An Overview of Bone Cement Compositions used in Vertebroplasty and Their Viability in Clinical Settings

Arion Frakulli, Gleb Levashov, Janneza Macaalay, Kian Nahad and Muhammad Hasibul Hasan

ABSTRACT
Vertebroplasty is a minimally invasive surgical procedure wherein a particular composition of bone cement is injected into a fractured vertebra in an attempt to restore joint mobility and reduce perceived pain. It is especially common in the treatment of osteoporotic vertebral compression fractures, most typically experienced by older women. The formulation of this bone cement takes on many forms, the most common being the group of cements known as polymethyl methacrylate acrylic bone cements. The different varieties of acrylic bone cements are investigated and compared, in addition to new potential rival materials being developed to rival the dominance of acrylic bone cements in the vertebroplasty bone cement industry. Factors such as biomechanical strength, handling, osteoconductivity/inductivity, biodegradability, additive delivery, and porosity are considered. While the main drawbacks of acrylic bone cements (significant biomechanical mismatch with vertebrae and lack of biodegradability and osteoconductivity) present opportunities for new solutions to enter the market to compete, the industry standard in vertebroplasty remains the most widely applicable, and thus wisest, cement choice for the procedure.
Keywords: Vertebroplasty, Minimally Invasive Surgery, Biodegradability, Bone Cement

1 INTRODUCTION

Two hundred million people worldwide (most commonly postmenopausal women) are affected by osteoporosis, resulting in muscle weakness and chronic bone pain (Zhu et al., 2020). Osteoporosis is a multifactorial, systemic disease causing bone mass loss and osteopenia, which can harm the bone microstructure and worsen bone durability. It becomes more common as the global population ages. Its effects leave bones vulnerable to osteopathy and systemic fracture. A common manifestation of osteoporosis is Osteoporotic Vertebral Compression Fractures (OVCFs). While traditional pain treatment methods for OVCFs, such as physical rehabilitation and oral medications, help reduce pain, they are not effective in relieving and quickly curing the suffering of patients, especially in cases involving spinal instability or neurological impairment (Lai et al., 2013; Chen et al., 2002; Denaro et al., 2009). Another treatment method is bone grafting, when bone from a donor, or a synthetic substitute, is used to fill a region of missing bone (Kumar et al., 2013). This is currently the primary method of traumatic bone defect treatment in spite of its disadvantages, such as its lack of availability, increased mortality risk in the donor, and potential postoperative complications (Yousefi, 2019). Naturally, bones have great regenerative abilities, but bone regeneration in the body can repair only small bone defects. Thus, if a person obtains trauma, infection, or experiences bone tumor resection which leads to large bone defects, their bones will not be able to heal themselves. Treatments such as allogeneic bone grafting, xenografting, and autologous bone grafting are often used to compensate for the body's inability to heal these large defects (Xia et al., 2022). Among these treatments, autologous bone grafting is considered the best option. Its success comes from its similarity to the natural bone, which allows it to have a high fitting and success rate, making it ideal for bone defect repair. Despite its positive attributes, autologous bone grafting has two big flaws: limited availability and poor compatibility with some patients. The other treatment options are expensive however, and have many requirements for preservation. Xenografts and allografts specifically have been known to transmit diseases. New versions of synthesized biomaterials are being created to tackle the disadvantages of these traditional treatments.

Vertebral body stabilization/augmentation procedures such as balloon kyphoplasty (BKP) and percutaneous vertebroplasty (PVP) are often used to combat the limitations of conservative pain-treating methods and bone grafting (Zhu et al., 2020). Vertebroplasty is highly effective at relieving pain from vertebral fractures and dramatically reduces the risk of future impairments associated with vertebral compression fractures (Hopkins et al., 2020).

Arion Frakulli, Gleb Levashov, Janneza Macaalay, Kian Nahad, Muhammad Hasibul Hasan ✉
Faculty of Engineering and Architectural Science, Toronto Metropolitan University
350 Victoria Street Toronto, ON M5B 2K3, Canada
E-mail: hasibulhasan@torontomu.ca

Vertebroplasty involves injecting injectable bone cement (IBC) into the affected vertebra via a cannula, as shown in Figure 1 (Lai et al., 2013). polymethyl methacrylate acrylic (PMMA) bone cement would relieve pain associated with the fracture by stabilizing the site of the fracture and inducing necrosis of nerve endings via the heat from its exothermic polymerization reaction (Lieberman et al., 2005). Different types of IBCs include acrylic bone cements (ABCs), PMMA modified with mineralized collagen (MC-PMMA), calcium phosphate cements (CPCs), and filamentary composite materials (Yousefi, 2019).

Figure 1: Fluorescent image of the injection of bone cement into a fractured vertebra. (Lai et al., 2013)

There are required properties that biomaterials must have to be considered safe and be used instead of bone grafts. These include biological histocompatibility, movement of nutrient metabolites, mechanical tolerance, and osteogenesis. Biological histocompatibility is the biocompatibility of material with the surrounding tissue. Materials of bone cement must be accepted by bone tissue to prevent cellular damage. Bone pore size affects the efficiency of the bone's nutrient metabolite movement between pores and bone regeneration. Small pore sizes limit cell movement and infiltration, while large pore sizes do not provide a large enough area for bone regeneration. Large pore sizes also worsen the stability of bone cement. Since bone cement is used to strengthen bones, it should have high enough mechanical strength to endure the loads commonly applied to the vertebrae. While having great mechanical properties, bone cement should also encourage osteogenesis. One major issue in current bone cements is the potential for bone cement implantation syndrome, which can cause hypotensive shock, severe cardiac arrhythmias, and cardiac arrest. (Xia et al., 2022)

Despite PVP being a minimally invasive procedure, it results in complications at an expected rate (Saracen et al., 2023). Cement leakage is the most frequently encountered complication, but it also can increase the risk of adjacent vertebral fractures, as summarized in Table 1. Systemic complications from PVP with PMMA cement are not common, however when they occur, they cause PMMA pulmonary, arterial, adipose, and or renal embolisms, permanent cardiac damage, and or epidural hemorrhages.

Table 1: Complications of Vertebroplasty in 1100 Augmented Vertebrae. (Saracen et al, 2023)

Complication Cause of Fractures	Paravertebral Veins Leakage	Surrounding Tissues Leakage	Leakage Into Spinal Canal	Intradiscal Leakage	Total
Osteoporosis (794-100%)	119 (15%)	204 (25.7%)	2 (0.25%)	74 (9.3%)	399 (50.2%)
Neoplastic Disease (137-100%)	19 (13.9%)	12 (8.8%)	7 (5.1%)	9 (6.6%)	47 (34%)
Trauma (69-100%)	2 (2.9%)	2 (2.9%)	0	7 (10.1%)	11 (15.9%)
Vertebral Hemangioma (100-100%)	2 (2%)	0	0	0	2 (2%)
Total	142 (13%)	218 (19.8%)	9 (0.8%)	90 (8.2%)	459 (41.7%)

1.1 Handling Techniques

Polymerization of bone cement often takes about 2-5 mins (Lai et al., 2013). The surgeon has a short time frame in which they deliver the bone cement with ideal viscosity. Injecting the bone cement before it has reached the ideal viscosity can result in it entering the venous system. The bone cement would not be able to properly connect to the bone if its viscosity is too high and it is injected too late. The relevant equation, the Arrhenius equation, can be found in Figure 2 (Laidler, 1984).

$$k = A * exp(E_a/RT)$$

k = Rate Constant of Chemical Reactions
A = Frequency Factor or Pre-Exponential Factor
E_a = Activation Energy
R = Gas Constant
T = Absolute Temperature (K)

Figure 2: The Arrhenius Equation for the rate constant k of chemical reactions

The variable A represents the pre-exponential factor, and R represents the gas constant. In this equation, temperature (T) is inversely proportional to the rate constant of the reaction (k). This expression implies that a lower handling temperature of the bone cement would extend polymerization time (Lai et al., 2013). The duration during which the bone cement is injectable can be increased by cooling the mixture, as doing so decreases the rate of polymerization. This can be done by refrigerating the components of bone cement overnight or by cooling the mixture with ice water before injecting it. No side effects are associated with these cooling methods. Longer handling times allow for increased monitoring of the process and multiple injections of the bone cement, resulting in more efficient procedures.

