

1 **Emerging Modified Poly(Methyl Methacrylate)**
2 **(PMMA) Bone Cements for Augmentation of**
3 **Osteoporosis-Induced Compression Fractures**
4 **of Vertebral Bodies: Present Status and**
5 **Future Prospects**

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10 **ABSTRACT**
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Background: Minimally-invasive vertebral body cement augmentation methods, notably percutaneous vertebroplasty (PVP) and percutaneous balloon kyphoplasty (PKP), are now well established as surgical modalities for treating persistent and/or severe pain arising from osteoporosis-induced vertebral body (VB) compression fracture(s). The essence of each of these procedures is the injection of a dough of a bone cement (almost invariably, poly methyl methacrylate (PMMA) cement either directly into the fractured VB(s) (as in PVP) or into a space created in the fractured VB(s) (as in PKP). Only a few commercially-formulated PMMA bone cement brands are specifically indicated for use in PVP and PKP, among which are Mendec®Spine and Osteopal®V. Recognition of the many shortcomings of these brands, such as compressive modulus that is markedly higher than that of the contiguous cancellous bone, has spurred the formulation and characterization of a large assortment of new PMMA bone cements. A review of the literature on these cements, which, herein, are designated “emerging modified PMMA bone cements” (EMPBCs), is lacking. Additionally, only a few fatigue and clinical studies of EMPBCs have been reported.

Purpose: To present a comprehensive, detailed, and critical review of the literature on EMPBCs, and, hence, identify the most promising of these cements.

Methodology: Using appropriate keywords and guided by strict acceptance and exclusion criteria, a thorough search of widely-used scientific databases, such as Google Scholar and PubMed, was conducted, which led to selection of 40 relevant English-language articles on EMPBCs.

Conclusions: Four particularly promising EMPBCs were identified, among which is one in which mineralized collagen particles were blended with Mendec®Spine. In addition, eleven shortcomings of the literature are presented, prompting several areas for future study. Among these areas are development of a standard for determining the *in vitro* compression-compression fatigue performance of EMPBCs and conduct of well-designed prospective randomized controlled trials.

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13 *Keywords: Poly(methyl methacrylate) bone cement; osteoporotic vertebral body compression*
14 *fracture; vertebroplasty; percutaneous vertebroplasty; balloon kyphoplasty; percutaneous*
15 *kyphoplasty*

16 **1. INTRODUCTION**
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18 Osteoporosis, a chronic systemic skeletal disease, is one of the most common diseases.
19 As such, myriad aspects of it are well known, among which are its causes, incidence,
20 common clinical presentations, methods of diagnosis, methods of treatment/management,
21 and ramifications [1-20]. In terms of causes, the most common type, the primary type

22 (hereafter, simply, osteoporosis (OP)), is the consequence of imbalance of homeostasis;
23 specifically, osteoclast-mediated bone resorption exceeds osteoblast-mediated bone
24 formation [1]. Osteoporosis-induced fracture(s) (or, simply, osteoporotic fracture(s)
25 vertebral body/bodies (hereafter, called osteoporotic vertebral compression
26 fracture(s) (OVCFs)) are the most common type of fragility fractures, accounting
27 for ~50% [21]. For most people, OVCF(s) result in mild to moderate pain and are
28 treated/managed with conservative methods, such as oral prescription medications,
29 physical therapy, and wearing of braces(s)/orthotic device(s) [22, 23]. However, in cases
30 where OVCF(s) lead(s) to segmental spinal deformity, the resulting pain is severe and/or
31 persistent, in which case treatment involves use of a minimally-invasive surgical modality,
32 the most established being percutaneous vertebroplasty (PVP) and percutaneous balloon
33 kyphoplasty (PKP) [24-28]. For example, in the National Health Service in England, between
34 2017/2018 and 2019/2020, the number of patients aged 55-74 years and >75 years who
35 underwent PVP or PKP increased by 19%, and 28%, respectively [26].
36 Newer or emerging surgical methods include use of expandable implant systems
37 (such as OsseoFix[®], SpineJack[®], and the Titanium Tri-blade Fixed Device) and robot-assisted
38 PVP or PKP [29-40].
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40 One feature that is common to PVP, PKP, and some of the newer and other emerging surgical
41 methods is the use of bone cement for either stabilization of the fractured VB(s)
42 (as in PVP) or restoration of the fractured VB(s) to their pre-fracture height(s) followed by their
43 stabilization (as in PKP). Over the years, there has been much debate about the efficacy of
44 PVP and PKP compared to a placebo or conservative measures, in particular, oral prescription
45 medications [35]. However, the consistent finding in meta-analyses of recent large-scale
46 real-world studies is that clinical and radiological outcomes from either PVP or PKP are
47 significantly better than from conservative methods [41, 42]. Thus, it appears that it is justified
48 for PVP and PKP to be continued to be part of the treatment options available to patients while
49 research continues on these methods [36-38] and/or replacement of them by
50 novel ones [39,40].
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52 Although many bone cement chemistries have been used in PVP and PKP or are being
53 evaluated for use in emerging variants of PVP and PKP and novel surgical methods, such as
54 poly (methyl methacrylate) (PMMA), calcium phosphate, calcium sulfate, and calcium silicate
55 cements, the predominant choice is PMMA bone cement [43-46]. The many advantages of
56 PMMA bone cement for this application are well known, among which are ease of preparation
57 and delivery to the fractured VB(s), excellent biocompatibility, and widespread familiarity given
58 its long history of use in anchoring total joint replacements [43-46]. However, the cement has
59 its share of shortcomings, five of which are of particular clinical relevance to
60 PVP and PKP [43-46]. First, its polymerization involves an exothermic reaction, with the
61 maximum temperature typically reached being much higher than that postulated to cause
62 thermal necrosis of contiguous tissues (50 °C) [47]. Second, there are myriad reports that
63 during PVP and PKP, there is extravasation or leakage of the cement dough into neighboring
64 tissues and/or organs [48-50]. Third, the residual monomer concentration in the cured cement
65 is high, which, it has been posited, increases the likelihood for chemical necrosis of contiguous
66 tissues. Fourth, its quasi-static compressive elastic modulus is much higher than that of
67 vertebral cancellous bone (by a factor of between ~2-~370), with the same trend seen for its
68 quasi-static compressive strength (by a factor of between ~7 and ~1140).
69 It has been postulated that these property mismatches increase the potential for or play a role
70 in the creation of new fracture(s) in VB(s) that are adjacent to or far removed from the one(s)
71 treated with PVP or PKP (what collectively have been called, “new symptomatic osteoporotic
72 vertebral compression fractures” (NSOVCFs)) [51]. The fifth highlighted shortcoming of PMMA
73 bone cement is that it is a biologically inert; as such, osseointegration between the cured
74 cement zone in the augmented VB(s) and the contiguous bone is very poor.

75 In addition to the shortcomings of PMMA bone cement, the literature on its *in vitro* and *ex vivo*
 76 fatigue performance relevant to PVP and PKP and clinical studies when the cement is used
 77 in PVP and PKP is very sparse.

