successfully applied to many spine disorders including OVCFs, vertebral metastasis of malignant tumours, multiple myeloma, and even traumatic VCFs. In 2004, the Food and Drug Administration (FDA) formally approved PMMA bone cements for treating vertebral fractures resulting from osteoporosis and tumours. Advantages such as bio-inertness, ease of handling, considerable mechanical strength, and cost-effectiveness make PMMA an ideal choice for bone cement. To date, ABCs represent the vast majority of bone cements for VP and BKP.

Compositions of ABCs

The main components of ABCs are acrylic compounds that are capable of self-curing. All of them are composed of solid and liquid phases. When the solid and liquid phases of an ABC are mixed, curing occurs rapidly at room or body temperatures. The compositions of ABCs only vary slightly. A large number of cement brands have been developed and are commercially available (Table 1).

The solid phase of an ABC mainly comprises PMMA prepolymer and/or copolymers of acrylic acid (AA), ethyl acrylate (EA), methyl acrylate (MA), MMA, and styrene. The average molecular weight of the prepolymers ranges from 44,000 to 1,980,000, and the bead size ranges from 30 μm to 150 μm. The prepolymer powder accounts for approximately 80 wt% of bone cement. The solid phase also contains benzoyl peroxide (BPO) as the initiator, at a concentration of 0.75–2.5 wt%. In addition, radiopacifiers, such as barium sulfate, zirconium dioxide, tantalum, and tungsten powders, are included in the powder to make the cement radiographically visible. Their concentration is generally 10–30 wt% of powder, and their particle size is

around 5 μm [12,13]. In order to prevent infection, some commercial products also supplement antibiotics, including gentamicin, keflin, erythromycin, and colistin, to the powder. Occasionally, dyes or pigments such as chlorophyll may also be supplemented to provide additional features to cements.

The main composition of the liquid phase is MMA monomer, usually at a concentration of 95 wt%. In order to initiate polymerization, an activator N-N-dimethyl-p-toluidine (DMPT) is usually supplied (0.89–2.7 wt%). In addition, the liquid phase contains an inhibitor, usually hydroquinone (HQ), which functions to inhibit premature polymerization during storage [12,13].

Current development of ABCs

Although the ABC industry is mature and a broad range of products have appeared in the market, some drawbacks of ABCs cannot be ignored, including nondegradability and significant mechanical mismatch with the VB. As such, many efforts have been made to improve the products in terms of mechanical characteristics, porosity, biodegradability, and to provide additional merits such as osteoconductivity and drug delivery capability [14–16]. Such improvements are mainly achieved by fabricating composite materials using ABCs and filling materials of desired properties.

Cortoss Bone Augmentation Material represents a typical composite ABC. It is a polymer–inorganics composite consisting of crosslinking resins and reinforcing glass ceramic particles. It consists of a terpolymer resin containing Bisphenol-A-glycidyl dimethacrylate (Bis-GMA), Bisphenol-A-ethoxy dimethacrylate (Bis-EMA), and triethyleneglycol dimethacrylate (TEGDMA). It is supplemented with bioactive combeite glass–ceramic particles for stimulating bone apposition at the interface, barium boroaluminosilicate glass for providing radiopacity and strength, and silica particles for achieving adequate viscosity [17]. It functions to strengthen weakened bone and achieves a compressive strength equal to approximately 75% of human cortical bone (210 megapascals, MPa) within 15 minutes of application [18].

The porosity of ABC significantly affects its mechanical and biological performance. Ideally, the cured cement as an implant material within the VB should contain pores of varying size and distribution to mimic the trabecular-like structure of the VB. However, such a porous structure inevitably weakens the mechanical properties of the cement. Therefore, it is desired to have a composite cement in which biodegradable fillers are embedded throughout the cement to provide enough initial mechanical strength. When they degrade, new bone ingrowth happens so that the voids are filled with new bone tissue to continuously provide adequate mechanical support to the VB [19].

A radiopacifier is an essential component in VP and BKP cements. However, addition of traditional radiopacifiers significantly lowers the mechanical strength of ABCs. In order to provide the ABC with adequate radiopacity yet minimize mechanical property loss, new radiopacifiers have been developed. For example, owing to the high

Table 1 Commercially available acrylic bone cements (ABCs).

