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Review Article

Bisphosphonate releasing dental implant surface coatings and osseointegration: A systematic review

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الملخص

أهداف البحث: تعتبر البايفوسفونيت من فئات الأدوية المستخدمة لعلاج هشاشة العظام. ولقد تم الاقتراح بأن تغطية الزرعات السنية بالبايفوسفونيت يؤثر إيجابا على تشكيل عظم جديد. والهدف من هذه المراجعة هو تحليل البيانات المتاحة حاليا حول الفاعلية السريرية والتجريبية لزرعات التيتانيوم السنية المحررة للبايفوسفونيت من أجل التحقق من إمكاناتها في الزرعات الفمية في طب الأسنان.

طرق البحث: تمت صياغة سؤال محدد؛ بحسب القواعد الإرشادية PRISMA ونظام PICO ؛ وكان السؤال المحدد: ما هو تأثير البايفوسفونيت المتحرر من الزرعات السنية المغطاة به على الاندماج العظمي مع زرعات التيتانيوم السنية؟ وتم البحث في قواعد البيانات الالكترونية PubMED/MEDLINE; ISI Web of Knowledge; Embase and Google Scholar باستخدام الكلمات المفتاحية "زرع الأسنان"؛ "البايفوسفونيت" و"التيتانيوم". تم تلخيص وتحليل الجودة منهجيا والخصائص العامة والنتائج لكل دراسة.

النتائج: توافقت١١ مقالة مع معايير هذه المراجعة. وكانت ثمانية منها دراسات تجريبية، ودراستان سريرية، ودراسة واحدة تجريبية وسريرية. وحققت الزرعات المغطاة بالبايفوسفونيت في ٩ دراسات (٨٢٪)؛ اندماجا عظميا أعلى كما هو مبين من قبل بواسطة قيم أعلى لتردد الرنين، وإزالة عزم الدوران، والاتصال العظمي الزرعي، وتشكيل العظام الجديد. ولم يكن هناك فرق بين الاندماج العظمي في دراستين فقط (١٨٪) للزرعات المغطاة بالبايفوسفونيت والضوابط.

الاستنتاجات: زرعات الأسنان المحملة بالبايفوسفونيت يمكن أن يكون لها تأثير إيجابي على الاندماج العظمي. ولكن هناك حاجة إلى المزيد من الدراسات السريرية لتأكيد دلائل تأثيراتها العظمية.

الكلمات المفتاحية: البايفوسفونيت؛ مواد الأسنان الحيوية؛ توصيل الأدوية؛ الاندماج العظمي

Abstract

Objectives: Bisphosphonates (BPs) are a class of drugs that are used to treat osteoporosis. It has been suggested that BP coatings on dental implants have a positive effect on new bone formation. The purpose of this review is to analyse the currently available data concerning the clinical and experimental efficacy of BP-releasing titanium implants such that their potential in clinical oral implant dentistry may be ascertained.

Methods: Based on a literature review, a focused research question was constructed: what is the effect of a BP-releasing coating on the osseointegration of titanium dental implant? The databases of PubMED/MEDLINE; ISI Web of Knowledge; Embase and Google Scholar were searched electronically using the keywords 'dental implant'; 'bisphosphonate' and 'titanium.' The quality; general characteristics and outcomes of each study were summarized and analysed systematically.

Results: A total of eleven articles fulfilled the criteria to be included in this review. Eight studies were experimental; two studies were clinical; and one study was experimental and clinical. In nine studies (82%), BP-

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coated implants resulted in higher osseointegration, as indicated by higher resonance frequency values, removal torque, bone-implant contact and new bone formation. In two studies (18%), there was no difference between the osseointegration of BP-coated implants and controls.

Conclusions: Bisphosphonates-loaded implants may have a positive effect on osseointegration. However, more well-designed clinical studies are required to demonstrate their osseoconductive effects.

Keywords: Bisphosphonate; Dental biomaterials; Drug delivery; Osseointegration

Introduction

Dental implants are devices that are surgically placed in the mandibular or maxillary bone to support or retain prosthodontic or orthodontic appliances.[1,2] For a long-term clinical success of dental implants, a direct and intimate contact between the bone and the implant surface must exist. The formation of such an implant–bone interface is termed osseointegration.[3–5] If the implant does not osseointegrate, it leads to failure, resorption of the alveolar bone and loss of the implant.[6] Currently, the most widely used dental implant material is titanium.[7] A number of factors may lead to failure of osseointegration, such as poor bone quality and volume, periodontitis, poor systematic health, tobacco use, and poor oral hygiene.[8,9] Additionally, implant characteristics, such as surface texture, shape and material, also play key roles towards osseointegration.[7,10]

