Review Article

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

ABSTRACT

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.

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

1. INTRODUCTION

Osteoporosis, a chronic systemic skeletal disease, is one of the most common diseases. As such, myriad aspects of it are well known, among which are its causes, incidence, common clinical presentations, methods of diagnosis, methods of treatment/management, and ramifications [1-20]. In terms of causes, the most common type, the primary type (hereafter, simply, osteoporosis (OP)), is the consequence of imbalance of homeostasis; specifically, osteoclast-mediated bone resorption exceeds osteoblast-mediated bone formation [1]. Osteoporosis-induced fracture(s) (or, simply, osteoporotic fracture(s) of vertebral body/bodies (hereafter, called osteoporotic vertebral compression fracture(s) (OVCFs)) are the most common type of fragility fractures, accounting for ~50% [21]. For most people, OVCF(s) result in mild to moderate pain and are treated/managed with conservative methods, such as oral prescription medications, physical therapy, and wearing of braces(s)/orthotic device(s) [22, 23]. However, in cases where OVCF(s) lead(s) to segmental spinal deformity, the resulting pain is severe and/or persistent, in which case treatment involves use of a minimally-invasive surgical modality, the most established being percutaneous vertebroplasty (PVP) and percutaneous balloon kyphoplasty (PKP) [24-28]. For example, in the National Health Service in England, between 2017/2018 and 2019/2020, the number of patients aged 55-74 years and >75 years who underwent PVP or PKP increased by 19%, and 28%, respectively [26]. Newer or emerging surgical methods include use of expandable implant systems (such as OsseoFix®, SpineJack®, and the Titanium Tri-blade Fixed Device) and robot-assisted PVP or PKP [29-40].

One feature that is common to PVP, PKP, and some of the newer and other emerging surgical methods is the use of bone cement for either stabilization of the fractured VB(s) (as in PVP) or restoration of the fractured VB(s) to their pre-fracture height(s) followed by their stabilization (as in PKP). Over the years, there has been much debate about the efficacy of PVP and PKP compared to a placebo or conservative measures, in particular, oral prescription medications [35]. However, the consistent finding in meta-analyses of recent large-scale real-world studies is that clinical and radiological outcomes from either PVP or PKP are significantly better than from conservative methods [41, 42]. Thus, it appears that it is justified for PVP and PKP to be continued to be part of the treatment options available to patients while research continues on these methods [36-38] and/or replacement of them by novel ones [39,40].

Although many bone cement chemistries have been used in PVP and PKP or are being evaluated for use in emerging variants of PVP and PKP and novel surgical methods, such as poly (methyl methacrylate) (PMMA), calcium phosphate, calcium sulfate, and calcium silicate cements, the predominant choice is PMMA bone cement [43-46]. The many advantages of PMMA bone cement for this application are well known, among which are ease of preparation and delivery to the fractured VB(s), excellent biocompatibility, and widespread familiarity given its long history of use in anchoring total joint replacements [43-46]. However, the cement has its share of shortcomings, five of which are of particular clinical relevance to PVP and PKP [43-46]. First, its polymerization involves an exothermic reaction, with the maximum temperature typically reached being much higher than that postulated to cause thermal necrosis of contiguous tissues (50 ^{o}C) [47]. Second, there are myriad reports that during PVP and PKP, there is extravasation or leakage of the cement dough into neighboring tissues and/or organs [48-50]. Third, the residual monomer concentration in the cured cement is high, which, it has been posited, increases the likelihood for chemical necrosis of contiguous tissues. Fourth, its quasi-static compressive elastic modulus is much higher than that of vertebral cancellous bone (by a factor of between ~2-~370), with the same trend seen for its quasi-static compressive strength (by a factor of between ~7 and ~1140).

It has been postulated that these property mismatches increase the potential for or play a role in the creation of new fracture(s) in VB(s) that are adjacent to or far removed from the one(s) treated with PVP or PKP (what collectively have been called, “new symptomatic osteoporotic vertebral compression fractures” (NSOVCFs)) [51]. The fifth highlighted shortcoming of PMMA bone cement is that it is a biologically inert; as such, osseointegration between the cured cement zone in the augmented VB(s) and the contiguous bone is very poor. In addition to the shortcomings of PMMA bone cement, the literature on its *in vitro* and *ex vivo* fatigue performance relevant to PVP and PKP and clinical studies when the cement is used in PVP and PKP is very sparse.

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

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

2. STUDY SELECTION METHODOLOGY

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

Table 1. Some features of studies included in the review

Cement shortcoming or literature gap addressed[a]	Control cement specifically for PVP/PKP	Control cement radiopacifier (loading, in wt./wt.%)	Intended use of experimental cement for treatment of OVCF(s)	Ref. #
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 *in vitro* fatigue performance	Yes	$BaS0_4$ (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 *in vitro* 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 *in vitro* 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® ($BaSO_4$; 25)	Yes	Boger et al. [78]
High E_c	Yes	Vertecem® ($BaSO_4$; 25)	Yes	Boger et al. [79]
Paucity of data on *ex vivo* 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]

[a]T_{max}: maximum polymerization temperature; E_c: quasi-static compressive modulus.
[b]Authors 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.
[c]Radiopacifier 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 $SrTiO_3$		Carrodeguas 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	Diatrizoate sodium (DTA)		Han et al. [61]
Mendec®Spine	MC powder[b]		Zhu et al. [62]
Experimental cement		A gel comprising HyA and poly(ethylene glycol)	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	Tungsten carbide (WC) particles		Xu et al. [67]

F20®		Linoleic acid (LA)	Robo et al. [68]
V-Steady™; Resilience®		LA	Robo et al. [69]
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]
"Traditional"	MC powder[b]	Luo et al. [91]

[a]Commercially-formulated brands are the following: Vertecem® (Synthes GmbH, Oberdorf, Switzerland); Mendec®Spine (Tecres SpA, Verona, Italy); Osteopal®V (Heraeus Medical GmbH, Hanau, Germany); Spineplex® (Stryker, Kalamazoo, MI, USA); F20® (Teknimed SAS, France); V-Steady™ (G21 Srl, San Possidonio, Italy); Resilience®: a commercially-formulated "low-modulus" cement for use in PVP or PKP but which is no longer available in the market (per 2021)[67]; VertaPlex™ (Stryker, Kalamazoo, MI, USA); Vertecem®V+ (Synthes GmbH). Note that, per July 2024, a commercially-formulated cement brand listed here may no longer be produced and/or marketed by the stated commercial entity.
[b]Different methods were used to combine MC particles with the powder and liquid of the control cement; for details, see the literature report.
[c]Added to other powder and liquid constituents of the cement before dough was prepared.
[d]In preparing the dough of the modified cement formulation, fetal bovine serum was added to the mixture of powder and liquid of the control cement.