1.2 Preparation Methods
Polymerization is initiated when the liquid and powder components of the bone cements are combined (Lai et al., 2013). Polymerization at room temperature occurs only in the presence of free radicals, which are released when benzoyl peroxide (BPO) reacts with methyl methacrylate (MMA). Polymerization continues as the created unstable compound reacts with other MMA monomers.

The four phases of applying bone cement are the mixing phase, the liquid phase, the working phase, and the hardening phase (Lai et al., 2013; Kuehn et al., 2005). During the mixing phase, the powder and the liquid components of the bone cement are mixed for about 1 minute to homogenize them thoroughly. This process can be done with a bowl and spatula. During the liquid phase, the cement reaches a non-sticky state after several minutes. The exact time depends on the chemical composition of the cement and the temperature it is exposed to.

During the working phase, the cement is injected within 2-4 minutes. Again, the exact time depends on the cement type and temperature. After injection, the cement enters the hardening phase, wherein it hardens quickly and develops heat from polymerization. The citric acid cycle converts the remaining monomers to water and carbon dioxide. During polymerization, the volume of the bone cement shrinks by a theoretical value of 6-7% (Kuehn et al., 2005). This is due to the distance between the free monomers decreasing as they bond to form polymers together. The volume shrinks by a percentage more significant than the theoretical shrinkage value due to air in its dough.

1.3 Current Limitations
Different compositions of bone cements are used, with PMMA being most commonly used due to its outstanding mechanical properties and injectability (Zhu et al., 2020). Compared to trabecular bone, plain PMMA bone cement displays much higher stiffness, with the modulus of elasticity of bone ranging from 10-900 MPa, and modulus of elasticity of PMMA ranging from 1700-3700 MPa. Due to raw PMMA having a greater Young's modulus, the risk of the adjacent vertebrae fracturing or collapsing (stress shielding) is increased.

Furthermore, PMMA has been shown to cause aseptic loosening within implants, likely due to its biological inactivity and hydrophobicity, preventing it from bonding efficiently to the existing bone (Zhao et al, 2018). Stress shielding and subsequent fracturing can also occur due to this loosening, thus improving the bone-cement bond is essential to improve the viability of PMMA cement usage in future orthopedic surgery. This can be done by combining PMMA with a bioactive filler, such as titania (TiO_2), mineralized collagen (MC), natural bone powder, and calcium phosphate (CaP). All of these implementations led to improved biocompatibility and several other properties. They could not, however, solve the issue of aseptic loosening due to the microstructure of the cement not being interconnected with the bone.

Radiopacity is another property useful in bone cements, allowing surgeons to trace its position via fluoroscopy during the surgical procedure (Lai et al., 2013). PMMA lacks this property, so a radiopaque additive must be included in the cement (Li et al., 2019; Nussbaum et al., 2004). Agents such as zirconium dioxide (ZrO2), tantalum, tungsten, and several others can be considered, but barium sulfate ($BaSO_4$) is the most commonly used due to its excellent optical properties and stability.

Due to $BaSO_4$ being an inorganic compound, it is chemically inert, preventing it from forming stable bonds with the particles of the PMMA matrix, which can impair the mechanical properties of the cement. It also causes aseptic loosening of the implant due to its cytotoxic effect. Micro/nano-sized particles of $BaSO_4$ can solve this issue, as it increases the surface area to enhance its biocompatibility. Barium particles must be evenly distributed to prevent the formation of fractures (Lai et al., 2013).

Implementing the $BaSO_4$ microparticles into a porous coating is done through Polydopamine (PDA)-assisted modification, a technique used for surface modification that would allow the agent to have a therapeutic effect as well as antibacterial traits (Zhao et al., 2018). The self-polymerization of dopamine forms excellent adhesion on many surfaces when under slightly alkaline conditions.

2 DISCUSSIONS
2.1 Parameters for Consideration
PVP is a surgical procedure that is considered to be relatively safe; however, it commonly leads to post-surgical complications. It relieves the individual's relative pain and is a viable alternative to other invasive procedures that yield more severe complications, such as open surgery. Kyphoplasty is another quick vertebral fracture treatment procedure, which is also an excellent pain reduction technique; however, it is much more expensive. (Saracen et al., 2023)

PVP is recommended when a patient is experiencing intense pain due to a vertebral fracture, and conservative treatment shows no restorative effect for a minimum of 3-4 weeks (Lai et al., 2013). This procedure is much more effective at treating pain than conservative treatments (Klazen et al., 2010). Pain can be reduced to the point where analgesics are not required. Vertebroplasty reduces the need for major spinal surgery and may accelerate rehabilitation (Lai et al., 2013). A study by Klazen et al. comparing vertebroplasty and conservative treatment found that the development of new fractures was similar in both treatment methods. Kyphoplasty is another method used to treat vertebral compression factors. It is similar to vertebroplasty, such that bone cement is injected into the area of interest; however, a balloon is first placed at the fracture site and expanded to create space for the cement. This method relieves a similar amount of pain to vertebroplasty; however, the process requires the patient to be administered anesthesia, while vertebroplasty can be done with an analgesic.

Osteoporotic, traumatic, or neoplastic vertebral fractures are generally treated with the minimally invasive PVP procedure. Generally, a PMMA-based cement is utilized to fill in the necessary voids present after any implantations are made. The bone cement must meet various parameter requirements to be implemented safely in bone treatment to ensure no further complications arise. Biocompatibility is crucial to withstand the harsh physiological environment while preventing any corrosion or degradation. Materials used in bone cements should not cause an immunological or toxic response and preferably have no adverse effect on tissue growth and cellular function. Preventing negative immunological responses is accomplished through the bioactivity of a material, which can encourage osseointegration and bone growth. Strong cement-bone interconnectivity allows for minimal aseptic loosening to occur. The injectability of bone cement is another contributing factor to the immunological response, as well as the curing characteristics of the cement. Smooth injectability ensures the material distributes evenly amongst any voids between the implant and vertebral body. However, if blood enters the bone cement, its strength would decrease (Lai et al., 2013). To prevent this, the viscosity of the bone cement must be high enough to withstand blood pressure. A higher viscosity consequently reduces its injectability.

Cured post-injection bone cement must provide sufficient strength and stiffness to stabilize the fractured bone and withstand further fracture or deformation under load. In addition to having good mechanical properties, fluoroscopy-guided methods require bone cement to repel electromagnetic radiation for better visibility. Therefore, the cement must also include a radio pacifier to ensure it is radiopaque. Since bone cement inevitably degrades, the degradation rate should be predictable and modifiable to allow sufficient remodeling and tissue regeneration time. Bone cement should possess all of these characteristics and should ideally be cost-effective simultaneously. The manufacturing process of bone cement should be simplified and optimized in a way that prevents excess waste of materials to minimize costs.