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 79 The present review is of a subset of literature reports on the formulation and characterization
 80 of PMMA bone cements that 1) address one or more of the aforementioned five shortcomings
 81 and/or the aforementioned two lacunae in the literature; and 2) satisfy three other criteria.
 82 The first of these criteria is that the control cement used in the study must be a cement
 83 brand/formulation that is used or suggested for use in PVP or PKP in cases where there are
 84 no other type(s) of fracture(s) in addition to VB fracture(s), such as superior endplate fractures.
 85 The second criterion is that the radiopacifier loading (RL) in the cement must be ≥ 25 wt./wt.%
 86 of the total mass of the powder, this being the minimum RL in commercially-formulated cement
 87 brands used in PVP and PKP, such as Mendec®Spine, OPACITY+®, Osteopal®V, and
 88 Vertecem™V+. The third criterion is that even though pathological fracture(s) occur in the spine
 89 (for example, arising from benign lesions (such as hemangioma) or malignant lesions
 90 (such as metastatic cancer [35]), the study must be on use of the cement for treatment of
 91 OVCFs. In the present work, the cements in the subset (as defined above) are designated,
 92 “emerging-modified PMMA bone cements” (EMPBCs). Although there are reviews of the
 93 literature on studies of PMMA bone cements that address their shortcomings
 94 in general [43-46; 52-54], the present review is the only one that exclusively focuses
 95 on studies on EMPBCs.

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 97 The present work, whose purpose is to present a comprehensive, detailed, and critical review
 98 of the literature on EMPBCs, is organized in eight sections. In the immediate
 99 next section (Section 2), the methodology used for selecting the articles that are reviewed is
 100 explained. After that, the next three sections comprise compact presentations of the
 101 compositions of the cements used in the reviewed studies (Section 3) and a selection of results
 102 of studies of determination of clinically-relevant properties *in vitro* tests, *ex vivo* tests
 103 (cement embedded in extracted tissue), *in vivo* (animal model) tests (cement plug surgically
 104 inserted into a part of an animal) (Section 4), and clinical studies (Section 5).
 105 Summarized perspectives on the results, as given in Sections 3 and 4, which led to identifying
 106 the most promising experimental cements, are presented in Section 6.
 107 A discussion of shortcomings of the literature (as evidenced in the studies reviewed) and,
 108 hence, suggestions of areas for future research are the subjects of Section 7.
 109 The review ends with a summary of the key points (Section 8).

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112 **2. STUDY SELECTION METHODOLOGY**

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114 A detailed search was conducted of open-access scientific research databases, such as
 115 Google Scholar, PubMed, ScienceDirect, and Scopus, using terms such as “osteoporosis”,
 116 “vertebral compression fracture”, “poly (methyl methacrylate) bone cement”,
 117 “percutaneous vertebroplasty”, “vertebroplasty”, “percutaneous kyphoplasty”,
 118 “percutaneous balloon kyphoplasty”, and “balloon kyphoplasty”. Only peer-reviewed full-text
 119 English-language articles published in archival journals between January 2000 and
 120 June 2024 (inclusive) were selected for review. A total of 40 articles met all the inclusion
 121 criteria (Table 1).

122 **Table 1. Some features of studies included in the review**

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Cement shortcoming or literature gap addressed ^a	Control cement specifically	Control cement radiopacifier (loading, in wt./wt.%)	Intended use of experimental cement for	Ref. #
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	for PVP/PKP		treatment of OVCF(s)	
High T_{max}	Yes	BaTiO ₃ (30-50) SrTiO ₃ (30-50)	Yes	Carroudeguas et al. [55]
High T_{max} ; high E_c	Yes	Vertecem® (BaSO ₄ ; 25)	Yes	Boger et al. [56]
High T_{max} ; high E_c	Yes	BaSO ₄ (25.6-30)	Yes	Cisneros-Pineda et al. [57]
High T_{max} ; high E_c	Yes	Mendec®Spine (BaSO ₄ ; 30); Osteopal®V (ZrO ₂ ; 45); Spineplex™ (BaSO ₄)	Yes	Jiang et al. [58]
High T_{max} ; high E_c	Yes	Mendec®Spine (BaSO ₄ ; 30)	Yes	Sun et al. [59,60]
High T_{max} ; high E_c	Yes	BaSO ₄ (30)	Yes	Han et al. [61]
Poor osteointegration; paucity of clinical studies	Yes	Mendec®Spine (BaSO ₄ ; 30)	Yes	Zhu et al. [62]
High T_{max} ; high E_c	Yes	ZrO ₂ (34)	Yes	Faruq et al. [63]
High E_c	Yes	ZrO ₂ (34)	Yes	Park et al. [64]
High T_{max} ; high E_c	Yes	Mendec®Spine (BaSO ₄ ; 30)	Yes	Zhang et al. [65]
High E_c ; paucity of data on <i>in vitro</i> fatigue performance	Yes	BaSO ₄ (15) ^b ZrO ₂ (15) ^b	Yes	Boger et al. [66]
High E_c	Yes	WC (30)	Yes	Xu et al. [67]
Poor osseointegration	Yes	F20® (ZrO ₂ ; 45)	Yes	Robo et al. [68]
Paucity of data on <i>in vitro</i> fatigue performance	Yes	V-Steady™ (ZrO ₂ ; 45)	Yes	Robo et al. [69]
High E_c	Yes	VertaPlex® (BaSO ₄ ; 30)	Yes	Jacobs et al. [70]
Paucity of data on <i>in vitro</i> fatigue performance	Yes	F20® (ZrO ₂ ; 45) Resilience® (ZrO ₂ ; 39.2)	Yes	Robo et al. [71]
High T_{max} ; lack of bioactivity	Yes	BaSO ₄ (NS ^c)	Yes	Hernandez et al. [74]
High E_c	Yes	Osteopal® V (ZrO ₂ ; 45)	Yes	Carlsson et al. [76]
High E_c	Yes	Mendec®Spine (BaSO ₄ ; 30)	Yes	Zhang et al. [77]
High E_c	Yes	Vertecem®	Yes	Boger et al. [78]

		(BaSO ₄ ; 25)		
High E _c	Yes	Vertecem [®] (BaSO ₄ ; 25)	Yes	Boger et al. [79]
Paucity of data on <i>ex vivo</i> fatigue performance	Yes	Vertecem [®] + (ZrO ₂ ; 40)	Yes	Kolb et al. [82]
High E _c	Yes	Osteopal [®] V (ZrO ₂ ; 45)	Yes	Lopez et al. [83]
High E _c	Yes	Osteopal [®] V (ZrO ₂ ; 45)	Yes	Holub et al. [84]
Paucity of clinical studies	Yes	“Osteopal- polymethylmethacrylate (PMMA)” (NS ^c)	Yes	Bai et al. [88]
Paucity of clinical studies	Yes	“Traditional PMMA” (NS ^c)	Yes	Wang et al. [89]
Paucity of clinical studies	Yes	Mendec [®] Spine (BaSO ₄ ; 30)	Yes	Zhu et al. [90]
Paucity of clinical studies	Yes	“Traditional PMMA” (NS ^c)	Yes	Luo et al. [91]

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^aT_{max}: maximum polymerization temperature; E_c: quasi-static compressive modulus.
^bAuthors of report stated that with the low radiopacifier used, their cadaver study results were evaluated by an experienced neurosurgeon, who declared the radiopacity provided by the cement to be comparable to that seen in clinical work.
^cRadiopacifier loading not stated in the report.

3. CEMENT COMPOSITIONS, SPECIMEN PREPARATION, AND TEST PROTOCOLS

A few aspects of the compositions of the cements used in many of the reviewed studies are given in **Table 2**, with emphasis on modification(s) to a given composition. Thus, **Table 2** serves as a complement to the summaries given in Sections 4 and 5.