Brand	Prepolymer	Monomer	Radiopacifier	Initiator and additives	Working time (min)	Setting time (min)	Viscosity	Bending modulus (MPa)	Bending strength (MPa)	Compressive strength (MPa)	Supplier
CMW1	PMMA: 88.85%	MMA: 99.18%	$BaSO_4$: 9.1%	BPO: 2.05% DMPT: 0.82% HQ: 0.0025%	6.5	11	High	2634	67.81	94.4	Depuy
CMW2	PMMA: 86.7%	MMA: 99.18%	$BaSO_4$: 11.3%	BPO: 2.0% DMPT: 0.82% HQ: 0.0025%	3	6	High	3008	74.3	97.8	Depuy
CMW3	PMMA: 88.0%	MMA: 97.5%	$BaSO_4$: 10%	BPO: 2.0% DMPT: 2.50% HQ: 0.0025%	5.5	11	Medium	2764	70.3	96.3	Depuy
Smartset HV	PMMA-co-PMA: 84%	MMA: 97.5%	ZiO_2: 15%	BPO: 1% DMPT: 2.5% HQ: 0.0075%	8.0	12.5	High	3010	64.32	86.54	Depuy
Endurance	PMMA: 67.5% PMMA-co-PS: 21.1%	MMA: 98.0%	$BaSO_4$: 10%	BPO: 1.85% DMPT: 2.0% HQ: 0.0011%	8.0	14	Low	2896	76.1	94	Depuy
Smartset MV	PMMA-co-PS: 15−30% PMMA: >50.0%	MMA: >50.0%	$BaSO_4$: 5−10%	BPO: 1−3% DMPT: ≤2.0%	8.0	14	Medium	3010	64.32	70	Depuy
Simplex P	PMMA-co-PS: 73.5% PMMA:15%	MMA: 97.45%	$BaSO_4$: 10%	BPO: 1.5% DMPT: 2.55% HQ: 0.008%	7	14.3	Medium	2681	71	90.32	Stryker
Spineplex	PMMA: 8.51% PMMA-co-PS: 58.3%	MMA: 97.5%	$BaSO_4$: 30%	BPO: 1.5% DMPT: 2.5% HQ: 0.0079%	10−12	8.7	Low		55.1	80.91	Stryker
Palacos® R	PMA: 83.9%	MMA: 97.98%	ZiO_2: 15.3%	BPO: 0.8% DMPT: 2.0%	5.0	12.5	High	2628	72.2	79.6	Heraeus
Osteopal V	PMMA-co-PMA: 54.6%	MMA: 97.87%	ZiO_2: 45%	BPO: 0.38% DMPT: 2.13% HQ	8	14	Low	3504 ± 235	46 ± 8	82 ± 3	Heraeus
Cobalt HV	PMMA-co-PMA: 83.55−84.65%	MMA: 98%	ZiO_2: 14.9%	BPO: 0.5−1.6% DMPT: 4.27%	5	10	High		67.84	96.04	Biomet
Osteobond	PMMA-co-PS: 88.75%	MMA: 99.26%	$BaSO_4$: 10%	BPO:1.25% DMPT: 0.745% HQ: 0.008%	5	14.5	Low	2828	73.7	104.6	Zimmer
KyphX HV-R	PMMA-co-PS: 68%	MMA: 99.11%	$BaSO_4$: 30%	BPO: 2% DMPT: 0.888% HQ: 0.0075%	8	20	High			111	Kyphon
ABC	PMMA-co-PS: 99.55%	MMA: 99%		BPO: 4.5% DMPT: 1% HQ: 0.006%	4.5−6.5	12	Medium	3300	68	93	Tianjin Institute of Synthetic Materials Industry

$BaSO_4$ = barium sulphate; BPO = benzoyl peroxide; DMPT = N−N-dimethyl-p-toluidine; HQ = hydroquinone; HV = high viscosity; MMA = methyl methacrylate; MPa = megapascals; MV = medium viscosity; PMA = poly(methyl acrylate); PMMA-co-PMA = methyl methacrylate-methylacrylate copolymer; PMMA-co-PS = methyl methacrylate-styrene copolymer; ZiO_2 = zirconium dioxide.

radiopacity of organobismuth, ABCs containing bismuth salicylate showed higher radiopacity and better injection properties compared to current commercial bone cements while retaining good mechanical properties [15]. Surface functionalization of existing radiopacifiers also appeared to effectively improve the mechanical properties of cements [20,21].

