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Alternative Radiopacifiers for Poly(Methyl Methacrylate) Bone Cement for Use in Cemented Arthroplasty and Augmentation of Osteoporotic Vertebral Compression Fracture

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Abstract

Background: Poly (methyl methacrylate) bone cement (or, simply, bone cement) is used in diverse applications, such as total arthroplasty, treatment/management of osteoporotic vertebral compression fractures, and bone filling. Micron-sized $BaSO_4$ or ZrO_2 particles (one of the powder constituents of the cement) act as the radiopacifying agent. One of the shortcomings of bone cement is that there are many undesirable effects of these particles, such as depreciation of the mechanical properties of the cement. Although there is a substantial body of literature in which this shortcoming is addressed by using alternative radiopacifiers, a review of it is lacking. **Purpose:** This was to conduct a comprehensive critical review of the literature on studies that focus on the synthesis of alternative radiopacifiers, the determination of radiopacity of cement specimens, and the determination of the influence of alternative radiopacifiers on various cement properties. **Methodology:** Using relevant keywords, an extensive search was conducted of applicable databases, such as Google Scholar, Scopus, and Web of Science, to identify relevant articles. After that, inclusion and exclusion criteria were applied to make a final selection of the articles. Each article was critically reviewed from the perspectives of the methods used to prepare test specimens and the determination of radiopacity. **Findings:** The final selection comprised 35 articles that covered studies on 38 different alternative radiopacifiers. In the vast majority of the studies, the experimental bone cement formulation was one in which an alternative radiopacifier was blended with the powder and x-radiography was used to determine radiopacity. Examples of alternative radiopacifiers are nano-sized $BaSO_4$ particles and iodine-containing methacrylate. Using a subset of radiopacity results, an index of effectiveness of an alternative radiopacifier was determined

as the increase of R (determined relative to the radiopacity of a radiopaque control cement specimen) (IEAR). IEAR ranged from 3% to 187%, with a Weibull median of 18%. Twelve shortcomings of the literature and associated suggestions for future studies are presented. **Summary:** The literature on studies on alternative radiopacifiers for bone cement is uneven in that, for example, some aspects of the topic are well covered whereas many others have attracted scant research attention, if any. This observation led to suggestions of twelve areas for future study.

Keywords

Poly (Methyl Methacrylate) (PMMA) Bone Cement, Radiopacity, Arthroplasty, Vertebral Fracture Augmentation

1. Introduction

Poly (methyl methacrylate) bone cement (also referred to as acrylic bone cement or bone cement) comes in two variants: plain (no antibiotic loaded) and antibiotic-loaded. Arguably, bone cement is the most well-known material in orthopaedic and spinal surgery because it is used in a plethora of applications, which may be collected into six groups. First, to anchor a primary total arthroplasty (PTA) [1]-[3]; second, in local antibiotic delivery systems, such as in antibiotic-loaded cement used to prevent/manage periprosthetic joint infection (PJI) in revision total arthroplasty (RTA) [1] [4] [5] or prophylactic placement of antibiotic-loaded bone cement discs with tissue expander insertion during a mastectomy [6]; third, to reduce surgical site infections in spine surgery [7]; fourth, for augmentation of osteoporosis-induced vertebral compression fractures (AOVCFs), in particular, percutaneous vertebroplasty (PVP) and percutaneous balloon kyphoplasty (PBK) [8] [9]; fifth, for local delivery of chemotherapeutic drugs [10] [11] or antimicrobial agents to the site of an infection, as is the case in infected diabetic foot ulcers [12]; and sixth, for bone filling in weight-bearing regions of the body following resection of a tumor [13] or repair of the skull vault defect following a craniectomy or a traumatic head injury [14].

In current clinical practice, the predominant uses of bone cement are for fixation of PTA and RTA (especially, of the hip and the knee), PVP, and BKP. Thus, for example, in 2023, 62%, 78%, and 96% of total knee arthroplasties (TKAs) performed in Australia, United States, and Germany, respectively, were cemented [15], 85% and 96% of total hip arthroplasties (THAs) in Sweden and the Netherlands, respectively, were cemented [16] [17], and, based on 2018, 2019, and 2020 volumes [18]-[20] and a rate of increase of volume of 5.6% per year [19], an estimated 44,000 PVP and BKP procedures were performed in the United States in 2025.

Because of its record of widespread use, many aspects of bone cement, such as its composition, polymerization process, attractive features, shortcomings, and

complications, are well-known [1] [2] [21]-[23]. Details of some of these aspects are common to the use of the material in PTA, RTA, PVP, and PBK, while others are specific to each of these uses. The principal attractive features of bone cement are its easy preparation and high injectability. The former simply involves mixing the cement powder and liquid parts, in the ambient operating room environment, until a dough is attained, after which it is inserted *in vivo* [2]. Plain bone cement and antibiotic-loaded bone cement (ALBC) share a long catalog of shortcomings [1] [2] [21]-[42], six of which are highlighted here. First, the radiopacifier is a constituent of the powder and comprises micron-sized particles of either $BaSO_4$ ($mBaSO_4$) or ZrO_2 ($mZrO_2$). Each of these inorganic materials has been identified as acting as stress risers in the cured cement and, hence, has a deleterious effect on the mechanical properties (especially, fatigue life) of the cured cement. There are at least two additional concerns when $mBaSO_4$ is used. One, detached particles may release toxic Ba ions, thereby reducing the biocompatibility of the cement. Two, the $mBaSO_4$-PMMA matrix is weak, so poor mechanical properties of the cement are obtained. Second, the polymerization process is an exothermic reaction, with, in the case of some cement formulations/commercial brands, a maximum temperature that is high enough to be the cause of or be implicated in thermal necrosis of periprosthetic tissue. Third, leaching of residual monomer constituents, in particular, *N*,*N* di-methyl-*p*-toluidine (DMPT) (the activator or accelerator of the polymerization process), which, it has been postulated, is toxic, and, in some brands, the concentration is high enough to be the cause of or be implicated in chemical necrosis of the periprosthetic tissue. Fourth, it has been postulated that released micron-sized radiopacifier particles cause or are implicated in processes that culminate in bone resorption and, hence, aseptic loosening of the implant. Fifth, the modulus of elasticity of bone cement is so much higher than that of the contiguous cancellous (trabecular) bone (typically, 1500 - 3600 MPa versus 100 - 800 MPa) that there is potential for stress shielding. Additionally, its fracture resistance is low, and, hence, its proneness to fatigue is high. Sixth, the bone cement layer in a cemented total arthroplasty (CTA) lacks (or has limited) bioactivity.

Four shortcomings of ALBC brands approved by relevant regulatory agencies, such as the European Medicines Agency, for use in CTA, are often cited [3] [32] [40] [42]-[45]. First, elution of the loaded antibiotic (usually, gentamicin, vancomycin, clindamycin, or a combination of the second and the third) is characterized by an initial burst, followed by a steady-state zone, and, finally, exhaustion all within, typically, 6 - 10 hours of deployment in an *in vitro* test (simulated body fluid (SBF), held at 37˚C ± 1˚C). Second, the eluate demonstrates reduced efficacy against certain bacterial species that are widely considered to be the causes of or are implicated in PJI, such as *Staphylococcus aureus* and *Staphylococcus epidermidis*. When used in a CTA, two complications of an ALBC are noted. One is bone cement implantation syndrome, which is characterized by presentations that include hypotension and cardiac instability (or, even, arrest) during various stages

during CTA, particularly during cemented THA and TKA [28] [46]. Two, because the cement is not degradable *in vivo*, cement debris that accumulates on the periprosthetic tissue, over the *in vivo* life of the arthroplasty, may cause chronic inflammation or cause or be implicated in prosthesis loosening and, eventually, osteolysis. When bone cement is used in PVP and BKP, two issues are highlighted. One is its high modulus, which may lead or contribute to the fracture of vertebra(e) adjacent to the treated one(s). The other is the possibility of cement leakage into paraveteral tissues (in particular, the lungs), which, in some cases, is fatal [47] [48]. A common complication with the cement is its involvement in the fracture of vertebral body/bodies adjacent to the treated one(s) [49]-[51].

Although there are many reviews of the literature on studies that address the stated shortcomings, concerns, and complications of plain and antibiotic-loaded bone cement in their use in CTA and plain bone cement in its use in AOVCFs [21]-[43] [52], only a few include coverage of studies on alternative radiopacifiers [21]-[24] [28] [35] [37] [38] [40] [52]. Among these studies, there are four issues. First, the coverage is either short [21]-[23] [28] [35] or moderate [24] [37] [38]. Second, in the case of one review [40], alternative radiopacifiers were mentioned in the context of the use of bone cement in drug delivery, not arthroplasty or vertebral augmentation. Third, the review was not on bone cement specifically, but rather, on polymeric biomaterials that are used in many other implant applications apart from CTA and AOVCF, examples being coronary artery stents and internal bone fracture fixation systems, and the coverage on enhancement of radiopacity was short [37] [52]. Fourth, each of the reviews that contained a section on enhancement of radiopacity [21]-[23] did not include a critical appraisal of the cited studies.