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

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

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.#]
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	10HyA-10PEG-PMMA	17% lower T_{max}	Park et al. [64]
Mendec®Spine	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 human vertebral cancellous bone	Boger et al. [56]
	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 land 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 with EDTA) was significantly < 4% (upper acceptable limit, per ISO/TR7405)	Sun et al. [59]
Mendec®Spine	15Hydrogel-PMMA	In Live-Dead staining test (BMSCs from 3 wk-old male Sprague-Dawley rats), significantly greater %live cells % 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)	Sun et al. [60]
Vertecem®	Aqueous fraction of 35% HyA to control cement liquid	In an *ex vivo* 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 *ex vivo* test (lumbar VBs taken from cadavers, age of donors: 78 ± 10 y), significantly higher force during cyclic loading at which there was a marked increase in the displacement-versus-time plot, adjusted for initial fracture force	Kolb et al. [82]
Mendec®Spine	5 or 10 wt./wt.% SIS particles to control cement powder	In an *ex vivo* 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 cavitary 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 and 12 wk post-surgery, significantly greater cortical bone thickness, osteoblast area, new bone area, and % bone growth	Zhu et al. [62]
Mendec®Spine	20Hydrogel-PMMA	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]
34 wt./wt.% ZrO_2-containing	10HyA-10PEG-PMMA	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]

Mendec®Spine	5 or 15 wt./wt.% SIS particles added to control cement powder	In an animal model test (mature male New Zealand white rabbits; mass: 2.5-3.0 kg) in which cement dough was injected into various positions on the L5 and L6 spinous processes), significantly higher BV/TV	Zhang et al. [65]

[a]Result for parameter obtained from test in which experimental cement was used compared to corresponding result from test in which control cement was used.
[b]HyA: hyaluronic acid; DMAEM: dimethyl amino ethyl methacrylate; MC; mineralized collagen; DTA: diatrizoate sodium; PEG: poly(ethylene glycol); SIS: small intestinal submucosa; Iopamiro-300®: a commercially-formulated organic iodine-containing hydrophilic radiopacifier;

Ultravist-370®: a commercially-formulated organic iodine-containing hydrophilic radiopacifier; LA: 9-cis,12-cis linoleic acid; CS: calcium silicate.
[c]T_{max}; maximum polymerization temperature; t_{set}: setting time; ALP: alkaline phosphate activity; OCN: osteocalcin; EDTA: ethylene diamine tetra acetic acid; VB: vertebral body; BV/TV: new bone volume/total tissue volume; Tb.N: trabecular bone number; Tb.Th: trabecular bone thickness.

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 mean intermediate vertebral height of fractured vertebra to mean anterior vertebra height of the superjacent vertebra (IVH) was significantly lower in Group 2 patients than in Group 1 patients, midline IVH was significantly larger for Group 2 patients than in Group 1 patients, and left lateral recess AVH was lower for Group 2 patients than in Group 1 patients; and 8) at 1 y follow-up, the computed tomography (CT) values of the fractured vertebrae were significant higher in Group 2 patients than in Group 1 patients. It was concluded that, overall, clinical and radiological results for Group 2 were better than those for Group 1 patients.

The study by Luo et al. [91] comprised two sets of very old osteoporotic patients (80-88 y) who suffered single-level VCFs at the thoracic/lumbar spine (T6-T12 and L1-L5) that were treated using PVP. For Group 1 patients, the cement used was a “traditional PMMA bone cement” (traditional PMMA cement group; 32 patients) and for Group 2 patients, the cement used was an experimental formulation obtained by incorporating MC particles into the traditional PMMA bone cement (31 patients). Trends in eight results were 1) the difference in operation time between the two groups was not significant; 2) the difference in cement leakage incidence between the two groups was not significant and, in cases where there was leakage, there were no accompanying clinical symptoms; 3) significantly lower fewer new VCFs occurred in Group 2 patients (1 case) than in Group 1 patients (7 cases); 4) at each follow-up, significantly lower VAS in each group compared to the pre-operative level, and, at 1 y follow-up, significantly lower VAS for Group 2 patients compared to Group 1 patients; 5) at each follow-up, significantly lower ODI score in each group compared to the pre-operative level, and, at 1 y follow-up, significantly lower ODI score for Group 2 patients compared to Group 1 patients; 6) at 1 y follow-up, the Cobb angle in Group 2 patients was significantly smaller than in Group 1 patients; 7) at 1 y follow-up, the vertebral height recovery of AVH and the vertebral height recovery of IVH was each significantly greater in Group 2 patients than in Group 1 patients; and 8) in Group 2 patients, the CT value of the injured VB, at 1 y follow-up, was significantly larger compared to the pre-operative value. It was concluded that, overall, clinical and radiological results were better for Group 2 patients than for Group 1 patients.

The retrospective study by Zhu et al. [62] was on two sets of osteoporotic middle-aged/old patients (64-84 y) who suffered single-level VCFs at levels that included T11, T12, L1, L2, L3, and L4 that were treated using PKP. For Group 1 patients, Mendec®Spine cement was used (12 patients) and for Group 2 patients, the cement used was an experimental formulation obtained by adding MC powder to the powder of Mendec®Spine (12 patients). Trends in three results were 1) the number of recurrent fractures of adjacent VBs were 8 and 0 in Groups 1 and 2 patients, respectively; 2) at 1 y follow-up, AVH and IVH were each significantly higher in Group 2 patients compared to the corresponding value in Group 1 patients; and 3) at 2 y follow-up, VAS and ODI scores for Group 2 patients were each significantly lower than the corresponding value for Group 1 patients. It was concluded that, overall, clinical and radiological results were better for Group 2 patients than for Group 1 patients.

6. PERSPECTIVE ON MOST PROMISING EXPERIMENTAL CEMENT FORMULATIONS

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

Table 4. Trends in properties of promising experimental cements

Promising experimental cement	Trend in property
Powder includes silanated radiopacifier [Ref. #55]	⋆ Significantly higher *in vitro* injectability[a]
Liquid includes hyaluronic acid (HyA) solution [Ref. #56]	⋆ *In vitro* quasi-static compressive modulus (E_c) (for 35 wt./wt.%HyA formulation, E_c = 477 ± 67 MPa) that is within the range for human vertebral cancellous bone[b] ⋆ *In vitro* quasi-static compressive strength (UCS) (for 45 wt./wt.%HyA formulation, UCS = 2.5 ± 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]	⋆ Significantly higher *in vitro* injectability[a] ⋆ Significantly lower *in vitro* T_{max}[a] ⋆ *In vitro* quasi-static compressive modulus (E_c) (for formulation that contains 30 wt./wt.% $BaSO_4$ and 10 vol.vol.% DMAEM), mean E_c = 236 MPa) that is within the range for human vertebral cancellous bone[b] ⋆ *In vitro* quasi-static compressive strength (UCS) (for formulation that contains 30 wt./wt.% $BaSO_4$ 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]	⋆ *In vitro* 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] ⋆ *In vitro* 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 *in vivo* (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]	⋆ Significantly lower *in vitro* T_{max}[a] ⋆ *In vitro* quasi-static compressive modulus (E_c) (for formulation that contains 34 wt./wt.% ZrO_2 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] ⋆ *In vitro* 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 *in vivo* (rabbit model) performance measures (such as area of newly formed bone tissue (BV^d/TV^d))[a].
Radiopacifier (Ioprama 300® or Ultramist 37®) is in liquid [Ref. #66]	⋆ Significantly higher *in vitro* radiopacity[a]
Radiopacifier is strontium-containing hydroxyapatite salt (untreated or treated with methyl methacrylate monomer) [Ref. #74]	⋆ Significantly higher *in vitro* biocompatibility measures[a]
Powder includes small intestinal mucosa particles [Ref. #s 65, 77]	⋆ Significantly lower *in vitro* T_{max}[a] ⋆ *In vitro* quasi-static compressive modulus (355-466 MPa) that is within the range for human vertebral cancellous bone[b] ⋆ *In vitro* 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) *in vivo* (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 *ex vivo* 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

[a]Compared to the value obtained with the control cement used in the study.
[b]352 ± 145 MPa, depending on the bone mineral density of the bone (especially, non-osteoporotic or osteoporotic) (see Öhman-Mägi et al.[[81]).
[c]2.27 ± 1.14 MPa, depending on the bone mineral density of the bone (especially, (non-osteoporotic or osteoporotic) (see Öhman-Mägi et al. [81]).
[d]BV: new bone volume; TV: total bone tissue volume; VAS: Visual Analog Score; ODI: Oswestry Disability Index.

