Review Article

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

Panteleimon N. Zogakis[1,2], Alisson R. Teles[3], Evangelos P. Zafeiris[4], Christos P. Zafeiris[1]

[1]Laboratory for Research of the Musculoskeletal System "Th. Garofalidis", Medical School, National and Kapodistrian University of Athens, KAT General Hospital of Athens, Greece;

[2]1st Department of Orthopaedics, General Children's Hospital "Aghia Sofia", Athens, Greece;

[3]Neurosurgery and Spine Program, Hospital Beneficente São Carlos, Farroupilha-RS, Brazil
McGill Scoliosis and Spine Group, Montreal-QC, Canada;

[4]2nd Department of Orthopaedics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece

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 skills[1,2].

Bone quality can also be compromised in situations of tumor induced osteolysis, like giant cell tumor, metastatic bone disease or multiple myeloma[3,4]. The presence of tumor cells in multiple cases triggers the secretion of markers like PTHrP, TNF-a, 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 procedure[5,6]. 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 pathway[5,7,8]. ZOL in particular, has been shown to
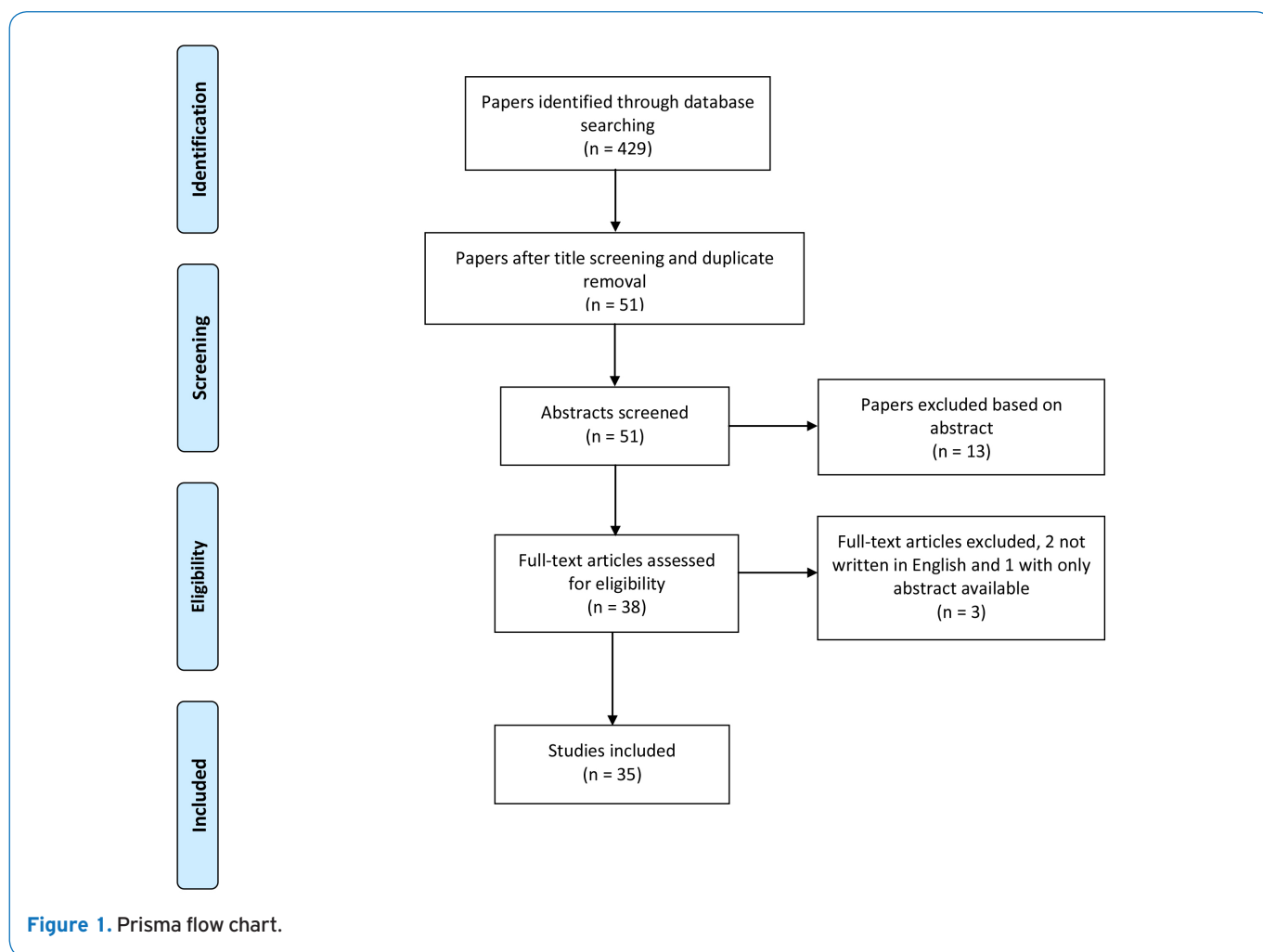
Figure 1. Prisma flow chart.