CPCs

A category of biodegradable bone cements, CPCs, were first invented by Brown and Chow in the early 1980s [22]. Compared to ABCs, CPCs hold a unique combination of osteoconductivity, injectability, mouldability, biodegradability, nonexothermic setting, and negligible shrinkage. CPCs upon mixing form a viscous paste that can be easily manipulated and moulded. Importantly, they can be injected into the defect area and harden *in vivo* without generating heat [23]. Therefore, CPCs are potentially an ideal filling material for VP and BKP applications.

In general, all CPCs consist of a powder phase containing one or more calcium phosphate (CaP) compounds (Table 2) and a liquid phase, which can be water or a calcium- or phosphate-containing aqueous solution. Despite the large number of CaP combinations in different CPC systems (Table 3), the setting chemistry is similar—dissolution and reprecipitation [22]. Based on the nature of the end hydration product, which depends on the pH of the cement paste, CPCs can be divided into two categories: apatite (hydroxyapatite, HA; or calcium-deficient hydroxyapatite, CDHA) (formed at pH > 4.2) and brushite (dicalcium phosphate dehydrate, DCPD) (formed at pH < 4.2) [24]. At a physiological pH, brushite is one to two orders of magnitude more soluble than apatite and degrades faster [25]. Due to the short setting time, low mechanical strength, and inferior injectability, brushite cements only have limited clinical applications [26].

Biocompatibility and degradability of CPCs

Since CPCs consist of a network of CaP crystals that resemble the HA in native bone tissue, they are considered biocompatible and osteoconductive. *In vivo*, CPCs may undergo passive and/or active absorption. The passive absorption relies mainly on solubility and dispersion of the materials. The active resorption is related to the activity of osteoclasts. Bone formation is initiated as soon as the active and/or passive resorption of CPCs starts. Woven bone usually forms after approximately 2 weeks. Depending on the specific characteristics of CPCs, the implanted site may be almost completely converted to bone within a few months to a couple of years [27]. In addition, CPCs may have bone-like elastic modulus, which helps prevent stress shielding and maintain adequate toughness to prevent fatigue fracture under cyclic loading [28].

Intrinsically, CPCs have nano/micron-sized pores. Their porosity is approximately 30–50% [29]. While porosity can be a limitation for them to be used in high load-bearing sites, such a porous structure enables fluid exchange and inclusion of growth factors, matrix proteins, and cells [30]. The micropores also significantly contribute to the resorption of CPCs and replacement of them by newly formed bone. Owing to their inherent porosity, CPCs have been widely used as carriers for controlled drug delivery [29,31]. Being able to function as both a supporting material and a delivery system to release bioactive substances, CPCs have been considered a promising cement material for bone defect repair and vertebral augmentation.

Reinforcement of CPCs

From a clinical point of view, the mechanical strength of a cement material should be similar to or greater than cancellous bone. Although CPCs are highly promising for bone regeneration, the usually poor mechanical properties constitute a major challenge toward their applications. To date, CPCs are mainly used at non- or moderate load-bearing sites [22]. Therefore, mechanical reinforcement has been a major challenge in CPC development. In addition to chemical composition (Table 3), the mechanical properties of CPCs are markedly affected by granularity, crystal type, powder/liquid ratio, and porosity.

Since CPCs are porous, decreasing the porosity by compacting the cement paste prior to hydration has an immediate boosting effect on their mechanical properties, while increasing pore density and size causes mechanical strength loss [32]. However, when CPC is compacted enough and its porosity reaches a critical level (< 30%), its strength becomes constant [33]. It should be noted that while

Table 2 Calcium orthophosphates commonly used in bone cements [64,74].