Therefore, a dental implant material must fulfil a number of requirements in order to be used in clinical settings.[7,11] First, the surface of the dental implant must be hydrophilic to promote cellular adhesion. Hydrophilicity may be increased by means of numerous surface treatments and coatings. Second, the shape of the implant must suit the site of application. In addition, coatings of osseoconductive materials, such as calcium phosphates and hydroxyapatite (HA), on the implant surface have been observed to promote the surface properties of dental implants.[12,13] However, even with the aforementioned surface treatments, implants are known to fail.[9] For example, the poor mechanical properties and delamination of the bioactive layer from the titanium surface contributes to the failure of osseointegration. The coating process involves implant treatment at high temperatures that leads to the formation of weaker calcium phosphate phases that might break off from the deeper layers of the coating.[7] More recently, immobilizing bioactive and osseoconductive drugs and growth factors have been advocated to improve osseointegration.[14]

Systematic bone diseases, such as osteoporosis, affect bone physiology and osseointegration.[15,16] The prevalence of osteoporosis is on the rise, posing a key healthcare problem.[17,18] Bisphosphonates (BPs) are a class of drugs that are commonly used to treat osteoporosis.[17–19] Although BPs' prolonged systemic use may cause bisphosphonate-related osteonecrosis of the jaws (BRONJ), their topical application has resulted in a positive effect on periodontal health and bone formation.[20–22] BPs reduce bone resorption by inhibiting osteoclasts by inhibiting the farnesyl diphosphate synthase (FPPS) enzyme in the HMG-CoA reductase pathway.[23] BPs have a higher affinity to bone cells compared to other tissues and are selective in their actions.[24] Due to BPs' anti-resorptive action, they have been immobilized on the surface of titanium dental implants. It has been further suggested that such coatings have a positive effect on new bone formation around the dental implants.[25] However, other studies have suggested that there is no difference between BP-releasing implants, HA-coated and uncoated implants.[26] Hence, there seems to be a controversy regarding the use of BP-releasing dental implants. Therefore, the aim of this systematic review is to analyse the currently available data concerning the clinical and experimental efficacy of BP-releasing titanium implants such that their potential in clinical oral implant dentistry may be ascertained.

Materials and Methods

Focused question

A focused question was constructed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and Participants Intervention Control Outcomes (PICO) protocol.[27] The focused question was, 'What is the effect of a bisphosphonate-releasing coating on the osseointegration of titanium dental implants?'

Literature search and eligibility criteria

A number of databases (PubMED/MEDLINE, ISI Web of Knowledge, Embase and Google Scholar) were searched electronically using the combination of keywords 'dental implant'; 'bisphosphonate' and 'titanium' from 1978 up to and including May 2016 for articles addressing the focused question. The inclusion criteria were the following: (1) Human studies, (2) Animal studies, (3) Original studies, (4) Articles published in English, and (5) BP-coated titanium implants. The following types of studies were excluded: (1) Cell studies, (2) Reviews, (3) Non-titanium implants, and (4) Letters to the editor.

Two reviewers, S.N. and Z.K., conducted the literature search using the above keywords and eligibility criteria. Additionally, the reference lists of the acquired full-texts were scanned manually for any additional articles relevant to the review. Any disagreements were settled by discussion among the reviewers. All included studies were analysed for the focused question, and relevant information was extracted. A flow diagram for the search methodology employed for conducting this review is illustrated in Figure 1.