provide an additional cytotoxic antitumor effect[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[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[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)[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[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[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 "**bisphosphonates**", "**cement**" combined with 'AND' amongst the search terms. The sentences "**bisphosphonate loaded cement**" and "**bisphosphonates 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 al[12] and Zhu et al[20], 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 pits[21].

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 strength[22]. 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 cement[23].

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 modulus[24]. 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 effective[12]. 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 additives[25].

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 instead[8,10,11,26-26]. 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 method[11].

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 antiosteoclastic effect[27]. 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 levels[28]. 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 times[7,29]. Schnitzler 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 release[30]. 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 strength[31].

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[32].

Matuszewski et al. and Mazurkiewicz et al. investigated the effect of PAM loaded cement, documenting a significant decrease in TNF-a 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[4,33].

Van Houdt et al. put to the test ALN and CaP cement enhanced with the porogenous material polylactic-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[29].

Gong et al. initially used calcium silicate cement as a carrier, trying to take advantage of its superior mechanical strength over PMMA or CPC[34]. After loading with risedronate (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[2].

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 analogic 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[40].

Last but not least, Verron et al., after concluding that CaP cement was a reliable bone drug carrier, advance on testings on animal models[41,42]. In a study of 2014, sheep osteoporotic vertebraes 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 intralesional 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 intralesional 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 antiosteoporotic 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[14]. 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[49]. 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[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[8,11,26,30,37]. 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[8]. 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[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 (7.0wt%)[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 antiosteoporotic effect of BPs can be reproduced in a local scale when a BP-bone cement composite is applied to the bone. This is confirmed by reduction of osteoclastic markers such as TNF-a and RANKL and elevation of osteogenic factors like ALP, OPG, Runx[24,33,35]. Osteoblast cultures have been shown to thrive after interaction with this mixture whereas osteoclast numbers saw a remarkable reduction7. Evidence were also found during radiological evaluation, with an enhancement of microarchitecture, bone regeneration, and augmentation of bone volume[1,33,37,39]. Finally, the halt in osseous loss and formation of new tissue is clearly confirmed via histological examination[12,40,43].

Most of the studies describe a short term observation, like the study of Sorensen et al. or Schnitzler et al., with a 3 to 4-week duration[30,32]. Longer studies are, to the best of our knowledge, the ones of Calvo-Fernandez et al. with a maximum duration of 24 weeks and the one of Verron et al. at 12 weeks[40,43]. A longer-term observation period would help to better understand the impact of BP on the osseous environment after being released from its scaffold.

Several clinical applications are to be considered based on the aforementioned results. A commercially available BP-loaded bone cement could be used for injection in osteoporotic vertebrae in order to improve bone quality before arriving to a compression fracture or function as a supplementary for already existing procedures such as vertebroplasty and balloon kyphoplasty in order to upgrade the level of osseous restoration[40,43]. Joint arthroplasty industry may find benefit as well, given that a cement was to be provided that does not only ensure the stability of orthopedic implants but also continues *in vivo* to work against wear-debris induced osteolysis[20,36]. By these means, a valuable aid against aseptic loosening could be established, helping against a growing problem with high medical and economic impact[51].