Table 2. Summary of compositions of cements^a in reviewed studies

Control cement	Modification by addition to		Source [Ref. #]
	Powder	Liquid	

Experimental cement	Unsilanated BaSO ₄ Unsilanated SrTiO ₃ Silanated BaSO ₄ Silanated SrTiO ₃		Carrodegua et al. [55]
Vertecem®		Hyaluronic acid (sodium hyaluronate solution) (HyA)	Boger [56]
Experimental cement		Dimethyl amino ethyl methacrylate (DMAEM)	Cisneros-Pineda et al. [57]
Mendec®Spine; Osteopal®V; Spineplex™	Commercially-formulated mineralized collagen (MC) powder ^b		Jiang et al. [58]
Mendec®Spine	Calcium silicate		Sun et al. [59]
Mendec®Spine	Hydrogel comprising oxidized HyA and carboxymethyl chitosan		Sun et al. [60]
Experimental cement Mendec®Spine Experimental cement	Diatrizoate sodium (DTA) MC powder ^b	A gel comprising HyA and poly(ethylene glycol)	Han et al. [61] Zhu et al. [62] Faruq et al. [63]; Park et al. [64]
Mendec®Spine	Small intestinal submucosa (SIS) powder		Zhang et al. [65]
Experimental BaSO ₄ -containing and ZrO ₂ -containing cements	Lipiodol®	Iopamiro-300®; Ultravist-370®	Boger et al. [66]
Experimental cement F20®	Tungsten carbide (WC) particles	Linoleic acid (LA)	Xu et al. [67] Robo et al. [68]
V-Steady™;		LA	Robo et al. [69]

Resilience®			
VertaPlex™	Au-containing PMMA microspheres ^c		Jacobs et al. [70]
F20® Resilience®			Robo et al. [71]
Experimental cement	Strontium-containing hydroxyapatite without or with treatment with methyl methacrylate monomer		Hernandez et al. [74]
Osteopal®V		LA; Castor oil (CO)	Carlsson et al. [76]
Mendec®Spine	SIS powder		Zhang et al. [77]
Vertecem®		HyA solution	Boger et al. [78]
Vertecem®		HyA solution	Boger et al. [79]
Vertecem®V+	Fetal bovine serum ^d		Kolb et al. [82]
Osteopal®V		LA	Lopez et al. [83]
Osteopal®V		LA	Holub et al. [84]
Osteopal®	“Artificial bone-mineralized collagen” (MC) powder ^b		Bai et al. [88]
“Traditional”	“Biomimetic MC” (“orderly-arranged type I collagen and nano-hydroxyapatite”) powder ^b		Wang et al. [89]
Mendec®Spine	Commercially-formulated MC powder ^b		Zhu et al. [90]

150 ^aCommercially-formulated brands are the following: Vertecem[®] (Synthes GmbH, Oberdorf,
 151 Switzerland); Mendec[®]Spine (Tecres SpA, Verona, Italy); Osteopal[®]V (Heraeus Medical
 152 GmbH, Hanau, Germany); Spineplex[®] (Stryker, Kalamazoo, MI, USA); F20[®] (Teknimed SAS,
 153 France); V-Steady[™] (G21 Srl, San Possidonio, Italy); Resilience[®]: a commercially-formulated
 154 “low-modulus” cement for use in PVP or PKP but which is no longer available in the market
 155 (per 2021)[67]; VertaPlex[™] (Stryker, Kalamazoo, MI, USA); Vertecem[®]V⁺ (Synthes GmbH).
 156 Note that, per July 2024, a commercially-formulated cement brand listed here may no longer
 157 be produced and/or marketed by the stated commercial entity.

158 ^bDifferent methods were used to combine MC particles with the powder and liquid of the control
 159 cement; for details, see the literature report.

160 ^cAdded to other powder and liquid constituents of the cement before dough was prepared.

161 ^dIn preparing the dough of the modified cement formulation, fetal bovine serum was added to
 162 the mixture of powder and liquid of the control cement.

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166 **4. IN VITRO CHARACTERIZATION, EX VIVO CHARACTERIZATION, AND**
 167 **IN VIVO (ANIMAL) STUDIES**

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169 A summary of a selection of notable trends in the results is presented in **Table 3**.

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Table 3. Summary of a selection of notable trends in results^a in the reviewed studies

Control cement	Experimental cement^b	Notable trend^c	Source [Ref.#]
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Vertecem®	Aqueous fraction of 30 vol/vol/% HyA solution added to control cement liquid	Significantly higher injectability	Boger et al. [56]
25.6-30 wt./wt.% BaSO ₄ -containing	10 vol./vol.% DMAEM added to control cement liquid	31% higher injectability	Cisneros-Pineda et al. [57]
Spineplex®	5-20 wt./wt.% MC particles added to control cement	15% lower T _{max}	Jiang et al. [58]
30 wt./wt.% BaSO ₄ -containing	10-20 wt./wt.% DTA added to control cement powder	15% lower T _{max}	Han et al. [61]
34 wt./wt. % ZrO ₂ -containing	Hydrogel comprising 10HyA and 10 PEG added to cement (10HyA-10PEG-PMMA)	16% longer t _{set}	Faruq et al. [63]; Park et al. [64]
34 wt./wt. % ZrO ₂ -containing Mendec®Spine	10HyA-10PEG-PMMA	17% lower T _{max}	Park et al. [64]
	5 or 10 wt./wt.% SIS powder added to control cement powder	14-34% lower T _{max}	Zhang et al. [65]
15 wt./wt.% BaSO ₄ -containing and 15 wt./wt.% ZrO ₂ -containing	40% aqueous fraction Iopamiro-300® added to cement liquid	30% higher radiopacity	Boger et al. [66]
	40% aqueous fraction Ultravist-370® added to cement liquid	32% higher radiopacity	
Vertecem®	45 or 50 vol/vol.% HyA solution added to control cement liquid	Quasi-static compressive strength within the range of that for	Boger et al. [56]

		human vertebral cancellous bone	
	35 vol/vol.% HyA solution added to control cement liquid	Quasi-static compressive modulus within the range of that for human vertebral cancellous bone	
Mendec®Spine	15 % hydrogel (comprising oxidized HyA and carboxymethyl chitosan) added to control cement powder (15Hydrogel-PMMA)	Mean quasi-static compressive modulus within the range of that for human vertebral cancellous bone	Sun et al. [60]
Osteopal®V	1.5 wt./wt.% LA added to control cement liquid	In a cytotoxicity test (human osteoblast-like SaOs-2 cells; 2×10^4 cells cm^{-2}), with 4-fold diluted extracts, at 3 d, significantly lower cell numbers	Carlsson et al. [76]
Mendec®Spine	20 wt./wt.% SIS particles added to control cement powder	After 7 d of culture, MC3T3-E1 cells showed significantly higher relative ALP mRNA and OCN mRNA levels (hence, enhanced mineralization)	Zhang et al. [77]
Mendec®Spine	10, 20, or 30 wt./wt.% CS added to control cement powder	% hemolysis (based on test using red blood cells from rabbit blood stabilized	Sun et al. [59]