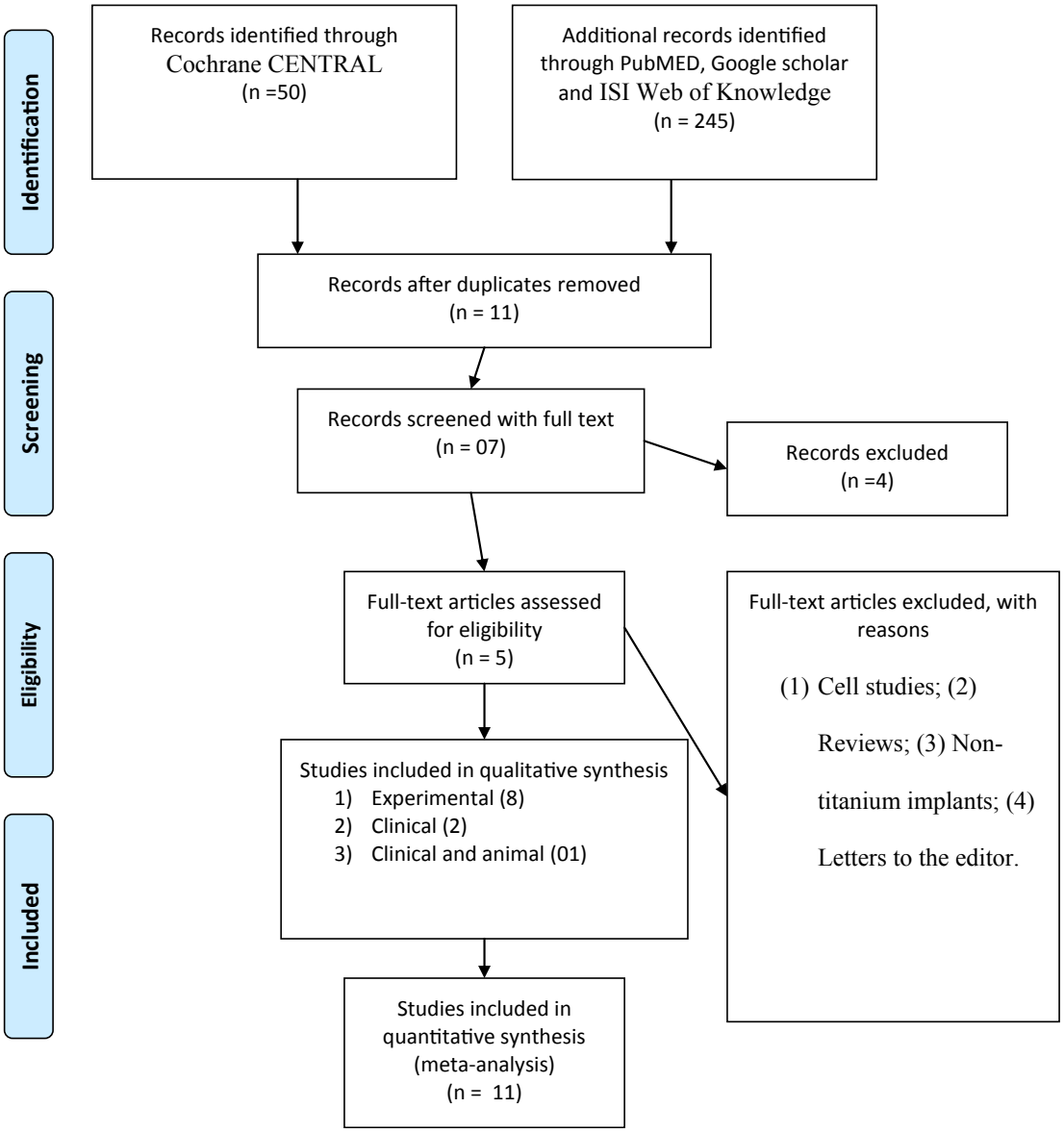

Figure 1: Search methodology employed for this study.

Quality assessment

The quality of the included studies was assessed using a modified scale previously described by Antczak et al.[28] and Jadad et al.[29] The following characteristics of the studies were assessed: calculation of sample size, description of appropriate measurement methods, appropriate statistics, error analysis and blinding. The quality of each study was hence designated as low, medium and high.

Results

Search results

Of the 255 articles that resulted in the primary search, 11 articles fulfilled the criteria to be included in this review. Eight studies were experimental,[25,30–35] two studies were clinical,[36,37] and one study was both-clinical and animal.[26] The general characteristics and main outcomes of included studies are displayed in Table 1.

Main outcomes and quality of studies

In nine studies (82%),[25,30–37] BP coated implants resulted in higher osseointegration, as indicated by higher resonance frequency values, removal torque, bone-to-implant contact and new bone formation. In two studies (18%),[26,38] there was no difference between the osseointegration of BP-coated implants and controls. Additionally, in one study, it was observed that BP remained within 500 µm of implant site.[33] As shown in Table 2, the quality of seven studies was rated as low[25,32–35,37,38] while four studies were rated as medium.[26,30,31,36]

Table 1: General characteristics and main outcomes of the selected studies.