Complications in relation to PVP are common; however not considered statistically significant in a clinical setting. Cement leakage is the most common complication, with polymethylmethacrylate (PMMA) cement frequently used. The treatment of 1100 vertebral disks using PMMA cement was analyzed, with particular notice to the clinical manifestations and severity of the complications. These disc treatments were performed in 616 patients, with 468(76%) and 148(24%) women and men, respectively, aged 24-94 (mean 68) years old. 50% of osteoporotic fractures occurred in complications, alongside 34% in neoplastic, 16% in traumatic, and 2% in vertebral hemangiomas. PMMA leakage was the most common of these complications, with 20% leaking into surrounding tissues, 13% manifesting as paravertebral vein embolisms, 8% as intradiscal leakages, and 0.8% leakage into the spinal canal. Despite the overwhelmingly high incidence of complications, approximately 95% do not escalate to produce clinical symptoms. (Saracen et al., 2023)

2.2 Antibiotic-Loading [AL]
In a study by Chen et al., the mechanisms affecting drug release behavior in ABCs were investigated (Chen et al., 2021). They found strong evidence suggesting the elution efficacy rate of antibiotics is correlated with several features of the bone cement: liquid/powder ratio, radio pacifier ratio, and antibiotic dose. A decreased liquid/powder ratio also facilitated increased antibiotic elution. However, the mechanical implications of the decreased liquid/powder ratio remain contested, with one study by Belkoff et al. finding that weakened compressive mechanical properties correlated inversely with the liquid/powder ratio and another by Pascual et al. suggesting no correlation at all. A high radio pacifier ratio was also observed to correlate with better antibiotic elution. Finally, a high antibiotic concentration was found to do the same. The mechanism by which these outcomes were caused was through the increased porosity of the cement caused by these three factors mentioned. The increased surface area provided by the cement pores facilitated the diffusion of the antibiotics in the cement into the surrounding area (see Figure 3).
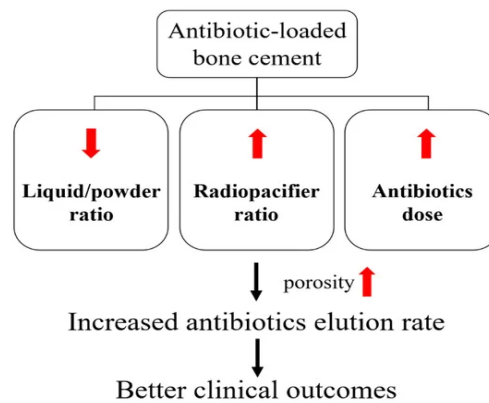
Figure 3: Diagram explaining the factors affecting antibiotic elution rate (Chen et al., 2019)

2.3 Radiopacifiers

Radiopacifiers (RP) are an integral component of any prosthetic implemented in the human body, and bone cements are no exception. Although radio pacifiers are needed for fluoroscopy visibility during the injection process, they can diminish the fatigue life of the bone cement (Lai et al., 2013). They can significantly lower the mechanical strength of the cement, as well as change setting behavior. Local stress concentrations can also form at the site of $BaSO_4$ masses, which decreases tensile strength and fatigue life. Due to this, only 10%-15% of the bone cement powder is delegated to pacifiers.

To compensate for this, new radio pacifiers have been developed, such as difunctional agent surface-treated $BaSO_4$ or zirconia dioxide, which allow for the interface between the radio pacifier and PMMA to be ameliorated, enhancing mechanical properties in ABCs (He et al., 2014). Another radiopacifying agent developed is bismuth salicylate, which, when used in ABCs, results in higher radiopacity and improved injection properties compared to common commercial options without compromising mechanical properties.
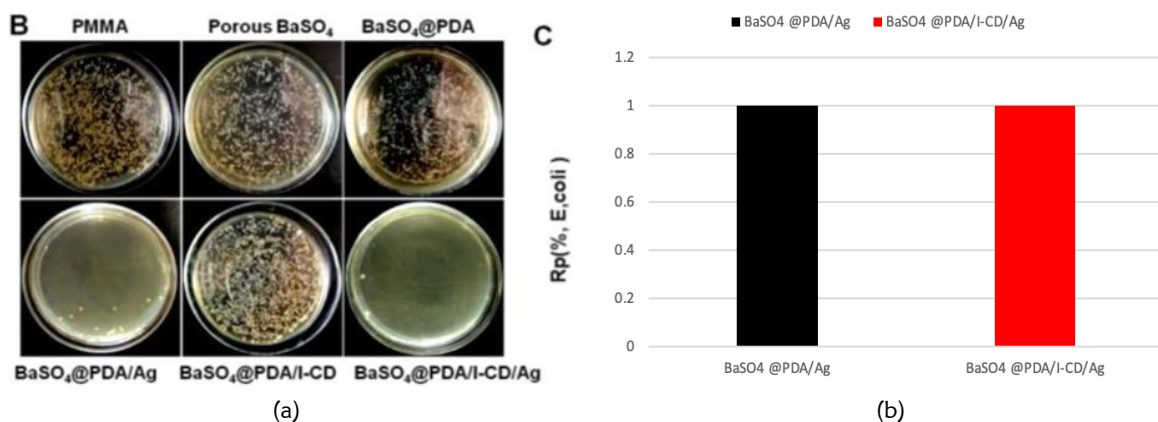

Figure 4: SEM Images of PMMA, Porous $BaSO_4$ and $BaSO_4$ with a PDA coating implemented respectively, with E. coli colonies. (Li et al, 2019)

2.3, 2.2 Coatings [AL+RP]

A study by Li et al. utilized a coating that simultaneously serves as an antibacterial and a radiopaque agent. This was done by utilizing $BaSO_4$ microparticles with hexakis-(6-iodo-6-deoxy)-alpha-cyclodextrin (I-CD) and silver (Ag) to form a $BaSO_4$@PDA/I-CD/Ag porous coating layer. This layer yielded a 99% antibacterial rate against Escherichia Coli (E. coli) and Staphylococcus aureus (S. aureus), as seen in Figure 4, two common bacterial infections. This also had no net effect on the biocompatibility while allowing the PMMA cement to have superior radiopacity, antibacterial performance, and the ability to deliver drugs in a controlled manner through the pores of the PDA and I-CD microparticle coating. (Li et al., 2019)

Ag nanoparticles in PDA-assisted coating can elicit a strong antibacterial effect due to the material properties of Ag. Ag nanoparticles implemented through PDA-assisted modification have been used in previous studies to modify poly(ether ether ketone) (PEEK) implants and had success in the antibacterial defense against both E. coli and S. aureus in vivo. This indicates that the PDA-assisted coating technique could also be suitable for $BaSO_4$ implementation. (Li et al., 2019).

5

2.4 Porogens

Implementing a porogen within the PMMA matrix of the cement used in vertebroplasty can assist in the regrowth and interconnectivity of the bone with the implant structure. As mentioned in the Parameters for Consideration, aseptic loosening of the implant is a major cause of pain and implant failure. Due to its bioinert properties, there is a lack of bone interconnectivity within the PMMA matrix. (Zhao et al., 2018). The implementation of Mg microspheres is an example of an effective porogen and is discussed in further detail in section 2.5.3.

2.5 Cement Compositions

There are several different material compositions for bone cements, consisting of composite resins, Cap, calcium sulfate, or variations of PMMA. The two general components of bone cement are a liquid and a polymer powder. Particles shaped as beads, with a diameter of about 40 microns, make up the powder component. BPO is the initiator of the powder, allowing for accelerated polymerization. The radio-opaque elements of the bone cement are found in the powder. MMA copolymers are also incorporated into the powder. The liquid component of bone cement generally consists of (MMA) monomers.

2.5.1 PMMA ABC

The most common implementation of this type is the polymethyl methacrylate acrylic bone cement (PMMA ABC), accounting for the vast majority of bone cements used for vertebroplasty procedures (He et al., 2014). It boasts a variety of advantages, including bio-inertness, ease of handling, high mechanical strength, and cost-effectiveness.

The solid phase of the cement is predominantly composed of PMMA prepolymers of acrylic acid, ethyl acrylate, methyl acrylate, MMA, and styrene, with bead sizes between 30µm and 150µm (Kühn, 2000; Liu-Snyder & Webster, 2008). The PMMA particles make up around 82-89% of the powder's total weight. $BaSO_4$ and zirconium dioxide are also included for radiographic visibility at a concentration of 10-30 wt%. In addition, it also contains BPO as the radical initiator for polymer chain growth, accounting for ~0.75-2.5 wt% of the powder. Situationally, supplement antibiotics may be added as well to prevent infection if it is a concern in the particular patient on whom the operation is being performed. This powder accounts for ~80 wt% of the bone cement.