The first promising experimental cement was obtained by adding15 wt./wt% of a hydrogel (comprising oxidized HyA and carboxymethyl chitosan) to the powder of a control cement [60]. It was explained that in specimens of this cement immersed in simulated body fluid, at 37 ^{o}C, for up to 28 d, there was partial degradation of the hydrogel, creating holes at the surface of the specimen, which served as spaces for the formation of new bone [60]. The second promising experimental cement was obtained by adding a gel comprising a mixture of 10 vol./vol.% HyA and 10 vol./vol.% PEG to the liquid of an experimental cement whose powder includes ZrO_2 as the radiopacifying agent (10HyA-10PEG-PMMA cement) [63,64]. It was postulated that, *in situ*, the gel in the 10HyA-10PEG-PMMA cement degrades, which, in turn, accounts for the extensive bone regeneration seen when cement specimens were implanted in the femurs of New Zealand white rabbits [64]. The third is one in which 10 wt./wt.% SIS particles were added to the powder of the control cement [65, 77]. The attractive performance of SIS particles-loaded cement in a New Zealand white rabbit vertebral defect model was attributed to 1) increased osseointegration, which is provided by the SIS particles, 2) the fact that there is degradation of SIS and its replacement by host tissue after implantation, and 3) as SIS degrades, there is release of growth factors, which promote processes such as osteoblast proliferation [65, 77]. The fourth promising experimental cement was obtained by blending MC particles with the dough formed by the mixture of the powder and the liquid of a control cement [62, 88-91]. A few clinical studies have been reported in which OVCFs were treated with PVP or PKP using this cement formulation [62, 88-91], and, even though each of these studies has its limitations, the reported clinical and radiological outcomes are encouraging. This performance was explained to be the consequence of many phenomena associated with the MC particles, such as 1) having a composition and microstructure similar to those of native vertebral cancellous bone and, as such, promote active osteoinduction and formation of new bone and increase of the viscosity of the cement dough, and 2) yielding an H-type of distribution of the cement dough within the augmented fractured VB which, among other things, provides support of the VB and maintains its stability [88-91]. It is worth noting that in a recent meta-analysis, the many advantages of MC-modified PMMA bone cement for use in PVP were highlighted while underscoring the need for further study of this cement formulation, especially in high-quality randomized controlled trials [92].

7. SHORTCOMINGS OF THE LITERATURE AND AREAS FOR FUTURE STUDY

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

First, a number of studies had methodological issues that precluded them from being included in the present review (**Table 5**). Furthermore, in the clinical study by Bai et al. [88], there is ambiguity about the appropriateness of the control cement used; specifically, in the report, it was stated that the cement used was Osteopal®, but this brand is approved for use in cemented total arthroplasties. It is possible that the authors intended to state that they used Osteopal®V, but this brand is formulated for use in PVP, whereas the study was on PKP [88]. Thus, the lack of clarity persists. In future studies, all the aforementioned methodological issues should be avoided. Most importantly, the control cement must be one that is either in current clinical use for augmentation of OVCFs or is being evaluated for such use. Thus, among other cement characteristics, its radiopacifier loading must be appropriately high; for example, when incorporated in the cement powder, loading must be $\geq$ 25 wt./wt.%.

Table 5. Some features of excluded studies

Excluded study	Reason(s) for exclusion
Heini et al. [93]	⋆ 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]	⋆ No control cement was used ⋆ The experimental cement used did not contain a radiopacifer (in either the solid or liquid phase) and hydroquinone in the liquid phase
Loeffel et al. [95]	⋆ A comparison cement brand or formulation was not used
Lewis et al. [96]	⋆ A comparison cement brand or formulation was not used
Calvo-Fernandez et al. [97]	⋆ 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]	⋆ The control cement brand used (KyphX®) has been withdrawn from clinical use
Aghyarian et al. [99]	⋆ 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]	⋆ The control cement used (Simplex®P) is a brand that is not specifically indicated for cement augmentation of OVCF(s)
Li et al. [101]	⋆ 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

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

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

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

Seventh, heterogeneity is observed in the reported *ex vivo* studies; namely, simulated prophylactic vertebroplasty of vertebrae in osteoporotic human thoracolumbar spine section [78], simulated prophylactic augmentation of human thoracic vertebrae [79], simulated augmentation of osteoporotic L2-L5 goat vertebrae following a simulated vertebral compression fracture [65], simulated augmentation of vertebrae in osteoporotic human lumbar spine section following a simulated vertebral compression fracture [82], prophylactic augmentation of bovine tibiae [83], and filling of bone defect created in the femoral condyle of sheep [68]. All future work should involve simulated augmentation of simulated OVCF(s), with 1) the protocols used in creating the fracture and 2) the metrics used for characterizing the VB(s) (prior to and after the simulated augmentation) having first been established in preliminary studies. Such work should involve not only PVP and PKP but, also, augmentation methods that have entered clinical use recently, examples being decompressed

percutaneous kyphoplasty [105], the Vertebral Body Stenting System [106, 107], and a poly(etheretherketone) transpedicular vertebral system [108].

Eighth, only a few studies on biocompatibility, biodegradability, osteogenic capacity, and immune response in *in vivo* (animal model) studies have been conducted, these being on female goats (L3, L4, and L5 VBs [59]), male New Zealand white rabbit (femoral condyle [60] and distal femoral head [64]), female sheep (femoral condyle and major tubercle of the humerus [68]), female Wistar rats (dorsal muscle) [74], and male Sprague-Dawley rats [76]. Future work should establish the appropriate animal model, validate it, and, then, use it in determining the aforementioned performance metrics of EMPBCs.

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

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

Eleventh, in terms of statistical analysis of results obtained (specifically, tests of significance of difference between means of study groups (hereafter, “test of significance”)), the information given in the reports may be assembled into six groups. In the first, no information was given [56, 57, 66, 67, 74]. In the second group, a parametric method only was used (t-test [58, 60, 64, 88, 89, 90], chi-squared [89], multifactor one-way analysis of variance (ANOVA) [55], one-way ANOVA [60, 63, 82], one-way analysis of covariance [82], and two-way ANOVA [64]). In the third group, a parametric method followed by a *post-hoc* test

was used (one-way ANOVA followed by Bonferroni test [59, 65], one-way ANOVA followed by Scheffe's test [71], one-way ANOVA followed by Dunnett's test [76], one-way ANOVA followed by LSD [77], one-way ANOVA followed by Tukey honestly significant difference test [78], and one-way ANOVA followed by Tamhane test [83]). In the fourth group, a test for normality of each of the populations being compared was performed first, which was followed by a parametric test (Kolmogorov-Smirnov test followed by one-way ANOVA [62], Shapiro-Wilk test and Levene test followed by Welch's robust ANOVA, and, then, followed by Tamhane post-hoc test [69], and Shapiro-Wilk test followed by paired t-test [70]). In the fifth group, a nonparametric method was used (Mann-Whitney test [70, 79]). In the sixth group, a mixture of parametric and non-parametric methods was used (one-way ANOVA followed by Mann-Whitney test [61]). In all future studies, a test of significance must be performed as this is a robust way of identifying whether the influence of a study variable on a determined cement property is significant or not. For this purpose, it would be both appropriate and economical to use a non-parametric method.