Authors; year	Study design	Subjects (n)	No. of implants placed (n)	Duration of study	Implant surface		BP used	Main outcomes
					Control	Test		
Denissen et al.; 2000[26]	Experimental/clinical	15 goats; 10 patients	Animals: 80; clinical: 23	Animal: 3 months; clinical: 1 year	HA	BP + HA	Alendronate	Comparable outcomes in both groups.
Langhoff et al.; 2008[38]	Experimental	1 sheep	7	8 weeks	Uncoated (sand-blasted; etched)	BP; CaP; anodized heat treatment; Collagen I + Chondroitin Sulphate	Alendronate	Comparable outcomes in all groups.
Abtahi et al.; 2010[37]	Clinical	5 patients	35	6 months	Uncoated	BP + Fibrinogen	Pamidronate and ibandronate	Resonance frequency values and radiographic bone formation suggests BP improves osseoinegration.
Lee et al.; 2011[35]	Experimental	18 rats	36	4 weeks	Uncoated	BP + anodized heat treatment; heat treatment	Ibandronate	BP increased removal torque and enhanced osteoblast activity.
Abtahi et al.; 2012[36]	Clinical	16 patients	32	6 months	Uncoated	BP + Fibrinogen	Pamidronate and ibandronate	BP increased resonance frequency values and decreased marginal bone loss
Abtahi et al.; 2013[25]	Experimental	40 rats	40	2 weeks	Uncoated	Local BP + Fibrinogen; systemic BP	Zoledronate	BP increased removal torque.
Alghamdi et al.; 2014[30]	Experimental	30 osteoporotic rats; 30 healthy rats	60	4 weeks	Uncoated	BP; BP-CaP; CaP	Alendronate	BP-CaP increased new bone formation.
Nepal et al.; 2014[34]	Experimental	8 rats	8	4 weeks	Uncoated (Ti−Zr alloy)	BP + anodized heat treatment	Ibandronate	BP increased new bone formation and resonance frequency values.
Pyo et al.; 2014[31]	Experimental	20 rats	40	8 weeks	CaP	BP + CaP (8−800 μg/mL)	Zoledronate	BP increased volume of new bone formed but had no effect on bone-implant contact.
Karlsson et al.; 2015[33]	Experimental	20 rats	40	8 weeks	Mesoporous TiO_2	Mesoporous BP-TiO_2	Alendronate	BP increased new bone formation and remained bound to bone within 500 μm of implant site.
Pura et al.; 2016[32]	Experimental	15 dogs	30	12 weeks	Porous; HA-porous	BP - porous (0.02−0.18 mg/cm^2)	Alendronate	BP (0.06 mg/cm^2) increased new bone formation but had no effect on bone ingrowth.

BP; bisphosphonate; HA; hydroxyapatite; CaP; calcium phosphate; TiO_2; titanium oxide.

Table 2: Results of the quality assessment of the selected studies.

Authors; year	Sample size calculation provided	Appropriate measurement methods	Appropriate statistics	Error analysis provided	Blinding	Quality
Denissen et al.; 2000[26]	No	Yes	Yes	Yes	No	Medium
Langhoff et al.; 2008[38]	No	Yes	Yes	No	No	Low
Abtahi et al.; 2010[37]	No	Yes	Yes	No	No	Low
Lee et al.; 2011[35]	No	Yes	Yes	No	No	Low
Abtahi et al.; 2012[36]	No	Yes	Yes	No	Yes	Medium
Abtahi et al.; 2013[25]	No	Yes	Yes	No	No	Low
Alghamdi et al.; 2014[30]	No	Yes	Yes	No	Yes	Medium
Nepal et al.; 2014[34]	No	Yes	Yes	No	No	Low
Pyo et al.; 2014[31]	No	Yes	Yes	No	Yes	Medium
Karlsson et al.; 2015[33]	No	Yes	Yes	No	No	Low
Pura et al.; 2016[32]	No	Yes	Yes	No	No	Low

Discussion

Studies suggested that BP-releasing dental implants may have a positive effect on osseointegration. BPs reduce bone resorption by inhibiting and promoting apoptosis of osteoclasts.[39,40] Periodontal effects of BPs have been observed previously. The topical application of BP gel has been suggested to augment the efficacy of scaling and root planning resulting in improved periodontal parameters.[20,21] Similarly, BP-releasing dental implants have been observed to reduce the marginal bone loss compared to those without a BP-releasing coating.[36] Previously, such growth factors as bone morphogenetic protein 2 (BMP-2) have been immobilized on dental implants to improve osseointegration.[41] To date, BPs have been coated on dental implants in numerous ways. Due to BPs' high affinity to hydroxyapatite (HA) and calcium phosphates, they may be complicated with sprayed plasma or biomimetic coatings on dental implants.[26,31] Alternatively, BPs have been attached to the titanium surface via fibrinogen,[25] by anodization and heat treatment[35] or by immobilization on a porous surface.[33] For effective drug delivery, a slow sustained release of the pharmacological agent from the delivery device or medium is required.[42] Hence, dental implants delivering osseoconductive agents at a slow and sustained manner into the surrounding bone may improve osseointegration. There are differences among the various types of different BPs in affinities for binding to HA.[43] To the best of our knowledge, to date, there have been no studies conducted to investigate the difference in release and effect of different BPs from coated implants. Hence, studies are indeed needed to find the optimal BP for immobilization on dental implants. Moreover, bisphosphonates are known as to be anti-resorptive drugs that inhibit osteoclasts mostly by bone metabolism. In a clinical trial on 16 patients, bisphosphonate-eluting fibrinogen coating on implants revealed markedly improved mechanical fixation.[24]