		with EDTA) was significantly < 4% (upper acceptable limit, per ISO/TR7405)	
Mendec®Spine	15Hydrogel-PMMA	In Live-Dead staining test (BMSCs from 3 wk-old male Sprague-Dawley rats), significantly greater %live cells	Sun et al. [60]
		% hemolysis (based on test using red blood cells from 3 wk-old male Sprague-Dawley rats stabilized with EDTA) was significantly < 4% (upper acceptable limit, per ISO/TR7405)	
Vertecem®	Aqueous fraction of 35% HyA to control cement liquid	In an <i>ex vivo</i> test (thoracic-lumbar VBs taken from cadavers, age of donors: 79 ± 11.2 y), lower ratio of incidence of endplate fracture to that of wedge-shaped fracture	Boger et al. [78]
Vertecem V+®	8 mL fetal bovine serum added when the control cement powder and liquid were mixed	In an <i>ex vivo</i> test (lumbar VBs taken from cadavers, age of donors: 78 ± 10 y),	Kolb et al. [82]

			significantly higher force during cyclic loading at which there was a marked increase in the displacement-versus-time plot, adjusted for initial fracture force	
Mendec®Spine	5 or 10 wt./wt.% SIS particles to control cement powder		In an <i>ex vivo</i> test, higher strength of augmented model (L2-L5 of goats)	Zhang et al. [65]
Mendec®Spine	20 or 40 wt./wt.% SIS particles added to control cement powder		In an animal model test (24 mature male Sprague-Dawley rats, 300-350 kg) in which a small cavitory bone defect was created in the L2 VB, significantly greater new bone formation	Zhang et al. [77]
Mendec®Spine	10 % or 20% CS added to control cement powder		In an animal model test (10 female goats, mass: 30 ± 5 kg) in which cement dough was injected into the L3, L4, L5 VBs, at 6 mo post-surgery, significantly higher BV/TV, Tb.N, and Tb.Th	Sun et al. [59]
Mendec®Spine	15 wt./wt.% MC particles added to control cement powder		In an animal model test (42 rabbits, age: 5 mo and mass: 3.02 ± 0.25 kg), at both 4 wk	Zhu et al. [62]

		and 12 wk post-surgery, significantly greater cortical bone thickness, osteoblast area, new bone area, and % bone growth	
	20Hydrogel-PMMA		
Mendec®Spine		In an animal model test (20 male New Zealand white rabbits, mass: 2.5-3.0 kg) in which cement dough was injected into a hole created in the femoral condyle, significantly greater BV/TV	Sun et al. [60]
	10HyA-10PEG-PMMA		
34 wt./wt.% ZrO ₂ -containing		In an animal model test (male New Zealand white rabbits) in which cement dough was injected into a small defect created in the femur, after 1 mo post-surgery 1) significantly higher BV/TV and 2) markedly smaller amount of tissue necrosis close to the specimen	Park et al. [64]
	5 or 15 wt./wt.% SIS particles added to control cement powder		
Mendec®Spine		In an animal model test (mature male New Zealand white rabbits; mass: 2.5-3.0 kg) in which	Zhang et al. [65]

cement dough was
injected into
various positions
on the L5 and L6
spinous
processes),
significantly higher
BV/TV

196 ^aResult for parameter obtained from test in which experimental cement was used compared
197 to corresponding result from test in which control cement was used.
198 ^bHyA: hyaluronic acid; DMAEM: dimethyl amino ethyl methacrylate; MC: mineralized collagen;
199 DTA: diatrizoate sodium; PEG: poly(ethylene glycol); SIS: small intestinal submucosa;
200 Iopamiro-300[®]: a commercially-formulated organic iodine-containing hydrophilic radiopacifier;
201 Ultravist-370[®]: a commercially-formulated organic iodine-containing hydrophilic radiopacifier;
202 LA: 9-cis,12-cis linoleic acid; CS: calcium silicate.
203 ^cT_{max}; maximum polymerization temperature; t_{set}: setting time; ALP: alkaline phosphate
204 activity; OCN: osteocalcin; EDTA: ethylene diamine tetra acetic acid; VB: vertebral body;
205 BV/TV: new bone volume/total tissue volume; Tb.N: trabecular bone number;
206 Tb.Th: trabecular bone thickness.

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5. CLINICAL STUDIES

The study by Bai et al. [88] was on two sets of osteoporotic middle-aged/old patients (51-75 y) who suffered single-level vertebral compression fractures (VCFs) at the thoracic/lumbar spine (T11, T12, L1, and L2) that were treated using PKP. For Group 1 patients, the cement used was “Osteopal polymethylmethacrylate (PMMA)” (47 patients) and for Group 2, “part of the bone cement” (used for Group 1 patients) “was replaced with an equal amount of artificial bone-mineralized collagen” (48 patients). Maximum follow-up was 16 mo. Trends in two results were at 3 mo follow-up, 1) decreases in Visual Analog Score (VAS), Oswestry Disability Index (ODI), and Cobb angle (relative to pre-operation values) were each greater in Group 2 patients than in Group 1 patients; and 2) CT showed clear demarcation between the cement and the vertebral bone tissue in Group 1 patients, whereas, in Group 2 patients, such demarcation was not visible. It was concluded that, overall, better clinical and radiological results were obtained in Group 2 patients than in Group 1 patients.

The work by Wang et al. [89] was on 2 sets of middle-aged/old patients (56-88 y) who suffered single-level VCFs at the thoracic/lumbar spine that were treated using PVP. For Group 1 patients, the cement used was “traditional PMMA” (30 patients) and for Group 2 patients, the cement used was an experimental cement obtained by adding 15 wt./wt.% MC particles to the dough formed by mixing the powder and liquid of the “traditional PMMA” cement (50 patients). Trends in four results were 1) significant longer cement injection time for Group 2 patients compared to that for Group 1 patients; 2) significantly higher bone cement injection volume used in the procedure on Group 2 patients than in Group 1 patients; 3) significantly lower incidence of cement leakage in Group 2 patients than in Group 1 patients; and 4) significantly lower number of postoperative adjacent VCFs in Group 2 patients compared to that in Group 1 patients. It was concluded that, overall, better clinical and radiological results were obtained in Group 2 patients than in Group 1 patients.

The study by Zhu et al. [90] was on two sets of osteoporotic middle-aged/old patients (61-84 y) who suffered single-level VCFs at the thoracic/lumbar spine (T11, T12, L1, L2, L3, and L4) that were treated using PKP. For Group 1 patients, the cement used was Mendec®Spine (48 patients) and for Group 2 patients, the cement used was an experimental formulation obtained by mixing the powder and liquid of Mendec®Spine and, then, adding MC particles to the dough (46 patients). Trends in eight results were 1) no significant difference between the groups in terms of the operation time; 2) significantly lower incidence of cement leakage in Group 2 cases (6.5%) compared to Group 1 cases (28.3%), although in each case, leakage was asymptomatic; 3) in each group, at each follow-up time (3 d, 3 mo, 6 mo, and 1 y), VAS and ODI scores were each significantly lower compared to pre-operation values; 4) at each follow-up, VAS and ODI score were each lower for Group 2 patients compared to the corresponding value for Group 1 patients, although the difference was significant only at follow-up of 1 y; 5) at follow-up of both 3 d and 1 y, Cobb angle for patients in each group was significantly smaller than pre-operative value, and Cobb angle was significantly smaller in Group 2 patients compared to Group 1 patients; 6) the incidence of refracture in Group 2 patients (1 case) was significantly lower than in Group 1 patients (8 cases); 7) at 1 y follow-up, the ratio of right lateral recess mean anterior vertebral height of the fractured vertebra to mean anterior vertebral height of the superjacent vertebra (AVH) was significantly higher in Group 2 patients than in Group 1 patients, the ratio of right lateral recess