The liquid phase of the ABC comprises mainly an MMA monomer, which accounts for ~95 wt%. It also contains an activator, usually N-N-dimethyl-p-toluidine (DMPT), to catalyze polymerization at 0.89-2.7 wt% (He et al., 2014). Finally, an inhibitor like hydroquinone (HQ) is added to prevent premature polymerization when stored. PMMA ABC has proven to improve hip fracture fixation stability due to its high mechanical strength. The addition of starch-stabilized polyethylene glycol or chitosan to PMMA has, in the past, reduced the maximum curing temperature. Hydroxyapatite (HA) has proven to be an osteoconductive material that improves biocompatibility when added to PMMA. The viscosity of bone cements, such as ABC, has been found to increase with temperature. In addition, bioactive agents with Ag have been proven to lower the risk of infection in bone cement. (Yousefi, 2019)

As a result of PMMA's poor biocompatibility, degradation, and potentially toxic nature, it inhibits bone formation (He et al., 2014). Since the polymerization process of the bone cement requires high temperatures, osteoblasts surrounding it can potentially die and have fibrous membrane form in their place, decreasing the osseointegration between PMMA and the bone. Some studies have discovered that bone tissue death occurs within one minute in an environment over 50 degrees Celsius.

Not all additions of minerals to bone cement help its performance. For example, the compressive strength of PMMA lowers when HA is added. A study found that when PMMA was modified with magnesium-based polylactic acid micro sheets, its surrounding osteoblasts received less damage from the high temperature needed for polymerization and delivered magnesium (Mg) ions simultaneously, encouraging osteogenesis. In another study by Sharma et al., PMMA experienced a drop in cytotoxicity and an increase in toughness with the addition of amine group-functionalized graphene. With this addition, major calcification occurred 20 days after the bone was damaged. Other additions that improved PMMA's biocompatibility were magnesium oxide and CaP, which encouraged bone formation. (Xia et al., 2022)

2.5.2 MC-PMMA

Mineralized collagen, an organic type-I collagen and nano-hydroxyapatite (nHA) material, has been used to modify PMMA. This material mimics the matrix microstructure and chemical makeup of the natural bone. The modified version of PMMA cement with MC is named MC-PMMA. MC-PMMA bone cement is made by mixing PMMA bone cement powder with MC particles and liquid MMA. For ideal properties, MC particles should make up 15% of the mixture's total weight. In the experiment conducted by Zhu et al. (2020), PMMA bone cement's compressive strength (111.61 ± 11.43 MPa) and compressive module (1.63 ± 0.23 GPa) were determined to be higher than those of MC-PMMA (79.12 ± 3.65 MPa and 1.13 ± 0.07 GPa). SEM imaging displayed that both MC particles closely interlock with PMMA cement with no gaps in between in MC-PMMA.

MC particles had practically no effect on the porosity of MC-PMMA since its (7.22 ± 0.53%) and PMMA's (5.61 ± 0.16%) porosity values are almost identical. 5 and 7 days after the injection of the bone cements into the test subjects, MC-PMMA's cell spreading area became much more extensive than that of PMMA, proving that it promotes the attachment of bone cells to the bone cement. Additionally, MC-PMMA bone cement's proliferation rate was higher than PMMA's, showing that it has no significant cytotoxicity and promotes cell growth. Four weeks into the

experiment, the subject with MC-PMMA bone cement injected displayed better bone repair than the subject with PMMA injected. As seen in Figure 5, at the eight-week mark, the new bone began to develop around the MC-PMMA cement, while the PMMA cement had no new bone around it. Once 12 weeks passed, the amount of mineralized collagen in the MC-PMMA cement was reduced, and osteoblasts displayed new bone growth. The PMMA test subject showed minor bone repair.

Overall, MC-PMMA had more bone growth than PMMA due to the degraded MC, which promoted bone growth. After four weeks, the PMMA and MC-PMMA tests had almost no inflammatory cells. Although the addition of MC particles to PMMA makes MC-PMMA more biocompatible than plain PMMA, it results in a worsening of mechanical properties. With a low elastic modulus, bone cement can reduce the stress concentration of bone tissue around it, improving stability in the original vertebral body. Human trabecular bone has a compressive strength of 2-12 MPa, while PMMA bone cement has a strength of 80-120 MPa. While very low bone cement compressive strength can cause deformation in the vertebral body under heavy pressure, very high compressive strength creates a stiffness mismatch between bone cement and bones, resulting in adverse effects such as unusual load transfer, secondary bone fracture, and a stress shielding effect. These effects are mainly prevalent in patients with osteoporosis. Although the compressive strength of MC-PMMA was lower than the strength of PMMA, it was greater than 70MPa. This means that it could still lessen the amount of compressive pressure taken by the vertebral body while minimizing the strength mismatch. The improved fusion between MC-PMMA and vertebrae, compared to that of PMMA and vertebrae, lowers the risk of cement shedding and loosening, making it a safer option. While PMMA bone cement's inferior interlocking with surrounding vertebrae makes it less biocompatible, it provides mechanical support for longer than MC-PMMA since it degrades at a slower rate. Although both bone cements caused the height of the test subjects to lower after two years, MC-PMMA had a smaller decrease than PMMA. (Zhu et al., 2020).
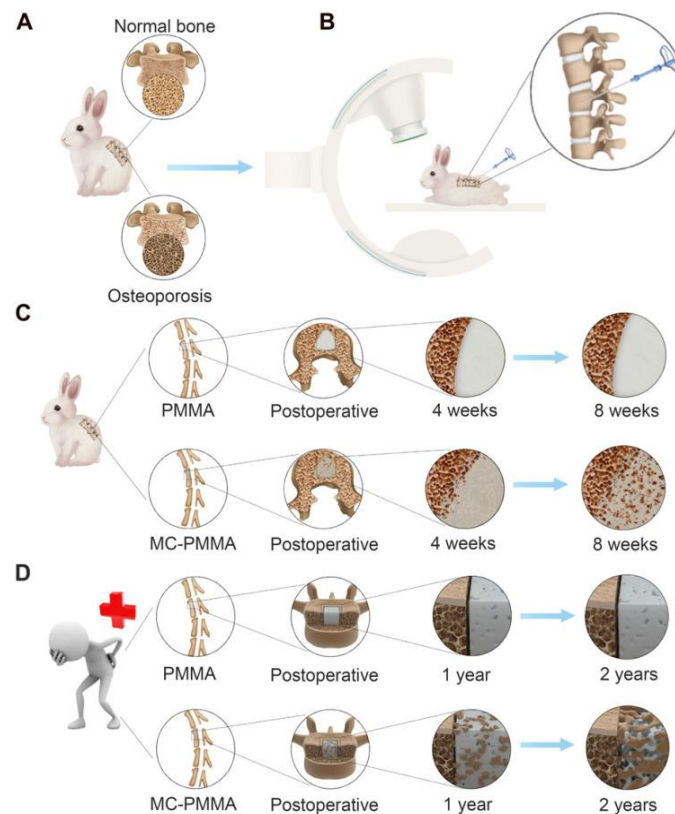

Figure 5: Bone growth in osteoporotic rabbit and human over time after bone cement injection (Zhu et al., 2020)

2.5.2 Calcium Phosphate Cements (CPCs)

The main prospective competitor to ABCs in vertebroplasty are calcium phosphate cements (CPCs), a collection of biodegradable bone cement (He et al., 2014; Turner et al., 2008). These hold a highly unique combination of properties, including osteoconductivity, injectability, mouldability, biodegradability, non-exothermic curing, and negligible curing shrinkage. Generally, they consist of a powder phase with one or more calcium phosphate (CaP) compounds and a liquid phase consisting of water of calcium or a phosphate-containing aqueous solution. When the powder and liquid phases are mixed, it forms an easily manipulable and mouldable viscous paste. Despite the vast array of CaP combinations, their setting chemistry is an essentially consistent process of dissolution and reprecipitation. While ABCs are mainly used for withstanding high and medium loads, CPCs, alongside calcium sulfate cements (CSCs), are mostly used for medium and low loads. Unlike older models, these current IBC models contain

materials, such as collagen and HA, that encourage osseointegration and improve biocompatibility. The Young's modulus of collagen and HA are 1-2 GPa and 130 GPa, respectively, alongside ultimate tensile strengths of 50-1000 and 100 MPa, respectively. When collagen and HA are combined, the collagen contributes viscoelasticity, toughness, and rigidity, while HA provides sufficient stiffness and structural reinforcement. Since bone grafts, especially autologous ones, can be hard to obtain, hydraulic cements are often used as a substitute, which includes CPCs, magnesium phosphate cements (MPCs), and calcium sulfate hemihydrates (CSHs). Strontium (II) is also commonly used in osteoporotic treatment, as it has the ability to improve bone formation and minimize bone resorption (Yousefi, 2019).

