Bisphosphonate-loaded bone cement: Background, clinical indications and future perspectives

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Abstract

Bisphosphonates represent an established treatment against bone resorption and osseous loss. Local application could help increase bone mineral density while minimizing their systemic use side-effects. Bone cement, used on a large scale in orthopedic surgery and a historically successful drug carrier, could represent an effective scaffold. The aim of this review was to investigate the alterations produced on the cement’s structure and properties by this mixture, as well as its antiosteoporotic and antitumor effect. After a thorough research of articles, title screening and duplicate removal we retained 51 papers. Two independent authors performed abstract and full-text reading, finally leaving 35 articles included in this review. In the current literature, acrylic and calcium phosphate bone cement have been used as carriers. A combination with nitrogen-containing bisphosphonates, e.g., zoledronic acid, provokes modifications in terms of setting time prolongation and mechanical strength decline within acceptable levels, on the condition that the drug’s quantity stays beneath a certain plateau. Bisphosphonates in bone cement seem to have a powerful anti-osteoclastic and osteogenic local impact as well as a direct cytotoxic effect against several neoplastic lesions. Further investigation on the subject is required, with specifically designed studies focusing on this method’s advantages and potential clinical applications.

Keywords: Bisphosphonates, Bone Cement, Osteoporosis, Osteolysis, Bone Regeneration

Introduction

Osteoporosis is becoming a sharp problem affecting millions of people across the globe every year as population ages and life expectancy increases. Osteoporotic bone becomes fragile and more vulnerable to deforming forces, resulting in fractures caused by a relatively low amount of energy. In addition, osteoporotic fractures are usually a challenge to treat, mostly due to the bone’s poor reconstruction skills1,2.

Bone quality can also be compromised in situations of tumor induced osteolysis, like giant cell tumor, metastatic bone disease or multiple myeloma3,4. The presence of tumor cells in multiple cases triggers the secretion of markers like PTHrP, TNF-α, IL-6 and RANKL, leading to increased bone resorption and pathologic fractures. Furthermore, factors released during this procedure such as TGF-β1, calcium and IGF-1 stimulate tumor cells, creating a positive feedback loop and aggravating the osteolytic procedure5,6. In that context, it is imperative to halt this osteolytic pathway in order to aid bone regeneration and slow down osseous loss.

Bisphosphonates (BP) inhibit osteoclastic activity and have been widely used for the past few decades in order to reverse excessive osseous loss. Their administration, either oral or intravenous, has been proved to decrease bone resorption considerably and especially nitrogen-containing BP, such as zoledronic acid (ZOL), demonstrate a powerful effect towards this direction by disrupting the osteoclast mevalonate pathway5,7,8. ZOL in particular, has been shown to
provide an additional cytotoxic antitumor effect\textsuperscript{3,5,9}. However, despite their favorable action, BP’s systemic administration presents low bioavailability and has been associated with complications, such as jaw osteonecrosis, gastrointestinal issues and low energy subtrochanteric fractures\textsuperscript{10}. Local administration could be considered as an alternative in order to take full advantage of their use and achieve high local concentrations while limiting their undesirable side-effects\textsuperscript{11}.

Bone cement is used as means to stabilize orthopedic implants to the bone or fill substantial osseous defects, caused by fractures and skeletal tumors (ex.vertebroplasty)\textsuperscript{12,13}. Next to its initial clinical applications, it also plays the role of drug carrier, the most popular example being the addition of antibiotics (ex.vancomycin), in order to achieve high drug concentration around the bone\textsuperscript{5,6,12}. This practice has also been expanded in the fields of orthopedic oncology, where cement was mixed with antitumor agents, like methotrexate, in order to locally halt tumor growth\textsuperscript{14–19}.

In light of the above, there is a growing interest regarding BP delivered in bone cement and their potential uses against e.x. osteoporotic vertebral fractures as well as wear-debris mediated osteolysis leading to implant loosening. The present review assembles all studies with information regarding BP-loaded cement, its mechanical properties, cytotoxic effects against malignant cells as well as its impact on bone growth and resorption.