Compound name	Abbreviation	Chemical formula	Ca/P ratio
Amorphous calcium phosphate	ACP	$Ca_3(PO_4)_2 \cdot nH_2O$	1.2–2.2
Calcium-deficient hydroxyapatite	CDHA	$Ca_{10-x}(HPO_4)_x(PO_4)_{6-x}(OH)_{2-x}$ ($0 < \times < 1$)	1.5–1.67
Dicalcium phosphate anhydrous	DCPA	$CaHPO_4$	1.00
Dicalcium phosphate dihydrate	DCPD	$CaHPO_4 \cdot 2H_2O$	1.00
Hydroxyapatite	HA	$Ca_{10}(PO_4)_6(OH)_2$	1.67
Monocalcium phosphate anhydrous	MCPA	$Ca(H_2PO_4)_2$	0.50
Monocalcium phosphate monohydrate	MCPM	$Ca(H_2PO_4)_2 \cdot H_2O$	0.50
Octacalcium phosphate	OCP	$Ca_8H_2(PO_4)_6$	1.33
Tetracalcium phosphate	TTCP	$Ca_4(PO_4)_2O$	2.00
α-Tricalcium phosphate	α-TCP	α-$Ca_3(PO_4)_2$	1.50
β-Tricalcium phosphate	β-TCP	β-$Ca_3(PO_4)_2$	1.50

Table 3 Commercially available calcium phosphate cements (CPCs).

Brand	Powder composition	Initial setting time	Full hardening time	End product	Porosity	Pore size (μm)	Degradability	Injectability	Compressive strength (MPa)	Supplier
BoneSource	72.3% TTCP, 27.7% DCPA	7 min	4 h	Apatite	5—10%	33.4 ± 6.2	Minimal	No	26	Stryker
Norian SRS	α-TCP, CaCO$_3$, MCPM	10—15 min	12 h	Carbonated apatite	50%	47.2 ± 21.9	Yes	Yes	50	Synthes
α-BSM	ACP, DCPD	15—20 min	1 h	Apatite	80%	<1	Yes	Yes	4	ETEX
Biopex	75% α-TCP, 18% TTCP, 5% DCPD, 2% HA	7—10 min	24 h	Apatite	40—50%		Yes	Yes	80	Mitsubishi
Calcibon	α-TCP, DCPA, CaCO$_3$, HA	10 min	6 h	Carbonated apatite	30—40%	41.6 ± 22.0	Yes	Yes	60	Biomet-Merck
Cementek	α-TCP, TTCP, Ca(OH)$_2$	3—15 min	24—48 h	Apatite	50%	26	Yes	Yes	13	Teknimed
Graftys HBS	HA, TCP	15 min	72 h	Apatite	65—70%	100—300	Yes	Yes	12	Graftys
Graftys Quickset	HA, TCP	8 min	24 h	Apatite	70%	10—100	Yes	Yes	24	Graftys
Ostim	HA	20 min		Apatite	53%	70	Yes	Yes	0.24	Hereaus
chronOS Inject	β-TCP, DCPD	6—12 min	24 h	Brushite	60—75%	70—170	Yes	Yes	3	Synthes
Embarc	ACP, DCPD			Apatite			Yes			Lorenz Surgical
Fracture Grout	α-TCP, CaCO$_3$			Apatite			Yes			Norian
Eurobone	TCP, DCPD	3—15 min		Apatite	2%	162.2 ± 107.1	Yes		17	FH Orthopedics
KyphOs FS		5 min	24 h	Apatite			Yes		61	Kyphon

ACP = amorphous calcium phosphate; DCPD = dicalcium phosphate dihydrate; HA = hydroxyapatite; MCPM = monocalcium phosphate monohydrate; TCP = tricalcium phosphate; TTCP = tetracalcium phosphate.

pressurization improves the mechanical strength of CPCs, it also deteriorates their injectability, making it difficult for them to be used in MIS procedures [22].

Supplementation of certain compounds, including small organic molecules, biodegradable polymers, proteins, polysaccharides, inorganic molecules, bioceramics, and bioglass, has proven effective in improving the mechanical properties of CPCs. For example, adding citric acid into an apatite cement paste increased both the injectability and strength of the cement. This is likely because the citrate ions facilitated the sliding and dispersion of apatite crystals, inducing their growth and entanglement to form a stronger matrix [34]. When CPC was blended with a silanised-hydroxypropyl methylcellulose (Si-HPMC) hydrogel, the mechanical and handling properties were improved, yet the rheological property was not affected [35]. Recently, we found that supplementing silk fibroin (SF) to CPCs helped improve their mechanical strength and washout resistance [36]. Further, when a mineralized complex, HA—SF, was supplemented to the CPC/SF composite, the compressive strength of the composite increased in a HA—SF content-dependent fashion, likely due to the improved interfacial integrity and the presence of nucleation seeds, which induced oriented growth of HA crystals [37].