CPCs consist of a network of CaP crystals mirroring HA in human bone. The release of calcium and phosphate ions as the bone cement degrades encourages osteogenesis and osteoconduction in the body. In vivo, CPCs have been found to be able to undergo passive and active absorption, with passive absorption relying on solubility and dispersion of materials and active absorption on the body's osteoclasts. Bone formation begins in correspondence with the active and/or passive resorption of the CPC, with woven bone usually forming after around two weeks (He et al., 2014). Depending on the specific characteristics of the CPC being used, the implant site could become entirely bone within a few months up to a couple of years. The rate at which the bone cement degrades in the body is determined by the calcium to phosphorus ratio, along with the type of filler (Yousefi, 2019). Adding foaming agents, calcium carbonate, and polymers can help improve CPC's porosity. Adding polyvinyl alcohol (PVA) to CPC has been proven to improve the cement's injectability significantly. Adding fine fillers, which are around one micrometer in diameter, has also been shown to increase the injectability of CPCs. Gelatinized starch, a type of additive, has the ability to improve the compressive modulus of strength of CPCs, alongside the strain energy density. Based on the nature of the compound and the end product of hydration, and depending on the pH of the cement paste, CPCs can be divided into two general categories: apatite (formed at pH>4.2) and brushite (formed at pH<4.2) (He et al., 2014). At the human body's pH, brushite is one to two orders of magnitude more soluble than apatite and degrades faster. It also has a short setting time, lower mechanical strength, and inferior injectability, limiting its applicability compared to apatite. Absorbable CPCs have also been found to treat large vertebral defects, given short and long injection periods (Lai et al., 2013; Turner et al., 2008). Despite the substantial benefits of CPCs, they have been shown to be absorbed and replaced by lamellar bone at a rate that may pose a risk of early vertebral collapse. (Lai et al., 2013).

Another important aspect of CPCs is their incredibly high porosity, of around 30-50%, depending on the mixture (He et al., 2014). This porosity is highly effective in helping to facilitate resorption and bone ingrowth and encouraging fluid exchange by aiding the transfer of additives contained in the cement, such as growth factors and antibiotics. The drawback to high porosity is low biomechanical properties. Although CPCs can allow for the close mirroring of the modulus of elasticity of human vertebrae (Lewis, 2006), it is generally not strong enough to withstand the various stresses that vertebrae that tend to carry more load endure. As such, it is generally used in non- or moderate load-bearing places.

2.5.3 Magnesium "Sacrifices"

A study by Zhao et al. (2018) developed a method to counteract the unfavorable aspects of PMMA, by implementing microspheres composed of magnesium (Mg) within the PMMA matrix to create a better bone-cement bond. These microspheres were denominated as "Mg sacrifices" (MgSs) and served as sites for partial biodegradation of the cement and bone ingrowth. The mechanical properties of the bone cement were not significantly different, and the bone ingrowth was considerably greater, which indicates that it may be an excellent option for orthopedic surgeries.

The implementation of Mg microparticles within the matrix of the PMMA cement acts as a porogen, which allows the cement to interconnect with the bone tissue as the Mg is absorbed into the body, as it will gradually decay within the physiological environment. This encourages the regeneration of bone, does not provoke any inflammatory response, and can also increase certain bone growth factors such as bone morphogenetic proteins, such as BMP-2, and vascular endothelial growth factor (VEGF) within the physiological system. (Zhao et al., 2018).

As more Mg sacrifices were implemented, the cement became more viscous and had reduced injectability (Chen et al., 2015). PMMA-25Mg and PMMA-41Mg cement still retained a good level of injectability; however, PMMA-58Mg was barely injectable. Alongside this, the maximum temperature during the cement formation decreases as more Mg microspheres are added, which is beneficial as higher PMMA polymerization temperatures can result in thermal necrosis of the tissue that surrounds the injection site. (Zhao et al., 2018).

Mechanical strength was better compared to PMMA cement for PMMA-25Mg and PMMA-41Mg (Liu et al., 2023); however, once the percentage of Mg exceeded 58 (PMMA-58Mg), the mechanical properties of the cement decreased. This is a significant advantage compared to other porogens such as CaP, gelatin microparticles, calcium sulfate, and several others. Animal experiments indicate that the PMMA-Mg composite yields no tissue abnormalities and that relatively large pores (>300μm) lead to better osteogenesis when compared to smaller pores due to the organism's ability to oxygenate and vascularize these micropores more effectively. (Zhao et al., 2018).

In ideal physiological conditions, the degradation rate of the Mg microspheres is approximately the same rate of osteogenesis (Miao et al., 2023; Shi et al., 2021), which alongside its hydrophilic and mineralizing properties, offers excellent bioactivity and osseointegration (Tan et al., 2021). 25% and 41% Mg microsphere implementation may be a good cement for orthopedic surgeries. (Zhao et al., 2018)

Figure 6: Schematic illustration of a partially degradable PMMA bone cement based on the "magnesium sacrifice" strategy. (Zhao et al., 2018)

Preparation of the Mg microspheres was done through a 2:1 ratio of solid and liquid for the PMMA cement. The solid component amounted to approximately 88.5 wt% of PMMA. Then, 10 wt% $BaSO_4$ was implemented as a radiopacifier, alongside 1.5 wt% BPO, which was used for increasing polymerization of the solid component. The liquid component of the cement was composed of 98.9 wt% Methyl methacrylate (MMA), and the remainder (1.1 wt%) dimethyl propiothetin (DMPT), which was utilized for an increased rate of polymerization within the liquid component, while the MMA provided the structural components. Mg microspheres, with a particle size in the range of 300-500 μm, were incorporated in a proportional amount based on the total weight of the PMMA cement, as seen in Figure 6, and were added 5 minutes post combination of the solid and liquid components of the cement. (Zhao et al., 2018)

2.5.4 Borate/Borosilicate
Borate bone cement is a type of bioactive class created through the total or partial replacement of silicon dioxide (SiO_2) with boron trioxide (B_2O_3). From observations, boron has been found to lower the speed of solidification reactions. This property has allowed borate cement to repair 87% of bone defects with vancomycin in osteomyelitis treatment. Strontium, another element used in certain bone cements, has been proven to lower osteoclast activity, promote the expression of mesenchymal stem cells genes, and promote bone regeneration. In a study by Zhang et al, the mixture of borate bone cement with chitosan and strontium produced cement that promoted bone formation via the release of strontium. The setting time for the mixture (Sr-BBG) was 10.6 ± 1.2 minutes. With the addition of extra strontium, the setting time of the cement increased while the compressive strength stayed the same (Xia et al., 2022).

2.5.5 Calcium Aluminate
Compared to calcium phosphate bone cement (CPC), calcium aluminate cement (CAC) has a lower curing temperature and greater mechanical properties. The disadvantage of CAC is that it has an extensive setting time, making it difficult to use in clinical procedures. Xia et al discovered that lithium chloride shortens CAC's setting time, while preserving its compressive strength and preventing cytotoxicity. Since lithium chloride lacks calcium, insufficient amounts of calcium ions get released in the area of injection, preventing the promotion of bone growth. A calcium chloride modification for the bone cement can help the cement spread calcium ions throughout the bone for approximately 84 hours. However, CAC has poor bio biocompatibility and relatively difficult fabrication methods when compared to other types of bone cements, which validates why it is not currently widely used. (Xia et al., 2022).