8. CONCLUSION

The following are the key points made in this review:

1. The incidence of primary osteoporosis is high, especially among post-menopausal women and people aged > 50 years. Osteoporotic people are particularly susceptible to compression fracture(s) of vertebral body/bodies (VB(s)). When the pain due to such fracture(s) is high and/or persistent, a surgical treatment method is commonly used, with this involving augmentation of the fractured VB(s) using a minimally-invasive procedure (usually, percutaneous vertebroplasty (PVP) or percutaneous kyphoplasty (PKP)). In the preponderance of cases, a poly(methyl methacrylate) (PMMA) bone cement is used for the augmentation. This cement has many shortcomings, such as high maximum exotherm temperature (hence, high potential for thermal necrosis of contiguous tissues), high compressive modulus (hence, high potential for fracture(s) of non-augmented VB(s), and poor osseointegration (hence, high potential for cement zone loosening). Over the years, there have been many literature reports on studies of PMMA bone cements that are modifications of or based on the composition of commercially-formulated brands used in PVP and PKP that address one or more shortcomings of the cement. A subset of this body of literature comprising studies that meet the aforementioned criterion as well as three others is herein designated studies on "emerging modified PMMA bone cements" (EMPBCs). Many EMPBCs have been characterized in *in vitro*, *ex vivo*, and *in vivo* (animal model) tests, and a few have been the subject of clinical studies. The present contribution is a review of the literature on EMPBCs.

2. A careful examination of the results of the reviewed literature studies leads to identification of four particularly promising EMPBCs, which, it is proposed, should be the subject of rigorous and extensive future studies. These cements are one in which a hydrogel (comprising a mixture of oxidized hyaluronic acid (HyA) and carboxymethyl chitosan) was added to the powder of a commercially-formulated cement brand that is used in PVP and PKP ("predicate cement brand"), another in which a gel (comprising a mixture of HyA and poly(ethylene glycol) was added to the liquid of an experimental bioactive cement, a third in which small intestinal submucosa particles were added to the powder of a predicate cement brand, and a fourth in which mineralized collagen particles were blended with the powder and liquid of a predicate cement brand.

3. Eleven shortcomings of the literature on EMPBCs are highlighted, such as lack of *in vitro* testing standards, lack of *in vitro* determination of many clinically relevant properties, lack of consensus on an appropriate animal model, and paucity of clinical studies, thereby pointing the way to many future studies.

4. When items 1)-3) above are taken into consideration, all future work in this field should be conducted in an efficient manner by concentrating on three aspects. First, a complete list of and rationale for all the desirable properties of a PMMA bone for use in cement augmentation of OVCF(s) should be presented. Second, instead of modifying the compositions of existing commercially-formulated PMMA bone cements used in PVP and PBK, novel cements that simultaneously possess all the desirable properties should be designed from first principles. Central to this approach should be analytical work that results in specification of the full collection of *in vitro* cement properties that significantly influence the performance of the cement in clinical studies, in particular, incidence of cement leakage and incidence of NSOVCFs [48, 110-112]. In this regard, artificial intelligence (in particular, deep learning algorithms, such as the Long Short-Memory [113] and/or machine learning algorithms, such as random forest, support vector machine, and gradient boosting machine) [114]) could be a particularly useful tool. Third, these novel cements should be comprehensively characterized in a battery of *in vitro*, preclinical, and clinical studies.

REFERENCES

1. Sabri SA, Chavarria JC, Ackert-Bicknell C, Swanson C, Burger E. Osteoporosis: an update on screening, diagnosis, evaluation, and treatment. Orthopedics 2023;46(1):e20-e26. https://doi.org/10.3928/01477447-20220719-03.
2. Ebeling PR, Nguyen HH, Aleksova J, Vincent AJ, Wong P, Milat F. Secondary osteoporosis. Endocrine Reviews 2022;43:240-313. https://doi.org/10.1210/endrev/bnab028.
3. Xiao PL, Cui AY, Hsu CJ, Peng R, Jiang N, Xu XH, et al. Global, regional prevalence, and risk factors of osteoporosis according to the World Health Organization diagnostic criteria: a systematic review and meta-analysis. Osteoporosis International 2022;33:2137-2153. https://doi.org/10.1007/s00198-022-06454-3.
4. Sarafrazi N, Wambogo EA, Shepherd JA. Osteoporosis or low bone mass in older adults: United States, 2017–2018. NCHS Data Brief; no. 405. 2021. http://dx.doi.org/10.15620/cdc:103477.
5. Wang L, Yu W, Yin X, Cui L, Tang S, Jiang N, et al. Prevalence of osteoporosis and fracture in China: the China Osteoporosis Prevalence Study. JAMA Network Open 2021 4(8):e2121106. doi:10.1001/jamanetworkopen.2021.21106.

6. World Organization Organization (WHO). Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: report of a WHO study group [meeting held in Rome from 22 to 25 June 1992]. WHO Technical Report Series. 1994;843: 1-129. https://iris.who.int/handle/10665/39142.