260 mean intermediate vertebral height of fractured vertebra to mean anterior vertebra height of
261 the superjacent vertebra (IVH) was significantly lower in Group 2 patients than in
262 Group 1 patients, midline IVH was significantly larger for Group 2 patients than in
263 Group 1 patients, and left lateral recess AVH was lower for Group 2 patients than in
264 Group 1 patients; and 8) at 1 y follow-up, the computed tomography (CT) values of the
265 fractured vertebrae were significant higher in Group 2 patients than in Group 1 patients.
266 It was concluded that, overall, clinical and radiological results for Group 2 were better than
267 those for Group 1 patients.
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269 The study by Luo et al. [91] comprised two sets of very old osteoporotic patients (80-88 y) who
270 suffered single-level VCFs at the thoracic/lumbar spine (T6-T12 and L1-L5) that were treated
271 using PVP. For Group 1 patients, the cement used was a “traditional PMMA bone cement”
272 (traditional PMMA cement group; 32 patients) and for Group 2 patients, the cement used was
273 an experimental formulation obtained by incorporating MC particles into the traditional PMMA
274 bone cement (31 patients). Trends in eight results were 1) the difference in operation time
275 between the two groups was not significant; 2) the difference in cement leakage incidence
276 between the two groups was not significant and, in cases where there was leakage, there
277 were no accompanying clinical symptoms; 3) significantly lower fewer new VCFs occurred in
278 Group 2 patients (1 case) than in Group 1 patients (7 cases); 4) at each follow-up,
279 significantly lower VAS in each group compared to the pre-operative level, and,
280 at 1 y follow-up, significantly lower VAS for Group 2 patients compared to Group 1 patients;
281 5) at each follow-up, significantly lower ODI score in each group compared to the pre-operative
282 level, and, at 1 y follow-up, significantly lower ODI score for Group 2 patients compared to
283 Group 1 patients; 6) at 1 y follow-up, the Cobb angle in Group 2 patients was significantly
284 smaller than in Group 1 patients; 7) at 1 y follow-up, the vertebral height recovery of AVH and
285 the vertebral height recovery of IVH was each significantly greater in Group 2 patients than in
286 Group 1 patients; and 8) in Group 2 patients, the CT value of the injured VB, at 1 y follow-up,
287 was significantly larger compared to the pre-operative value. It was concluded that, overall,
288 clinical and radiological results were better for Group 2 patients than for Group 1 patients.
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290 The retrospective study by Zhu et al. [62] was on two sets of osteoporotic middle-aged/old
291 patients (64-84 y) who suffered single-level VCFs at levels that included T11, T12, L1, L2, L3,
292 and L4 that were treated using PKP. For Group 1 patients, Mendec®Spine cement was used
293 (12 patients) and for Group 2 patients, the cement used was an experimental formulation
294 obtained by adding MC powder to the powder of Mendec®Spine (12 patients).
295 Trends in three results were 1) the number of recurrent fractures of adjacent VBs were
296 8 and 0 in Groups 1 and 2 patients, respectively; 2) at 1 y follow-up, AVH and IVH were each
297 significantly higher in Group 2 patients compared to the corresponding value in
298 Group 1 patients; and 3) at 2 y follow-up, VAS and ODI scores for Group 2 patients were each
299 significantly lower than the corresponding value for Group 1 patients. It was concluded that,
300 overall, clinical and radiological results were better for Group 2 patients than for
301 Group 1 patients.
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306 **6. PERSPECTIVE ON MOST PROMISING EXPERIMENTAL CEMENT** 307 **FORMULATIONS**

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A careful examination of the results of the characterization studies, as detailed in Sections 4 and 5, shows that only a few EMPBCs have properties that are unambiguously significantly better than the corresponding values for the control cement. (Note that for some properties, better means higher and for others, better means lower.) When the results of all

313 the four types of studies (*in vitro*, *ex vivo*, *in vivo* (animal model), and clinical) reviewed in the
 314 present work are considered against the background of their relative importance
 315 (clinical study being the most important), four experimental cements appear to be particularly
 316 promising (Table 4).

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Table 4. Trends in properties of promising experimental cements

Promising experimental cement	Trend in property
Powder includes silanated radiopacifier [Ref. #55]	<ul style="list-style-type: none"> * Significantly higher <i>in vitro</i> injectability^a
Liquid includes hyaluronic acid (HyA) solution [Ref. #56]	<ul style="list-style-type: none"> * <i>In vitro</i> quasi-static compressive modulus (E_c) (for 35 wt./wt.% HyA formulation, $E_c = 477 \pm 67$ MPa) that is within the range for human vertebral cancellous bone^b * <i>In vitro</i> quasi-static compressive strength (UCS) (for 45 wt./wt.% HyA formulation, $UCS = 2.5 \pm 1$ MPa) that is within the range for human vertebral cancellous bone^c
Powder includes BaSO ₄ and liquid includes dimethyl amino ethyl methacrylate (DMAEM) [Ref. #57]	<ul style="list-style-type: none"> * Significantly higher <i>in vitro</i> injectability^a * Significantly lower <i>in vitro</i> T_{max}^a * <i>In vitro</i> quasi-static compressive modulus (E_c) (for formulation that contains 30 wt./wt.% BaSO₄ and 10 vol./vol.% DMAEM), mean $E_c = 236$ MPa) that is within the range for human vertebral cancellous bone^b * <i>In vitro</i> quasi-static compressive strength (UCS) (for formulation that contains 30 wt./wt.% BaSO₄ and 10 vol./vol.% DMAEM), mean $UCS = 8$ MPa) that is within the range for human vertebral cancellous bone^c
Powder includes a hydrogel comprising of oxidized hyaluronic acid and carboxymethyl chitosan [Ref. #60]	<ul style="list-style-type: none"> * <i>In vitro</i> quasi-static compressive modulus (E_c) (for formulation that contains 15 wt./wt.% hydrogel, mean $E_c = 410$ MPa) that is within the range for human vertebral cancellous bone^b * <i>In vitro</i> quasi-static compressive strength (UCS) (for formulation that contains 15 wt./wt.% hydrogel, mean $UCS = 42$ MPa) that is within the range for human vertebral cancellous bone^c * Significantly higher and better <i>in vivo</i> (rabbit model) performance measures (such as area of newly formed bone tissue (BV^d/TV^d))^a.
Liquid that contains a gel comprising HyA and poly(ethylene glycol) (PEG) [Ref. #s 63 and 64]	<ul style="list-style-type: none"> * Significantly lower <i>in vitro</i> T_{max}^a * <i>In vitro</i> quasi-static compressive modulus (E_c) (for formulation that contains 34 wt./wt.% ZrO₂ and a hydrogel made up of 10 vol./vol.% HyA and 10 vol./vol.% PEG, $E_c = 128-165$ MPa) that is within the range for human vertebral cancellous bone^b * <i>In vitro</i> quasi-static compressive strength (UCS)