The purpose of the present work was to give a detailed review in which the exclusive focus is on studies of alternative radiopacifiers for bone cement for use in CTAs and AOVCFs. The review is organized in seven sections. The period of the search for relevant articles and the strategy used to conduct the search (that is, the criteria used to include or exclude items) are described in the second section. In the third section, the rationale given in the cited studies for the selection of the various alternative radiopacifiers is discussed. Salient aspects of the methods used to determine radiopacity are presented in the fourth section. The focus of the fifth section is the introduction of the concept of an index of effectiveness of an alternative radiopacifier (IEAR), calculation of IEAR using radiopacity results given in the various literature studies, and a discussion of the trends in IEAR. The sixth section is devoted to highlighting shortcomings of the literature and, hence, suggestions for future studies. A summary of the key points made in the review is presented in the seventh section.

2. Search Strategy

The first step involved searching several relevant databases, such as Google Scholar, PubMed, Scopus, and Web of Science, for items published between Jan-

uary 1996 and June 2026 in which one or more of the search terms appeared. Those terms were "PMMA bone cement", "radiopacity", and "alternative radiopacifier." In the second step, inclusion and exclusion criteria were applied to all the items obtained in the first step. Inclusion criteria were that the item is a peer-reviewed article and is written in English. Exclusion criteria were that the item was an abstract or a conference presentation. The third step involved manually reviewing the reference lists of each of the articles that met the inclusion criteria for additional articles. In the fourth step, the stated inclusion and exclusion criteria were applied to the additional articles. Through this four-step process, 35 articles were finally selected. Thus, the present review is of these articles.

3. Gold Standard Radiopacifier and Alternative Radiopacifiers

In an approved cement brand (which, herein, is defined as a patented commercial-prepared formulation that is approved by a relevant regulatory agency, such as the US Food and Drug Administration and the European Medicines Agency, for use in a specified clinical procedure, such as cemented primary arthroplasty, cemented revision arthroplasty, PVP, and PBK), the radiopacifier comprises either $mBaSO_4$ or $mZrO_2$ particles added to the cement powder. Herein, these particles are referred to as the gold standard radiopacifiers. Examples of these brands with the accompanying gold standard radiopacifier and its loading are given in Table 1. In experimental bone cement formulations, an alternative radiopacifier (that is, one that is not $mBaSO_4$ or $mZrO_2$) is used.

Table 1. Gold standard radiopacifier ($mBaSO_4$ or $mZrO_2$ particles) and loading in a sample of plain and antibiotic-loaded bone cement brands for use in cemented primary and revision arthroplasties.

Brand	Cement type[a]	$mBaSO_4$[a] loading (wt./wt.% of cement powder)	$mZrO_2$[a] loading (wt./wt.% of cement powder)
Biomet® Bone Cement[b]	Plain		10.0
Cemex® RX[c]	Plain	9.0	
Palacos®R[d]	Plain		15.3
Simplex®P[e]	Plain	10.0	
Copal®G + C[d]	ALBC		10.0
Palacos®R + G[d]	ALBC		15.0
Simplex™P with Tobramycin[e]	ALBC		10.0
SmartSet®GMV[f]	ALBC		10.0

[a]ALBC: antibiotic-loaded bone cement; $mBaSO_4$: micron-sized barium sulfate particles; $mZrO_2$: micron-sized zirconium dioxide particles. [b]Manufacturer/distributor: Biomet Orthopaedics Switzerland GmbH, Ried b. Kerzers, Switzerland/Zimmer Biomet, Warsaw, IN, USA. [c]Manufacturer: Tecres SpA., Sommacampagna, Verona, Italy. [d]Manufacturer: Heraeus Medical GmbH, Wehrheim, Germany. [e]Manufacturer: Stryker Howmedica Osteonics, Mahwah, NJ, USA. [f]Manufacturer/distributor: DePuy International Ltd., Blackpool, UK/DePuy Synthes.

Various alternative radiopacifiers were the subject of the studies selected for review [53]-[87]. In the preponderance of these studies, the radiopacifier was

blended with the powder of the cement formulation, examples being 2,5 diiodo-8-8-hydroquinone, iodixanol (an iodine-containing agent), micron-sized $SrTiO_3$, graphene oxide-embedded baghdadite particles, and BiInSn powder (Table 2). In six studies, the radiopacifier was blended with the liquid of the control formulation, these being triphenyl bismuth, 2[2',3',5'-triiodobenzoyl] ethyl methacrylate (TIBMA), 3,5-diiodine salicyclic methacrylate (DISMA), and nanoTiO_2 particles (Table 2). In many of the literature reports, the rationale for the choice of the alternative radiopacifier used in the study is given. A summary of this information is presented in Table 3.

Table 2. Alternative radiopacifiers used in experimental bone cement formulations in literature studies.

Alternative radiopacifier	Added to cement powder	Added to cement liquid	Source (Reference number for literature study shown [ ])
2,5-diiodo-8-hydroquinoline (IHQ)	+		[53]
2,5-diiodo-8-quinolyl methacrylate (IHQM)		+	[53] [56]
Triphenyl bismuth (TPB)	+	+	[55]
Iodixanol (IDX)	+		[54] [59] [60] [63]
Iohexol (IHX)	+		[54] [59] [63]
2[2',3',5'-triiodobenzoyl] ethyl methacrylate (TIBMA)		+	[57]
3,5-diiodine salicyclic methacrylate (DISMA)		+	[57]
Micron-sized $BaTiO_3$	+		[58]
Micron-sized $SrTiO_3$	+		[58]
2-[4-iodobenzoyl]-oxo-ethyl methacrylate (4-IEMA)	+		[61]
A covalently-bound iodine-containing copolymer	+		[62]
Tantalum	+		[64]
Iodine-containing methacrylic copolymer	+		[65]
Nano-sized $BaSO_4$	+		[66] [67]
Micron-sized MgO	+		[66]
Nano-sized MgO	+		[67]
Nano-sized ZrO_2 particles	+		[68] [81]
Acrylic-coated ZrO_2 fibers	+		[69]
Covalently-bound iodine-containing copolymer	+		[70]
Nano-sized TiO_2 particles		+	[71] [72]
Microspheres having composition of 32.5 molar ratio of methyl methacrylate (MMA), 13.9 molar ratio of 4-IEMA, and 1.0 molar ratio of tetraethylene glycol dimethacrylate (TEGDMA)	+		[73]
Gold particles embedded in PMMA microspheres	+		[74]
Hydroxyapatite (HA) microspheres	+		[75]
Poly[(methyl methacrylate-co-(N-4-iodophenyl) acrylamide)]	+		[76]
Poly[(methyl methacrylate-co-(N-3,4,5-triiodophenyl) acrylamide)]	+		[76]

Continued

Silane-treated anatase TiO_2	+	[77]
Yttria-stabilized ZrO_2	+	[77]
Hydroxyapatite (HA) powder	+	[78]
Diatrizoate sodium	+	[79]
Tungsten carbide	+	[80]
$Ca_3ZrSi_2O_9$ (baghdadite)	+	[82]
Graphene oxide-encapsulated baghdadite	+	[82]
Tantalum carbide	+	[83]
Poly (dimethyl siloxane) (PDMS)	+	[84]
Calcium tungstate	+	[85]
Bismuth oxychloride	+	[85]
BiInSn powder	+	[86]
Bismuth chalcogenides Bi_2X_3 (X= 0, S, Se)	+	[87]

Table 3. Stated rationale for selection of alternative radiopacifiers.

Alternative radiopacifier	Stated rationale	Source (Reference number for literature study shown [ ])
2,5-diiodo-8-quinolyl methacrylate (IHQM)	Iodine-containing methacrylate	[53] [56]
2[2',3',5'-triiodobenzoyly] ethyl methacrylate (TIBMA)	Iodine-containing methacrylate	[57]
3,5-diiodine salicylic methacrylate (DISMA)	Iodine-containing methacrylate	[57]
Iodixanol (IDX)	Iodine-based contrast agent	[63]
Iohexol (IHX)	Iodine-based contrast agent	[63]
2-[4'-iodobenzoyl]-oxo-ethyl methacrylate (4-IEMA)	Iodine-containing methacrylate	[61]
Nanoparticles of $BaSO_4$	High surface area	[66] [67]
Nanoparticles of ZrO_2	High surface area	[66]
Nanoparticles of MgO	High surface area	[67]
Microspheres having composition of 32.5 molar ratio of methyl methacrylate (MMA),13.9 molar ratio of 4-IEMA, and 1.0 molar ratio of tetraethylene glycol dimethacrylate (TEGDMA)	Iodine-containing agent	[73]
Microspheres having composition of 32.5 molar ratio of MMA, 13.9 molar ratio of 4-IEMA, 1.0 molar ratio of TEGDMA, and 0.7 molar ratio of $I_4C_2B_{10}H_8$	Iodine-containing agent	[73]
TiO_2	In the clinic, x-radiography is, typically, performed using x-ray tube voltage of 70 kV. At this level, it is expected that the intensity of the transmitted x-rays through specimens of cement that contain this radiopacifier would be large	[77]