An impressive finding remains the composite's direct cytotoxic, anti-tumor action. BP used as antineoplastic treatment is not a new idea. It is known that "*bisphosphonates may induce apoptosis in neoplastic cells via modulation of the activity of small GTPases*"[52]. Nishisho et al. describe the therapeutic effect of ZOL when injected directly into a proximal tibia giant cell tumor lesion[9]. Tse et al. notes how systemic BP administration worked perfectly as adjuvant therapy next to intralesional curettage[44] while Forsea et al. talk about the regression PAM and ZOL provoked on human melanoma cell cultures[53].

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[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.[3]. 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-BP 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 vertebraes 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.

References

1. van Houdt CIA, Gabbai-Armelin PR, Lopez-Perez PM, et al. Alendronate release from calcium phosphate cement for bone regeneration in osteoporotic conditions. Sci Rep 2018;8(1):1-13.

2. Gong T, Chen Y, Zhang Y, et al. Osteogenic and anti-osteoporotic effects of risedronate-added calcium phosphate silicate cement. Biomed Mater 2016;11(4).

3. Chen KH, Wu PK, Chen CF, Chen WM. Zoledronic acid-loaded bone cement as a local adjuvant therapy for giant cell tumor of the sacrum after intralesional curettage. Eur Spine J 2015;24(10):2182-2188.

4. Mazurkiewicz T, Matuszewski Ł, Matuszewska A, Jaszek M. Implanted bisphosphonates in bone cement affect bone markers in rat serum. Int Orthop 2013;37(5):969-974.

5. Koto K, Murata H, Sawai Y, Ashihara E, Horii M, Kubo T. Cytotoxic effects of zoledronic acid-loaded hydroxyapatite and bone cement in malignant tumors. Oncol Lett 2017;14(2):1648-1656.

6. Zwolak P, Manivel JC, Jasinski P, et al. Cytotoxic effect of zoledronic acid-loaded bone cement on giant cell tumor, multiple myeloma, and renal cell carcinoma cell lines. J Bone Jt Surg - Ser A 2010;92(1):162-168.

7. Dolci LS, Panzavolta S, Albertini B, et al. Spray-congealed solid lipid microparticles as a new tool for the controlled release of bisphosphonates from a calcium phosphate bone cement. Eur J Pharm Biopharm 2018;122(September 2017):6-16.

8. Shen Z, Yu T, Ye J. Microstructure and properties of alendronate-loaded calcium phosphate cement. Mater Sci Eng C 2014;42:303-311.

9. Nishisho T, Hanaoka N, Endo K, Takahashi M, Yasui N. Locally administered zoledronic acid therapy for giant cell tumor of bone. Orthopedics 2011;34(7):e312-5.

10. Bigi A, Boanini E. Calcium phosphates as delivery systems for Bisphosphonates. J Funct Biomater 2018; 9(1):6.

11. Panzavolta S, Torricelli P, Bracci B, Fini M, Bigi A. Alendronate and Pamidronate calcium phosphate bone cements: Setting properties and *in vitro* response of osteoblast and osteoclast cells. J Inorg Biochem 2009;103(1):101-106.

12. Yu NYC, Ruys AJ, Zenios M, et al. Bisphosphonate-laden acrylic bone cement: Mechanical properties, elution performance, and *in vivo* activity. J Biomed Mater Res - Part B Appl Biomater 2008;87(2):482-491.

13. Bodde EWH, Kowalski RSZ, Spauwen PHM, Jansen JA. No increased bone formation around alendronate or omeprazole loaded bioactive bone cements in a femoral defect. Tissue Eng - Part A 2008;14(1):29-39.

14. Hernigou P, Thiery JP, Benoit J, et al. Methotrexate diffusion from acrylic cement. Local chemotherapy for bone tumours. J Bone Jt Surg - Ser B 1989;71(5):804-811.

15. Wang HM, Crank S, Oliver G, Galasko CSB. The effect of methotrexate-loaded bone cement on local destruction by the VX2 tumour. J Bone Jt Surg - Ser B 1996;78(1):14-17.

16. Kirchen ME, Menendez LR, Lee JH, Marshall GJ. Methotrexate eluted from bone cement: Effect on giant cell tumor of bone *in vitro*. Clin Orthop Relat Res 1996;(328):294-303.

17. Özben H, Eralp L, Baysal G, Cort A, Fiarkalkan N, Özben T. Cisplatin loaded PMMA: Mechanical properties, surface analysis and effects on Saos-2 cell culture. Acta Orthop Traumatol Turc 2013;47(3):184-192.