	(for formulation that contains 34 wt./wt.% ZrO ₂ and a hydrogel made up of 10 vol./vol.% HyA and 10 vol./vol.% PEG, UCS = 14-35 MPa) that is within the range for human vertebral cancellous bone ^c
	* Significantly higher and better <i>in vivo</i> (rabbit model) performance measures (such as area of newly formed bone tissue (BV ^d /TV ^d)) ^a .
Radiopacifier (Ioproma 300 [®] or Ultramist 37 [®]) is in liquid [Ref. #66]	* Significantly higher <i>in vitro</i> radiopacity ^a
Radiopacifier is strontium-containing hydroxyapatite salt (untreated or treated with methyl methacrylate monomer) [Ref. #74]	* Significantly higher <i>in vitro</i> biocompatibility measures ^a
Powder includes small intestinal mucosa particles [Ref. #s 65, 77]	* Significantly lower <i>in vitro</i> T _{max} ^a
	* <i>In vitro</i> quasi-static compressive modulus (355-466 MPa) that is within the range for human vertebral cancellous bone ^b
	* <i>In vitro</i> quasi-static compressive strength (21-31 MPa) that is within the range for human vertebral cancellous bone ^c
	* Significantly higher index of new bone formation (BV ^d /TV ^d) <i>in vivo</i> (a rabbit model) ^a
Fetal bovine serum added to mixture of powder and liquid [Ref. #82]	* Significantly higher fatigue fracture force adjusted for initial fracture force in <i>ex vivo</i> test ^a
Mineralized collagen particles are combined with cement powder and liquid in a variety of ways [Ref. #s 88-91]	* Significantly higher biocompatibility measures, such as VAS ^d score and ODI ^d score ^a , as obtained in clinical percutaneous vertebroplasty and balloon kyphoplasty studies
	* Significantly lower incidence of post-operative adjacent vertebral body fracture ^a , as obtained in clinical percutaneous vertebroplasty and balloon kyphoplasty studies

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^aCompared to the value obtained with the control cement used in the study.

^b352 ± 145 MPa, depending on the bone mineral density of the bone (especially, non-osteoporotic or osteoporotic) (see Öhman-Mägi et al. [81]).

325 2.27 ± 1.14 MPa, depending on the bone mineral density of the bone (especially,
326 (non-osteoporotic or osteoporotic) (see Öhman-Mägi et al. [81]).
327 ^aBV: new bone volume; TV: total bone tissue volume; VAS: Visual Analog Score;
328 ODI: Oswestry Disability Index.

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333 The first promising experimental cement was obtained by adding 15 wt./wt% of a hydrogel
334 (comprising oxidized HyA and carboxymethyl chitosan) to the powder of a control cement [60].
335 It was explained that in specimens of this cement immersed in simulated body fluid, at 37 °C,
336 for up to 28 d, there was partial degradation of the hydrogel, creating holes at the surface of
337 the specimen, which served as spaces for the formation of new bone [60].
338 The second promising experimental cement was obtained by adding a gel comprising
339 a mixture of 10 vol./vol.% HyA and 10 vol./vol.% PEG to the liquid of an experimental cement
340 whose powder includes ZrO₂ as the radiopacifying agent (10HyA-10PEG-PMMA cement)
341 [63,64]. It was postulated that, *in situ*, the gel in the 10HyA-10PEG-PMMA cement degrades,
342 which, in turn, accounts for the extensive bone regeneration seen when cement specimens
343 were implanted in the femurs of New Zealand white rabbits [64]. The third is one in which
344 10 wt./wt.% SIS particles were added to the powder of the control cement [65, 77].
345 The attractive performance of SIS particles-loaded cement in a New Zealand white rabbit
346 vertebral defect model was attributed to 1) increased osseointegration, which is provided by
347 the SIS particles, 2) the fact that there is degradation of SIS and its replacement by host tissue
348 after implantation, and 3) as SIS degrades, there is release of growth factors, which promote
349 processes such as osteoblast proliferation [65, 77]. The fourth promising experimental cement
350 was obtained by blending MC particles with the dough formed by the mixture of the powder
351 and the liquid of a control cement [62, 88-91]. A few clinical studies have been reported in
352 which OVCFs were treated with PVP or PKP using this cement formulation [62, 88-91],
353 and, even though each of these studies has its limitations, the reported clinical and radiological
354 outcomes are encouraging. This performance was explained to be the consequence of many
355 phenomena associated with the MC particles, such as 1) having a composition and
356 microstructure similar to those of native vertebral cancellous bone and, as such, promote
357 active osteoinduction and formation of new bone and increase of the viscosity of the cement
358 dough, and 2) yielding an H-type of distribution of the cement dough within the augmented
359 fractured VB which, among other things, provides support of the VB and maintains
360 its stability [88-91]. It is worth noting that in a recent meta-analysis, the many advantages of
361 MC-modified PMMA bone cement for use in PVP were highlighted while underscoring the
362 need for further study of this cement formulation, especially in high-quality randomized
363 controlled trials [92].

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372 **7. SHORTCOMINGS OF THE LITERATURE AND AREAS FOR FUTURE STUDY**

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374 Eleven shortcomings of the literature are highlighted, which indicated areas for future study.

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376 First, a number of studies had methodological issues that precluded them from being included
377 in the present review (**Table 5**). Furthermore, in the clinical study by Bai et al. [88], there is

378 ambiguity about the appropriateness of the control cement used; specifically, in the report,
 379 it was stated that the cement used was Osteopal[®], but this brand is approved for use in
 380 cemented total arthroplasties. It is possible that the authors intended to state that they used
 381 Osteopal^{®V}, but this brand is formulated for use in PVP, whereas the study was on PKP [88].
 382 Thus, the lack of clarity persists. In future studies, all the aforementioned methodological
 383 issues should be avoided. Most importantly, the control cement must be one that is either in
 384 current clinical use for augmentation of OVCFs or is being evaluated for such use.
 385 Thus, among other cement characteristics, its radiopacifier loading must be appropriately high;
 386 for example, when incorporated in the cement powder, loading must be ≥ 25 wt./wt.%.
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389 **Table 5. Some features of excluded studies**
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Excluded study	Reason(s) for exclusion
Heini et al. [93]	<ul style="list-style-type: none"> * The control cement used (Palacos E-Flow[®]) is a brand that is not specifically indicated for cement augmentation of osteoporotic vertebral compression fracture(s) (OVCF(s)) * The comparison cement used (an experimental CaP bone cement formulation) is not a PMMA bone cement
Hernandez et al. [94]	<ul style="list-style-type: none"> * No control cement was used * The experimental cement used did not contain a radiopacifier (in either the solid or liquid phase) and hydroquinone in the liquid phase
Loeffel et al. [95]	<ul style="list-style-type: none"> * A comparison cement brand or formulation was not used
Lewis et al. [96]	<ul style="list-style-type: none"> * A comparison cement brand or formulation was not used
Calvo-Fernandez et al. [97]	<ul style="list-style-type: none"> * In both the control and comparison cements used, the radiopacifier loading (10 wt./wt.%) was less than the minimum in cement brands specifically indicated for PVP and PKP (30 wt./wt.%)
Rodrigues et al. [98]	<ul style="list-style-type: none"> * The control cement brand used (KyphX[®]) has been withdrawn from clinical use
Aghyarian et al. [99]	<ul style="list-style-type: none"> * The control cement brand used (KyphX[®]) has been withdrawn from clinical use * The comparison cements used (experimental CaP bone cement formulations) are not PMMA bone cements
Tai et al. [100]	<ul style="list-style-type: none"> * The control cement used (Simplex^{®P}) is a brand that is not specifically indicated for cement augmentation of OVCF(s)
Li et al. [101]	<ul style="list-style-type: none"> * The control cement used (Palacos^{®MV}) is a brand that is not specifically indicated for cement augmentation of OVCF(s)

Panpisut et al. [102]

- * One of the two control cement brands used (Simplex®P) is not specifically indicated for cement augmentation of OVCF(s)
- * The other control brand used (Cortoss®) is not a PMMA cement
- * The comparison cements used (experimental composite bone cement formulations) are not PMMA bone cements

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Second, in the case of experimental formulations in which an extra constituent was added to the powder of the control cement, in some studies, specifics of the blending method used were not stated [61, 62, 65, 77], whereas, in others, it was (for example, ground evenly [67]). Similarly, in the case of experimental formulations in which an extra constituent was added to the liquid of the control cement, in some studies, the mixing method used was not stated [76], whereas, in others, it was (for example, vortex mixing [68, 83]). Additionally, with the exception of a few studies [59, 63, 64, 68, 69, 83, 90], the method used to mix the final powder and the final liquid to obtain the cement dough was not stated.