Continued

Yttria-stabilized $BaSO_4$	Silane treatment leads to enhanced dispersion of a radiopacifier	[77]
Diatrizoate sodium	It is an ionic iodine-containing agent	[79]
Nanoparticles of TiC	• High atomic number • Low solubility • Not toxic	[80]
$SrTiO_3$	Mass absorption (K_{a1}) is comparable to that of $mBaSO_4$	[58]
Micron-sized $BaTiO_3$	Mass absorption (K_{a1}) is comparable to that of $mBaSO_4$	[58]
Nanoparticles of ZrO_2	Zr has larger atomic number than each of the constituents of PMMA (C, H, O)	[81]
Nanoparticles of $Ca_3ZrSi_2O_9$ (baghdadite)	Contains large amount of Zr in the form of $ZrO(NO_3)_2{\cdot}6H_2O$	[82]
Nanoparticles of graphene oxide-encapsulated baghadite	Contains large amount of Zr in the form of $ZrO(NO_3)_2{\cdot}6H_2O$	[82]
Calcium tungstate	Not stated explicitly	[85]
Bismuth oxychloride	Not stated explicitly	[85]
BInSn powder	"Good radiographic visibility"	[86]
Bismuth chalcogenides Bi_2X_3 (X = O, S, Se)	• High atomic number (83), which results in high photoelectric absorption of x-rays • K-edge of 90.5 keV (= 5.74 $cm^2\ g^{-1}$, at 100 keV)	[87]

4. Methods of Determination of Radiopacity

4.1. Overview

The methods of determination described in the reviewed studies [53]-[87] may be grouped into two categories, namely, qualitative and quantitative. There is one similarity and one difference between these categories. The similarity is that in each category, an instrument was used in the determination of radiopacity. The difference is summarized thus. In the qualitative category, the results were presented as images (for example, x-ray images) and a method whereby those images are translated to a numerical measure of radiopacity (herein, designated, a conversion method) is lacking. In contrast, in the quantitative category, various conversion methods were used.

4.2. Qualitative Method

This method was used in 11 studies [1] [53]-[55] [57] [59] [61] [73] [75] [84] [86].

In the first study [53], a control cement that contained 10 wt./wt.% $BaSO_4$ particles and an experimental cement (5 vol./vol.% of an iodine-containing methacrylate (2,5-diiodo-8-quinolyl methacrylate (IHQM)) was dissolved in the cement liquid) were used. Tensile test specimens were exposed to x-rays (55 kV; 4 mA; 0.2 s) and radiopacity was described based on visual observation of the radio-

graphs even though a standard stained steel wedge (1 - 5 cm in height), rather than an Al wedge, was used in the test. Radiographs of experimental cement specimens were shown but those of control cement specimens were not.

The second study [1], involved fabricating rectangular test specimens (15.0 mm × 10.0 mm × 3.2 mm), gluing the specimens to a sheet of paper, and, then, taking x-rays of the glued assembly. Radiopacity was described in terms of the appearance of each of the specimens compared to that of the background material (darker (low radiopacity) versus lighter (high radiopacity)). The settings of the x-ray machine were 40 kV and 2 mAs. It was found that $mZrO_2$ provided greater radiopacity than $mBaSO_4$ (Table 4 and Table 5).

Table 4. Qualitative radiopacity results for specimens of various micron-sized $BaSO_4$ particles-loaded bone cement brands (Taken from results given in the study by Kuhn [1]).

Cement brand	Radiopacifier loading (wt./wt.%)	Appearance of image on x-radiograph
CMW®2000 Gentamicin	8.0	Dark
Cemex®LV	9.0	Dark
CMW®1 Radiopaque	9.1	Dark
CMW®1 Gentamicin	9.1	Dark
Durus®H	9.1	Dark
AKZ (Antibiotic Simplex®)	10.0	Dark
C-Ment®1	10.0	Dark
Genta C-Ment®1	10.0	Dark
C-Ment®3	10.0	Dark
Genta C-Ment®3	10.0	Dark
CMW®3	10.0	Dark
CMW®3G	10.0	Dark
Osteobond®	10.0	Dark
Simplex®P	10.0	Dark
Subiton®G	10.0	Dark
Subiton®RO	10.0	Dark
Zimmer ®Dough-Type Radiopaque	10.0	Dark
CMW®2	11.3	Dark
CMW®2G	11.3	Dark
Cemex®HV	13.0	Dark

Table 5. Qualitative radiopacity results for specimens of various micron-sized ZrO_2 particles-loaded bone cement brands (Taken from results given in the study by Kuhn [1]).

Cement brand	Radiopacifier loading (wt./wt.%)	Appearance of image on x-radiograph
Cerafix®LV	9.2	Light
Cerafixgenta	9.2	Light

Continued

Allofix®-G	9.5	Light
Duracem®3	9.8	Light
Copal®	10.0	Light
Osteopal®HA	10.0	Light
Palavit®HV	10.2	Light
Palamed®	12.0	Light
Palamed®G	12.0	Light
Osteopal®G	15.0	Light
Osteopal®VS	15.0	Light
Palacos®	15.0	Light
Palacos®E-Flow	15.0	Light
Palacos®E-Flow with Gentamicin	15.0	Light
Palacos®LV	15.0	Light
Palacos®R with Gentamicin	15.0	Light
Palacos®R with Gentamicin	15.0	Light

In the third study [54], x-rays (70 kV; 80 mAs; focal distance = 1 m; 113 ms) were taken of fractured tensile test specimens, while they were under 0.1 m of water. The cements used were Palacos®R and Simplex®P (control cements) and two experimental cements, with the radiopacifiers being 8% wt./wt. iodixanol (IDX) and 6, 8, or 16 wt./wt.% of iohexol (IHX). The control bone cement specimens showed higher radiopacity than each of the experimental bone cement specimens.

In the fourth study [55], x-rays (70 kV; 7 mA; focal distance = 0.35 mm) were taken of 1 mm- and 2.5 mm-thick specimens of control cement (CMW®1 RO; contained 12.5 wt./wt.% $BaSO_4$ particles) and those fabricated using experimental cements in which an alternative radiopacifier (triphenyl bismuth (TPB) was either mixed with the powder of the cement) or dissolved in the liquid of the cement. TPB loadings used were 10, 15, and 25 wt./wt.%. The results showed that the three sets of specimens had comparable radiopacities.

The cements used in the fifth study [57] were one that contained 10 wt./wt.% $BaSO_4$ (control cement) and two experimental cements (5 vol./vol.% of an iodine-containing monomer, 2-[2',3',5'-triiodobenzoyl] ethyl methacrylate (TIBMA) was substituted for MMA and 5 vol./vol.% of another iodine-containing monomer, 3,5-diiodine salicylic methacrylate (DISMA) was substituted for MMA). In the test, 1 mm-thick specimens were exposed to x-rays (55 kV; 2.5 mAs). It appeared that the radiopacities of each of the experimental cement specimens were lower than those of the control cement specimens.

The sixth study involved a comparison between specimens of Palacos®R (the control cement), an IDX-containing cement, and an IHX-containing cement [59].

The specimens (5 mm wide x 1 mm thick) were examined using micro computed tomography (mCT), with scanning carried out at 70 kV. The radiopacities of the IDX-containing cement specimens and the Palacos®R specimens appear to be comparable.

In the seventh study [61], the cements used were C-ment3 (radiopacifier: 11.4 wt./wt. $BaSO_4$) (B-cement) and one in which an alternative radiopacifier (a copolymer of methylmethacrylate and 2-[4-iodobenzoyl]-oxo-ethylmethacrylate (4-IEMA)) was added to the powder of the cement (I-cement). Tension-tension fatigue test specimens were exposed to x-rays (77 kV; 1 mAs). The radiopacities of the two sets of specimens were comparable.

In the eighth study [73], the control cement was a commercially prepared one (Vertaplex™; radiopacifier: 30 wt./wt.% $mBaSO_4$). Two alternative radiopacifiers in the form of microspheres were synthesized on the basis of 3 methacrylic monomers. Then, iodine was included in one of two ways in these microspheres; namely, covalently linked to the methacrylic polymer (I microspheres) and as a constituent of a stable cluster $C_2B_{10}H_8$ (IC microspheres). The microspheres were mixed with the powder of a control cement to obtain two experimental formulations, namely, I cement and IC cement, respectively. Cylindrical specimens (diameter = height = 8 mm) were exposed to x-rays (46 kV; 1.04 mAs). It appears that the radiopacities of the specimens were in the order of control cement > IC cement > I cement.

The focus of the ninth study was the influence of the form of HA on radiopacity [75]. Two forms of HA were considered, namely microspheres and powder. HA microspheres were synthesized using a spray drying method, with the final sizes being in the 100 - 500 mm range. Five study groups were used, with the radiopacifier being $mBaSO_4$ (control group), HA microspheres (5, 20, and 40 vol./vol %), and 20 vol./vol.% HA powder. Radiopacity results were presented in a qualitative manner as mCT images. It was reported that the intensity signals from the control cement specimen were low and for the specimens of cements that contained HA microspheres, the intensity of signals from the specimens was high and it increased with an increase in HA microsphere content.

In the tenth study [84], the cements used were CMW®3 (control cement) and an experimental cement in which the radiopacifier was 10 wt./wt.% poly(dimethylsiloxane) (PDMS). In the test, the specimens (cylinder, with height and diameter of 12 mm and 6 mm, respectively) were examined using x-rays (44 kV; 1.29 mA). It appeared that the radiopacities of the two groups of specimens were about the same.

