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Systematic Review
Dental Implants

Role of local alendronate delivery on the osseointegration of implants: a systematic review and meta-analysis☆

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Abstract. There is controversy regarding whether locally delivered alendronate enhances osseointegration. The aim of this systematic review was to assess the role of local alendronate delivery (topical, or as a coating on implant surfaces) in the osseointegration of implants. The focused question was, ''Does the local delivery of alendronate affect osseointegration around implants?''. To address this question, indexed databases were searched, without time or language restriction, up to and including January 2017. Various combinations of the following key words were used: ''alendronate'', ''bisphosphonates'', ''osseointegration'', and ''topical administration''. letters to the editor, historic reviews, commentaries, case series, and case reports were excluded. In total, 18 experimental studies were included: alendronate-coated implants were used in 13 of these studies and local delivery in five studies. The results of 11 of the studies showed that alendronate coating increased new bone formation, the bone volume fraction, or bone-to-implant contact (BIC) and biomechanical properties. Results from two studies in which alendronate was administered topically indicated impaired BIC and/or biomechanical fixation around implants. On experimental grounds, local alendronate delivery seems to promote osseointegration. From a clinical perspective, the results in animal models support phase 1 studies in healthy humans (without co-morbidities other than edentulism).

Key words: bisphosphonates; osseointegration; implants; alendronate; topical administration.

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Dental implants are a predictable and successful treatment strategy for the replacement of missing teeth in partially and totally edentulous patients[1]. Local factors that may influence the overall success and survival of implants include primary stability at the time of implant placement, the formation of a direct bone to implant contact (BIC)[2], and the quantity and/or quality of the residual bone[3]. Substantial efforts have been made to accelerate healing around implants. In this regard, adjunct therapies such as the placement of osteogenic coatings on implant surfaces[3–6]

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have been proposed in an attempt to enhance BIC and new bone formation (NBF) around implant surfaces. Modifications in implant surface chemistry have also been reported to enhance the proliferation and differentiation of osteoprogenitor cells and to increase alkaline phosphatase (ALP) activity and the expression of osteogenic genes (which helps to enhance BIC and promote osseointegration)[7]. Such implant surface modifications have been shown to improve osseointegration in systemically healthy as well as immunosuppressed patients, such as those with osteoporosis or poorly controlled diabetes mellitus[8–10].

Alendronate, which belongs to the bisphosphonate class of drugs, is an anticatabolic agent that inhibits bone resorption and is therefore widely used for the treatment of skeletal disorders such as osteoporosis, bone metastases, and Paget's disease[11]. It has been suggested that alendronate influences the three phases of bone remodeling, which are microinjury, osteoclastogenesis, and osteogenesis, thereby stimulating NBF by enhancing the proliferation and differentiation of osteoblasts and inhibiting osteoclast function[12,13]. In addition to the bone antiresorptive effect, in vitro studies have shown that the administration of alendronate modulates osteoprotegerin (OPG) production by fibroblasts[14], and decreases phosphatase activity and the expression of osteoclast markers[15].

According to Hazzaa et al., the systemic administration of alendronate significantly improves osseointegration around titanium implants placed in animals with induced osteoporosis[16]. A recent systematic review also concluded that systemic bisphosphonate supplementation promotes implant osseointegration in animals with induced osteoporotic conditions[17]. However, in a clinical scenario, the potential risk of bisphosphonates related to osteonecrosis of the jaw cannot be disregarded[17]. Other complications related to the systemic administration of alendronate such as nausea, epigastric pain, vomiting, and dyspepsia, could be avoided by local alendronate release directly from the implant to the surrounding bone[18].

Conflicting results have been reported regarding whether local alendronate delivery (topical, or as a coating on implant surfaces) enhances osseointegration and NBF around implants[18–35]. Therefore, the aim of this systematic review was to assess the role of local alendronate delivery (topical, or as a coating on implant surfaces) in the osseointegration of implants.

Materials and methods

Focused question

Based on the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[36], a specific question was constructed according to the PICO principle (participants, interventions, control, outcomes). The focused question was, ''Does the local delivery of alendronate affect osseointegration around implants?" Participants (P) had to have undergone implant treatment. The intervention of interest (I) was the effect of local delivery of alendronate on osseointegration. The control intervention (C) was implant placement without adjunctive local alendronate administration. Outcome measures (O) included BIC, NBF, bone volume/tissue volume (BV/TV), and/or biomechanical fixation around implants with and without alendronate local delivery.

Eligibility criteria

The eligibility criteria were as follows: (1) original studies, (2) randomized controlled trials, (3) prospective and retrospective studies, (4) cohort studies, (5) experimental studies (animal models), (6) studies with a control group, (7) intervention: effect of local alendronate (topical or coating) on osseointegration. Letters to the editor, historic reviews, commentaries, in vitro studies, case series, case reports, and studies where alendronate was delivered systemically were excluded. Articles available online in electronic form ahead of print were considered eligible for inclusion.

Literature search protocol

In order to identify studies relevant to the focused question, an electronic search without time or language restriction was conducted in January 2017 in the PubMed (National Library of Medicine, Washington, DC, USA), Google Scholar, Scopus, Embase, MEDLINE (OVID), and Web of Knowledge databases. The following medical subject headings (MeSH) were used: (1) alendronate, (2) bisphosphonates, (3) osseointegration, (4) topical administration, and the combinations 1 or 2 and 3; 1 or 2 and 4; and 1, 2, and 3 or 4. Other relevant non-MeSH words were used in the search process to identify articles discussing osseointegration parameters and/or alendronate administration. These included: ''local delivery", ''local administration", ''coating", ''coated", ''bone-to-implant contact", and ''new bone formation".

Titles and abstracts of studies identified using the protocol described above were screened by two authors (SVK and VRM) and checked for agreement to exclude irrelevant articles and duplicates. The full texts of studies judged by title and abstract to be relevant were read and evaluated independently for the stated eligibility criteria. Reference lists of potentially relevant original and review articles were hand-searched to identify studies that had remained unidentified in the previous step. Once again, the articles were checked for disagreement via discussion among the authors. Kappa scores (Cohen's kappa coefficient) were used to determine the level of agreement between the two reviewers ($\kappa = 0.90$)[37]. Data were extracted using standardized evaluation forms. Authors of the studies included were contacted via e-mail in the case of missing data or for additional information regarding their studies if required. Fig. 1 summarizes the literature search strategy according to the PRISMA guidelines.

Quality assessment

A quality assessment of the studies that were included was performed in an attempt to increase the strength of the systematic review. The studies that were included underwent a quality assessment with the Critical Appraisal Skills Program (CASP) cohort study checklist[38]. The CASP tool uses a systematic approach based on 12 specific criteria, which are (1) study issue is clearly focused (effect of local alendronate delivery on osseointegration); (2) cohort is recruited in an acceptable way; (3) exposure (alendronate delivery) is accurately measured; (4) outcome (osseointegration and/or NBF around implants) is accurately measured; (5) confounding factors are addressed; (6) follow-up is long and complete; (7) results are clear; (8) results are precise; (9) results are credible; (10) results can be applied to the local population; (11) results fit with available evidence; and (12) there are important clinical implications. Each criterion was given a response of either 'yes', 'no', or 'cannot tell'. Each study could have a maximum score of 12. CASP scores were used to grade the methodological quality of each study assessed in the present systematic review.

Data analysis

A meta-analysis was performed for four studies in which the effect of local alen-