7. Yang TL, Shen H, Liu A, Dong SS, Zhang L, Deng FY, et al. A road map for understanding molecular and genetic determinants of osteoporosis. Nature Reviews Endocrinology 2020;16:91-103. https://doi.org/10.1038/s41574-019-0282-7.
8. He L, Liu Z, Liu C, Gao Z, Ren Q, Lei L, et al. Radiomics based on lumbar spine magnetic resonance imaging to detect osteoporosis. Academic Radiology 2021;28(6):e165-e171. https://doi.org/10.1016/j.acra.2020.03.046
9. Vadera S, Osborne T, Shah V, Stephenson JA. Opportunistic screening for osteoporosis by abdominal CT in a British population. Insights into Imaging 2023;14(1):57. https://doi.org/10.1186/s13244-023-01400-1
10. Xu W, Li Y, Zhang X, Chen L, Wang S, Wang Y, et al. A novel approach for assessing osteoporosis utilizing DXA, HU and VBQ. Biomedical Technology 2024;5:102-108. https://doi.org/10.1016/j.bmt.2023.08.001
11. Anish RJ, Nair A. Osteoporosis management-current and future perspectives-a systematic review. J Orthopaedics 2024;53:101-113. https://doi.org/10.1016/j.jor.2024.03.002
12 Gosh D, Sahu PK. Osteoporosis detection with microwave signals: An investigation into natural resonance frequencies. Sensors and Actuators A: Physical 2024;365:114867. https://doi.org/10.1016/j.sna.2023.114867.
13 Pivonka P, Calvo-Gallego JL, Schmidt S, Martinez-Reina J. Advances in mechanobiological pharmacokinetic-pharmacodynamic models of osteoporosis treatment-pathways to optimise and exploit existing therapies. Bone 2024;11710. https://doi.org/10.1016/j.bone.2024.117140.
14 Pickering M-E, Javier R-M, Malochet S, Pickering G, Desmeules. Osteoporosis treatment and pain relief: a scoping review. Eur Pain J 2024;28:3-20. https//doi: 10.1002/epj.2156.
15 Ren M, Ahmed AF, Li M, Li M, Yan Z, Wang J. A review: the mechanism of plant-derived polysaccharides on osteoblasts and osteoclasts. Journal of Future Foods 2024;4: 183-192. https://doi.org/10.1016/j.jfutfo.2023.07.001.
16 Cheng C, Xing Z, Hu Q, Kong N, Liao C, Xu S, et al. A bone-targeting near-infrared luminescence nanocarrier facilitates alpha-ketoglutarate efficacy enhancement for osteoporosis therapy. Acta Biomaterialia 2024;173:442-456. https://doi.org/10.1016/j.actbio.2023.11.022.
17 Kanis JA, Johnell O, Oden A, Sernbo I, Redlund-Johnell I, Dawson A, et al. Long-term risk of osteoporotic fracture in Malmö. Osteoporosis International 2000;11:669-674. https://doi.org/10.1007/s001980070064.
18 Moayyeri A, Warden J, Han S, Suh HS, Pinedo-Villanueva R, Harvey NC, et al. Estimating the economic burden of osteoporotic fractures in a multinational study: a real-world data perspective. Osteoporosis International 2023;34:2121-2132. https://doi.org/10.1007/s00198-023-06895-4.
19 Chen K, Wang T, Tong X, Song Y, Hong J, Sun Y, et al.. Osteoporosis is associated with depression among older adults: a nationwide population-based study in the USA from 2005 to 2020. Public Health 2024;226:27-31. https://doi.org/10.1016/j.puhe.2023.10.022.
20 Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. J Am Med Assoc 2009;301:513-521. doi:10.1001/jama.2009.50.
21 Si L, Winzenberg TM, Jiang Q, Chen M, Palmer AJ. Projection of osteoporosis-related fractures and costs in China: 2010–2050. Osteoporosis International 2015;26: 1929-1937. https://doi.org/10.1007/s00198-015-3093-2.
22 Viswanathan M, Reddy S, Berkman N, Cullen K, Middleton JC, Nicholson WK, et al. Screening to prevent osteoporotic fractures: updated evidence report and systematic review for the US Preventive Services Task Force. J Am Med Assoc 2018;319: 2532-2551. doi:10.1001/jama.2018.6537.

23. Gelvez D, Dong K, Redlich N, Williams J, Bhandutia A. Treatment strategies in the osteoporotic spine. Orthopedic Clinics North America 2024;55:403-413. https://doi.org/10.1016/j.ocl.2024.01.001.
24. Beall DP, Phillips TR. Vertebral augmentation: an overview. Skeletal Radiol 2023; 52:1911–1920. https://doi.org/10.1007/s00256-022-04092-8.
25. Ong T, Kantachuvesiri P, Sahota O, Gladman JRF. Characteristics and outcomes of hospitalized patients with vertebral fragility fractures: a systematic review. Age Ageing 2018;47:17–25. https://doi.org/10.1093/ageing/afx079.
26. Tan CW, Sahota O. A 3-year retrospective analysis of patients admitted with clinical vertebral fragility fractures across hospitals in England, UK. Osteoporosis International 2023;34:607–611. https://doi.org/10.1007/s00198-022-06647-w.
27. Daher M, Kreichati G, Kharrat K, Sebaaly A. Vertebroplasty versus kyphoplasty in the treatment of osteoporotic vertebral compression fractures: a meta-analysis. World Neurosurg 2023;171:65–71. https://doi.org/10.1016/j.wneu.2022.11.123.
28. Gozel T, Ortiz AO. Vertebral augmentation for osteoporotic vertebral compression fractures: what is the current evidence pro and con? Radiologic Clinics 2024 (in press) https://doi.org/10.1016/j.rcl.2024.03.004.
29. Chu W, Tsuei YC, Liao PH, Lin JH, Chou WH, Chu WC, et al.. Decompressed percutaneous vertebroplasty: a secured bone cement delivery procedure for vertebral augmentation in osteoporotic compression fractures. Injury 2013; 44:813-818. https://doi.org/10.1016/j.injury.2012.10.017.
30. Trumm CG, Jakobs TF, Stahl R, Sandner TA, Paprottka PM, Reiser MF, et al. CT fluoroscopy-guided vertebral augmentation with a radiofrequency-induced, high-viscosity bone cement (StabiliT®): technical results and polymethylmethacrylate leakages in 25 patients. Skeletal Radiol 2013;42:113–120. https://doi.org/10.1007/s00256-012-1386-5.
31. Chen H, Tang P, Zhao Y, Gao, Y. Wang. Unilateral versus bilateral balloon kyphoplasty in the treatment of osteoporotic vertebral compression fractures. Orthopedics 2014;37(9):e828-835.https://doi.org/10.3928/01477447-20140825-61.
32. Sembrano JN, Yson SC, Polly DW, Ledonio CGT, Nuckley DJ, Santos ERG. Comparison of nonnavigated and 3-dimensional image-based computer navigated balloon kyphoplasty. Orthopedics 2015;38:17–2. https://doi.org/10.3928/01477447-20150105-51.
33. Lewis G. Alternatives to balloon kyphoplasty for surgical treatment of vertebral compression fractures: a state-of-the-art review. J Adv Med Med Res 2018; 26:1–19. https://doi.org/10.9734/JAMMR/2018/42418.
34. Long Y, Yi W, Yang D. Advances in vertebral augmentation systems for osteoporotic vertebral compression fractures. Pain Res Manag 2020;Article ID 3947368. doi: 10.1155/2020/3947368 .
35. Skjødt MK, Abrahamsen B. New Insights in the pathophysiology, epidemiology, and response to treatment of osteoporotic vertebral fractures. J Clin Endocrinol Metab 2023;108:e1175–e1185. https://doi.org/10.1210/clinem/dgad256.
36. Tan L, Wen B, Guo Z, Chen Z. Robot-assisted percutaneous vertebroplasty for osteoporotic vertebral compression fractures: a retrospective matched-cohort study. Int Orthop 2023;47:595–604. https://doi.org/10.1007/s00264-022-05654-0.
37. Wang X, Zhu Y, Zhu Q. Efficacy and safety of robot-assisted versus fluoroscopy-assisted PKP or PVP for osteoporotic vertebral compression fractures: a systematic review and meta-analysis. J Robot Surg 2023;17:2597–2610. https://doi.org/10.1007/s11701-023-01700-0.
38. Liu D, Zhang H, Fan X. Robot-assisted percutaneous vertebroplasty for osteoporotic vertebral compression fracture treatment and risk factor screening for postoperative refracture. Journal of Robotic Surgery 2024;18:23. https://doi.org/10.1007/s11701-023- 01776-8.