In the eleventh study [86], the bone cements used were Mendec®3 (which contains 30 wt./wt.% $BaSO_4$; control cement) and experimental bone cement formulations in which the radiopacifier was 10, 20, or 30 wt./wt.% $Bi_{32.5}In_{51.0}Sn_{16.5}$ powder. The study involved implanting a cement dough in the marrow cavity of fresh pig femurs and then examining them using CT. It appeared that the radiopacities of the experimental bone cement specimens were better than those of the control

cement specimens, with the radiopacity of the experimental cement specimens increasing with increase in radiopacifier loading.

4.3. Quantitative Methods

4.3.1. X-Radiography and Equivalent Aluminum Thickness Method

This method was used in 6 studies [58] [71] [72] [76] [83] [87].

In the study by Carrodeguas *et al.* [58], cement discs (diameter and thickness = 15 mm and 1.0 ± 0.1 mm, respectively) were glued on a piece of paper next to an Al wedge (0.5 mm steps) (in accordance with ISO 4049), the sheet was placed on an x-ray film that was between x-ray screens positioned 1 m below the exit window of the x-ray equipment. After that, the film was irradiated (40 kV, 0.8 mAs) for 2 ms and then developed. The absorbance of the developed film at the positions at which the discs and Al step were positioned (A) was determined using a combination of equipment (cold light source with a green filter, an optical conductor, a light detector, and a radiometer). The best-fit curve to the A versus Al wedge thickness results was obtained and the equivalent Al thickness of the cement disc was determined from this best-fit curve. Radiopacity of a cement disc (R) (in equivalent thickness of Al) was determined using Equation (1):

$$R = (\text{Equivalent thickness of Al})/(\text{Thickness of cement disc}) \quad (1)$$

This method was used to determine comparative radiopacities of specimens fabricated with two potential alternative radiopacifiers; namely, barium titanate ($BaTiO_3$) and strontium titanate ($SrTiO_3$). Two trends in the results are noted. First, at any radiopacifier loading (10 - 50 wt./wt.%), the radiopacity of a specimen fabricated using cement that contained an alternative radiopacifier was greater than that of the radiolucent control cement specimens. Second, for each of the cements when radiopacifier loading was ≥ 20 wt./wt.%, radiopacity of a specimen exceeded the minimum recommended for bone cements for use in arthroplasties.

This method was used in studies in which the alternative radiopacifiers were TiO_2 nanotubes [71], strontium-modified titania nanotubes (*n*-SrO-TiO_2 nanotubes) [71], *n* TiO_2 fibers functionalized using 2-propanol and methacrylic acid [72], and those synthesized using iodine-containing PMMA and graphene oxide nanoplatelets (< 32 layers; thickness = 2 - 18 nm) [76].

In the first-mentioned study [71], the mean radiopacities of specimens from each of the experimental cements were less than that from control cement specimens (0.17, 0.30, and 0.34 mm Al for the 2 wt./wt.% *n*-TiO_2 nanotube-containing cement specimens, 2 wt./wt.% *n*-SrO-TiO_2-containing cement specimens, and CMW®1 (control cement)) specimens, respectively.

In the second-mentioned study [72], provided the radiopacifier loading in an experimental cement was no more than 1.5 wt./wt.%, the radiopacities of experimental cement specimens were marginally greater than that of control cement specimens. In the third-mentioned study [76], the alternative radiopacifiers

were prepared using iodine-containing poly(methyl methacrylate-co-acrylamide) (P(MMA-co-AA)) and graphene oxide (GO (loading (X) = 1, 2, 5, and 10 wt./wt.%). P(MMA-co-AA) was synthesized via co-polymerization of methyl methacrylate and acrylic acid (AA) and modified with 4-iodophenyl isocyanate, and 3,4,5-triiodophenyl isocyanate, to form poly[(methyl methacrylate-co-(N-4-iodophenyl)acrylamide)]) (1I-P(MMA-co-AA) and poly[(methyl methacrylate-co-(N-3,4,5-triiodophenyl)acrylamide)]) (3I-P(MMA-co-AA), respectively. A non-iodinated copolymer was also prepared (PIC-P(PMMA-co-AA)). In the study, a control cement was not used. Thus, the three cement formulations are designated 1I-GO-X, 3I-GO-X, and PIC-GO-X, respectively. Even though a quantitative radiopacity determination method was used, the results were given in qualitative terms (radiographic images), which appeared to show that the radiopacities of specimens were in the order 3I-GO-5 better than 1I-GO-5 better than PIC-GO-5 [76].

This method was used to evaluate TaC nanotubes (size = 50 nm, 100 nm, 500 nm, 800 nm, and 10 mm) as alternative radiopacifiers [83]. For each experimental formulation, the nanotube loadings used were 2.5, 5.0, 7.5, 10, 20, and 30 wt./wt.%. The tests were conducted using four x-ray tube voltages (V) (75, 101, 120, and 140 kV). In a test, cement specimens were irradiated in a digital radiography (DR) mode. The grey-scale intensity from the image of the specimen was converted to Al-equivalent thickness using an 11-step Al calibration wedge (step height = 3 mm). Two trends in the results are noted. First, for a given combination of experimental formulation (that is, TaC particle size) and V, specimen radiopacity increased monotonically with an increase in radiopacifier loading. Second, regardless of V, the radiopacity of a specimen fabricated using an experimental formulation that contained 30 wt./wt.% of TaC particles of any size was greater than that of a control cement specimen (the cement contained 30 wt./wt. m$BaSO_4$ particles).

This method was used in the evaluation of nanoparticles of bismuth chalcogenides (Bi_2X_3, X = 0, S, Se) as alternative radiopacifiers for bone cement to be used in VP [87]. For each experimental formulation, loadings used were 2.5, 5.0, 7.5, 10, 20, and 30 wt./wt.%. The tests were conducted using four x-ray tube voltages (V) (80.9, 101.9, 120.9, and 140.9 kV). In a test, the cement specimens (discs, with a diameter and thickness = 10 mm and 3 mm, respectively) were placed on an x-ray imaging plate and irradiated in DR mode. The grey-scale intensity from the image of the specimen was converted to Al-equivalent thickness using an 11-step Al calibration wedge (step height = 3 mm). Two key trends in the results (**Table 6**) are noted. First, for a given combination of experimental formulation and V, specimen radiopacity increases monotonically with an increase in radiopacifier loading. Second, at any V, the radiopacity of a specimen of an experimental cement formulation that contains 30 wt./wt.% of either Bi_2S_3 or Bi_2Se_3 is about the same as that of a specimen of the control cement (experimental formulation that contained 30 wt./wt.% m$BaSO_4$ particles).

Table 6. Radiopacities of specimens (expressed in equivalent Al thickness (in mm)) of radiopaque control bone cement and experimental bone cements loaded with particles of various alternative radiopacifiers (Results taken from results given in the study by Xu *et al.* [87]).

Radiopacifier loading (wt./wt.%)	Radiopacifier: Bi_2S_3	Radiopacifier: Bi_2O_3	Radiopacifier: Bi_2Se_3
2.5[a]	3.0	3.0	2.5
5.0[a]	3.3	4.0	3.5
7.5[a]	4.7	4.5	4.5
10.0[a]	6.3	5.7	4.7
20.0[a]	13.5	5.8	6.2
30.0[a]	14.2	13.0	14.2
2.5[b]	3.0	3.0	2.5
5.0[b]	4.2	4.2	3.8
7.5[b]	5.0	4.6	5.0
10.0[b]	7.0	5.0	5.0
20.0[b]	12.8	6.0	7.0
30.0[b]	13.8	12.0	13.0
2.5[c]	3.7	3.5	2.5
5.0[c]	3.9	4.5	3.8
7.5[c]	5.7	5.0	5.0
10.0[c]	7.5	5.8	5.0
20.0[c]	13.0	6.5	7.8
30.0[c]	14.5	13.0	14.0
2.5[d]	3.7	4.0	3.0
5.0[d]	3.9	4.8	3.8
7.5[d]	5.7	5.0	5.0
10.0[d]	7.5	4.8	4.8
20.0[d]	13.0	4.9	7.5
30.0[d]	14.5	15.0	14.5

[a]For this sub-set of tests, radiopacity was determined using x-ray tube voltage of 80.9 kV. For specimens of the radiopaque control cement (radiopacifier: 30 wt./wt.% $mBaSO_4$ particles), radiopacity (in equivalent Al thickness, in mm) = 14.0. [b]For this sub-set of tests, radiopacity was determined using x-ray tube voltage of 101.9 kV. For specimens of the radiopaque control cement (radiopacifier: 30 wt./wt.% $mBaSO_4$ particles), radiopacity (in equivalent Al thickness, in mm) = 14.0. [c]For this sub-set of tests, radiopacity was determined using x-ray tube voltage of 121.9 kV. For specimens of the radiopaque control cement (radiopacifier: 30 wt./wt.% $mBaSO_4$ particles), radiopacity (in equivalent Al thickness, in mm) = 14.0. [d]For this sub-set of tests, radiopacity was determined using x-ray tube voltage of 140.9 kV. For specimens of the radiopaque control cement (radiopacifier: 30 wt./wt.% $mBaSO_4$ particles), radiopacity (in equivalent Al thickness, in mm) = 14.0.

4.3.2. X-Radiography and Other Calculation Methods

This method was used in 11 studies [59] [64] [65] [67] [68] [77]-[82].