**Methods**

**Literature search**

An initial search has been performed aiming to find out all available articles relevant to our topic thus making an estimation of the literature involved with the search criteria. The electronic databases used were PubMed, Cochrane Reviews and Google Scholar. The research conducted was unrestricted. Literature search was based on specific keywords decided beforehand, sufficient enough to cover all aspects of the subject investigated. Keywords used were “bisphophonates”, “cement” combined with ‘AND’ amongst the search terms. The sentences “bisphosphonate loaded cement” and “bisphophonates in bone cement” were also
used for the search. Additional searches were conducted in order to detect any other relevant articles that had not been included in the initial search. PRISMA guidelines were followed for the design and conduction of this review.

**Study selection**

Study selection was performed by two independent authors who realized a meticulous abstract screening in order to exclude articles irrelevant to the subject investigated. The same two authors reviewed the full text of the articles mentioned above. English language and full text availability were paramount inclusion criteria for the studies retained. More specifically, in this review all relevant studies investigating action, results and properties of BP-loaded cement were included. These could refer to its cytotoxic action against tumor cells, its biocompatibility, as well as its osteogenic and anti-osteoporotic effects **in vitro** and **in vivo**.

**Results**

In the initial search, 429 articles met with the search criteria provided. After title screening and duplicate removal, 51 articles remained. Abstract screening further reduced that number, leaving 38 articles for full text review. The subject of the excluded papers varied mainly from the effects of oral or intravenous BP administration to its applications in dentistry. Studies dealing with systemic BP delivery were not included, with the exception of two articles by Yu et al21 and Zhu et al20, where effects of subcutaneous and local delivery were compared. Two papers with available abstracts had to be excluded as they were not written in English and one was not included as the full text was not available. In the end, 35 articles were included in the review (Figure 1).

The first data on the use of BP-loaded cement come from Sabokbar et al. in 1998, where polymethyl methacrylate (PMMA) was mixed with different concentrations of etidronate, then added to mice monocyte cultures. Conclusions made were based on the calculation of tartrate resistant acid phosphatase (TRAP), a marker indicating cell maturation into osteoclasts. In the presence of etidronate-loaded cement, there was a decrease in the amount of TRAP, or else said in osteoclastic activity, indicating an inhibition of bone resorption, an assumption also supported by a decrease in bone resorption pits21.

**Biomechanical properties and search for the most suitable carrier**

Zenios et al. state disappointing results after adding liquid BP pamidronate (PAM) in the acrylic cement Palacos R. PAM addition resulted in unacceptable deterioration of the cement’s flexural modulus and bending strength22. Based on this study, Lewis et al. proposed addition of powder alendronate (ALN). Fatigue tests and porosity measurements were proven satisfactory, making the authors to strongly support this BP form for impregnation in bone cement23.

Matuszewski et al. mixed 40 g of cement with 60 mg PAM. They performed compressive and three-point flexural tests, concluding that BP addition did not have a significant difference neither on the biomechanical properties of the mixture nor on Young’s modulus24. Yu et al. also evaluated potential alterations of acrylic bone cement mixed with ZOL or PAM stating that the high dilution and not the addition of the BP led to the production of an abnormal, weaker substance.

A poor BP elution rate **in vitro** as well as a non-significant bone formation **in vivo**, underlined the necessity for higher BP concentrations in order to become clinically effective12. Last but not least, a 2018 article by Qu et al. examined alterations that occur in several PMMA’s properties, such as compressive, tensional and flexural strength, fatigue life etc. after BP addition. They observed a considerable decrease on the material’s fatigue life and suggested strengthening with additives25.

Next to the research conducted focusing on modifications of PMMA, there is a growing interest for the use of calcium phosphate cement (CPC) as a carrier instead8,10,11,26-26. Panzavolta et al. mixed ALN and PAM, in different concentrations (0.4 and 1 mM), with calcium phosphate (CaP) cement, observing a prolongation in the cement’s initial and final setting times analogic to BP’s addition. A negative impact was also observed on the compressive strength and Young’s modulus, with PAM group presenting the least satisfactory results, probably due to its low affinity to hydroxyapatite (HA). Nevertheless, these alterations led to acceptable results, permitting the potential clinical application of this method21.