Third, there were two ambiguities or inconsistencies in the studies in which an experimental cement was obtained by adding MC particles to the control cement. The first of these was in the method used to obtain the MC particles, with this being from a commercially-available “artificial bone graft” [58], “included hydroxyapatite and type-I collagen” [88], “consists of orderly arranged type I collagen and nano-hydroxyapatite” [89], and commercially formulated [90, 91]). The second was in the method used to combine the MC particles with the control cement, with this being 1) the powder and liquid of the control cement were mixed, producing a dough, and, then, the MC particles were stirred into the dough [58, 89, 90], 2) the MC particles were mixed with the powder of the control cement and the liquid of the control cement was added to the mixture [62], 3) the MC particles were poured into a mixing bowl (Part A), an amount equal to that of Part A was removed from the dough formed by mixing the powder and the liquid of the control cement (Part B), and, then, Parts A and B were mixed [88]; and 4) the control cement powder, the MC particles, and liquid of the control cement were mixed until a dough was obtained [91].

Fourth, for some *in vitro* properties, a variety of protocols was used for the determination. Examples are injectability [55, 57, 58, 59, 61, 66] and radiopacity [66, 67, 68]. Additionally, for some of these properties, the determination was either in accordance with a testing standard or was not. Specifically, this was the case for t_{set} and T_{max} (ISO 5833 was used [56, 57, 58, 61, 63] or a standard was not used [62, 65]), UCS and E_c (ISO 5833 was used [56, 58, 63, 65, 67], ASTM F 451 was used [71], or a standard was not used [55, 59, 62]), and flexural strength (UBS) and flexural modulus (E_B) (ISO 5833 was used [58, 61] and ISO 5833 and ISO 14125 were used [65]). Additionally, it is to be noted that in two studies [59, 60], 1) the method used to determine setting times (the Vicat needle method) is problematic because this method is appropriate for cements whose chemistries and/or polymerization mechanisms are different from those for

430 PMMA bone cement, an example being a glass ionomer cement [103]; and 2) the definition of
431 maximum setting temperature used is not the same as that given in either ISO 5833 or F 451.
432 These observations underscore the need for development of testing standards for *in vitro*
433 determination of the properties of EMPBCs.

434
435 Fifth, in some reports [55, 57, 58, 65], assessment of the suitability of experimental cements
436 from the perspective of t_{set} , T_{max} , UCS, UBS, or E_B was made with respect to acceptable range
437 of values for these properties given in testing standards for determining these properties of
438 PMMA bone cements (specifically, ISO 5833 and F 451 and the proposal that t_{set} should
439 be < 25 min [104]). This approach is flawed because this standard applies only to PMMA bone
440 cements for use in anchoring arthroplasties. Thus, in future studies, to facilitate valid
441 evaluation of PMMA bone cements for augmentation of OVCFs, it must be ensured that in
442 each of the proposed testing standards, the range of values for the property that is considered
443 acceptable for cements to be used in augmentation of OVCFs be stated.

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445 Sixth, very few studies on the *in vitro* fatigue performance of EMPBCs have been
446 reported [66, 69, 71]. Of these, only in the work by Robo et al. [69, 71] was a protocol used
447 that is deemed appropriate; thus, among other facets of the protocol, specimens with surface
448 defects > 0.25 mm in diameter or internal defects > 1 mm in diameter were rejected;
449 accepted specimens were conditioned in PBS, at 37 °C, for between 14 d and 60 d before
450 a test; the test was conducted in PBS solution, at 37 °C, with accepted specimens subjected
451 to a pre-load of 20 N before being subjected to compression-compression loading
452 at a frequency of 2 Hz; run-out was considered to be no fracture of a specimen after
453 either 2×10^6 or 5×10^6 load cycles; and fatigue strength of the cement was estimated from
454 the fit of the Olgive equation to the results (stress amplitude (S)-versus-number of load cycles
455 to fracture). As such, in future work in this area, this protocol should be used as the basis for
456 development of a standard for determination of *in vitro* compression-compression fatigue
457 performance of EMPBCs. In this effort, the following elements should be included in the
458 standard: a minimum of 15 accepted specimens be tested at each value of S (this will ensure
459 that the estimated fatigue limit is statistically meaningful), test conditions that are clinically
460 relevant (for example, spectrum loading that encompasses flexion, extension, right bending,
461 left bending, clockwise torsion, and counterclockwise torsion, and variable frequency),
462 test carried out in PBS solution, at 37 °C, and run-out being the number of cycles that is
463 imposed on the spine during a course of a year during normal activities of daily living.

464
465 Seventh, heterogeneity is observed in the reported *ex vivo* studies; namely, simulated
466 prophylactic vertebroplasty of vertebrae in osteoporotic human thoracolumbar spine
467 section [78], simulated prophylactic augmentation of human thoracic vertebrae [79],
468 simulated augmentation of osteoporotic L2-L5 goat vertebrae following a simulated vertebral
469 compression fracture [65], simulated augmentation of vertebrae in osteoporotic human lumbar
470 spine section following a simulated vertebral compression fracture [82],
471 prophylactic augmentation of bovine tibiae [83], and filling of bone defect created in the femoral
472 condyle of sheep [68]. All future work should involve simulated augmentation of simulated
473 OVCF(s), with 1) the protocols used in creating the fracture and 2) the metrics used for
474 characterizing the VB(s) (prior to and after the simulated augmentation) having first been
475 established in preliminary studies. Such work should involve not only PVP and PKP but, also,
476 augmentation methods that have entered clinical use recently, examples being decompressed
477 percutaneous kyphoplasty [105], the Vertebral Body Stenting System [106, 107],
478 and a poly(etheretherketone) transpedicular vertebral system [108].

479
480 Eighth, only a few studies on biocompatibility, biodegradability, osteogenic capacity, and
481 immune response in *in vivo* (animal model) studies have been conducted, these being on
482 female goats (L3, L4, and L5 VBs [59]), male New Zealand white rabbit (femoral condyle [60])

483 and distal femoral head [64]), female sheep (femoral condyle and major tubercle of the
484 humerus [68]), female Wistar rats (dorsal muscle) [74], and male Sprague-Dawley rats [76].
485 Future work should establish the appropriate animal model, validate it, and, then, use it in
486 determining the aforementioned performance metrics of EMPBCs.