In the study, digital x-radiography [59] was used and the focus was on bone

cements that contained a gold standard radiopacifier (5 or 10 wt./wt.% $BaSO_4$ particles and 5, 10, or 15 wt./wt.% ZrO_2) and an alternative radiopacifier, namely, 5 - 15 wt./wt.% iodixanol (IDX) (an iodine-containing material). Tensile test specimens were used. X-irradiation parameters were x-ray tube voltage (V) = 40 - 80 kV, 63 mAs, and focal distance of 1.1 m. Two series of tests were conducted, one with the test specimens in air and another with the specimens immersed under 100 mm of water contained in a thin-walled polypropylene (PP) box. Grey-scales of the images of a specimen and the immediately adjacent background were obtained by averaging over an area of 5 pixels x 5 pixels and these data were then used to calculate the contrast of the specimen (a measure of its radiopacity). Three trends in the results are noted. First, for a given cement, contrast determined in air decreased monotonically with an increase in V, although there was a marked difference in the rate of drop. Second, for a given combination of bone cement and V, the contrast of a specimen obtained under water was markedly lower than that obtained in air. Third, when clinically relevant conditions were used (V = 80 kV; 63 mAs; specimen under water), the contrast of the IDX-containing cement specimens, as a group, was about the same as that of control cement specimens.

In the study by Persson *et al.* [64], Ta was the alternative radiopacifier and a digital densitometer was used to obtain the optical density (a measure of radiopacity) of a specimen. The tests were conducted in air as well as with the specimen immersed under 150 mm of water. Two key trends in the results are noted. First, the radiopacity of a specimen fabricated using a 10 wt./wt.% Ta-containing cement was less than that of its 10 wt./wt.% $mBaSO_4$-containing counterpart. Second, the radiopacities of both the 20 wt./wt.% Ta-containing and 40 wt./wt.% Ta-containing cement specimens were each greater than that of 10 wt./wt.% $mBaSO_4$-containing cement specimens (this formulation is used in approved $mBaSO_4$-conatining cements).

In the study by Boelen *et al.* [65], the cements were an experimental $mBaSO_4$-containing one (BA cement) and an iodine compound-containing one (IO cement). Specimens (discs, with a diameter and thickness = 12 and 3 mm), respectively) were irradiated (46 kV, 1.04 mAs), after which a software package was used to determine the brightness of the specimen in the x-ray image, averaged over a region of interest (5 pixels x 5 pixels) (expressed as %). Radiopacity of a disc was determined as the ratio of (100-brightness) of the disc to (100-brightness) of an Al wedge (3 mm thick). It was found that the radiopacities of BA and IO cement specimens were found to be 132.9% ± 3.6% and 108.2% ± 8.3%, respectively.

In the study by Ricker *et al.* [67], the radiopacifiers used were $mBaSO_4$, $nBaSO_4$, mMgO, and nMgO, each with a loading of 10 wt./wt.%. X-ray images of the bone cement specimens were taken in air using an x-ray machine equipped with a digital detector (x-ray operating conditions: 40 kV and 63 mA), after which the pixel intensities of the images were determined using a commercially-available software

package. Two trends in the results (Table 7) are noted. First, using MgO particles of any size as the alternative radiopacifier did not increase the radiopacity of the control cement specimens (cement contained 10 wt./wt. $mBaSO_4$ particles). Second, radiopacity of cement specimens in which the cement contained 10 wt./wt.% $nBaS0_4$ particles were markedly higher than that of the control cement specimens (increase of ~184%).

Table 7. Radiopacities of specimens of radiopaque control bone cement and experimental $BaSO_4$- and MgO-containing bone cements (Taken from results in the study by Ricker *et al.* [67]).

Radiopacifier[a] and loading	Radiopacity (x-ray intensity, in %)
10 wt./wt.% $mBaSO_4$ (Radiopaque control cement)	12.5
10 wt./wt.% $nBaSO_4$	35.9
10 wt./wt.% mMgO	0.4
10 wt./wt. nMgO	0.5

[a]m and n: Denote micron- and nano-sized particles, respectively.

This method was used in the study by Gillani *et al.* [68] to compare radiopacities of specimens in which 3 alternative radiopacifiers were used (namely, $nanoBaSO_4$ functionalized using 3-(trimethoxysilyl) propyl methacrylate (TMS), unfuctionalized $nanoZrO_2$, and $nanoZrO_2$ functionalized using TMS) versus the case where the radiopacifier comprised mBaSO4 particles (control cement). X-rays were obtained of tensile test and compression test specimens after which the resulting images were scanned to obtain mean grey values as measures of optical density (OD). Two findings (Table 8) are noted. First, the radiopacity of specimens made using any of the three alternative radiopacifiers was greater than that of control cement specimens. Second, the greatest increase (~40%) was obtained when the cement used contained unfunctionalized $nZrO_2$.

Table 8. Radiopacities of specimens of radiopaque control bone cement and experimental $BaSO_4$- and ZrO_2-containing bone cements (Taken from results given in the study by Gillani *et al.* [68]).

Radiopacifier[a] and loading	Radiopacity (normalized mean grey value)
33 wt./wt.% $mBaSO_4$ (radiopaque control cement)	54.63
33 wt./wt.% functionalized $nBaSO_4$	63.44
33 wt./wt.% unfunctionalized $nZrO_2$	76.30
33 wt./wt. functionalized $nZrO_2$	72.66

[a]m and n: Denote micron- and nano-sized particles, respectively.

This method was used in the study by Ayre *et al.* [77] to compare radiopacities of specimens fabricated using two alternative radiopacifiers (anatase TiO_2 and yttria-stabilized ZrO_2 powder) and two commercially-available cement brands (Cemex®Isoplastic and Palacos®R) (control cements). For each test, x-radiographic images were obtained from the test specimens (10 mm × 10 mm × 2 mm) using an accelerating voltage of 35 kVp and current of 150 mA. It was

pointed out the dimensions of the test specimen were selected to be about the same as those for the minimum cement mantle thickness in CTA cases. OD of a test specimen was expressed as the average brightness of the pixels in the x-ray image. Radiopacity was calculated as mean grey value ranging from 0 (the image is completely black; all of the incident x-rays incident on the specimen are transmitted through it) to 255 (the image is completely white; the specimen absorbs all of the incident x-rays). Two key trends in the results are noted. First, for either anatase TiO_2 or yttria-stabilized ZrO_2 powder, specimen radiopacity increased monotonically with an increase in radiopacifier loading. Second, radiopacities of specimens fabricated using an experimental cement formulation (cement loading of at least 20 wt./wt.%) were each comparable to that of either of the two control cement specimens.

In the study by Montano *et al.* [78], the measure of radiopacity used was designated the contrast full-width-at-half-maximum (CFWHM). The first step that was used applying the method to determine CFWHM was to scan the x-ray film in order to obtain the contrast at different points (regions of interest (ROIs)) on the film. After that, an array set was generated by the mean Fast Fourier Transform for each ROI. The next steps comprised obtaining a three-dimensional (3D) surface plot for an array set, obtaining a 3D Gaussian fit to this plot, and, finally, calculating CFWHM by considering all the statistical parameters of the fit. In the study, cement dough was delivered into a vertebral column of a porcine model and, then, the model was irradiated (60 kV, 70 mA, 0.5 s, focal distance = 0.85 m). CFWHMs obtained for specimens of control cement (radiopacifier: 10 wt./wt.% $BaSO_4$ particles) and an experimental cement (radiopacifier: 50 wt./wt.% HA powder) were comparable, being 2.14 and 2.19, respectively.

The Red-Green-and-Blue (RGB) method was used in the study by Han *et al.* [79] with the alternative radiopacifier being DTA. This involved irradiating control cement specimens and experimental cement formulation specimens (each specimen one being a disc, diameter and thickness = 12 mm and 5 mm, respectively) and a 10-step Al wedge (step height = 2 mm), with the specimens being either in air or under 100 mm of water contained in a thin-walled PP box. Typical x-irradiation conditions were comparable to those used in the clinic (78.9 kV; 785 mA) and the radiographs were obtained at a focal distance of 1.1 m. From the radiographs, RGB values for the control cement specimens, the experimental cement formulation specimens, and the Al wedge were obtained. This procedure was repeated with 9 other Al wedges (thickness varied from 4 mm to 20 mm, in steps of 2 mm). From the collection of results, the best-fit equation between RGB value and Al wedge thickness was obtained (Equation (2)).

$$\text{RGB of Al wedge} = A + B\,(\text{thickness of Al wedge}), \tag{2}$$

where A and B are constants.

This allowed the radiopacity of a cement specimen to be expressed in equivalent Al thickness, in mm.

Alternatively, the relative radiopacity (or contrast) (RR) of a cement specimen

was calculated using Equation (3)

$$RR = (R1 - R2)/(R1), \quad (3)$$

where R1 and R2 are the RGB values for the specimen and for the black area that surrounded the specimen, respectively.

On each cement specimen, RGB values at 5 locations on it were obtained, thus allowing determination of the mean and standard deviation values of RR for that specimen.