Several efforts have been made in order to augment BP incorporation in CaP cement thus improving its carrier potentials. Kim et al. formed CaP in microspheres where ALN could be incorporated, thus increasing the amount of loaded BP, which was released from the cement for 40 days and was also proven capable enough to present an antosteoclastic effect27. Panzavolta et al. included gelatin in the mixture so as to reduce cement’s setting times and ameliorate its mechanical properties, thus equilibrating BPs’ negative impact. CaP cement was able to incorporate a larger dosage of BP whilst maintaining its strength and production phases in acceptable levels28. Dolci et al. planted ALN inside calcium-phosphate-gelatin cement in the form of spray-congealed Solid Lipid Microparticles, incorporating higher doses of BP in this form (7.0 wt%) while avoiding a direct cement-drug contact and eliminating ALN’s documented impact on setting times22,29. Schnitzius et al. (2011) mixed ALN with apatitic CPC on the condition that “…the BP was introduced chemisorbed on calcium-deficient apatite, one of the components of the cement...”. According to the results, there was a significant improvement in the time this material needed to stiffen next to a constant BP release30. Nosoudi et al. added etidronate to CPC, noticing a prolongation of the cement’s initial and final setting times until it reached a peak, with a decrease in its mechanical strength31.
Osteogenic and anti-osteoporotic action

Bodde et al. noticed no new bone production after inserting β-tricalcium phosphate cement with ALN into rabbit femur defects. Bone mineral density as well as its volume remained unchanged some weeks later and an evident reduction in contact areas was noted in the ALN group. According to the authors, an excessive amount of ALN incorporated in the cement (3-4 wt%) led to disorganization of osteoclast-osteoblast equilibrium and forbidding increase in the BP’s cytotoxic action.13

Zhu et al. compared BP’s impact on osseous resorption triggered by wear debris, following local and systemic administration, finding increased bone mineral density in both groups. Local anti-osteolytic effect increased analogically with the amount of mixed ALN (best results with 1 wt%) and was found satisfactory, although subcutaneous administration was slightly more effective.20 Positive osteogenic effect is also recorded by Sorensen et al. who performed an in vivo experiment using ZOL-loaded CaP cement, with a significant increase of bone area and bone-cement contact for the BP loaded cement at 3 weeks’ time, indicating ZOL’s important role in osteoclast inhibition. The necessity to estimate the precise BP quantity was underlined in order to produce a positive effect without weakening the scaffold.22

Matuszewski et al. and Mazurkiewicz et al. investigated the effect of PAM loaded cement, documenting a significant decrease in TNF-α values in blood tests. RANKL-OPG balance was also found to be affected in favor of the second, thus provoking a decrease of factors favoring osteoclastogenesis and leading to a reduction in bone resorption. This argument was supported by micro-CT findings with a notable augmentation in parameters such as bone volume and trabecular thickness.1, 33

Van Houdt et al. put to the test ALN and CaP cement enhanced with the porogenous material polyactic-co-glycocid-acid (PLGA) in order to boost the drug’s local release, leading to a long-term ALN release from the cement. This release was detectable even 148 days after the mixture, with acceptable results in terms of cement setting times and compressive strength. In the in vivo part of the study, BP presence ameliorated bone formation, regeneration and bone-implant contact area numbers.1 In line with the aforesaid, Dolci et al. marked a positive osteogenic impact of ALN loaded cement in vitro with an osteoblast-osteoclast co-culture. The loading of BP in the CaP cement, using Solid Lipid Microparticles, permitted to largely increase the amount of ALN incorporated in the scaffold. A clue not be omitted is the estimation of the exact dosage of ALN needed as it was mentioned that drug’s dosage greater than 30% w/w leads to severe alterations on the compressive strength.3

Gong et al. initially used calcium silicate cement as a carrier, trying to take advantage of its superior mechanical strength over PMMA or CPC. After loading with risendronate (RA) they noticed a dose-dependent weakening of the cement’s strength but also a slow and controlled BP release to the environment.35 In an attempt to optimize the carrier’s biomechanical properties, Gong et al tried calcium phosphate silicate cement (CPSC) as a carrier where they incorporated RA. Dosages of 0.5% RA and 1% RA were compared with the first declared as clinically significant without unacceptably modifying cement’s compressive strength and setting time. In vitro tests revealed elevation of osteoblast-related genes expressing ALP, OPG and runx2, while the aforementioned mixture was found to strongly promote new bone production locally and provide a greater bone-implant stability at radiological and histological testing performed in 10 weeks’ time.26