39. Wang Y, Zhou C, Liao Y, Meng X. Comparison between intraoperative target area cement-enhanced percutaneous vertebroplasty and conventional percutaneous vertebroplasty for osteoporotic thoracolumbar non-total vertebral fractures. Turkish Neurosurgery 2024;34:461-467. doi: 10.5137/1019-5149.JTN.43749-23.2.
40. Zhou Q, Wan Y, Ma L, Dong L, Yuan W. Percutaneous curved vertebroplasty decrease the risk of cemented vertebra refracture compared with bilateral percutaneous kyphoplasty in the treatment of osteoporotic vertebral compression fractures. Clinical Interventions in Aging 2024;289-301. doi: 10.2147/CIA.S438036.
41. Zhang Y, Ge J, Liu H, Niu J, Wang S, Shen H, et al. Kyphoplasty is associated with reduced mortality risk for osteoporotic vertebral compression fractures: a systematic review and meta-analysis. Eur Spine Journal 2024;33:1490-1497. https://doi.org/10.1007/s00586-023-08032-5.
42. Gao Q, Li Q, Wang L, Cen Y, Yang H. Percutaneous vertebroplasty versus Percutaneous kyphoplasty for osteoporotic vertebral compression fractures: an umbrella review protocol of systematic reviews and meta-analyses. BMJ Open 2024;14:e075225. https://doi:10.1136/bmjopen-2023-07522523.
43. Lewis G. Injectable bone cements for use in vertebroplasty and kyphoplasty: a state-of-the-art review. J Biomed Mater Res B Appl Biomater 2006;76B: 456–468. doi:10.1002/jbm.b.30398.
44. Quan Q, Gongping X, Ruisi N, Shiwen L. New research progress of modified bone cement applied to vertebroplasty. World Neurosurg 2023;176:10–18. https://doi.org/10.1016/j.wneu.2023.04.048.
45. Levashov G, Hasan MH, Frakulli A, Macaalay J, Nahad K. An overview of bone cement compositions used in vertebroplasty and their viability in clinical settings. International Journal of Engineering Materials and Manufacture 2024;9:1–14. https://doi.org/10.26776/ijemm.09.01.2024.01.
46. Williams TD, Adler T, Smokoff L, Kaur A, Rodriguez B, Prakash KJ, et al. Bone cements used in vertebral augmentation: a state-of-the-art narrative review. J Pain Res 2024;17:1029-1040. https://doi.org/10.2147/JPR.S437827
47. Luedke L, Mohammed H, Ducharme N. Decreasing polymethyl methacrylate bone cement concentration extends working and setting times in vitro. Am Journal of Veterinary Research 2023;26:84. https://doi.org/10.2460/ajvr.23.05.0110.
48. Rose L, Bateman G, Ahmed A. Clinical significance of cement leakage in kyphoplasty and vertebroplasty: a systematic review. Eur Spine J 2024;33: 1484-1489. doi: https://doi.org/10.1007/s00586-023-08026-3.
49. Jarrar S, Al Barbarawi MM, Daoud S, Jaradat A, Alkalbani R, Abu Qayyas L, et al. Cement extravasation as a complication for kyphoplasty and vertebroplasty procedure: a retrospective analysis of 171 cases. Med Glas (Zenica) 2024; 21:176-183. doi: https://doi.org/10.17392/1626-23.
50. McGarvey C, Nair A, Nawras Y, Oenick J, Vattipally V. Cement embolism after kyphoplasty. Cureus 2024; 16(1):e52821. https://doi.org/10.7759/cureus.52821
51. Feng ST, Yang Y, Li X, Zuo W-Y, Sun H-B. Risk factors of new symptomatic fractures after vertebroplasty: a retrospective cohort study of 268 patients with painful osteoporotic vertebral compression fracture. World Neurosurg 2024; in press: E1-E8. https://doi.org/10.1016/j.wneu.2024.05.007.
52. Zhu J, Jiang G, Qiu Z, Lu J, Shen F, Ciu F-Z. Modification of poly(methyl methacrylate) bone cement for vertebroplasty. J Biomater Tissue Eng 2018; 8:607-616. https://doi.org/10.1166/jbt.2018.1800.
53. Gong Y, Zhang B, Yan L. A preliminary review of modified polymethyl methacrylate and calcium-based bone cement for improving properties in osteoporotic vertebral compression fractures. Frontiers in Materials 2022;9:912713. https://doi.org/10.3389/fmats.2022.912713.

54. Mounika C, Tadge T, Keerthana M, Velyutham R, Kapusetti G. Advancements in poly(methyl methacrylate) bone cement for enhanced osteoconductivity and mechanical properties in vertebroplasty: a comprehensive review. Med Eng Phys 2023; 120:104049. https://doi.org/10.1016/j.medengphy.2023.104049.
55. Carrodeguas RG, Lasa BV, Del Barrio JS. Injectable acrylic bone cements for vertebroplasty with improved properties. J Biomed Mater Res (Appl Biomater) 2004; 68:94-104. https://doi.org/10.1002/jbm.b.20007.
56. Boger A, Bohner M, Heini P, Verrier S, Schneider E. Properties of an injectable low modulus PMMA bone cement for osteoporotic bone. J Biomed Mater Res (Appl Biomater) 2008; 86B:474-482. https://doi.org/10.1002/jbm.b.31044.
57. Cisneros-Pineda OG, Cauich-Rodríguez JV, Cervantes-Uc JM, Vázquez B, Román JS. Combined influence of barium sulfate content and co-monomer concentration on properties of PMMA bone cements for vertebroplasty. J Biomater Sci Polym Ed 2011; 22(12):1563-80. https://doi.org/10.1163/092050610X516780.
58. Jiang H-J, Xu J, Qiu Z-Y, Ma X-L, Zhang Z-Q, Tan X-X, et al. Mechanical properties and cytocompatibility improvement of vertebroplasty PMMA bone cements by incorporating mineralized collagen. Materials 2015; 8:2616-2634. https://doi.org/10.3390/ma8052616.
59. Sun X, Wu Z, He D, Shen K, Liu X, Li H, Jin W. Bioactive injectable polymethylmethacrylate/silicate bioceramic hybrid cements for percutaneous vertebroplasty and kyphoplasty. J Mech Behav Biomed Mater 2019; 96: 125–135. https://doi.org/10.1016/j.jmbbm.2019.04.044.
60. Sun X, Zhang X, Jiao X, Ma J, Liu X, Yang H, et al. Injectable bioactive polymethyl methacrylate–hydrogel hybrid bone cement loaded with BMP-2 to improve osteogenesis for percutaneous vertebroplasty and kyphoplasty. Biodes Manuf 2022;5:318–332. https://doi.org/10.1007/s42242-021-00172-1.
61. Han J, Zheng X, Liu J, Wang Y, Cui Z, Wu S, et al. Modification and evaluation of Diatrizoate sodium containing polymethyl methacrylate bone cement. J Biomater Appl 2023;37: 1300-1314. https://doi.org/10.1177/08853282221150359.
62. Zhu J, Yang S, Cai K, Wang S, Qiu Z, Huang J, et al. Bioactive poly (methyl methacrylate) bone cement for the treatment of osteoporotic vertebral compression fractures. Theranostics 2020;10:5444-6560. doi: 10.7150/thno.44428.
63. Faruq O, Sarkar K, Lee B-T. Physicochemical property and cytocompatibility of HyA-PEG loaded PMMA based bone cement. Materials Chemistry and Physics 2023; 295:127142. https://doi.org/10.1016/j.matchemphys.2022.127142.
64. Park S-s, Lim H, Lee B-T. *In vivo* evaluation of hyaluronic acid–polyethylene glycol amended PMMA bone cement for orthopaedic application. Journal of Biomaterials Science Polymer Edition 2024; May 30:1-16. https://doi.org/10.1080/09205063.2024.2359789.
65. Zhang C, Cai X, Li M, Peng J, Mei J, Wang F, et al. Preclinical evaluation of bioactive small intestinal submucosa-PMMA bone cement for vertebral augmentation. ACS Biomater Sci Eng 2024;10:2398-2413. https://doi.org/10.1021/acsbiomaterials.3c01629.
66. Boger A, Bisig A, Bohner M, Heini P, Schneider E. Variation of the mechanical properties of PMMA to suit osteoporotic cancellous bone. J Biomater Sci Polym Edition 2008;19:1125-1142. https://doi.org/10.1163/156856208785540154.
67. Xu TG, Liu DC, Wang Y, Chen S, Li B, Zhang F, He JH. Tungsten carbide-enhanced radiopaque and biocompatible PMMA bone cement and its application in vertebroplasty. Composites Communications 2023; 40:101615. https://doi.org/10.1016/j.coco.2023.101615.