Using Equation (3) and cements intended for use in PVP, RR values for specimens of an experimental formulation that contained 10, 15, or 20 wt./wt.% of DTA (an iodine-based radiopacifier) were compared to those of specimens of a control cement (radiopacifying provided by 30 wt./wt.% $mBaSO_4$ particles). Three trends in the results are noted. First, whether the test was conducted with the specimen being in air or under water, RR increased with an increase in the DTA loading of the experimental cement formulation. Second, whether the test was conducted in air or under water, RR of experimental cement specimens with DTA loading of 20 wt./wt. was not significantly lower than that of control cement brand specimens (respective means = 80% versus 81% in air and 36% and 38% under water). Third, for a given cement, RR under water was substantially lower than that in air (by a factor of between ~2 and 3). This trend indicates that RR should be determined under conditions that are clinically relevant (such as with specimens being held under water).

There were two parts in the study in which the suitability of WC as a radiopacifier for use in PVP was investigated [80]. In the first, which was an *in vitro* study, radiopacity was determined for specimens fabricated using 25 experimental formulations (radiopacifier: WC nanoparticles, with mean particle size (D_m) of 50 nm, 500 nm, 5 mm, 50 mm, and 100 mm) and loading of 0, 2.5, 5.0, 7.5, and 10.0 wt./wt.%. The tests were performed using digital radiography and four values of x-ray tube voltage (V = 80, 100, 120, and 140 kV). The results were presented as attenuation values (arbitrary units) as the mean of all the pixels in an ROI on the x-ray image. Two trends in the results are noted. First, for a given combination of radiopacifier loading and V, radiopacity decreased non-monotonically with an increase in D_m. Second, the highest radiopacity was obtained using specimens fabricated using a cement that contained 10 wt./wt.% WC nanoparticles having D_m = 50 nm with test conducted using V = 140 kV. In fact, when the review of results is limited to those obtained at V = 80 kV (a level that is commonly used in clinical work [60]), the highest radiopacity was obtained with the same combination of D_m and loading (**Table 9**).

The second set of tests was conducted using sheep vertebrae into which a bolus of the prepared cement was injected. In this case, the control cement was a commercially prepared one in which the radiopacifier was 30 wt./wt.% $mBaSO_4$ particles and the experimental cements used were those in which the radiopacifier was 50 nm WC particles (loading: 2.5, 5.0, 7.5, and 10.0 wt./wt.%). The results were given in qualitative terms, comprising radiographs only.

Table 9. Influence of mean size and loading of WC nanoparticles[a] on radiopacities of specimens[b] (Results taken from results given in the study by Xu *et al.* [80]).

Radiopacifier in cement formulation	Radiopacity (arbitrary units)
2.5 wt./wt.% WC nanoparticles (50 nm[a])	250
2.5 wt./wt.% WC nanoparticles (500 nm[a])	230
2.5 wt./wt.% WC nanoparticles (5 mm[a])	225
2.5 wt./wt.% WC nanoparticles (50 mm[a])	230
2.5 wt./wt.% WC nanoparticles (100 mm[a])	230
5.0 wt./wt.% WC nanoparticles (50 nm[a])	350
5.0 wt./wt.% WC nanoparticles (500 nm[a])	300
5.0 wt./wt.% WC nanoparticles (5 mm[a])	280
5.0 wt./wt.% WC nanoparticles (50 mm[a])	290
5.0 wt./wt.% WC nanoparticles (100 mm[a])	250
7.5 wt./wt.% WC nanoparticles (50 nm[a])	390
7.5 wt./wt.% WC nanoparticles (500 nm[a])	325
7.5 wt./wt.% WC nanoparticles (5 mm[a])	320
7.5 wt./wt.% WC nanoparticles (50 mm[a])	325
7.5 wt./wt.% WC nanoparticles (100 mm[a])	280
10.0 wt./wt.% WC nanoparticles (50 nm[a])	400
10.0 wt./wt.% WC nanoparticles (500 nm[a]	325
10.0 wt./wt.% WC nanoparticles (5 mm[a])	320
10.0 wt./wt.% WC nanoparticles (50 mm[a])	300
10.0 wt./wt.% WC nanoparticles (100 mm[a]	330

[a]Mean size of particles. [b]Radiopacities determined using x-ray tube voltage of 80 kV.

In the study by Sari *et al.* [81], the radiopacifier in the experimental cement consisted of $nZrO_2$ particles, with the loading used in preparing the experimental cements being 2.5, 5, and 7.5 wt./wt.%. Tensile test specimens were irradiated and a densitometer was used to measure their radiopacities. Radiopacity was expressed as the ratio of the intensity of the incoming light to the test specimen to that of the outgoing light from it. The influence of two processing variables used in the synthesis of the particles using a sol gel method on crystallinity, crystallite size, size distribution, and morphology of the particles was investigated. The variables were pH (6, 9, and 11) and calcination temperature (T_c) (700˚C and 1000˚C). Thus, there were six study groups. However, only a limited set of radiopacity results was presented, with no information given on the values of pH and T_c that were used to synthesize the radiopacifiers. The results show that radiopacity increased monotonically with an increase in radiopacifier loading.

This method was used by Tavakoli *et al.* [82] in a study on the comparative radiopacities of three cements; namely, Simplex®P (the control cement) and two experimental 2 wt./wt.% vancomycin-loaded formulations. For one of the formu-

lations, the radiopacifier consisted of nanoparticles of biodegradable silicate (Bgh) that were synthesized using a sol-gel method and were used as a radiopacifier. For the other formulation, 0.5 wt./wt.% of nanoparticles of graphene oxide (GO) were added to Bgh nanoparticles in an ethanolic reaction medium followed by sonication and, then, the solution was magnetically stirred and the resulting powder was dried and, finally, ground. The specimens (discs with diameter and thickness = 12 mm and 3 mm, respectively) were irradiated (46 kV and 1.04 mAs). On a specimen, the brightness of the image in an area encompassing 5 pixels x 5 pixels was measured using a commercially-available software package. Then, Equation (4) was used to calculate the radiopacity of the specimen (R).

R (in %) = 100(Brightness of specimen)/(Brightness of an Al sheet (3 mm thickness) (4)

The results showed that each of the experimental formulation specimens was ~74% - 76% more radiopaque than the control cement specimens.

4.3.3. Computed Tomography

This method was used in the study by Jacobs *et al.* [74], which involved a comparison of the radiopacities of cements for use in VP: a commercial-prepared control cement (VertaPlex^{TM}; radiopacifier: 30 wt./wt.% $mBaSO_4$ particles) and an experimental cement formulation in which the radiopacifier comprised cross-linked PMMA microspheres in which gold particles were embedded homogeneously (size range: 0 - 300 mm). In preparing the experimental cement, the microspheres were added to the cement powder. In the tests, the cement dough was injected into a synthetic VP model that included simulated wedge-shaped compression fracture in human vertebrae (T6-L5) and bipedicular injection of the cement dough into the vertebra. High-resolution peripheral quantitative computed tomography (HR-pQCT) was used to determine the apparent density (r_{app}), a parameter that was used a measure of radiopacity of the cemented models. The radiopacity of the model when the experimental cement was used was markedly less than that when the control cement was used (r_{app} values were 1261 ± 42 and 1878 ± 80, respectively).

5. Effectiveness of Alternative Radiopacifiers

In the present work, an index of effectiveness of an alternative radiopacifier (IEAR) is introduced. IEAR is defined as the % increase in the radiopacity of a specimen (R) fabricated using an alternative radiopacifier compared to that of a specimen when a radiopaque control cement was used for the fabrication. Thus, an acceptable alternative radiopacfier is one for which IEAR > 0. The following stratification of effectiveness of radiopacifier is offered: low (1% < IEAR ≤ 30%), moderate (31% ≤ IEAR ≤ 70%), high (71 ≤ IEAR ≤ 90%), and very high (IEAR > 91%). It is to be noted that two additional requirements for an alternative radiopacifier to be deemed acceptable are 1) that its radiopacity determined under clinically-relevant test conditions meets a defined clinical or regulatory visibility threshold and 2) it does not have adverse effects on clinically-relevant cement

properties, notably fatigue life, hemolysis, and cytotoxicity.

The steps used to calculate IEAR are now described. The first step was to assemble a first sub-set of literature studies as those in which R results were presented in quantitative terms. The second step involved identifying a second subset of literature studies as those in the first sub-set in which x-radiography was used to determine R and, for the determination, the tube voltage (V_t) used was in the order of 75 - 80 kV. It is pointed out that, in THA and TKA, almost invariably, x-radiography is carried out using the stated range of V_t [60].

The IEAR values, as calculated from the second sub-set of studies (8), are presented in **Table 10**, from it is seen that among the 23 radiopacifiers used in this sub-set of studies (yielding 27 values of IEAR), 19 may be classified as having low effectiveness, 4 as being moderately effective, 2 as being highly effective, and 2 as being very highly effective.

Two methodologies were used to determine measures of centrality and dispersion of the population of IEARs. First, a test of normality (the Anderson-Darling (AD) Test) was conducted to see if the population followed a normal distribution. It was found that this was not the case (AD statistic = 2.750; critical value of the AD statistic (AD*) = 2.835; level of significance (p) ≤ 0.0005). Thus, an appropriate method to use to determine the stated statistical measures is the three-parameter Weibull method. When this was done, the minimum value, the Weibull modulus, and the characteristic value of IEAR were determined to be 2.45%, 0.714 and 25.98%, respectively. With these values, the Weibull median (a measure of centrality) and the Weibull standard deviation (a measure of dispersion) of the IEAR population were calculated to be 18% and 46%, respectively.

