

Does Local Ibandronate and/or Pamidronate Delivery Enhance Osseointegration? A Systematic Review

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Keywords

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Abstract

Purpose: To our knowledge from indexed literature, the present study is the first one to systematically review the influence of local delivery of pamidronate (PAM) and/or ibandronate (IBA) on osseointegration enhancement. The aim of the present systematic review was to assess the efficacy of IBA and/or PAM local delivery (topically or coating on implants surfaces) in promoting osseointegration.

Materials and Methods: To address the focused question, “Does local IBA and/or PAM delivery enhances osseointegration?,” indexed databases were searched without time or language restrictions up to and including May 2016 using various combinations of the following keywords: “pamidronate,” “ibandronate,” “bisphosphonates,” “osseointegration,” and “topical administration.” Letters to the Editor, historic reviews, commentaries, case series, and case reports were excluded.

Results: Fifteen studies were included. Fourteen studies were performed in animals and 2 were clinical trials. One study reported an experimental model and a clinical trial in the same publication. Results from 12 experimental studies and 2 clinical studies reported improved biomechanical properties and/or osseointegration around implants with PAM and/or IBA. Two experimental studies showed that PAM and/or IBA did not improve osseointegration.

Conclusions: On experimental grounds, local IBA and/or PAM delivery seems to enhance osseointegration; however, from a clinical perspective, further randomized control trials are needed to assess the effectiveness of IBA and PAM in promoting osseointegration around dental implants.

Bone-to-implant contact (BIC) and primary stability are fundamental parameters that influence the overall success and survival of dental implants.¹⁻⁴ However, additional parameters that may also influence BIC and osseointegration include implant surface roughness and coating.⁵ It is well known that collagen synthesis and osteogenic cell proliferation, attachment, and differentiation are significantly higher around rough-surfaced implants compared with machined-surfaced implants.^{5,6} Various techniques such as airborne-particle abrasion, acid etching, and heat treatment have been used to modify the implant surfaces to enhance osseointegration.⁷ It has also been reported that the systemic supplementation and/or local delivery (coatings or topical) of adjunctive therapies can improve osteogenesis and enhance new bone formation (NBF) around implants.⁸⁻¹⁰ One

such adjunct therapy is local delivery of bisphosphonates (BPs), including topical application (BP-soaked morselized allografts or intracavity irrigation) and BP-coated implants.¹¹⁻¹³

BPs are anticatabolic drugs commonly used to treat resorptive skeletal disorders, such as bone metastasis, osteoporosis, Paget’s disease, and hypercalcemia associated with malignancies.^{14,15} Nitrogen-containing BPs such as zoledronate, alendronate, ibandronate (IBA), and pamidronate (PAM) are much more potent and act on the cholesterol pathway by inhibiting diphosphate synthase in the mavalonate pathway.¹⁶⁻¹⁸ BPs have a strong affinity to hydroxyapatite and calcium compounds and are able to induce osteoclastic inactivation, resulting in the inhibition of bone resorption.¹⁴ However, substantial differences among the pharmacological and

biological properties of BPs affect their binding to hydroxyapatite.¹⁹ In terms of speed and duration of action, IBA is a drug 50 times more potent than PAM.²⁰ Clinical and experimental studies²¹⁻³⁵ have explored the role of local IBA and/or PAM delivery (topically or coatings on implant surfaces) on the osseointegration and NBF around implants. Wermelin *et al*³³ reported increased strength of fixation and biomechanical properties around titanium (Ti) and stainless steel (SS) screws coated with a fibrinogen, IBA, and PAM solution, compared with uncoated Ti and SS surfaces. Baas *et al*²² reported higher strength of fixation and NBF around implants coated with hydroxyapatite grafted with morselized allograft soaked in PAM solution compared to allograft without PAM. Similar results were reported in other studies.^{21,24,25,35} However, conflicting results have also been reported. Wermelin *et al*³² reported comparable BIC in SS screws coated with fibrinogen, PAM, and IBA, compared with uncoated SS screws. Likewise, Skoglund *et al*²³ reported no significant difference in BIC and bone mineral density (BMD) around implants with and without IBA topical delivery. Therefore, the efficacy of IBA and PAM local delivery in terms of improving osseointegration seems debatable.

The aim of the present systematic review was to assess the efficacy of IBA and/or PAM local delivery (topically or coating on implant surfaces) on the osseointegration of implants.