18. Tani T, Okada K, Takahashi S, Suzuki N, Shimada Y, Itoi E. Doxorubicin-loaded calcium phosphate cement in the management of bone and soft tissue tumors. *In Vivo* (Brooklyn) 2006;20(1):55-60.

19. Greco F, De Palma L, Specchia N, Jacobelli S, Gaggini C. Polymethylmethacrylate-antiblastic drug compounds: An *in vitro* study assessing the cytotoxic effect in cancer cell lines - A new method for local chemotherapy of bone metastasis. Orthopedics 1992;15(2):189-194.

20. Zhu FB, Cai XZ, Yan SG, Zhu HX, Li R. The effects of local and systemic alendronate delivery on wear debris-induced osteolysis *in vivo*. J Orthop Res 2010; 28(7):893-899.

21. Sabokbar A, Fujikawa Y, Murray DW, Athanasou NA. Bisphosphonates in bone cement inhibit PMMA particle induced bone resorption. Ann Rheum Dis 1998; 57(10):614-618.

22. Zenios M, Nokes L, Galasko CSB. Effect of a bisphosphonate, disodium pamidronate, on the quasi-static flexural properties of Palacos R acrylic bone cement. J Biomed Mater Res - Part B Appl Biomater 2004;71(2):322-326.

23. Lewis G, Janna S. Alendronate in bone cement: Fatigue life degraded by liquid, not by powder. Clin Orthop Relat Res 2006;(445):233-238.

24. Matuszewski Ł, Olchowik G, Mazurkiewicz T, et al. Biomechanical parameters of the BP-enriched bone cement. Eur J Orthop Surg Traumatol 2014;24(4):435-441.

25. Qu GX, Ying ZM, Zhao CC, Yan SG, Cai XZ. Mechanical properties and porosity of acrylic cement bone loaded with alendronate powder. Int J Med Sci 2018; 15(13):1458-1465.

26. Parasaram V, Chowdhury A, Karamched SR, Siclari S, Parrish J, Nosoudi N. Bisphosphphonate-calcium phosphate cement composite and its properties. Biomed Mater Eng 2019;30(3):323-331.

27. Kim CW, Yun YP, Lee HJ, Hwang YS, Kwon IK, Lee SC. *In situ* fabrication of alendronate-loaded calcium phosphate microspheres: Controlled release for inhibition of osteoclastogenesis. J Control Release 2010;147(1):45-53.

28. Panzavolta S, Torricelli P, Bracci B, Fini M, Bigi A. Functionalization of biomimetic calcium phosphate bone cements with alendronate. J Inorg Biochem 2010;104(10):1099-1106.

29. Dolci LS, Panzavolta S, Torricelli P, et al. Modulation of Alendronate release from a calcium phosphate bone cement: An *in vitro* osteoblast-osteoclast co-culture study. Int J Pharm 2019;554(August 2018):245-255.

30. Schnitzler V, Fayon F, Despas C, et al. Investigation of alendronate-doped apatitic cements as a potential technology for the prevention of osteoporotic hip fractures: Critical influence of the drug introduction mode on the *in vitro* cement properties. Acta Biomater 2011;7(2):759-770.

31. Nosoudi N, Hasanzadeh A, Holman D, et al. Calcium phosphate/etidronate disodium biocement: Etidronate, retarder or accelerator. Nano Biomed Eng 2014;6(1):40-45.

32. Sörensen TC, Arnoldi J, Procter P, et al. Locally enhanced early bone formation of zoledronic acid incorporated into a bone cement plug *in vivo*. J Pharm Pharmacol. 2013;65(2):201-212.

33. Matuszewski Ł, Turżańska K, Matuszewska A, Jabłoński M, Polkowska I, Mazurkiewicz T. Effect of implanted bisphosphonate-enriched cement on the trabecular microarchitecture of bone in a rat model using micro-computed tomography. Int Orthop 2013;37(6):1187-1193.

34. Zhao W, Wang J, Zhai W, Wang Z, Chang J. The self-setting properties and *in vitro* bioactivity of tricalcium silicate. Biomaterials 2005;26(31):6113-6121.