2.5.6 Inorganic Nanohybrid Bone Cement
The stabilization and crosslinking of polymer bone cements, as seen in organic-inorganic nanohybrid cement, is based on double bonds and thienyl groups. This type of cement is composed mostly of esters and propylene glycol fumarate, and the gelation time of the cement is determined by the ratio of these substances. The minimum gelation time of the cement ranges from several minutes to half an hour. Approximately 21 days after injection, organic-inorganic nanohybrid bone cement caused the number of osteogenic markers and mesenchymal stem cells (cells that have the ability to differentiate into osteoblasts) to increase, and bone formation was observed a month after the injection. Overall, the polymer bone cement had good degradability, low toxicity, and encouraged mesenchymal stem cell differentiation. Despite these positive characteristics and its superior availability, polymer bone cement is speculated to have lower strength than other bone cements. (Xia et al., 2022).

2.6 Surgical Limitations

A majority of the issues associated with vertebroplasty result from the bone cement leaking into the vascular system or the spinal canal (Lai et al., 2013). Common sites of leakage are the intervertebral and paravertebral soft tissues, intervertebral discs, epidural and vertebral veins, the spinal canal and needle tract, alongside the neural foramina. Leakage of bone cement can result in motor, sensory, or cognitive complications. Once in the circulatory system, bone cement particles may block major vessels, such as the right cardiac chambers or the pulmonary artery, the risk of a pulmonary blocking for osteoporotic fractures ranged from 3.5% to 23%. Leakage has been found to occur in about 40% of cases, with less than 1% of these cases being severe, however most patients with leakage are asymptomatic (Klazen et al., 2010; Hulme et al., 2006; Wardlaw et al., 2009). Neurological issues may also arise as a result of compression acting on neural tissue by the bone cement (Lai et al., 2013). The heat emitted from the exothermic polymerization reaction may also damage surrounding tissue, and fractures could form adjacent to the site of vertebroplasty, most often in cranial vertebrae, and out of 106 patients, 18.9% of them experienced the formation of new fractures adjacent to the site of vertebroplasty. Fractures are more likely to form if the cement was not evenly distributed, which may be a sign of poor injectability. At the cost of being so effective, vertebroplasty is more expensive than conservative treatment (Hopkins et al., 2020).

2.7 Drawbacks of ABCs

ABCs are extremely widely used in vertebroplasty, and the industry is mature with a broad range of products available, but they do not come without drawbacks (He et al., 2014). The two most problematic are their nonbiodegradability, and significant mechanical mismatch with human vertebrae (Lopes et al., 2013; Vallo & Schroeder, 2005). Efforts are continually being made to ameliorate these shortcomings.

One such example is the cortoss bone augmentation material, a polymer-inorganics composite material made of crosslinked resins and reinforced with glass ceramic particles (He et al., 2014). It is comprised of a terpolymer resin made of bisphenol-A-glycidyl (Bis-EMA) and triethylene glycol dimethacrylate (TEGDMA), and supplemented with bioactive combeite glass-ceramic particles to help bone apposition. This particular formulation can strengthen weakened bone, achieving a compressive strength equivalent to ~75% of that of human cortical bone.

Another major drawback of ABCs is their lack of porosity (He et al., 2014). Porosity is a very desirable feature of bone cement as it allows for the ingrowth and eventual replacement of cement with new bone, as well as facilitating transfer of components such as antibiotics mixed in the cement. The porosity of different commercial bone cements varies within the range of 5-16%, which is very low compared to CPCs, whose porosity comes at the expense of mechanical strength.

Vertebrae are subjected to very high shear, compressive and tensile stresses supporting the wide variety of activities required of the body (He et al., 2014). As such, the choice of cement must be based on comprehensive biomedical considerations such as fracture configuration, rotational and flexional stability, load-bearing capacity, and the bone mineral density of the vertebrae. Stiffness must also be considered, as ABCs are up to 11 times stiffer than osteoporotic cancellous vertebral bone. This type of bone augmented by rigid cement is not only stiffer, but 35 times stronger than untreated bone. The comparatively significantly higher stiffness leads to a load increase in the adjacent structures of the spine, potentially stopping the normal endplate bulge into the augmented vertebra, pressurizing the disks adjacent to it and causing increased loading to those adjacent disks, potentially leading to fracture.

2.8 Shortcomings of CPCs

It is logical to expect a cement meant to mimic the mechanical properties of cancellous bone (He et al., 2014). While CPCs are highly promising due to their biodegradability and their ability to facilitate bone regeneration, as previously mentioned their mechanical properties tend to be poor, limiting their use to low or non-weight bearing areas. Mechanical properties are generally affected by crystal type, powder to liquid ratio, granularity, and porosity. A trivial solution would be to decrease the porosity by compacting the paste pre-hydration, which does boost mechanical properties, but only up to a critical porosity of <30%, where strength plateaus: Which comes at the expense of injectability.

The supplementation of various compounds such as biodegradable polymers, inorganic compounds, small organic molecules, polysaccharides, proteins, bioceramics and bioglass have been shown to help mechanical performance (He et al., 2014). One example is the addition of citric acid to apatite cement, which caused an increase in injectability and strength, most probably as a result of citrate ions facilitating sliding and dispersion of the apatite crystals, inducing the formation of a stronger matrix. The inclusion of fibers, biodegradable or otherwise, has also shown promise in strengthening CPCs. Depending on volume fraction, fiber-matrix interfacial properties, orientation of the fibers, strength and length the mechanical properties of fiber-reinforced CPCs (frCPCs) can come out to up to two orders of magnitude stronger than CPCs alone, potentially allowing for use in load-bearing areas.

The inconsistency in degradation of CPCs is another enormous limitation in the clinical use of CPCs (He et al., 2014). This could be due to the complexity in composition and setting chemistry of CPCs, as well as the harsh environment of the human body. One brand of CPCs, BoneSource, demonstrated in one study no resorption several years post-implantation, but in another 30% resorption after 12 weeks and 90% after 40 weeks. Being a marquee feature of this type of cement, it is critical that there be some sort of consistent outcome in the resorption of the implant.

2.9 Commercial Viability

Longterm, vertebroplasty ensures better survival than conservative methods, rendering its large short term cost more beneficial than that of conservative treatments (Hopkins et al., 2020). Around one in three women and one in five men 50 years of age or older experience fractures as a result of osteoporosis, and in the United States, around 2 million cases of disease-related bone fracture or trauma occur each year. The treatment cost is considered to be approximately $10 billion yearly. (Yousefi, 2019) Furthermore, the costs of vertebroplasty can be up to 20 times lower than that of kyphoplasty (Klazen et al., 2010; Mathis et al., 2004).

The growing geriatric population who experiences osteoporosis is another contributing factor to the growth of the market of vertebroplasty and other related industries. Annually, more than 8.9 million fractures are created as a result of osteoporosis (Pouresmaeili et al., 2018). In 2022, 18.7% of the European and North American population is 65 years and older. This population is expected to grow to 22.0% in 2030. Analysis conducted by NASDAQ OMX (2021) predicts that by 2027, the global vertebroplasty market will reach $301.7 million USD with a compound annual growth rate (CAGR) of 5.2% between the years of 2020 and 2027. To reach this conclusion, the vertebroplasty of different countries from all continents, apart from Antarctica, were considered. An analysis conducted by MordorIntelligence (n.d.) expects the orthopedic bone cement and casting material market to develop a CAGR of about 8.4% between the years of 2018 and 2028. For this study, market trends of 17 different countries of major regions were studied. The increase in demand of bone cements would be due to the rising incidence of orthopedic and musculoskeletal disorders. The PMMA industry has expanded in favour of the increasing aging population and the Food and Drug Administration's guidelines in reducing the use of harmful plastics in medical applications (Global Market Insights, 2016). According to an analysis conducted by Global Market Insights (2016), the PMMA market is anticipated to reach a market value of 235 million USD in 2024 with a compound annual growth rate (CAHR) of 7.5% between the years of 2016 and 2024.