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489 Ninth, only a few clinical studies have been reported [62, 88-91]. Various aspects of these
490 studies are problematic, such as 1) type was not stated (for example, prospective or
491 retrospective) [62, 88-91]; 2) vague information given with regard to the control cement
492 brand/formulation used [88, 89, 91]; 3) number of study sites (1 [62, 88-91]); 4) location of
493 study sites (only in China [62, 88-91]); 5) small sample size in each of the study groups
494 (12 [62]; 47 and 48 [88]; 46 and 48 [90]; 31 and 32 [91]); 6) subjects that were middle-aged to
495 old (51-75 y [88], 64-84 y [62], and 61-83 y [90]); old (64-84 y [62] and 66-78 y [89]),
496 or very old (81-88 y [91]); and 7) short maximum follow-up (3 mo [88], 12 mo [89, 90, 91], and
497 24 mo [62]). In addition to the enumerated problematic aspects, in each of the clinical
498 studies [62, 88-91], the same experimental cement formulation was used, this being obtained
499 by combining MC particles with the powder and liquid of either Mendec[®]Spine or Osteopal[®].
500 Thus, there is scope for enhanced clinical studies, which would involve investigation of the
501 MC-modified variant of other cement brands being used for augmentation of OVCFs or of
502 novel cement formulations. Additionally, an enhanced clinical study must, at the minimum,
503 possess the following characteristics: prospective randomized clinical trials, carried out in at
504 least 20 sites spread over at least 10 countries (preferably, distributed among at least four
505 continents), at least 100 subjects in each study group, and follow-up of least 3 y.
506 Reports of clinical studies must include measures that are critical in the assessment of the
507 clinical performance of an augmentation method, such as incidence of cement leakage and
508 incidence of post-operative fractures in all non-augmented VBs.

509

510 Tenth, there are cement properties that are critical to the assessment of the suitability of an
511 EMPBC for use in augmentation of OVCFs but either have been reported in very few studies
512 or not all. Among the former are *in vitro* determination of the porosity profile of the cement
513 (for example, number of pores, porosity, and pore size distribution) [56, 66], flexural properties
514 of the cement [57, 58, 61, 65]), determination of biological safety parameters in a
515 mouse model [65], and determination of bone formation indexes in a goat model and in
516 a New Zealand white rabbit model [59, 60, 62, 64]. Among cement properties not reported are
517 *in vitro* determination of complex viscosity-versus-time from commencement of preparation of
518 cement dough (results that provide a key insight into the handling of the cement in
519 the clinic) [109] and circularity or spreading distance of the cement upon injection into the
520 fractured VB in a simulated augmentation in an *ex vivo* study. These deficiencies should be
521 addressed in future studies.

522

523 Eleventh, in terms of statistical analysis of results obtained (specifically, tests of significance
524 of difference between means of study groups (hereafter, "test of significance")), the information
525 given in the reports may be assembled into six groups. In the first, no information was
526 given [56, 57, 66, 67, 74]. In the second group, a parametric method only was used
527 (t-test [58, 60, 64, 88, 89, 90], chi-squared [89], multifactor one-way analysis
528 of variance (ANOVA) [55], one-way ANOVA [60, 63, 82], one-way analysis of covariance [82],
529 and two-way ANOVA [64]). In the third group, a parametric method followed by a *post-hoc* test
530 was used (one-way ANOVA followed by Bonferroni test [59, 65], one-way ANOVA followed by
531 Scheffe's test [71], one-way ANOVA followed by Dunnett's test [76], one-way ANOVA followed
532 by LSD [77], one-way ANOVA followed by Tukey honestly significant difference test [78],
533 and one-way ANOVA followed by Tamhane test [83]). In the fourth group, a test for normality
534 of each of the populations being compared was performed first, which was followed by a
535 parametric test (Kolmogorov-Smirnov test followed by one-way ANOVA [62],

536 Shapiro-Wilk test and Levene test followed by Welch's robust ANOVA, and, then, followed by
537 Tamhane post-hoc test [69], and Shapiro-Wilk test followed by paired t-test [70]).
538 In the fifth group, a nonparametric method was used (Mann-Whitney test [70, 79]).
539 In the sixth group, a mixture of parametric and non-parametric methods was used
540 (one-way ANOVA followed by Mann-Whitney test [61]). In all future studies, a test of
541 significance must be performed as this is a robust way of identifying whether the influence of
542 a study variable on a determined cement property is significant or not.
543 For this purpose, it would be both appropriate and economical to use a non-parametric
544 method.

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547 **8. SUMMARY**

548

549 The following are the key points made in this review:

550

- 551 1. The incidence of primary osteoporosis is high, especially among post-menopausal women
552 and people aged > 50 years. Osteoporotic people are particularly susceptible to
553 compression fracture(s) of vertebral body/bodies (VB(s)). When the pain due to such
554 fracture(s) is high and/or persistent, a surgical treatment method is commonly used, with
555 this involving augmentation of the fractured VB(s) using a minimally-invasive procedure
556 (usually, percutaneous vertebroplasty (PVP) or percutaneous kyphoplasty (PKP)).
557 In the preponderance of cases, a poly(methyl methacrylate) (PMMA) bone cement is used
558 for the augmentation. This cement has many shortcomings, such as high maximum
559 exotherm temperature (hence, high potential for thermal necrosis of contiguous tissues),
560 high compressive modulus (hence, high potential for fracture(s) of non-augmented VB(s),
561 and poor osseointegration (hence, high potential for cement zone loosening).
562 Over the years, there have been many literature reports on studies of PMMA bone
563 cements that are modifications of or based on the composition of commercially-formulated
564 brands used in PVP and PKP that address one or more shortcomings of the cement.
565 A subset of this body of literature comprising studies that meet the aforementioned
566 criterion as well as three others is herein designated studies on "emerging modified PMMA
567 bone cements" (EMPBCs). Many EMPBCs have been characterized in *in vitro*, *ex vivo*,
568 and *in vivo* (animal model) tests, and a few have been the subject of clinical studies.
569 The present contribution is a review of the literature on EMPBCs.
570
- 571 2. A careful examination of the results of the reviewed literature studies leads to identification
572 of four particularly promising EMPBCs, which, it is proposed, should be the subject of
573 rigorous and extensive future studies. These cements are one in which a hydrogel
574 (comprising a mixture of oxidized hyaluronic acid (HyA) and carboxymethyl chitosan) was
575 added to the powder of a commercially-formulated cement brand that is used in
576 PVP and PKP ("predicate cement brand"), another in which a gel (comprising a mixture
577 of HyA and poly(ethylene glycol) was added to the liquid of an experimental bioactive
578 cement, a third in which small intestinal submucosa particles were added to the powder
579 of a predicate cement brand, and a fourth in which mineralized collagen particles were
580 blended with the powder and liquid of a predicate cement brand.
581
- 582 3. Eleven shortcomings of the literature on EMPBCs are highlighted, such as lack of *in vitro*
583 testing standards, lack of *in vitro* determination of many clinically relevant properties,
584 lack of consensus on an appropriate animal model, and paucity of clinical studies, thereby
585 pointing the way to many future studies.
586
- 587 4. When items 1)-3) above are taken into consideration, all future work in this field should be
588 conducted in an efficient manner by concentrating on three aspects. First, a complete list

589 of and rationale for all the desirable properties of a PMMA bone for use in cement
590 augmentation of OVCF(s) should be presented. Second, instead of modifying the
591 compositions of existing commercially-formulated PMMA bone cements used in PVP and
592 PBK, novel cements that simultaneously possess all the desirable properties should be
593 designed from first principles. Central to this approach should be analytical work that
594 results in specification of the full collection of *in vitro* cement properties that significantly
595 influence the performance of the cement in clinical studies, in particular, incidence of
596 cement leakage and incidence of NSOVCFs [48, 110-112]. In this regard,
597 artificial intelligence (in particular, deep learning algorithms, such as the
598 Long Short-Memory [113] and/or machine learning algorithms, such as random forest,
599 support vector machine, and gradient boosting machine) [114]) could be a particularly
600 useful tool. Third, these novel cements should be comprehensively characterized in a
601 battery of *in vitro*, preclinical, and clinical studies.

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