35. Gong T, Wang Z, Zhang Y, et al. Preparation, characterization, release kinetics, and *in vitro* cytotoxicity of calcium silicate cement as a risedronate delivery system. J Biomed Mater Res - Part A 2014; 102(7):2295-2304.

36. Song DY, Mao XZ, Ding ML, Ni JD. Effects of alendronate sodium content on the interface strengths of composite acrylic bone cement. Int J Endocrinol 2015;2015.

37. Zhao J, Tang H, Wang J, Li G. Local treatment of osteoporosis with alendronate-loaded calcium phosphate cement. Chin Med J (Engl) 2014;127(22):3906-3914.

38. Zhao J, Tang H, Gu J, Wang B, Bao L, Wang BQ. Evaluation of a novel osteoporotic drug delivery system *in vitro*: Alendronate-loaded calcium phosphate cement. Orthopedics 2010;33(8): 10.3928/01477447-20100625-15.

39. Wu CC, Wang CC, Lu DH, Hsu LH, Yang KC, Lin FH. Calcium phosphate cement delivering zoledronate decreases bone turnover rate and restores bone architecture in ovariectomized rats. Biomed Mater 2012;7(3):035009.

40. Calvo-Fernández T, Parra J, Fernández-Gutiérrez M, et al. Biocompatibility of alendronate-loaded acrylic cement for vertebroplasty. Eur Cells Mater 2010;20:260-273.

41. Verron E, Gauthier O, Janvier P, et al. *In vivo* bone augmentation in an osteoporotic environment using bisphosphonate-loaded calcium deficient apatite. Biomaterials 2010;31(30):7776-7784.

42. Faucheux C, Verron E, Soueidan A, et al. Controlled release of bisphosphonate from a calcium phosphate biomaterial inhibits osteoclastic resorption *in vitro*. J Biomed Mater Res - Part A 2009;89(1):46-56.

43. Verron E, Pissonnier ML, Lesoeur J, et al. Vertebroplasty using bisphosphonate-loaded calcium phosphate cement in a standardized vertebral body bone defect in an osteoporotic sheep model. Acta Biomater 2014; 10(11):4887-4895.

44. Tse LF, Wong KC, Kumta SM, Huang L, Chow TC, Griffith JF. Bisphosphonates reduce local recurrence in extremity giant cell tumor of bone: A case-control study. Bone 2008;42(1):68-73.

45. Errani C, Ruggieri P, Asenzio MAN, et al. Giant cell tumor of the extremity: A review of 349 cases from a single institution. Cancer Treat Rev 2010;36(1):1-7.

46. Greenberg DD, Lee FY. Bisphosphonate-loaded Bone Cement as a Local Adjuvant Therapy for Giant Cell Tumor of Bone. Am J Clin Oncol Cancer Clin Trials 2019;42(3):231-237.

47. Bobyn JD, McKenzie K, Karabasz D, Krygier JJ, Tanzer M. Locally delivered bisphosphonate for enhancement of bone formation and implant fixation. J Bone Jt Surg - Ser A 2009;91(Suppl. 6):23-31.

48. Peter B, Pioletti DP, Laïb S, et al. Calcium phosphate drug delivery system: Influence of local zoledronate release on bone implant osteointegration. Bone 2005; 36(1):52-60.

49. Özben H, Eralp L, Baysal G, Cort A, Fiarkalkan N, Özben T. Cisplatin loaded PMMA: Mechanical properties, surface analysis and effects on Saos-2 cell culture. Acta Orthop Traumatol Turc 2013;47(3):184-192.

50. Ginebra MP, Traykova T, Planell JA. Calcium phosphate cements as bone drug delivery systems: A review. J Control Release 2006;113(2):102-110.

51. Nosoudi N, Moztarzadeh F, Rabiee S, Gelinsky M,

Nezafati N. Using bisphosphonate as a part of calcium phosphate cement in osteoporotic patients for local loosening prevention. Bone 2009;44:S88.

52. Macedo F, Ladeira K, Pinho F, et al. Bone metastases: An overview. Oncol Rev 2017;11(1):321.

53. Forsea AM, Müller C, Riebeling C, Orfanos CE, Geilen CC. Nitrogen-containing bisphosphonates inhibit cell cycle progression in human melanoma cells. Br J Cancer 2004;91(4):803-810.