Inclusion of fibres, either nondegradable or biodegradable, into CPCs can also improve their mechanical strength, probably through a crack-arresting mechanism [22,38]. Depending on the strength, length, volume fraction, and orientation of fibres, and fibre—matrix interfacial adhesion, the mechanical properties of fibre-reinforced CPCs (frCPCs) may be up to two orders of magnitude higher than CPCs, which permits their potential in load-bearing applications [24,38]. Commonly used nondegradable fibres include polyamides, carbon fibres, and glass fibres. Biodegradable fibres include natural biomolecules such as proteins (e.g., collagen) and polysaccharides (e.g., chitosan) or synthetic polymers such as poly(glycolic acid) (PGA), polylactide (PLA), poly(lactic-co-glycolic acid) (PLGA), and polycaprolactone (PCL). In addition to the relatively long fibres, whiskers made of HA, calcium carbonate, silicon nitride, silicon carbide, or bioglass have also been used for improving the mechanical strength of CPCs [39,40].

CPCs for VP and BKP

While no commercially available CPC products have been approved specifically for VP and BKP purposes, there have indeed been many off-label uses of CPCs (Table 3) for vertebral augmentation and spinal fusion. According to biomechanical tests of vertebra filled with CPCs or PMMA by VP/KP procedures, CPCs could restore the strength but not stiffness of vertebra [41]. In the treatment of fractured vertebra, both PMMA and CPCs restored strength and stiffness and resulted in similar anterior vertebral height restoration [42].

Using a canine VP model, Turner et al [43] compared the histological responses and mechanical characteristics of VBs injected with CPC (BoneSource, Stryker) or PMMA. Histologically, both cement materials were well integrated to VB bone tissue. Unlike PMMA, CPC underwent resorption

and remodelling with vascular invasion and bone ingrowth, indicating its excellent biocompatibility and osteoconductivity. There was no significant difference in VB height and compressive strength between PMMA- and CPC-treated VBs. Interestingly, the compressive strength of CPC-treated VBs continuously increased, whereas PMMA-treated VBs presented decreased compressive strength, indicating that CPC injection might have both intermediate and short-term effects in treating vertebral defects.

The inconsistency of degradability of CPCs, possibly due to the complexity in their composition, setting chemistry, and environment, may present a major limitation toward their clinical usage. For example, it has been reported that no resorption of BoneSource was observed after several years of implantation [44]. However, Turner et al [43] found that BoneSource indeed degraded in a canine VP model. Another study reported that approximately 30% of Bone-Source was resorbed and replaced with bone after only 12 weeks, and 90% degraded after 40 weeks [45].

Strontium-substituted CPCs

Strontium belongs to the same family as calcium in the Periodic Table of Elements. Systematic administration of strontium ranelate has been used to prevent bone loss and stimulate bone regeneration [46]. Taking advantage of the dual functions of strontium, strontium-modified CPC systems (Sr-CPCs) have recently been explored in order to develop novel bioactive bone cements [47—51]. Different ways to introduce strontium into the CPC paste, however, may result in very different end products. When amorphous Sr-substituted CaP and DCPD were mixed half and half, strontium could be doped into the lattice of the HA, which increased the lattice dimension and volume. However, when a mixture of amorphous CaP and amorphous strontium phosphate (SrP) were blended with DCPD, the HA and Sr-hydroxyapatite (Sr-HA) precipitated separately in the hydrated cement [52]. Therefore, in the majority of studies, Sr-containing CaP was first synthesized and then supplemented to the CPCs.

The supplementation of strontium to CPCs causes the release of biologically effective doses of Sr^{2+}, which stimulates bone formation in and around the implant and enhances osseointegration. In a critical-size metaphyseal defect in the femur of ovariectomised rats filled with Sr-CPC and CPC, a significant increase in bone formation was achieved in the Sr-CPC group compared to the CPC group [48]. However, the release of strontium from the Sr-CPC implants did not lead to a serum Sr^{2+} level that was sufficiently high to induce systemic bone mass increase [49].

In addition to promoting bone formation, Sr-CPCs also show improved mechanical properties. Compared to non-substituted CPCs, the compressive strength of Sr-CPCs can achieve a high of 74.9 MPa [50,53] and may be further improved upon surface treatment of the Sr compounds. When the Sr-HA powder was surface-treated using acrylolpamidronate, the compression strength and stiffness of the Sr-HA cement were improved by 22% and 14%, respectively [54].