Materials and methods

Participants, interventions, control, outcomes (PICO) principle

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,³⁶ a specific question was constructed according to the participants, interventions, control, outcomes (PICO) principle.

(P) Participants: Subjects must have undergone implant treatment.

(I) Types of interventions: The intervention of interest was the local delivery of PAM and/or IBA on osseointegration.

(C) Control intervention: Osseointegration without PAM or IBA local delivery.

(O) Outcome measures: BIC, NBF, bone volume/tissue volume (BV/TV), and/or biomechanical fixation around implants with and without PAM and/or IBA local delivery.

Focused question

The addressed focused question was “Does local IBA and/or PAM delivery enhance osseointegration?”

Eligibility criteria

The eligibility criteria were as follows: (1) clinical and experimental original studies; (2) inclusion of a control group (osseointegration around implants without local IBA and/or PAM delivery); and (3) intervention: effect of local IBA and/or PAM (topical or coating) on osseointegration. Articles available online in electronic form ahead of print were considered eligible for inclusion. Letters to the Editor, historic reviews, commentaries, case series, and case reports were excluded.

Literature search protocol

An electronic search without time or language restrictions was conducted up to May 2016 using PubMed (National Library of Medicine, Washington, D.C.), Google Scholar, Scopus, EMBASE, MEDLINE (OVID), and Web of Knowledge databases. The following Medical subject headings (MeSH) were used: (1) pamidronate, (2) ibandronate, (3) bisphosphonates, (4) osseointegration, and (5) topical administration, and combinations of 1 or 2 or 3 and 4; 1 or 2 or 3 and 5; and 3, 4, and 5. Other relevant non-MeSH words were used in the search process to identify articles discussing osseointegration parameters and IBA and/or PAM 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 above-described protocol were screened by two authors (SVK and FJ) and checked for agreement. Full texts of studies judged by title and abstract to be relevant were read and independently evaluated for the stated eligibility criteria. Reference lists of potentially relevant original and review articles were hand searched to identify studies that remained unidentified in the previous step. Once again, the articles were checked for disagreement via discussion among the authors. Kappa scores (Cohen kappa coefficient) were used to determine the level of agreement between the two reviewers (Kappa score = 0.95).³⁷ Figure 1 summarizes the literature search strategies according to the PRISMA guidelines.

Quality assessment

A quality assessment of included studies was performed using the Critical Appraisal Skills Program (CASP) Cohort Study Checklist.³⁸ The CASP tool uses a systematic approach based on the following 12 specific criteria: (1) Study issue is clearly focused (effect of local IBA and/or PAM delivery on osseointegration); (2) Cohort is recruited in an acceptable way; (3) Exposure 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 received 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.

Results

Study selection

Two hundred ninety-eight potential articles were initially identified. In the first step 239 publications, which were either duplicates or did not answer the focused question, were excluded. In the second step 44 more articles were excluded. A total of 15 studies²¹⁻³⁵ were included in the present systematic review and processed for data extraction, out of which 14 studies²¹⁻³⁴ were performed in animals, and 2 studies^{21,35} were clinical trials in