Song et al. used ALN added into acrylic bone cement and investigated the shear strengths and bone densities in the bone-cement area of rabbit femurs. At 60 days post-surgery, shear strength forces remained practically the same, with a positive effect in bone densities, in contrast to a remarkable decrease noticed in the control group. Best results were recorded after addition of 100 mg of ALN into 50 g of bone cement powder. However, shear strengths on metal-bone cement interface were inversely analogical to the amount of ALN mixed. It was assumed that the addition of BP may be useful in preventing aseptic loosening of joint prostheses, on the condition that it is to be kept below a certain plateau that does not drastically affect metal-bone cement shear strengths.36 Zhao Jindong et al. also used different ALN concentrations incorporated in CPC, testing its properties and release in vitro but also their osteogenic impact in vivo. ALN-loaded CPC led to a decrease of mechanical strength, which remained within acceptable levels, in accordance with the study conducted by Panzavolta et al.11, 37, 38 BP release peaked in the first 5 days, with a starting point analogous to the amount of ALN, then slowing down only to reach a certain plateau at 21 days. A significant augmentation regarding bone mineral density and trabecular number showed that an ALN-loaded CPC implanted in the bone halts the microarchitecture changes provoked by osteoporosis and improves osseous quality, with the best results coming from 5% ALN group.37, 38

Wu et al. observed in vivo the antiosteoporotic effects of a ZOL-CPC composite, noting a reduction in the bone resorption (fragments of C-telopeptides of type I collagen) and bone formation markers (ALP and osteocalcin). Osteopontin levels were also decreased, indicating a negatively affected osteoclastic activity. Finally, the bone’s radiological evaluation with micro-CT demonstrated a ZOL-CPC beneficial impact on the bone’s microarchitecture and volume.39

A research conducted by Calvo-Fernandez et al. (2010), investigates features of an ALN-loaded acrylic cement in vitro and in vivo. Addition of 1.5wt% ALN caused signs of cytotoxicity in vitro when placed into osteoblast cultures during the first days when the drug presented the maximum release from PMMA while, in vivo, ALN-loaded cement helped with bone reconstruction and promoted osseous regeneration. An explanation for the in vitro elevated cytotoxicity was the excess of ALN accumulated in the osteoblast cultures, which can be balanced in vivo by the
removal of an important drug quantity via blood circulation\(^6\).

Last but not least, Verron et al., after concluding that C\(\text{aP}\) cement was a reliable bone drug carrier, advance on testings on animal models\(^{41,42}\). In a study of 2014, sheep osteoporotic vertebrae were identically filled with 0.56 mg ALN per g of cement. Three months later, radiological and histological study of vertebral segments demonstrated a strong osteogenic effect on the sheep’s bones, more powerful in a short distance from the implant, as well as an improved microarchitecture and cortical bone thickness, an outcome which CPC by itself wasn’t able to evoke\(^43\).

**Cytotoxic and antineoplastic effects**

A study by Zwolak et al. is the first to deal with ZOL’s cytotoxic action against neoplastic cells when released locally by bone cement. ZOL-PMMA mixture was placed in different tumor cell cultures (multiple myeloma, giant tumor and renal cell carcinoma cells) and its cytotoxicity was put to the test. BP loaded cement showed a cytotoxic impact, as tumor cells number was reduced significantly in all cultures\(^6\).

Similar results were recorded in a study conducted by Koto et al. where the authors created three different groups of 2.0 mg of ZOL mixed with two different types of PMMA (with different polymerization temperatures) and HA. Their effect was observed on multiple malignant tumor cells culture lines, including osteosarcoma, synovial sarcoma etc. BP-loaded bone cement and HA demonstrated indeed an antitumor activity as proliferation of all cell lines was halted whereas positive feedback was also noticed in vivo. ZOL was proven to not getting affected by polymerization heat but taking part in the destruction of cancerous cells in a non-negligible way\(^5\).