68. Robo C, Hulsart-Billström G, Nilsson M, Persson C. In vivo response to a low-modulus PMMA bone cement in an ovine model. Acta Biomaterialia 2018; 72: 362-370. https://doi.org/10.1016/j.actbio.2018.03.014.
69. Robo C, Öhman-Mägi C, Persson C. Long-term mechanical properties of a novel low-modulus bone cement for the treatment of osteoporotic vertebral compression fractures. J Mech Behav Biomed Mater 2021; 118:104437. https://doi.org/10.1016/j.jmbbm.2021.104437
70. Jacobs E, Saralidze K, Roth AK, de Jong JJ, van den Bergh JP, Lataster A, et al. Synthesis and characterization of a new vertebroplasty cement based on gold-containing PMMA microspheres. Biomater 2016; 82:60-70. https://doi.org/10.1016/j.biomaterials.2015.12.024.
71. Robo C, Öhman-Mägi C, Persson C. Compressive fatigue properties of commercially available standard and low-modulus acrylic bone cements intended for vertebroplasty. J Mech Behav Biomed Mater 2018; 82:70-76. https://doi.org/10.1016/j.jmbbm.2018.03.001.
72. Dixon WJ. The up-and-down method for small samples. J Am Stat Assoc 1965; 60:967-978. https://doi.org/10.2307/2283398.
73. Schwartz EN, Steinberg D. Detection of vertebral fractures. Current Osteoporosis Reports 2005;3:126-135. https://doi.org/10.1007/s11914-996-0015-4.
74. Hernández L, Gurruchaga M, Goni I. Injectable acrylic bone cements for vertebroplasty based on a radiopaque hydroxyapatite. Formulation and rheological behaviour. J Mater Sci:Mater Med 2009;20:89-97. https://doi.org/10.1007/s10856- 008-3542-y.
75. Clifford CJ, Downes S. A comparative study of the use of colorimetric assays in the assessment of biocompatibility. J of Mater Sci:Mater Med 1996;7:637-643. https://doi.org/10.1007/BF00058204.
76. Carlsson E, Mestres G, Treerattrakoon K, López A, Karlsson Ott M, Larsson S, et al. In vitro and in vivo response to low-modulus PMMA-based bone cement. BioMed Res Int 2015;Article ID 594284. https://doi.org/10.1155/2015/594284.
77. Zhang C, Zhu J, Zhang T, Li M, Jiang G, Zhao J. Small intestinal submucosa/polymethyl methacrylate composite bone cement for vertebral repair. Materials and Design 2018; 154:254-265. https://doi.org/10.1016/j.matdes.2018.05.045.
78. Boger A, Heini P, Windolf M, Schneider E. Adjacent vertebral failure after vertebroplasty: a biomechanical study of low-modulus PMMA cement. Euro Spine J 2007;16:2118-2125. https://doi.org/10.1007/s00586-007-0473-0.
79. Boger A, Bohner M, Heini P, Schwieger K, Schneider E. Performance of vertebral cancellous bone augmented with compliant PMMA under dynamic loads. Acta Biomater 2008;4:1688-1693. https://doi.org/10.1016/j.actbio.2008.06.019.
80. Wilke H-J, Neef P, Caimi M, Hoogland T, Claes LE. New in vivo measurements of pressures in the intervertebral disc in daily life. New in vivo measurements of pressures in the intervertebral disc in daily life. Spine 1999;24:755-762. doi:10.1097/00007632-199904150-00005.
81. Öhman-Mägi C, Holub O, Dan D, Hall RM, Persson C. Density and mechanical properties of vertebral trabecular bone-a review. JOR Spine 2021;4(4):e1176. doi.10.1002/jsp2.1176.
82. Kolb JP, Kueny RA, Püschel K, Boger A, Rueger JM, Morlock MM, et al. Does the cement stiffness affect fatigue fracture strength of vertebrae after cement augmentation in osteoporotic patients? Euro Spine J 2013;22:1650-1656. https://doi.org/10.1007/s00586-013-2809-2.

83. López A, Mestres G, Ott MK, Engqvist H, Ferguson SJ, Persson C, et al. Compressive mechanical properties and cytocompatibility of bone-compliant, linoleic acid-modified bone cement in a bovine model. J Mech Behav Biomed Mater 2014;32:245-256. https://doi.org/10.1016/j.jmbbm.2014.01.002.
84. Holub O, López A, Borse V, Engqvist H, Kapur N, Hall RM, Persson C. Biomechanics of low-modulus and standard acrylic bone cements in simulated vertebroplasty: A human ex vivo study. J Biomech 2015;48:3258-3266. https://doi.org/10.1016/j.jbiomech.2015.06.026.
85. Furtado N, Oakland RJ, Wilcox RK, Hall RM. A biomechanical investigation of vertebroplasty in osteoporotic compression fractures and in prophylactic vertebral reinforcement. Spine 2007;32:E480-E487. doi: 10.1097/BRS.0b013e31811ea2ee.
86. Buckley JM, Parmeshwar R, Deviren V, Ames CP. An improved metric for quantifying the stiffnesses of intact human vertebrae. Proc Inst Mech Eng Part H: J Eng Med 2009;223:537-543. https://doi.org/10.1243/09544119JEIM524.
87. Ryhänen J, Kallioinen M, Tuukkanen J, Junila J, Niemelä E, Sandvik P, et al. In vivo biocompatibility evaluation of nickel-titanium shape memory metal alloy: muscle and perineural tissue responses and encapsule membrane thickness. J of Biomed Mater Res 1998;41:481-488. https://doi.org/10.1002/(SICI)1097-4636(19980905)41:3<481::AID-JBM19>3.0.CO;2-L.
88. Bai M, Yin H, Zhao J, Li Y, Yang Y, Wu Y. Application of PMMA Bone cement composited with bone cement-mineralized collagen in percutaneous kyphoplasty. Regenerative Biomaterials 2017;251-255. https://doi:10.1093/rb/rbx019.
89. Wang X, Kou J-M, Yue Y, Weng X-S, Qiu Z-Y, Zhang X-F. Clinical outcome comparison of polymethylmethacrylate bone cement with and without mineralized collagen modification for osteoporotic vertebral compression fractures. Medicine 2018;97(37):e12204. doi:10.1097/MD.0000000000012204.
90. Zhu J, Zhang K, Luo K, Qiu Z, Yang S, Cui F, et al. Mineralized collagen modified polymethyl methacrylate bone cement for osteoporotic compression vertebral fracture at 1-year follow-up. Spine 2018;44:827-838. doi:10.1097/BRS.0000000000002971.
91. Luo K, Jiang G, Zhu J, Lu B, Lu J, Zhang K, et al. Poly (methyl methacrylate) bone cement composited with mineralized collagen for osteoporotic vertebral compression fractures in extremely old patients. Regenerative Biomaterials 2020;7:29-34. https://doi.org/10.1093/rb/rbz045.
92. Li S-f, Li X-y, Bai X-h, Wang Y-l, Han P-f, Li H-z. A meta-analysis comparing the efficacy of mineralized collagen-polymethylmethacrylate and polymethylmethacrylate bone cements in the treatment of vertebral compression fractures. PLoS ONE 2024;19:e299325. https://doi.org/10.1371/journal.pone.0299325.
93. Heini PF, Berlemann U, Kaufmann M, Lippuner K, Fankhauser V, Landuyt PV. Augmentation of mechanical properties in osteoporotic vertebral bones – a biomechanical investigation of vertebroplasty efficacy with different bone cements. Eur Spine J 2001;10:164–171. https://doi.org/10.1007/s005860000204.
94. Hernández L, Gurruchaga M, Goñi I. Influence of powder particle size distribution on complex viscosity and other properties of acrylic bone cement for vertebroplasty and kyphoplasty. J Biomed Mater Res B Appl Biomater 2006; 77B: 98–103. https://doi.org/10.1002/jbm.b.30409.
95. Loeffel M, Ferguson SJ, Nolte LP, Kowal JH. Vertebroplasty. Spine 2008;33: 1352-1359. https://doi.org/10.1097/BRS.0b013e3181732aa9.
96. Lewis G, Koole SJ, Hooy-Corstjens CSJV. Influence of powder-to-liquid monomer ratio on properties of an injectable iodine-containing acrylic bone cement for vertebroplasty and balloon kyphoplasty. J Biomed Mater Res B Appl Biomater 2009; 91B:537–544. https://doi.org/10.1002/jbm.b.31427.