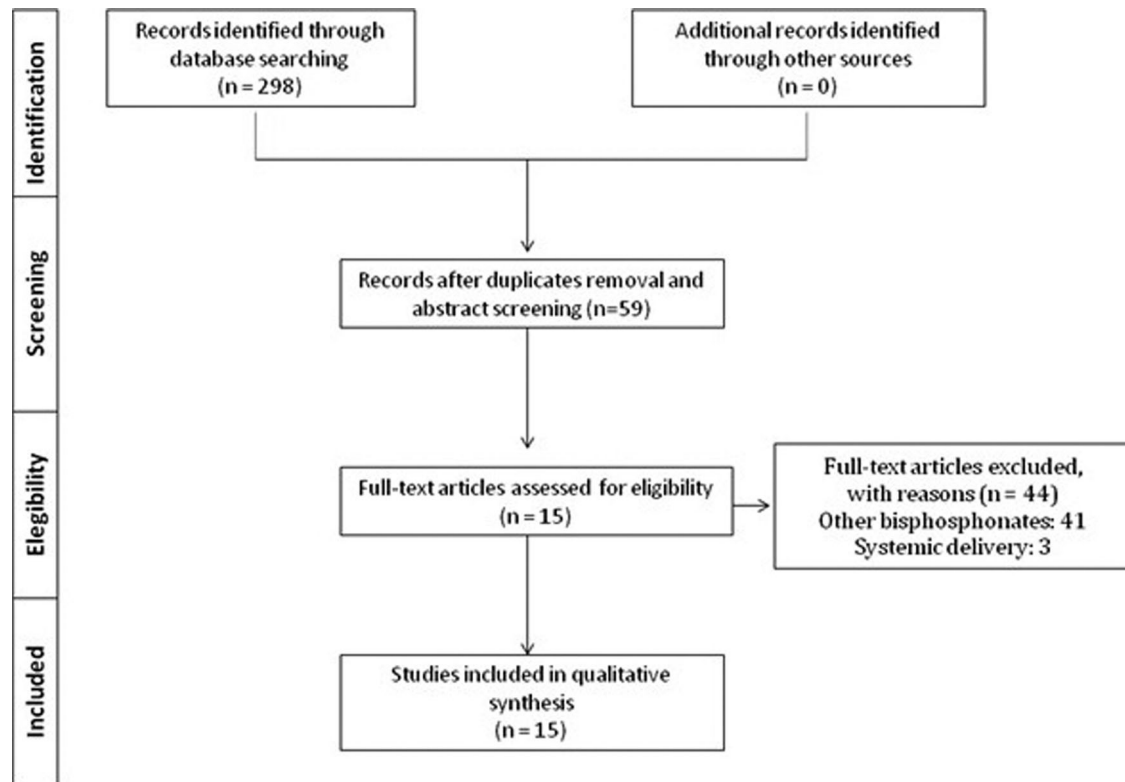


Figure 1 Article selection flow chart for the systematic review according to PRISMA guidelines.

humans. Abtahi *et al*²¹ reported an animal model and a clinical trial in the same study.

Experimental studies

General characteristics

Fourteen experimental prospective studies²¹⁻³⁴ were included. Male and female rats were used as study subjects in 10 studies^{21,23-25,27-30,32,33} and one study,²⁶ respectively. In one study³¹ rodents' sex was not reported. Yoshinari *et al*³⁴ used male dogs, and in Baas *et al*'s study²² the dogs' sex was unclear.

In six studies,^{21,24,26,30-33} a combination of IBA and PAM was immobilized into the implant surfaces. In five studies,^{22,25-27,34} PAM was delivered locally, out of which PAM-coated implants were used in four studies^{22,25-27,34} and morselized allograft soaked in PAM solution in one study.²² IBA was incorporated into the implant surfaces in three studies.^{26,28,29} In one study,²³ the bone cavity was irrigated with IBA solution prior to implant placement.

In 13 studies,^{21-25,27-34} the role of IBA and/or PAM in the promotion of NBF around implants was assessed in healthy animals, whereas Gao *et al*²⁶ assessed the effectiveness of PAM and IBA on osseointegration in rats with induced osteoporosis. In all studies,²¹⁻³⁴ the follow-up period ranged between 5 hours and 12 weeks (Table 1).

Implant-related characteristics

Ti implants were used in seven studies,^{22,26-29,31,34} of which two^{28,29} used Ti dioxide nanotubes to serve as BP's carriers. SS screws were used in seven studies.^{21,23-25,30,32,33} Eight studies^{21,22,24-26,28,29,34} reported the total numbers of implants placed in the subjects, ranging between 10 and 109. In six studies,^{23,27,30-33} the total number of implants was not reported. In 12 studies,^{21,23-33} implants were placed in tibiae. Baas *et al*²² and Yoshinari *et al*³⁴ placed implants in dogs' humeri and mandibles, respectively.

In 13 studies,²²⁻³⁴ implant dimensions (diameter × length) ranged between 1 × 2 and 3 × 11 mm. Implant dimensions were not reported in Abtahi *et al*'s study.²¹ Screw-type and cylindrical implants were placed in nine studies^{21,23-25,28,30-33} and four studies,^{22,26,27,34} respectively. In one study,²⁹ the implants' shape was not reported. Nine studies^{22,24-26,29-32,34} used rough-surfaced implants, and machined-surfaced implants were used in two studies.^{23,27} Lee *et al*²⁸ and Wermelin *et al*³³ used implants with machined and roughened surfaces. One study²¹ did not report the implant surface characteristics (Table 2).