Furthermore, Sr-CPCs are radiopaque cements. The radiopacity of brushite cements containing 10 wt%

strontium halides was similar to or higher than that of commercial radiopaque cements, which usually contain 20 wt% or more radiopacifiers [55]. With moderate mechanical strength yet without the need for the addition of another radiopacifier, Sr-CPCs may be good candidates for repairing nonloading sites or reinforcing osteoporotic vertebrae through MISs [51].

Other types of bone cements

Besides ABCs and CPCs, there are also some other types of bone cements. Taking advantage of the controllable degradation, rapid solidification, excellent biocompatibility, and osteoconductivity of calcium sulfate (CaS), calcium sulfate cements (CSCs) have been developed [28]. Compared to CPCs, CSCs have relatively higher mechanical strength. However, CSCs not only cure very fast, but also degrade fast. They may be fully absorbed within 6 weeks upon implantation *in vivo*. Such fast degradation of the filling material does not match the bone formation process. Therefore, the development and clinical applications of CSCs are relatively limited compared to CPCs [56].

Magnesium phosphate cement (MPC) is another type of biodegradable bone cement. Because the released magnesium ions can enhance the activity of osteoblasts, MPC may function as a bioactive bone cement. However, the setting time of MPCs is as short as 3 minutes, which largely limits their applications. Similar to CSCs, MPCs are often used in combination with other cement systems such as CaPs and CaSs. Yang et al [57] mixed CaS powder with magnesium phosphate (MgP) to form a CaP/MgP bone cement. The setting time could be controlled up to 6 minutes by adjusting the content of MgP in the composite cement. The compressive strength was up to 70 MPa.

Future development of VP/BKP cements

Ideally, the next generation of cements for VP and BKP should have (a) adequate injectability, setting property, cohesion, and radiopacity for best handling property; (b) sufficient mechanical strength for immediate reinforcement; (c) adequate porosity to allow body fluid circulation, cell migration, and new bone ingrowth; (d) excellent osteoconductivity and osteoinductivity for promoting new bone formation; (e) moderate biodegradability so that the resorption of cement material matches new bone formation; and (f) high efficiency of drug delivery [28]. In addition, future development of VB/BKP cements should also take into consideration the following issues.

Mechanical characteristics

Bone cement is subjected to high stress and a challenging body environment. As such, improving mechanical properties has been one of the main topics of bone cement development. It should be noted, however, that higher compressive strength of bone cements does not necessarily mean a better choice. When a complex 3D load is applied *in vivo*, the shear and tensile stresses, in addition to compressive stress, indeed play a prominent role [58]. The

choice of cement for augmentation of a fractured VB should be based on comprehensive biomechanical considerations including fracture configuration, rotational/flexional fracture stability, load-bearing capacity, and the bone mineral density of the VB [59].

The stiffness of VP/BKP cements should also be seriously evaluated. Vertebrae augmentation using rigid ABCs (stiffness being as high as 11 times that of osteoporotic vertebral cancellous bone) may cause massive vertebrae stiffness change [60]. Osteoporotic cancellous bone augmented by rigid bone cement can be at least 12 times stiffer and 35 times stronger than untreated bone [61]. The rigid cement augmentation leads to load increase in the structures adjacent to the augmented VB, which may inhibit the normal endplate to bulge into the augmented VB and thus pressurizes adjacent discs, leading to increased loading of untreated vertebra and even VB fracture. In addition, finite element analyses showed that the compressive stiffness of the spinal unit increased over 10% after VP using ABCs, yet the hydrostatic pressure within the nucleus pulposus increased by about 15% [62]. The stiffening effect of regular cement, however, can be largely avoided by using low-modulus cements, which cause less stiffness alteration of vertebrae and therefore better preservation of vertebrae strength [60].

Incorporation of bioactive additives and cells

Bone cements usually lack sufficient osteoinductivity. Therefore, various bioactive, osteogenic agents are supplemented in order to promote osteogenic differentiation of progenitor cells and new bone formation. The incorporation of several bioactive ions, for example, strontium, magnesium, zinc, copper, and fluoride, has been shown to improve the biological performance of CPCs by promoting bone metabolism [63].