There are two clinical studies in the recent literature dealing with ZOL-loaded bone cement for the treatment of patients with giant cell tumor which, although mostly benign, usually provokes severe bone loss due to the presence of giant cells resembling to osteoclasts and stromal cells producing RANKL\(^44\). Chen et al. published a case series of four patients with cauda equine syndrome due to sacral giant cell tumor. The void created after intraslesional curettage was filled with spheres formed by hand and made up of a mixture of 40 g PMMA with 4 mg ZOL acid and 1 g Vancomycin. The outcome was impressive as new bone formation was detected during the 28-month follow-up, clinically all patients had neurological recovery and no local recurrence of the tumor was noticed. The results of the study were highly encouraging although the presence of antibiotic remains an issue as it could have potentially biased the results\(^3\).

Greenberg et al. use a combination of 40 g PMMA with 4 mg/100 ml ZOL. In this study, 17 patients with giant cell tumor of the extremities, were treated with intraslesional curettage followed by adjuvant treatment. The cavity’s remplissage was then performed either by BP-PMMA alone or with the addition of bone graft. During 1 to 12 years follow-up, there was one case of local recurrence (5.9%), a significantly lower rate than the one reported in older series\(^45\) and significant improvement in function and quality of life, demonstrating the potential of combining PMMA and ZOL in reducing tumor local recurrence\(^46\).

**Discussion**

BP systemic use against osteoporosis and tumor induced osteolysis is a thoroughly investigated subject. Several studies focus on their enhancing effect on the osteoporotic bone as well as their contribution in halting the osseous destruction of tumoral origin\(^5,43,46\). Next to the undoubted advantages, limitations of their systemic use have also been well documented which can complicate patients’ therapeutic algorithm\(^20,29\).

BPs antosteoporotic local use has been partially studied, although there have been several ideas in the past. In a study of Bobyn et al. orthopedic implants were bathed in ZOL solution before placed into the bone whereas Peter et al. insert BP in the HA coating of implants. All these efforts help increase bone’s density and material anchorage leading to the assumption that these beneficial effects are to be maintained when BP are loaded to a carrier and applied directly into a bone defect\(^47,48\).

Bone cement has already given credentials as a successful antibiotic scaffold in order to prevent and treat skeletal infectious situations\(^5,6,12\). It was also used as a delivery system for cytotoxic agents in an attempt to locally contribute in tumor cell reduction. Hernigou et al. mixed methotrexate with PMMA without altering the drug’s properties, producing positive results when used locally against osteosarcoma\(^49\). Wang HM et al. and Kirchen et al. demonstrated the effectiveness of methotrexate-loaded PMMA against different tumor cells and its ability to decrease the amount of associated osteolysis\(^15,16\). Finally, Ozben et al. successfully used cisplatin-loaded PMMA against Saos-2 cells without noticing any grave alteration of the cement’s properties\(^50\). With this rationale in mind, the clinical application of BP loaded cement was found to be intriguing as it concerns a therapeutic agent combining a potential cytotoxic effect with a simultaneous osteogenic action.

Next to the first promising results coming from the addition of BP in terms of bone regeneration and osteoclast inhibition, alteration of cement’s setting times and mechanical properties was a concern from the very beginning\(^21,22\). A vast majority of studies concluded that the impact on acrylic cement composites was not of dramatic clinical significance and the mixture could be applied in clinical practice, on the condition that BP concentration stayed below a low plateau of 1.5-2.0 wt\%\(^3,4,5,12,24,36,40\).

In the recent years, the use of CaP cement as a more suitable BP carrier has provoked a great interest. This biomaterial, already popular in medical and dental surgical procedures, may be used instead of PMMA with a highly satisfactory performance in terms of bio-compatibility and injectability. Thanks to its resemblance to HA, it can be further remodeled and replaced by new bone in vivo, once placed into the osseous defect. In addition, unlike PMMA,
it does not pass through exothermic reaction, avoiding the inflammatory response provoked by temperature elevation and permitting CPC to become an ideal carrier for a variety of substances without allowing the heat to alter their form.\textsuperscript{10,26,50}