Osseointegration assessment

Six studies^{22,24-26,32,34} assessed osseointegration using histomorphometric analysis. In 12 studies,^{21-26,28-33} biomechanical testing was performed to assess the strength of newly formed bone around implants, of which four studies^{23,24,28,32}

Table 1 Experimental studies with local delivery of pamidronate and/or ibandronate

Authors	Study subjects (mean age)	Study groups	Bisphosphonate dose and route of administration	Follow-up	Analysis methods	Outcome
Implants with bisphosphonates-coated surfaces						
Abtahi et al ²¹	50 male rats (NA)	<ul style="list-style-type: none"> Group 1: FIB Group 2: FIB + PAM + IBA Group 3: FIB + PAM + IBA + 5 kGy Group 4: FIB + PAM + IBA + 15 kGy Group 5: FIB + PAM + IBA + 25 kGy 	Groups 2, 3, 4, and 5: PAN + IBA solution (NA)	4 weeks	Pull-out test	Group 1 presented lower strength of fixation than groups 2, 3, 4, and 5.
Agholme et al ²⁴	60 male rats (NA)	<ul style="list-style-type: none"> Group 1: FIB + PAM + IBA Group 2: HA Group 3: Uncoated SS 	Group 1: PAM solution 1 mg/ml, IBA solution 50 µg/ml	4 weeks	Pull-out test, Removal torque, HIST, BEM-SEM	Group 1 presented higher strength of fixation, BIC, and BV/TV than groups 2 and 3.
Andersson et al ²⁵	109 male rats (2.1-month-old)	<ul style="list-style-type: none"> Group 1: PAM + FIB Group 2: ZOL + FIB Group 3: FIB Group 4: Uncoated SS 	Group 1: PAM solution, 1 mg/ml, 279 ng/cm ² ; Group 2: ZOL solution, 15 mg/ml, 108 ng/cm ²	2 and 6 weeks	Pull-out test, HIST	Group 1 presented higher strength of fixation and BMD than groups 3, and 4, but lower than group 2.
Gao et al ²⁶	40 female rats(NA)	<ul style="list-style-type: none"> Group 1: OVX + HA Group 2: OVX + HA + PAM Group 3: OVX + HA + IBA Group 4: OVX + HA + ZOL 	Group 2: PAM solution 1 mg/ml; Group 3: IBAL solution 1 mg/ml; Group 4: ZOL solution 1 mg/ml	12 weeks	DEXA, Micro-CT, HIST, push-out test	Groups 2 and 3 presented higher BIC, BV/TV, NBF and strength of fixation than group 1, but lower than group 4.
Kajiwara et al ²⁷	30 male rats (2.5-month-old)	<ul style="list-style-type: none"> Group 1: Uncoated Ti Group 2: Ca-coated Ti Group 3: Ca coated Ti + PAM 	Group 3: PAM 3 mg/ml	4 weeks	Fluorescent labeling, SEM	Group 3 presented higher NBF than groups 1 and 2.
Lee et al ²⁸	18 male rats (3-month-old)	<ul style="list-style-type: none"> Group 1: Uncoated Ti Group 2: AH Ti Group 3: AH Ti + IBA 	Group 3: 1 mg/ml IBA solution	2 and 4 weeks	Removal torque, Western Blot, micro-CT	Group 3 presented higher strength of fixation, NBF, BIC, and bone formation markers than groups 1 and 2.
Nepal et al ²⁹	8 male rats (NA)	<ul style="list-style-type: none"> Group 1: AH Ti Group 2: AH Ti + IBA 	Group 2: 1 mg/ml IBA solution	4 weeks	Histology, micro-CT, push-out test	Group 2 presented higher removal torque, BV/TV, BIC, and strength of fixation than group 1.

(Continued)