Because of their intrinsic porosity and high surface area, CPCs are an ideal carrier system for growth factor (GF) and drug delivery. GFs such as bone morphogenetic proteins (BMPs), basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF) have been incorporated into CPCs, which improved their osteogenic and angiogenic capabilities [64]. The GFs may be mixed with CPC components alone, or be encapsulated within microspheres of chitosan, gelatin, or hyaluronic acid before incorporation into the CPC for best preservation of their bioactivity [65]. Plasmids or small interfering RNAs (siRNAs) may also be incorporated into CPCs to achieve gene delivery to cells at the injection area [64,66]. Recently, platelet-rich plasma (PRP) and autologous bone marrow concentrate (BMC) have been used together with CPCs as autologous bone substitutes [67].

In general, the bone metabolism of VP/BKP patients is impaired due to the significantly reduced number and functionality of osteogenic stem/progenitor cells. Delivery of mesenchymal stem cells (MSCs) along with injection of biodegradable bone cements such as CPCs, therefore, is desirable for regenerating fractured VBs [68]. Since the potential chemical or heat release during the cement setting reaction may harm the cells, appropriate short-term protection of cells is needed during cement handling.

Various biodegradable carriers including chitosan, alginate, and fibrin have been used as encapsulating gels to protect the cells [69]. With such protection, the cells remained in the CPC with a high survival rate (close to 90%) and showed excellent proliferation, osteo-differentiation, and mineralization upon implantation [70].

Radiopacifiers

The addition of traditional radiopacifiers to VP/BKP cements may affect cement setting behaviour and significantly reduce the mechanical strength of cements. It may even significantly increase bone resorption, likely as a result of enhanced macrophage/osteoclast differentiation [71]. In the development of new radiopacifiers, the surface functionalization of existing radiopacifiers appears to be an effective way to overcome such problems. Using barium sulfate or zirconia dioxide nanoparticles that were surface-treated with a difunctional agent, usually an acrylated compound which can be copolymerized with MMA, the interface between radiopacifier particles and PMMA was ameliorated, resulting in enhanced mechanical properties of ABCs [20,21]. Supplementing MMA-treated, Sr-HA to ABCs not only improved the handling property and compressive strength of ABCs, but also enhanced their radiopacity and bioactivity [72].

Hybrid cements

Currently, various PMMA-based hybrid or composite cements have been developed by incorporating CaPs or polymers in order to combine the bone augmentation characteristics of ABCs and biodegradability of CPCs. Such studies may eventually lead to the development of a range of bone cements that are tailored for specific VP or BKP needs. For example, for young patients with traumatic burst fractures, excellent biocompatibility and degradability of cement are required to facilitate bone formation and remodelling. In elderly OVCF patients, however, immediate weight-bearing stability is more important. Therefore, cements that provide long-term multidirectional stability and are slowly resorbed are needed. For application in metastatic lesions or osteoid osteomata, the cement could be designed to produce local heat and resolve quickly. Developing cements with characteristics matching the needs of specific VP/BKP indications, therefore, may help solve many practical issues and lead to better treatment outcomes yet reduced complications [59].

Concluding remarks

To date, a broad range of bone cements have been approved for clinical applications and many have been used for VP and BKP procedures. While ABCs still prevail as the VP/BKP filling material of choice, their intrinsic non-degradability constitutes a formidable obstacle toward broader applications. By contrast, given the unique combination of biodegradability, osteoconductivity, mouldability, nonexothermic setting, and negligible shrinkage, CPCs are determined to play a significant role in the development of next-generation VP/BKP cements. Being able to simultaneously promote bone formation yet suppress bone resorption, Sr-CPCs represent a promising type of bone cement for augmentation of fractured vertebra.

New technical advances in the development of VP/BKP cements rely on innovative concepts and interdisciplinary knowledge. With the advent of new biodegradable and mechanically matched bone cements, the indications of VP/BKP will likely be broadened, for example, to VCFs with no neurological symptoms in the elderly or even traumatic VCFs in young adults. These types of fractures require bone cements with adjustable mechanical properties that meet the loading requirements early and can be absorbed to avoid stress shielding in the later stage of treatment. If achieved, patients suffering from such fractures may no longer need extra vertebral fixation surgeries. Therefore, a wide spectrum of spinal lesions that were previously left untreated may potentially benefit from these ongoing advancements of bone cements.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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