As demonstrated by Nepal et al.[34] Karlsson et al.[33] and Lee et al.,[35] anodization of titanium surfaces creates a layer of porous TiO_2, which makes it easier to load BPs for effective *in-situ* delivery to periodontal bone. However, the long-term efficacy of such coatings, owing to the lack of clinical studies, is not clear. Although animal studies suggest that such coated implants may have an osseoconductive effect, animal studies do not necessarily translate to positive clinical effects. Therefore, more studies are required to investigate anodized BP coatings on dental implants. Attachment of BP to titanium surfaces via an intermediate layer of fibrinogen may also be an effective way to improve osseointegration. A series of animal and human studies by Abtahi et al.[25,36,37] suggests that BP-coated dental implants may reduce marginal bone loss. However, in the human trials, the patient follow-up period was only 6 months,[36,37] and hence, the long-term clinical efficacy of such coatings is not unknown.

Although the systematic effect of BPs on osseointegration is not clear,[19,44] the major concern of BRONJ due to BP still exists. Local delivery of BPs to via immobilization on dental implants may overcome the risk of BRONJ. Abtahi et al.[25] have observed that local delivery of BPs has a positive impact on the osseointegration in rats receiving systemic BPs. Additionally, in a study by Karlsson et al.,[33] BP delivered via dental implants remained within 500 μm of the implant site. These results suggest that BPs may be safe and may have minimal risk of inducing necrosis of the bone. However, these results should be confirmed by more in-depth studies before BP-coated dental implants may be used in clinics.

Osseointegration of BP-releasing implants have been monitored in patients in only two studies.[36,37] The follow-up of both of these two studies was only 6 months. To date, no follow-up articles have been published documenting the long-term outcomes of those studies. Furthermore, it is unclear whether the effect of BP release is dose-dependent. Pyo et al.[31] have reported that increasing the dose of BP from 8 to 80 μg/mL increases new bone formation in rats but has little effect on bone-implant contact. However, Pura et al.[32] have observed that 0.06 mg/cm^2 of BP on implant surface is optimal for enhancing bone formation, but no effect is observed on bone-in growth *in vivo*. Similarly, clinical studies by Abtahi et al.[36,37] have used BPs in a concentration of less than 1 μg/cm.^{2} But none of the studies reported to date had investigated the effect of altering the dose of BP in human subjects.

Conclusions

Bisphosphonate-loaded surface coatings may have a positive effect on osseointegration of dental implants.

However, more well-designed clinical studies are required to confirm the coatings' osseoconductive effect. Alendronate is the most frequently used BP in the studies in combination with HA, collagen 1, chondroitin sulphate, and calcium phosphate, heat treatment and titanium oxide that revealed significant new bone formation. The pamidronate and ibandronate used together and separately were assessed in combination with fibrinogen and heat treatment and resulted in improved osseointegration and decreased marginal bone loss. However, the use of zoledronate with fibrinogen and calcium phosphate in two studies showed increased bone formation and increased removal torque with no bone implant effect. To date, the above-mentioned four types of BP coated implants were treated and analysed through animal and human studies to determine the effect. These studies sought to improve the osseointegration and fixation of dental implants. However, more research and clinical trials with various other implant coatings are needed to establish better evidence for successful outcomes.

Limitations

Although the outcomes of the reviewed studies are promising, this study has several limitations. For instance, the quality assessment of the literature revealed that there might be numerous sources of bias. These findings are based on data extracted primarily from animal studies and only two clinical studies.[36,37] None of the studies supported its sample size by a suitable statistical calculation. Furthermore, the error analysis was included in only one study,[26] and only three studies were blinded.[30,31,36] These sources of bias may have contributed to a number of the positive outcomes documented in the studies. There is not sufficient evidence to validate the efficacy of BP-coated dental implants. Further research and unbiased clinical trials are warranted.

Authors' contributions

SN and ZK proposed the study design and literature search. SN and MSZ did data acquisition and drafted major part of the manuscript. SZ and SH collected, organized and interpreted the data and wrote a part of discussion. RK performed general discussion and critically reviewed the manuscript. All of the authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Conflicts of interest

The authors have no conflict of interest to declare.

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