Table 1 Continued

Authors	Study subjects (mean age)	Study groups	Bisphosphonate dose and route of administration	Follow-up	Analysis methods	Outcome
Tengvall <i>et al</i> ³⁰	16 male rats (NA)	<ul style="list-style-type: none"> Group 1: FIB + PAM + IBA Group 2: Uncoated SS 	Group 1: PAM solution 1 mg/ml, IBA solution 50 µg/ml	2 weeks	Pull-out test	Group 1 presented higher pullout force and pullout energy than group 2.
Wermelin, Aspenberg, <i>et al</i> ³¹	60 male rats (NA)	<ul style="list-style-type: none"> Group 1: FIB + PAM + IBA Group 2: Uncoated Ti 	Group 1: PAM solution 1 mg/ml, IBA solution (NA)	2 weeks	Pull-out test	Group 1 presented higher pullout force and pullout energy than group 2.
Wermelin, Suska, <i>et al</i> ³²	99 rats (2.5-month-old)	<ul style="list-style-type: none"> Group 1: FIB + PAM + IBA Group 2: FIB Group 3: Uncoated SS 	Group 1: PAM solution 1 mg/ml, 530 ng/cm ² (44 A), IBA solution 50 µg/ml, 380 ng/cm ² (32 A)	1 and 8 weeks	Histology, HIST, removal torque	Group 1 presented higher BA and removal torque than groups 2 and 3. Group 1 presented higher BIC than group 2, but similar to group 3.
Wermelin, Tengvall, <i>et al</i> ³³	278 male rats (NA)	<ul style="list-style-type: none"> Group 1: FIB + PAM + IBA Group 2: FIB 	Group 1: PAM solution 1 mg/ml, IBA solution 50 µg/ml	5 hours, 4 days, 1 week, 2,4, and 8 weeks	Pull-out test	Group 1 presented enhanced mechanical fixation compared with group 2.
Yoshinari <i>et al</i> ³⁴	5 male dogs (12-month-old)	<ul style="list-style-type: none"> Group 1: Blasted Group 2: Blasted + CaP Group 3: Blasted + CaP + PAM 	Group 3: PAM solution 10 ⁻² M	4 and 12 weeks	Histology, HIST	Group 3 presented higher BIC than groups 1 and 2.

Topical delivery of bisphosphonates						
Baas <i>et al</i> ²²	16 dogs (14.5-month-old)	<ul style="list-style-type: none"> Group 1: HA Group 2: HA + rhBMP-2 Group 3: HA + PAM Group 4: HA + PAM + rhBMP-2 	Group 3: Morselized allograft soaked in 4 ml PAM (9 mg × ml × 3 minutes); Group 4: Morselized allograft soaked in 4 ml PAM (9 mg × ml × 3 minutes) and 0.45 mg rhBMP-2	4 weeks	Push-out, Histology, HIST	Groups 3 and 4 presented significantly higher strength of fixation and NBF compared with groups 1 and 2.
Skoglund <i>et al</i> ²³	76 male rats (NA)	<ul style="list-style-type: none"> Group 1: SO IBA Group 2: SQ SAL Group 3: Local IBA Group 4: Local SAL 	Group 3: IBA solution 0.1 ml injected into the cavity	2 weeks	Pull-out test, removal torque, histology	Group 3 presented higher pullout force and removal torque than group 4. No significant difference between groups in BIC and BMD.

NA: Not available; FIB: Fibrinogen; PAM: Pamidronate; IBA: Ibandronate; kGy: Kilogray; HA: Hydroxyapatite; SS: Stainless steel; HIST: Histomorphometry; BEM: Backscattered electron microscopy; SEM: Scanning electron microscope; BIC: Bone-to-implant contact; BV/TV: Bone volume/tissue volume; ZOL: Zoledronate; BMD: Bone mineral density; HA: Hydroxyapatite; Ti: Titanium; SAL: Saline; OVX: Ovariectomized; DEXA: Dual energy X-ray absorptiometry; Micro-CT: Microcomputed tomography; NBF: New bone formation; Ca: Calcium; AH: Anodized and heat treated; BA: Bone area; ELISA: Enzyme-linked immunosorbent assay; CaP: Calcium phosphate; SQ: subcutaneous; rhBMP-2: recombinant human bone morphogenetic protein-2.