In light of the aforementioned caveats as well as the fact that among the 8 studies (23 different alternative radiopacifiers) whose results were used to calculate IEAR, different radiopacity determination methods were used and different specimen testing environments were used, the present methodology used to calculate IEAR should be taken as exploratory, rather than definitive. Thus, the IEAR values and the associated stratification of the radiopacifiers based on IEAR must be treated cautiously.

Table 10. Calculated values of index of effectiveness of alternative radiopacifiers.

Alternative radiopacifier[a]	Index of effectiveness (IEAR)\(%)	Calculation done using results reported in cited literature study indicated by [ ]
15 wt./wt.% IDX	22.8[b]	[60]
10 wt./wt.% IDX	5[c]	[60]
15 wt./wt.% IDX	51[c]	[60]
20 wt./wt. Ta	21[d]; 9[e]	[64]
40 wt./wt. Ta	111[d]; 43[e]	[64]
10 wt./wt.% nano-sized $BaSO_4$ particles	187	[67]
30 wt./wt.% functionalized $nBaSO_4$	16.1	[68]

Continued

30 wt./wt.% unfunctionalized $nZrO_2$	39.7	[68]
30 wt./wt.% functionalized $nZrO_2$	33.0	[68]
0.5 wt./wt.% functionalized TiO_2 fibers	2.8	[72]
1.0 wt./wt.% functionalized TiO_2 fibers	5.7	[72]
1.5 wt./wt.% functionalized TiO_2 fibers	5.7	[72]
20 wt./wt.% anatase TiO_2-based	3[f]	[77]
20 wt./wt.% yttria-stabilized ZrO_2-based	10[f]; 2.8[g]	[77]
25 wt./wt.% anatase TiO_2-based	7[f]	[77]
25 wt./wt.% yttria-stabilized ZrO_2-based	20[f]; 10.8[g]	[77]
20 wt./wt.% Bgh	76	[82]
20 wt./wt.% GOBgh	74	[82]
30 wt./wt.% 50-nm TaC particles	15[h]	[83]
30 wt./wt.% 100-nm TaC particles	30[h]	[83]
30 wt./wt.% 500-nm TaC particles	9[h]	[83]
30 wt./wt.% 800-nm TaC particles	26[h]	[83]
30 wt./wt.% 10-mm TaC particles	4[h]	[83]

[a]IDX: iodixanol; Bgh: baghdadite; GO: graphene oxide-encapsulated baghdadite. [b]Relative to $mBaSO_4$-containing control cement. [c]Relative to $mZrO_2$-containing control cement. [d]Determined with specimen in air. [e]Determined with specimen under water. [f]Relative to Palacos®R (radiopaque control cement). [g]Relative to Cemex®Isoplastic (radiopaque control cement). [h]Determined using x-ray tube voltage of 75 kV.

6. Literature Shortcomings and Suggested Future Studies

Eleven shortcomings of the literature and suggestions for future studies to address them are highlighted.

First, in some studies in which the focus was determination of the influence of radiopacifier on cement properties, radiopacity was not among the properties determined [56] [62] [63] [66] [69] [70] [85]. This deficiency must be avoided in future studies.

Second, the case in which the alternative radiopacifier was dissolved in the liquid of the cement was the subject of only a few studies [53] [55] [57] [71] [72]. Thus, there is an opportunity to develop and synthesize more alternative radiopacifiers that would be suited to be dissolved in the liquid.

Third, in some studies, a control cement was not included [53] [76] [80] or a control cement was used but it was radiolucent [58] [67] [81]. In other studies, the control cement was radiopaque and was formulated specifically for the use in the study [57] [64] [77] [79] [83] [87] rather than an approved cement brand. An experimental ALBC formulation (antibiotic: vancomycin) was used in one study [82] and a commercial-prepared ALBC (Cemteq®; antibiotic: vancomycin) was used in another [85]. In some studies, the control cement was an approved cement brand, namely CMW®1R1 [55]; C-ment®3 [61] [62]; Cemex®Isoplastic [77]; Cemteq®Ce-

ment [85]; CMW®1 [66] [71] [72]; CMW®3 [84]; Model 1230® (Tecres) [87]; Palacos®MV [88]; Palacos®R [63] [77]; Simplex® P [82]; and Vertaplex™ [73]. In future studies, a radiopaque control cement must be used, preferably an appropriate approved cement brand.

Fourth, in only three of the studies on bone cements that are designed for use CTAs were the cement powder and liquid vacuum mixed ("the combination") to prepare test specimens [54] [59] [60]. It is well-known that cement mixing method exerts a strong influence on cement properties. For example, for specimens of one commercial-prepared bone cement (Palacos®MV), when mixing was carried out using a bowl open to the atmosphere and in a vacuum cartridge (vacuum level = 86.7 kPa), the mean porosities were ~2.3 and ~0.3%, respectively, and the mean quasi-static compressive strengths were ~105 MPa and ~115 MPa, respectively [88]. Additionally, in contemporary CTA practice, the combination is mixed and delivered under vacuum to the prepared bone bed [2]. Thus, in future studies, the combination should be vacuum mixed.

Fifth, many different methods were used to determine radiopacity of bone cement, as detailed in Section 4. This makes interstudy comparison of results challenging. Although there is a Standard for determining radiopacity (ASTM F640-23), it suffers from two shortcomings. One, it is generic in the sense that it is for materials, products, or parts of a product intended for use as a medical device in the body, rather than for bone cement specifically. Two, the determination was done in ambient laboratory air, rather than in a biosimulating medium (such as SBF). Thus, there is scope to develop a standard for determining radiopacity in which the protocol is simple and covers all relevant aspects, such as specimen preparation conditions (medium and temperature), specimen configuration, specimen size, specimen aging conditions (medium, temperature of medium, and duration in medium), test equipment, and method of analysis of test results. In this regard, efforts should be made to ensure that four aspects are covered. First, the cost of the stipulated test equipment is modest so that the Standard could be adopted in many countries regardless of *per* capita income level. Second, the method should allow for determining radiopacity in a short time. Third, it should be possible to use the Standard to evaluate test specimens as well as animal models into which cement dough is delivered. Fourth, the test protocol should include features that are clinically relevant. Work on this aspect could build on the study by Kjellson *et al.* [60]. Cognizant of the first three aforementioned points, the recommendation is that a very-low-cost high-quality cone beam CT (VLCHQCBCT) be adopted as the equipment for use in this Standard after results using it have been validated using a counterpart standard cone beam CT (CBCT) that is in contemporary clinical use. Suggested settings for various parameters to be used are voltage = 100 kV, current = 900 mA, focal distance = 0.5 m, dose area product = 2200 mGy.cm^2, and exposure time = 0.5 s. A challenge of this recommendation is the need to design a VLCHQCBCT which, among other features, should have the advantages of clinical-quality CBCT but none of its shortcomings. Thus, image

acquisition time should be short (in order of 5 - 10 min) and spatial resolution of image should be in the sub-mm range but should not have beam hardening artifacts or be susceptible to scattering of radiation. Delivering this design should interest research and development professionals in fields such as radiation physics and biomedical engineering. A benefit that should accrue from employing this Standard would be a robust calculation of an index of effectiveness of a radiopacifier.

Sixth, in some studies [53] [57] [61] [73] [75] [84], radiopacity results were expressed in qualitative terms (visual observations), an approach that is viewer-dependent. In future studies, radiopacity results must be expressed in quantitative terms.

Seventh, cements intended for use in AOVCF were the subject of only a few studies and, in each of them, the target uses were PVP and BKP [58] [73] [78]-[81] [83] [84] [87]. Recent developments in the field of vertebral augmentation include third-generation implantable vertebral augmentation devices (TGIVADs) and innovative surgical techniques. The goal of each is to create an expanded and stable space within the fractured vertebral bodies in which the bolus of cement dough is injected. Examples of TGIVADs are Osseofix System, Sky Bone Expander System, SpineJack, and vertebral body stenting [89] [90]. Three examples of an innovative technique are percutaneous curvature kyphoplasty [89], the pedicle-to-pedicle technique [91], and a curved cement delivery system in VP [92]. In future studies, this paucity of research attention should be addressed through inclusion of at least one cement from three categories. One, those that are in current clinical use for PVP and BKP, such as Osteopal®V or VertePlex®. Two, novel formulations designed for use in PVP and BKP, examples being iodine-containing spheres-reinforced PMMA bone cement [73], a poly(dimethyl siloxane)-enhanced cement [84], a demineralized bone matrix-augmented PMMA bone cement [93], and a PMMA bone cement augmented with chitosan and human-derived bone powder [94].

Eighth, in many studies, statistical analysis of the results was not reported [53] [57] [60] [61] [64] [73] [76] [78] [80] [81] [83] [86] [87]. In many other studies, a parametric test of significance between the means of the populations (datasets) was used without any mention of *a priori* investigation to establish whether or not the conditions for using the test were satisfied (namely, normality and homogeneity of variance). In these studies, the parametric tests used were the t test [68] and analysis of variance (ANOVA) [58] [67] [71] [75] [82], ANOVA with the Bonferroni correction [65], and ANOVA in conjunction with another test (Tukey B rank-order test [72] and Tukey multiple comparisons test [84]). In only one study was a check for normality of the populations to be compared conducted first (Shapiro-Wilk test) and, if normality was shown, ANOVA was used, but, if deviation from normality was shown, a non-parametric test (Kruskal-Wallis test) was used followed by Dunn's *post hoc* test [77]. In one study, both ANOVA and a non-parametric test (Mann-Whitney U test) were used [79]. In future studies, the

results must be statistically analyzed using a non-parametric method.