One potential issue is the lack of cement, conclusive evidence of increased benefit of the vertebroplasty procedure as compared to sham procedures where a local anesthetic is injected into the periosteum, but no cement is injected in the treatment area (Ahn et al., 2013). Two randomized controlled trials published by Mayo Clinic researchers Kallmes et al. and Buchbinder et al. in 2009, both found that while positive clinical outcomes were observed in patients after receiving the vertebroplasty procedure, similar outcomes were observed in the sham set. A few issues have been identified with these studies, such as the discrepancy between patients screened and those ultimately enrolled into the study, the lack of required screening MRIs/bone scans, and the high crossover from the sham to the vertebroplasty group in one of the studies. Another study, published in 2018 by Firanescu et al, also found that throughout the 12-month follow-up period, there was not statistically significantly greater relief in pain compared to the sham procedure among patients being treated for acute OVCFs (Firanescu et al., 2018). There is, however, no question that vertebroplasty is vastly superior to optimal conservative approaches to treatment of OVCFs, even though there is contentious debate surrounding its efficacy as compared to sham trials (Ahn et al., 2013). While this could be cause for concern for the demand of bone cement in vertebroplasty procedures, it is abundantly clear that vertebroplasty significantly improves pain, disability, and quality of life in patients suffering from osteoporotic vertebral fracture. As such, the market is in no immediate danger.

3 SUMMARY AND CONCLUSIONS

Taking into consideration the advantages, limitations, and disadvantages of each bone cement type, PMMA ABC, alongside MC-PMMA, and Magnesium PMMA variations are the most clinically viable options.

1. PMMA's high compressive strength of 111.61 ± 11.43 MPa alongside the cost-effectiveness have contributed greatly to the reliability and popularity of its use in vertebroplasty procedures (Zhu et al., 2020). Despite having superior bioactive properties, CPC, borate/borosilicate, and inorganic nanohybrid bone cement have inferior compressive strengths compared to PMMA.
2. To compensate for its lack of bioactivity, inefficient degradation, PMMA variations with supplemented mineralized collagen (MC-PMMA) or Mg microparticles are promising, as they do not worsen the compressive strength of the PMMA matrix, unlike other additives. Both MC and Mg microparticles improve the cements bioactivity and osteogenesis. The addition of MC does decrease the compressive strength of the cement, however it is within an acceptable range for the external loading that may take place in vertebroplasty with lighter load bearing.
3. Acting as a porogen, the implementation of Mg microparticles introduces sites of biodegradation, increases interconnectivity of bones, promotes osteogenesis when added to PMMA, and has statistically insignificant effects on mechanical properties, and elicits no immune response.
4. For the optimization of PMMA's efficiency, coatings made up of antibiotic-loading agents and radiopacifiers can be used. The addition of antibiotic-agents prevents bacterial infection at the site of injection, which facilitates good biocompatibility.
5. Radiopacifiers provide visibility to bone cement during fluoroscopic procedures, which is vital, and by observing the location of the bone cement during injection, medical professionals are able to correctly and safely set bone cement in the body. Difunctional agent surface-treated barium sulfate, and or zirconia dioxide, are promising radiopacifying agents, as they do not decrease the mechanical properties and or fatigue strength of the cement, unlike traditional agents.

4 RESEARCH GAP AND FUTURE RESEARCH

Research into the next generation of bone cements is continually evolving (He et al., 2014). The ideal bone cement should have adequate cohesion, radiopacity, setting properties, and injectability, so as to maximize ease of handling and thus minimize the potential of complications during the procedure. It would also need to be sufficiently mechanically strong for the immediate reinforcement of the compromised vertebra it is meant to support, ideally having comparable mechanical properties to the bone. A level of porosity that can facilitate the circulation of bodily fluid, cell migration and the ingrowth of new bone should also be established. Excellent osteoconductivity and osteoinductivity is also desirable for the promotion of new bone growth, as well as a moderate level of biodegradability matching the rate of bone formation. Finally, high efficiency of drug delivery is also ideal.

The incorporation of bioactive additives is being experimented with in order to improve generally insufficient osteoinductivity observed in bone cements (He et al., 2014). The incorporation of strontium, magnesium, zinc, copper, and fluoride has proven to be effective in improving the biological performance of CPCs through the promotion of bone metabolism. Due to their high porosity, CPCs are the ideal delivery system for growth factor (GF) and drugs. Various growth factors such as BMPs, VEGF, and basic fibroblast growth factor (bFGF), have been incorporated into CPCs to increase osteogenesis. Plasmids or small interfering RNAs (siRNAs) can be mixed into CPCs for gene delivery to cells in the injection area as well. Finally, more recently platelet-rich plasma (PRP) with autologous bone marrow concentrate (BMC) have been used in conjunction with CPCs as autologous bone substitutes.

Currently, a variety of PMMA-based composite cements are in development through the incorporation of CaPs or polymers to combine the bone augmentation ability of ABCs with the biodegradability of CPCs (He et al., 2014). Research in this area of bone cements could yield the development of a wide array of products tailored to the specific implementations of vertebroplasty procedures. For example, if a young patient experiences a traumatic burst fracture, a high level of biocompatibility and biodegradability is required to facilitate the formation and remodeling of bone. Conversely, in the case of an elderly patient who experiences an OCVF, immediate weight-bearing stability, and therefore a cement with long-term multidirectional stability and a slow rate of resorption, is needed. In the application of metastatic lesions and osteoid osteomas, a cement that produces heat locally and cures quickly could be created. The development of bone cements that balance the characteristics of ABCs and CPCs to match the specific needs of a patient's ailment can solve a variety of practical issues, leading to improved treatment outcomes and reduced complications.

Despite many experiments and studies taking place in the field of bone cements, the optimal mixing ratios of commonly used bone cements and natural bioactive materials are still not definite. In each combination of bone cement and material, porosity, mechanical strength, and biocompatibility differ. Since an ideal bone cement for the repair of many bone defects has not been found yet, researchers are still actively looking for a solution. New types of bone cements have only been tested on animals, so their effects on humans are still untested. Since animals used in bone cement experiments are often small, it is not clear whether the cements can repair only small bone defects or large ones as well. Bone cements for larger bone defects have extensive filling repair times, and in some cases, patients with large bone defects have to undergo a second surgery or implantation of an autologous bone. At this time, the only tested treatment for large bone defects is 3D printing stent technology. (Xia et al., 2022)

REFERENCES

1. Ahn, S., & Jay, B. (2013). Vertebroplasty. Seminars in Interventional Radiology, 30(03), 297–306. https://doi.org/10.1055/s-0033-1353483
2. Chen, F., Song, Z., & Liu, C. (2015). Fast setting and anti-washout injectable calcium–magnesium phosphate cement for minimally invasive treatment of bone defects. Journal of Materials Chemistry B. 47(3), 9173-9181.
3. Chen, J. F., Lee, S. T., Lui, T. N., Wu, C. T., & Liao, C. C. (2002). Percutaneous vertebroplasty for the treatment of osteoporotic vertebral compression fractures: a preliminary report. Chang Gung medical journal, 25(5), 306–314.
4. Chen et al. (2021). Influence of antibiotic-loaded acrylic bone cement composition on drug release behavior and mechanism. Polymers, 13(14), 2240. https://doi.org/10.3390/polym13142240
5. Denaro, L., Longo, U. G., & Denaro, V. (2009). Vertebroplasty and kyphoplasty: reasons for concern?. The Orthopedic clinics of North America, 40(4), 465–viii. https://doi.org/10.1016/j.ocl.2009.05.004
6. Firanescu et al. (2018). Vertebroplasty versus sham procedure for painful acute osteoporotic vertebral compression fractures (VERTOS iv): Randomised sham controlled clinical trial. BMJ. https://doi.org/10.1136/bmj.k1551
7. Global Market Insights. (2016). PMMA Market Size In Healthcare Applications (Medical Ware, Pharmaceutical Handling, Laboratory Ware), Industry Analysis Report, Regional Outlook, Application Potential, Price Trends, Competitive Market Share & Forecast, 2016–2024.
8. He, Z., Zhai, Q., Hu, M., Cao, C., Wang, J., Yang, H., & Li, B. (2015). Bone cements for percutaneous vertebroplasty and balloon kyphoplasty: Current status and future developments. Journal of Orthopaedic Translation, 3(1), 1–11. https://doi.org/10.1016/j.jot.2014.11.002