Table 2 Characteristics of the implants included in experimental studies

Author	Material and number of implants	Implant dimensions (D × L in mm)	Location of implant placement	Implant shape	Implant surface characteristics
Abtahi <i>et al</i> ²¹	50 SS	NA	Tibia	Screw	NA
Agholme <i>et al</i> ²⁴	90 SS	1.7 × 3	Tibia	Screw	Rough
Andersson <i>et al</i> ²⁵	109 SS	1.7 × 3	Tibia	Screw	Rough
Baas <i>et al</i> ²²	64 Ti	6 × 10	Humerus	Cylinder	Rough (HA)
Gao <i>et al</i> ²⁶	80 Ti	1 × 10	Tibia	Cylinder	Rough (HA)
Kajiwarra <i>et al</i> ²⁷	Ti*	1 × 2	Tibia	Cylinder	Smooth
Lee <i>et al</i> ²⁸	36 Ti	2 × 4	Tibia	Screw	Smooth and rough (TiO ₂ nanotubes)
Nepal <i>et al</i> ²⁹	10 Ti	1.2 × 5 and 1.2 × 10	Tibia	NA	Rough (TiO ₂ nanotubes)
Skoglund <i>et al</i> ²³	SS*	1.7 × 3	Tibia	Screw	Smooth
Tengvall <i>et al</i> ³⁰	SS*	1.7 × 3	Tibia	Screw	Rough
Wermelin, Aspenberg, <i>et al</i> ³¹	Ti*	1.9 × 2.5	Tibia	Screw	Rough
Wermelin, Suska, <i>et al</i> ³²	SS*	1.7 × 3	Tibia	Screw	Rough
Wermelin, Tengvall, <i>et al</i> ³³	SS*	1.7 × 3	Tibia	Screw	Smooth and rough
Yoshinari <i>et al</i> ³⁴	40 Ti	3 × 11	Mandible	Cylinder	Rough

NA: Not available; Ti: Titanium; SS: Stainless steel; HA: Hydroxyapatite; TiO₂: Titanium dioxide; D: Diameter; L: Longitude; *: Number of implants was not reported.

used removal torque analysis, three studies^{22,26,29} assessed bone healing capabilities with push-out test, and seven studies^{21,23-25,30,31,33} used pull-out test. In three studies,^{26,28,29} NBF around implants was assessed using 3D microcomputed tomography. In five studies,^{22,23,29,32,34} osseointegration was assessed using histology. Scanning electron microscopy and dual energy X-ray absorptiometry were used to assess NBF around implants in two studies^{24,27} and one study,²⁶ respectively. In one study,²⁷ fluorescence markers were used to track patterns of NBF and apposition. Lee *et al*²⁸ used western blot analysis to evaluate the degree of mineralization based on levels of type I collagen and osteocalcin.

Main outcomes

Results from 12 studies^{21-26,28-33} reported improved biomechanical properties around implants with PAM and/or IBA local delivery (topical or coating) compared with implants without BP administration. In eight studies,^{22,24-29,34} local delivery of PAM and/or IBA resulted in enhanced BIC, NBF, BMD, and/or BV/TV. Lee *et al*²⁸ reported significantly higher levels of type I collagen and osteocalcin expression in the bone tissue around Ti implants coated with IBA, compared with uncoated controls; However, Wermelin *et al*³² reported similar BIC around SS screws coated with fibrinogen and immobilized PAM with IBA, compared with uncoated SS screws. Likewise, Skoglund *et al*²³ reported no significant difference in BIC and BMD around implants with and without IBA topical delivery.

Quality assessment

Quality assessment showed that all studies²¹⁻³⁴ were conducted on experimental animals, and the total quality score ranged from 7 to 9. The most common shortcomings among the studies were

short term and incomplete follow-up (up to 12 weeks) of the experimental groups and no assessment of confounder's variables. Furthermore, as all studies were performed in animals, these results cannot apply to the human population. Overall, the quality of included experimental studies on the impact of IBA and/or PAM local administration on the osseointegration of implants was good, but limitations of short-term follow-up, lack of confounder's assessment, and the need for clinical studies limit the clinical application of these study outcomes. Quality assessment of the individual papers is summarized in Table 4.

Clinical studies

General characteristics

Two clinical trials^{21,35} were included (Table 3). In Abtahi *et al*'s 2010 study,²¹ 5 patients with a mean age of 66 years were included. In 2012, Abtahi *et al*³⁵ included 16 patients, with a mean age of 65 years. Both studies^{21,35} reported the number of Ti implants placed: 16 and 36 for the control groups (nontreated implants) and 5 and 16 implants for the test groups (BP-coated implants). In both studies^{21,35} test groups received implants coated with a combination of fibrinogen, IBA, and PAM. In both studies^{21,35} the implants were placed exclusively in maxilla, and each patient received at least one control implant and one test implant.

Osseointegration assessment

Two studies^{21,35} used resonance frequency analysis and radiographic examination (periapical and/or panoramic) to assess implant stability. Abtahi *et al*²¹ removed two of the BP-coated implants en bloc with an osteotome after 6 months to perform histological analysis.