However, BP's great affinity for calcium creates problems, resulting in drug-HA binding and high interaction when mixed with the cement. The setting times prolongation and unacceptable mechanical strength decrease questions the role of CPC as a BP carrier as it limits the amount of incorporated drug.\textsuperscript{9,11,26,30,37} Shen et al. mentioned that CaP cement's setting time and mechanical strength were drastically degraded when the drug's concentration overpassed 2\%, indicating BP's effect to be dose-dependent.\textsuperscript{6} Therefore, the exact dosage needs to be determined in order to be effective and on the same time keep the carrier's properties in acceptable levels. Certain studies (Shen et al., Zhu et al., Dolci et al.) succeeded in striking that balance and suggest a BP dosage of 1.0-2.0 wt.% in the CaP bone cement.\textsuperscript{8,20,29}

Acknowledging the low BP concentration in the CaP cement composite, several studies aimed at revealing a method that could help incorporate a larger drug quantity. The addition of gelatin proved to be an effective solution (Panzavolta et al.) as well as ALN processing in order to be delivered to CaP cement in the form of Solid Lipid Microparticles (Dolci et al.), leading to a considerable BP amount augmentation (7.0 wt%)\textsuperscript{7,28,29}. Although promising, these methods should be put under further investigation before arriving to definite conclusions concerning their utility and it still stays unclear which is the ideal cement carrier for BP incorporation. It is possible that there are more than one possible answers, with clinical indications remaining a decisive factor, as CaP cement, for example, represents a competent scaffold when it comes to remplissage of low weight-bearing bone areas.

An undisputable conclusion during this review's preparation was the local osteogenic and antiosteoclastic activity of BP-bone cement application. Literature agrees that the beneficial properties while avoiding its systemic side-effects. Literature covering the topic of antineoplastic action of BP-enriched cement remains surprisingly limited. In vitro and in vivo trials performed up till now provide encouraging results, as cancerous cells cultures declined and tumor necrosis was observed.\textsuperscript{5,6} Most importantly, BP-loaded PMMA seems to be highly efficient combined with intralesional curettage, with very low rates of local recurrence. The most extraordinary outcome was the evident bone regeneration around cement balls, detected radiographically in sacrum X-rays on the study of Chen et al.\textsuperscript{2} It is a vital clue that should motivate more research on the subject. In addition, as the only data provided refer to the action of ZOL, utility of more nitrogen-BPs needs to be put to the test. Last but not least, the aforementioned clinical trials focus mostly on the treatment of giant cell tumor, an entity whose activity is based on osteoclast activation and bone resorption, therefore presenting a fertile ground for ZOL or other similar substances to thrive. In order to better understand BPs' antitumor action, more tumor types with different behavior must be examined.

Conclusions

BP-loaded bone cement represents an innovative therapeutic approach which maintains the substance's beneficial properties while avoiding its systemic side-effects. Alterations in the cement's setting times and biomechanical properties exist. In general terms, they produce a clinically applicable result, their intensity depending on the carrier type and drug concentration, but in any case, need to be further explored in the direction of achieving a higher substance incorporation. The mixture certainly reduces osteoclastic...
bone resorption while assisting in osseous regeneration and may potentially be applied in situations of inadequate bone stock, such as osteoporotic vertebrae and joint arthroplasty in elderly patients. Furthermore, it produces a local antineoplastic effect that can be proved a valuable adjuvant treatment next to tumor resection or radiotherapy, finding use in the prevention of local recurrence. Not least of all, its osteogenic properties can contribute to halt the metastatic osteolytic pathway and boost bone regeneration. There is evident necessity for further investigation on the subject aiming towards a future broad application that could possibly ameliorate patients’ quality of life.

Authors’ contributions

Panteleimon N. Zogakis performed the research design, acquisition and interpretation of data. He also contributed in the drafting and revision of the paper as well as the approval of the final version. Alisson R. Teles contributed in the critical revision of the paper and approval of the final version. Evangelos P. Zafeiris performed a critical revision of the paper and participated in the approval of the final version. Christos P. Zafeiris contributed in the research design, acquisition and interpretation of data as well as the drafting and revision of the paper and approval of the final version. All authors read and approved the final manuscript.

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