97. Calvo-Fernández T, Parra J, Fernández-Gutiérrez M, Vázquez-Lasa B, López-Bravo A, Collía F. Biocompatibility of alendronate-loaded acrylic cement for vertebroplasty. Eur Cell Mater 2010; 20: 260–273. https://doi.org/10.22203/eCM.v020a21.
98. Rodrigues DC, Gilbert JL, Hasenwinkel JM. Two-solution bone cements with cross-linked micro and nano-particles for vertebral fracture applications: effects of zirconium dioxide content on the material and setting properties. J Biomed Mater Res B Appl Biomater 2010; 92B:13–23. https://doi.org/10.1002/jbm.b.31484.
99. Aghyarian S, Rodriguez LC, Chari J, Bentley E, Kosmopoulos V, Lieberman IH, et al. Characterization of a new composite PMMA-HA/Brushite bone cement for spinal augmentation. J Biomater Appl 2014; 29: 688–698. https://doi.org/10.1177/0885328214544770.
100. Tai CL, Lai PL, Lin WD, Tsai TT, Lee YC, Liu MY, et al. Modification of mechanical properties, polymerization temperature, and handling time of polymethylmethacrylate cement for enhancing applicability in vertebroplasty. Biomed Res Int 2016;2016:7901562. doi:10.1155/2016/7901562.
101. Li T, Weng X, Bian Y, Zhou L, Cui F, Qiu Z. Influence of nano-HA coated bone collagen to acrylic (polymethylmethacrylate) bone cement on mechanical properties and bioactivity. PLoS ONE 2015;10:e0129018. https://doi.org/10.1371/journal.pone.0129018.
102. Panpisut P, Khan MA, Main K, Arshad M, Xia W, Petridis H, et al. Polymerization kinetics stability, volumetric changes, apatite precipitation, strontium release and fatigue of novel bone composites for vertebroplasty. PLoS ONE 2019; 14: e0207965. https://doi.org/10.1371/journal.pone.0207965.
103. Ghashami M, Nouri F, Heidari S, Mohammadpour M, Mirzadeh M, Asgari N. Comparative evaluation of net setting time and radiopacity in Fuji II (GC-Japan) restorative glass ionomer and Iranian glass ionomer. Dent Res J (Isfahan) 2022;19:109. PMCID: PMC9807932 .
104. Lv Y, Li A, Zhou F, Pan X, Liang F, Qu X, et al. A novel composite PMMA-based bone cement with reduced potential for thermal necrosis, ACS Applied Materials Interfaces 2015;7:11280–11285. https://doi.org/10.1021/ acsami.5b01447.
105. Cheng S-H, Chou W-H, Tsuei Y-C, Chu W, Chu W-C. Assessment of cement leakage in decompressed percutaneous kyphoplasty. J Clin Med 2024; 13:345. https://doi.org/10.3390/ jcm13020345.
106. Zhang T, Peng Y, Li J. Comparison of clinical and radiological outcomes of vertebral body stenting versus percutaneous kyphoplasty for the treatment of osteoporotic vertebral compression fracture: a systematic review and meta-analysis. Joint Diseases and Related Surgery 2024;35: 218-230. doi: 10.52312/jdrs.2023.1356.
107. Takemasa R, Konishi H, Minamide A, Kawasaki M, Kawaguchi Y, Watanabe K, et al. Effectiveness and safety of vertebral body stenting for acute spinal compression fractures due to primary osteoporosis: a multicenter prospective clinical study. Spine Surgery and Related Research 2024; ID:2023-0248 https://doi.org/10.22603/ssrr.2023-0248.
108. Barral M, Razakamanantsoa L, Tselikas L, De Baere T, Le Huec J-C, Cornelis FH. Polyetheretherketone polymer transpedicular vertebral system to treat vertebral compression fracture: a multicenter pilot study of feasibility and safety. Canadian Association of Radiologists Journal 2024 Feb 4:8465371241228256. doi: 10.1177/08465371241228256.

109. Trivedi Z, Wychowaniec JK, Gehweiler D, Sprecher CM, Boger A, Gueorguiev B, et al. Rheological analysis and evaluation of measurement techniques for curing poly(methacrylate) bone cement in vertebroplasty. ACS Biomaterials Science & Engineering 2024;10:4575-4586. https://doi.org/10.1021/acsbiomaterials.4c00417.
110. Dai X, Liao W, Xu F, Lu W, Xi X, Fang X, et al. External validation of predictive models for new vertebral fractures following percutaneous vertebroplasty. Eur Spine J 2024. doi: 10.1007/s00586-024-08274-x.
111. Gao Y, Zheng J, Yao K, Wang W, Tan G, Xin J, et al. Construction of a nomogram to predict the probability of new vertebral compression fractures after vertebral augmentation of osteoporotic vertebral compression fractures: a retrospective study. Frontiers in Medicine 2024;11:1369984. doi: 10.3389/fmed.2024.1369984.
112. Sun N, Zhang Y, Xie D, Chen Y, Liu Y. Enhancing percutaneous kyphoplasty efficacy in elderly osteoporotic fractures through optimal cement filling ratio. Frontiers in Endocrinology 2024;15:1359550. doi: 10.3389/fendo.2024.1359550.
113. Machrowska A, Szabelski J, Karpinski R, Krakowski P, Jonak J, Jonak K. Use of deep learning networks and statistical modeling to predict changes in mechanical parameters of contaminated bone cements. Materials 2020;13(23):5419. https://www.mdpi.com/1996-1944/13/23/5419.
114. Ma Y, Lu Q, Yuan F, Chen H. Comparison of the effectiveness of different machine learning algorithms in predicting new fractures after PKP for osteoporotic vertebral compression fractures. J Orthopaedic Surg Res 2023;18:62. https://doi.org/10.1186/s13018-023-03551-9.