Ninth, in only seven studies was determination of radiopacity conducted in an animal model, namely, defect created in the femoral condyles of New Zealand White rabbits (12 wk; 3 kg) [75], defect created in the proximal femur of Wistar rats (male; 4 mo; 0.24 kg) [82], sheep vertebrae [80] [83] [87], porcine lumbar vertebrae [84], and femurs from fresh pigs obtained from a licensed commercial market [86]. However, in four of these studies, some relevant information of the model was not provided, such as the breed of the sheep and the spinal level of the vertebrae [80] [83] [87] and the spinal level of the vertebrae [84]. In future studies, radiopacity should be determined both *in vitro* and in suitable animal models. For the latter, many details should be given, such as rationale for the selected model and anatomical location of the injected cement bolus.

Tenth, the following four categories of experimental cement formulations should be evaluated in future studies. One, those that include alternative radiopacifiers and have been the subject of studies in which the radiopacity was not determined or radiopacity was expressed in qualitative terms. Examples of these formulations are ones in which the radiopacifiers were PMMA-coated ZrO_2 fibers [69], an iodine-containing methacrylic copolymer [54] [62] [63] [70], I microspheres and IC microspheres [73], a commercial formulation of poly(dimethyl siloxane) (PDMS) [84], Ca tungstate [85], bismuth oxychloride [85], and BiInSn particles [86]. Two, novel/emerging plain formulations in which the influence of replacing a gold standard radiopacifier with an alternative radiopacifier on radiopacity has not been explored. Examples are a formulation that includes chemically functionalized graphene powder [95], a formulation that includes chitosan microgel to increase quasi-static properties of the cement [96], and a formulation that includes $Ca_2MgSi_2O_7$ (akermanite) and graphene oxide to impart bioactivity and increase quasi-static compressive properties and cellular response [97]. Three, novel/emerging ALBCs in which the influence of replacing a gold standard radiopacifier with an alternative radiopacifier on radiopacity has not been explored. Examples are a formulation that includes natural antibacterial agents, such as extracts of Aloe vera and Calendura [14], a formulation that contains a combination of a well-known antibiotic (vancomycin) and a lesser-known antibiotic (ceftazidime) [98], and a formulation that includes a combination of gentamicin and vancomycin (both of which are well-known antibiotics) and trimethoprim (a lesser-known antibiotic) [99]. Four, novel/emerging bone cements for use in AOVCFs, an example being a formulation that includes MoS_2 nanosheets to impart antibacterial activity to the cement [100].

Eleventh, the literature is uneven in terms of determination of radiopacities. For example, radiopacity was not determined (7 studies), radiopacity was reported in a qualitative manner (11 studies), and quantitative measures of radiopacity were reported but a radiopaque control cement was not among those used in the study (4 studies). A consequence of this unevenness is that in the present work, IEAR could not be determined for the alternative radiopacifiers used in the afore-

mentioned studies. The affected alternative radiopacifiers include triphenyl bismuth (TPB), 2,5 diiodo-8-quinolyl methacrylate (IHQM), polydimethyl siloxane (PDMS), calcium tungstate, and micron-sized $SrTiO_3$. This underscores the need for improved design of future studies.

Twelfth, there are no reports on first-principles design of alternative radiopacifiers. Such a design would entail deriving the composition of an alternative radiopacifier subject to desirable values of a varied list of properties in addition to radiopacity. For example, for radiopacifiers to be incorporated in ALBCs, at the minimum, the following additional cement properties must be considered: dough time (t_d); setting time (t_s); maximum temperature reached during cement polymerization (T_{max}); injectability (INJ); quasi-static compressive strength in SBF, at 37˚C; quasi-static four-point flexural strength in SBF, at 37˚C; fracture toughness, in SBF, at 37˚C (K_{IC}); multiaxial fatigue life, at 3 Hz, in SBF, at 37˚C; fatigue crack growth rate, in SBF, at 37˚C (FCGR); measures of *in vitro* biocompatibility and osteogenic activity (especially, attachment, proliferation, and differentiation of precursor osteoblast cell line, such as MC3T3-E1 and L929, and human osteoblasts, such as CRL-1137); blood compatibility (expressed as % hemolysis); a measure of *in vitro* bioactivity (for example, amount of apatite-like deposits formed on surface of a test specimen in SBF, at 37˚C, for 7 days); a measure of osteoconductivity in a relevant animal model (especially, volume of bone tissue formed around and within the implanted cement bolus); profile of the elution of the antibiotic from an ALBC, especially, duration of burst phase and time-to-exhaustion. For alternative radiopacifiers for use in cements intended for AOVCFs, at the minimum, the following additional cement properties should be considered: t_d; t_s; T_{max}; INJ, K_{IC}; compression-compression fatigue life, at 3 Hz, in SBF, at 37˚C; FCGR; rate of cement leakage; measures of *in vitro* biocompatibility; a measure of *in vitro* biocompatibility; and a measure of osteoconductivity in a relevant animal model. It is suggested that artificial intelligence methods (such as machine learning models) be used in these design studies [101] [102].

7. Summary

The following is a summary of the main points made in the present work:

- Poly (methyl methacrylate) bone cement ("bone cement") has a multitude of uses in surgery, ranging from providing the anchoring/grouting bed of an implant in an arthroplasty and augmentation of osteoporotic vertebral compression fracture(s) (for example, balloon kyphoplasty (BKP)) to delivery of chemotherapeutic drugs and filling of a bone void. The most common use is in primary and revision total hip arthroplasty (THA) and knee arthroplasty (TKA).
- Bone cement has many shortcomings. Three of them are (i) problems associated with the gold standard radiopacifier (micron-sized particles of $BaSO_4$ ($mBaSO_4$) or ZrO_2 ($mZrO_2$), which is a constituent of the powder of the cement), (ii) high temperature reached when the powder and liquid are mixed to form a dough (which, it has been postulated, may cause or be implicated in

thermal necrosis of periprosthetic tissue), and (iii) lack of or very limited bioactivity.

- Although the synthesis and characterization of bone cements that contain an alternative radiopacifier to m$BaSO_4$ and mZrO_2 have been the subject of many reports in the literature, a review of this body of work is lacking. The present contribution fills this gap. Ten key points made in this review are now highlighted. First, in the vast majority of studies, the alternative radiopacifier was added to the powder of the cement. Examples of these radiopacifiers are micron-sized particles of TaC, nano-sized particles of MgO, and an iodine-containing methacrylate. Second, in several of the studies, radiopaque control bone cement specimens were not used. Third, in some of the studies, radiopacity was not determined. Fourth, in studies where radiopacity was determined, several combinations of instrumentation and methods were used. Examples are x-radiography and the equivalent Al thickness method, computed tomography, and a densitometer. Fifth, the concept of an index of effectiveness of an alternative radiopacifier (IEAR) was introduced as the percentage increase in radiopacity when specimens of an alternative radiopacifier were used compared to when radiopaque control bone cement specimens were used. IEAR ranged from 3% when 25 wt./wt.% of yttria-stabilized ZrO_2 particles were added to the cement powder to 187% when 10 wt./wt.% of nano-sized $BaSO_4$ particles (particle size: 80 - 500 nm) were added to the cement powder. The Weibull median IEAR was 18%. Sixth, in many studies, statistical analysis of radiopacities was not reported or, in cases where it was, an inappropriate method was used (namely, analysis of variance (ANOVA method)). Seventh, radiopacities of specimens of antibiotic-loaded bone cements (ALBCs) were determined in only a few studies even though ALBCs are very widely used to prevent/manage peri-prosthetic joint infections in revision total hip and knee arthroplasties. Eighth, radiopacities of specimens of cements for use in vertebroplasty and balloon kyphoplasty (BKP) were determined in only a few studies. Ninth, in nearly all the studies, radiopacity was determined with the test specimen being in ambient laboratory atmosphere rather than in a biosimulating solution, such as simulated body fluid. Tenth, radiopacity was not determined for any specimens of novel/emerging plain or antibiotic-loaded bone cements, which have been the subject of recent reports in the literature.
- The shortcomings of the literature, as indicated above, suggest twelve areas for future work, four of which are summarized here. First, the development and validation of a test standard for the determination of radiopacity of bone cement specimens. Second, determination of radiopacity of a large collection of specimens fabricated from (i) commercial-prepared plain bone cements, commercial-prepared ALBCs, and experimental plain bone cements that were not included in the studies reviewed, (ii) novel/emerging experimental plain bone cements, and (iii) novel/emerging experimental ALBCs. Third, determination of radiopacity when bone cement dough/specimen is placed in appropriate an-

atomical locations in animal models, such as the thurl of a cow (for cements to be used in, for example, THA or TKA) and the third vertebra in the lumbar spine of a sheep (for cements to be used in, for example, BKP). Fourth, in every study, (i) radiopaque control bone cement specimens should be included and they must be immersed in a biosimulating solution and (ii) an appropriate statistical method should be used to analyze study results, an example being the Kruskal-Wallis method.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this work.

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