Table 3 Clinical studies with local delivery of pamidronate, and/or ibandronate

Authors	Number of patients (F/M)	Mean age in years (age range)	Implant location and dimensions	Study groups	Analysis methods	Follow-up	Outcome
Abtahi <i>et al</i> ²¹	5 (1/4)	66 (NA)	Maxilla 3.75 × 10 3.75 × 11	Group 1: 36 non-treated Ti implants; Group 2: 5 treated Ti implants (PAM + IBA + FIB)	RFA, histology, radiographs	6 months	No significant difference in MBL between groups 1 and 2. Group 2 presented higher ISQ values than group 1.
Abtahi <i>et al</i> ³⁵	16 (11/5)	65 (NA)	3.75 × 13 Maxilla 3.75 × 11.5	Group 1: 16 nontreated Ti implants; Group 2: 16 treated Ti implants (FIB + PAM solution 1 mg/ml + IBA solution 50 μg/ml)	RFA, radiographs	6 months	Group 2 presented higher ISQ values after 6 months than group 1. MBL was higher in group 1 than in group 2.

NA: Not available; F: Female; M: Male; PAM: Pamidronate; IBA: Ibandronate; FIB: Fibrinogen; Ti: Titanium; MBL: Marginal bone loss; ISQ: Implant stability quotient; RFA: Resonance frequency analysis.

Main outcome

The results of the two studies^{21,35} showed that the implants coated with fibrinogen, IBA, and PAM presented higher implant stability quotient (ISQ) compared with uncoated implants after 6 months follow-up. In one study,²¹ no significant difference in marginal bone loss (MBL) around implants with or without BP and fibrinogen coating was observed after 6 months. Abtahi *et al*³⁵ reported lower MBL in implants coated with BPs and fibrinogen compared with uncoated control after 6 months. Histological analysis after 6 months showed osseointegration of the BP-coated implants, with mature and lamellar bone formed around the implant, and without signs of active resorption or necrosis.²¹

Quality assessment

The total quality score were 8 and 10. The most common shortcomings in both studies were the short term (up to 6 months), and the incomplete follow-up of the groups. Thus, on average, the quality of included studies was good, but the limitations of short-term follow-up limit the application of these study outcomes (Table 4).

Discussion

To our knowledge from indexed literature, the present study is the first to systematically review the influence of local delivery of PAM and/or IBA on osseointegration and NBF around implants. It is noteworthy that results from ~93% of the ex-

perimental studies^{21,22,24-34} reported that local delivery of PAM and/or IBA enhanced osseointegration and NBF around implants. Therefore, it is tempting to speculate that local delivery of PAM and/or IBA promotes osseointegration; however, it is worth mentioning that several variables remained unaddressed in the studies.

First, it seems difficult to select the specific drug and dosage (PAM alone, IBA alone, or the combination of both) that might offer the most predictable outcome in terms NBF or BIC enhancement. For example, Agholme *et al*²⁴ and Tengwall *et al*³⁰ incorporated 1 mg/ml of PAM combined with 50 μg/ml IBA to SS screws precoated with fibrinogen, whereas Andersson *et al*²⁵ incorporated only 1 mg/ml PAM in SS screws precoated with fibrinogen, and Lee *et al*²⁸ used only 1 mg/ml IBA to coat anodized and heat-treated Ti implants. This reflects a lack of standardization regarding the methods and formulations to deliver IBA and/or PAM locally, and the need to be further optimized.

Second, different carriers such as fibrinogen,^{21,24,25,30-33} hydroxyapatite,²⁶ calcium,²⁷ and calcium phosphate³⁴ were used to bind BPs to the implants' metal surfaces. Studies have shown that the use of hydroxyapatite and other calcium compounds are suitable methods for binding BPs to implant surfaces.^{31,39,40} However, the heterogeneity in the methods used among the included studies^{21,24-34} to incorporate BPs into the Ti and SS surfaces makes difficult to draw a conclusion regarding the ideal carrier.