9. Hopkins, T. J., Eggington, S., Quinn, M., & Nichols-Ricker, C. (2020). Cost-effectiveness of balloon kyphoplasty and vertebroplasty versus conservative medical management in the USA. Osteoporosis International, 31(12), 2461-2471. https://doi.org/10.1007/s00198-020-05513-x

10. Hulme, P. A., Krebs, J., Ferguson, S. J., & Berlemann, U. (2006). Vertebroplasty and kyphoplasty: a systematic review of 69 clinical studies. Spine, 31(17), 1983–2001. https://doi.org/10.1097/01.brs.0000229254.89952.6b

11. Klazen et al. (2010). Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial. The Lancet, 376(9746), 1085-1092.

12. Kuehn, K. D., Ege, W., & Gopp, U. (2005). Acrylic bone cements: composition and properties. Orthopedic Clinics of North America, 36(1), 17-28. https://doi.org/10.1016/j.ocl.2004.06.010

13. Kumar, P, Vinitha, B., & Fathima, G. (2013). Bone grafts in dentistry. J Pharm Bioallied Sci, 5, 125-127. https://doi.org/10.4103/0975-7406.113312

14. Kühn, K.-D. (2000). Bone cements up to date comparison of physical and chemical properties of commercial materials; with 132 tables. Springer.

15. Lai, P. L., Chen, L. H., Chen, W. J., & Chu, I. M. (2013). Chemical and Physical Properties of Bone Cement for Vertebroplasty. Biomed J, 36(4), 167-167. https://doi.org/10.4103/2319-4170.112750

16. Laidler, K. J. (1984). The development of the Arrhenius equation. Journal of Chemical education, 61(6), 494-500. https://doi.org/10.1021/ed061p494

17. Lewis, G. (2006) Injectable bone cements for use in vertebroplasty and Kyphoplasty: State-of-the-art review. Journal of Biomedical Materials Research Part B: Applied Biomaterials, 76B(2), 456-468.

18. Li, J., Wang, H., Guo, Q., Zhu, C., Zhu, X., Han, F., Yang, H., & Li, B. (2019). Multifunctional coating to simultaneously encapsulate drug and prevent infection of Radiopaque agent. International journal of molecular sciences.

19. Lieberman, I. H., Togawa, D., & Kayanja, M. M. (2005). Vertebroplasty and kyphoplasty: filler materials. The spine journal, 5(6 Suppl), 305S–316S. https://doi.org/10.1016/j.spinee.2005.02.020

20. Liu, Q., Liu, C., Wang, W., Yuan, L., Wang, Y., Yi, X., Pan, Z., & Yu, A. (2023, January 26). Bioinspired strontium magnesium phosphate cement prepared utilizing the precursor method for Bone Tissue Engineering. Frontiers.

21. Liu-Snyder, P., & Webster, T. (2008). Developing a new generation of bone cements with nanotechnology. Current Nanoscience, 4(1), 111–118. https://doi.org/10.2174/15734130878359179

22. Lopes, P. P., Garcia, M. P., Fernandes, M. H., & Fernandes, M. H. V. (2013). Acrylic formulations containing bioactive and biodegradable fillers to be used as bone cements: Properties and biocompatibility assessment. Materials Science and Engineering: C, 33(3), 1289–1299. https://doi.org/10.1016/j.msec.2012.12.028

23. Mathis, J. M., Ortiz, A. O., & Zoarski, G. H. (2004). Vertebroplasty versus kyphoplasty: a comparison and contrast. AJNR. American journal of neuroradiology, 25(5), 840–845.

24. Mordor Intelligence. (n.d.). Orthopedic Bone Cement and Casting Material Market Size & Share Analysis - Growth Trends & Forecasts (2023 - 2028). mordorintelligence. https://www.mordorintelligence.com/industry-reports/orthopedic-bone-cement-and-casting-materials-market

25. NASDAQ OMX. (2021). (Global Vertebroplasty Market to Reach $301.7 Million by 2027: Project Details: StrategyR - A Trademark of Global Industry Analysts, Inc. - Project Edition: 8. - Influencer Pool: 1253. - MarketGlass™ Platform - Our influencer driven interactive research platform draws from unique perspectives of participating executives from featured companies.

26. Nussbaum, D. A., Gailloud, P., & Murphy, K. (2004). The chemistry of acrylic bone cements and implications for clinical use in image-guided therapy. Journal of vascular and interventional radiology: JVIR, 15(2), 121–126. https://doi.org/10.1097/01.rvi.0000109394.74740.56

27. Pouresmaeili, F., Kamalidehghan, B., Kamarehei, M., & Goh, Y. M. (2018). A comprehensive overview on osteoporosis and its risk factors. Therapeutics and Clinical Risk Management, 14, 2029-2049. https://doi.org/10.2147/TCRM.S138000

28. Saracen, A., & Kotwica, Z. (2016). Complications of percutaneous vertebroplasty: An analysis of 1100 procedures performed in 616 patients. Medicine.

29. Shi, Y., Yu, L., Gong, C., Li, W., Zhao, Y., Guo, W., & https://orcid.org/0000-0002-9093-9980, W. G. (2021, April 16). IOP Science. Biomedical Materials. https://iopscience.iop.org/article/10.1088/1748-605X/abf5c4

30. Turner, T. M., Urban, R. M., Singh, K., Hall, D. J., Renner, S. M., Lim, T. H., Tomlinson, M. J., & An, H. S. (2008). Vertebroplasty comparing injectable calcium phosphate cement compared with polymethylmethacrylate in a unique canine vertebral body large defect model. The spine journal: official journal of the North American Spine Society, 8(3), 482–487. https://doi.org/10.1016/j.spinee.2006.12.007

31. Tan, S., Zhang, S., Xiao, Y., Du, Y., & Wang, Y. (2021). Injectable bone cement with magnesium-containing microspheres enhances osteogenesis via anti-inflammatory immunoregulation. Bioactive Materials.

32. Vallo, C. I., & Schroeder, W. F. (2005). Properties of acrylic bone cements formulated with Bis-GMA. Journal of Biomedical Materials Research Part B: Applied Biomaterials, 74B(2), 676–685.

33. Wardlaw, D., Cummings, S. R., Van Meirhaeghe, J., Bastian, L., Tillman, J. B., Ranstam, J., Eastell, R., Shabe, P., Talmadge, K., & Boonen, S. (2009). Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial. Lancet (London, England), 373(9668), 1016–1024. https://doi.org/10.1016/S0140-6736(09)60010-6

34. Xia, Y., Wang, H., Li, Y., & Fu, C. (2022). Engineered bone cement trigger bone defect regeneration.

35. Frontiers in Materials, 9. https://doi.org/10.3389/fmats.2022.929618

36. Yousefi, A.-M. (2019). A review of calcium phosphate cements and acrylic bone cements as injectable materials for bone repair and implant fixation. Journal of Applied Biomaterials & Functional k3a Materials, 17(4). https://doi.org/10.1177/2280800019872594

37. Zhai, Q., Han, F., He, Z., Shi, C., Zhou, P., Zhu, C., Guo, Q., Zhu, X., Yang, H., & Li, B. (2018). The "Magnesium Sacrifice" strategy enables pmma bone cement partial biodegradability and osseointegration potential. International journal of molecular sciences.

38. Zhu, J., Yang, S., Cai, K., Wang, S., Qiu, Z., Huang, J., Jiang, G., Wang, X., & Fang, X. (2020). Bioactive poly (methyl methacrylate) bone cement for the treatment of osteoporotic vertebral compression fractures. Theranostics, 10(14), 6544–6560. https://doi.org/10.7150/thno.44428