Third, in two studies,^{25,26} the efficacy of implants coated with PAM or IBA to improve osseointegration was compared with

Table 4 CASP quality assessment of the reviewed papers

Authors	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Total quality score
<i>Experimental studies</i>													
Abtahi <i>et al</i> ²¹	Yes	Yes	Cannot tell	No	No	No	Yes	Yes	Yes	No	Yes	Yes	7
Agholme <i>et al</i> ²⁴	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	9
Andersson <i>et al</i> ²⁵	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	9
Baas <i>et al</i> ²²	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	9
Gao <i>et al</i> ²⁶	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	9
Kajiwara <i>et al</i> ²⁷	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	Yes	8
Lee <i>et al</i> ²⁸	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	Yes	8
Nepal <i>et al</i> ²⁹	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	9
Skoglund <i>et al</i> ²³	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No	Yes	8
Tengvall <i>et al</i> ³⁰	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	Yes	8
Wermelin, Aspenberg, <i>et al</i> ³¹	Yes	Yes	Cannot tell	No	No	No	Yes	Yes	Yes	No	Yes	Yes	7
Wermelin, Suska, <i>et al</i> ³²	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	9
Wermelin, Tengvall, <i>et al</i> ³³	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	Yes	8
Yoshinari <i>et al</i> ³⁴	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	9
<i>Clinical studies</i>													
Abtahi <i>et al</i> ²¹	Yes	Cannot tell	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	8
Abtahi <i>et al</i> ³⁵	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	10

Item 1: study issue is clearly focused; *item 2:* cohort is recruited in an acceptable way; *item 3:* exposure is accurately measured; *item 4:* outcome is accurately measured; *item 5:* confounding factors are addressed; *item 6:* follow-up is long and complete; *item 7:* results are clear; *item 8:* results are precise; *item 9:* results are credible; *item 10:* results can be applied to the local population; *item 11:* results fit with available evidence; *item 12:* there are important clinical implications.

implants coated with zoledronate. In both studies,^{25,26} zoledronate groups presented higher strength of fixation and NBF compared with PAM and IBA groups. Zoledronate is a nitrogen containing BP, which exhibits the more potent action inhibiting bone resorption among all the BPs.⁴¹ It is hypothesized that other BPs applied locally might be more effective in enhancing NBF and BIC around implants than IBA and/or PAM are. Therefore, further studies comparing the local delivery efficacy of different BPs to improve osseointegration are needed. These parameters should be considered in a future protocol for the clinical use of local BPs in implantology.

It is noteworthy that the experimental studies²¹⁻³⁴ were performed for a maximum 12-week follow-up period. Therefore, it remains unclear whether local delivery of IBA and/or PAM in patients receiving dental implants would increase BIC and contribute to long-term (at least 5 years or longer) success and survival of dental implants.

In Skoglund *et al*'s²³ study, the topical delivery of IBA did not improve BIC or BMD around SS screws. Some possible explanations can be hypothesized for these findings. First, the SS screws used had smooth surfaces. It is well known that rough-surfaced implants present higher proliferation of osteoprogenitor cells, and enhanced osseointegration compared with

implants with turned surfaces.⁴²⁻⁴⁴ Second, the follow-up period was relatively short (2 weeks). It is speculated that a longer follow-up period may have resulted in an increment of NBF. Third, the delivery method used was an intracavity injection with 0.1 ml IBA solution. Intracavity injection with BP has been reported to increase NBF and osseointegration around implants;^{45,46} however, the dosage (5 ml) and the irrigation time (60 seconds) were significantly higher in these studies^{45,46} than in Skoglund *et al*'s study.²³

From the literature reviewed, it is noteworthy that two studies^{21,35} were clinical trials, where 21 Ti implants were soaked in a solution of fibrinogen, IBA, and PAM, and placed in the maxilla of 21 patients. After 6 months, the implants coated with BPs presented higher ISQ compared with uncoated Ti implants. The authors of the present systematic review applaud the results of Abtahi *et al*;^{21,35} however, several limitations, such as the lack of an ideal BP formulation, dose, protocol, and/or method for delivery, short follow-up (6-month), and uncertainty regarding systemic effects of the local BP delivery, seem to have biased the results reported. Furthermore, of all the studies included, only one study²⁹ was published after 2012, suggesting that this issue has ceased to be relevant to the current literature. Moreover, the significant heterogeneity among all the studies

(experimental and clinical) did not allow pooling of results and statistical analysis. In this regard, the conclusions of the studies included in the present systematic review should be interpreted with caution.

Conclusions

On experimental grounds, local IBA and/or PAM delivery seems to enhance osseointegration; however, from a clinical perspective, further randomized control trials are needed to assess the effectiveness of IBA and PAM in promoting osseointegration around dental implants.

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