

Medication-Related Osteonecrosis of the Jaw and Dental Implants Failures: A Systematic Review

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No well-established evidence supporting safe use of bisphosphonates (BPs) or other antiresorptive agents prior, during, or after dentoalveolar surgery, are currently available; moreover, the real risk of osteonecrosis of the jaw (ONJ) development is still unknown. The aim of the present systematic review was to assess the scientific literature concerning the implants placement in antiresorptive agent users and the related risk of implants failure and ONJ development. English papers published from January 2003 until December 2014 were identified on the MEDLINE database. Titles and abstracts retrieved from electronic search were screened separately by 2 examiners; thus, original studies dealing with dental implants placement during or before bone antiresorptive agent therapy and the relative risk of implant failure or development of osteonecrosis were evaluated. Due to the heterogeneity of the included studies and the high risk of bias, there is no evidence of the safe use of oral antiresorptive agents prior or after dental implant surgery. Indeed, implant failure and ONJ development can occur and represent a devastating side effect that should be considered during treatment. Within the limitation of the present systematic review, high quality studies are needed to provide an adequate level of evidence regarding the safety of dentoalveolar surgery during or before bone resorption inhibition therapy and the increase predisposition to osteonecrosis of the jaw (ONJ) development. Therefore, antiresorptive agent therapy should be considered a risk factor until further evidence is prospectively obtained.

Key Words: antiresorptive drugs, bisphosphonates, dental implants, implant failure, ONJ

INTRODUCTION

Osteonecrosis of the jaw (ONJ) is an oral lesion characterized by exposure of necrotic bone in the maxillofacial region, persisting for more than 8 weeks, first described by Marx in 2003.¹ Etiology of the disease is unknown and the pathogenesis seems to be multifactorial.² Though occurrence could be spontaneous,³ treatment with bisphosphonates (BPs) was highly correlated with ONJ. Particularly, bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a well-known adverse side effect of long-term BP treatment without previous history of radiation therapy to the jaws.^{1,4} Recently, other non-BP drugs seemed to be related to the development of ONJ;⁵ therefore, additional and revised definitions of the pathology were proposed: according to Ikebe,⁶ newly developed molecule-targeting drugs, such as denosumab (a monoclonal antibody acting on receptor activator of nuclear factor kappa-B ligand or RANKL of osteoclast), bevacizumab (a monoclonal antibody targeting vascular endothelial growth factor or VEGF), and sunitinib (a

multikinase inhibitor) would cause drug-related ONJ or “drug-related osteoclastic disease of the jaw.” Schipmann et al⁷ proposed a definition of ONJ, in relation with bone resorption inhibitor treatment: “osteopathology associated with bone resorption inhibitor therapy (BRIOJ).” Moreover, an increasing number of reports have shown an association between the use of antiresorptive medication (ARM; bisphosphonates, human monoclonal antibody against nuclear factor-kappa B ligand (RANKL), and cathepsin K inhibitors) and osteonecrosis of the jaw, that was defined as “antiresorptive agent-induced osteonecrosis of the jaws (ARONJ).”⁸ The latest position paper of American Association of Oral and Maxillofacial Surgeons (AAOMS)⁹ defined “medication-related osteonecrosis of the jaw (MRONJ)” as exposed, unhealed necrotic bone caused by current or previous treatment with antiresorptive or antiangiogenic agents.

ONJ lesions are localized in the jaw bone matrix, mainly in the mandible than in the maxilla (2:1 ratio),⁴ due to the great vascularization, high bone turnover rate, high risk of surgical trauma, and local infections of jaws.^{2,3} Moreover, BPs possessed a strong affinity to the hydroxyapatite, and 80% of the administered drugs were accumulated into the bones⁵ and released over time, from months to years.

Several systemic and local risk factors were correlated with the high frequency of ONJ development.² Time of exposure, drug potency, and way of administration were considered

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drug-related risk factors,⁴ particularly, intravenous (IV) administration in the treatment of multiple myeloma and bone metastases, expose a risk of ONJ development 100 times higher than oral administration for treatment of osteopenia, osteoporosis, and Paget's disease.⁹ Furthermore, oral and maxillofacial surgery are considered the major local risk factors for ONJ occurrence, mainly in cancer patients treated with intravenous BPs or antiresorptive agents. Though this correlation was unanimously accepted, the possibility to perform tooth extractions and dental implants placement in BP- or antiresorptive agent-users has been widely debated in the literature. Regarding dentoalveolar surgery in patients undergoing intravenous antiresorptive therapy, current opinion contraindicates implant surgery according to the position paper of the American Association of Oral and Maxillofacial Surgeons.⁹ Although dentoalveolar surgery performed on patients receiving oral antiresorptive treatment seems not to be contraindicated,⁹ the presence of comorbidities, such as diabetes, use of glucocorticoids,⁶ use of antiangiogenic drugs, and time of exposure >4 years, should be taken into account,^{9,10} since the risk of ONJ development appears to increase.

Nevertheless, there is no strong evidence supporting safe use of BPs or other antiresorptive agents prior, during, or after dentoalveolar surgery, and more data are needed to determine the real risk of ONJ development, in both cancer and noncancer patients, which is, to date, still unknown.⁹

Of key importance is to define whether BPs and antiresorptive agents in general should be considered as "risk factors" in implant dentistry and dentoalveolar surgery fields, and how the type of drugs, time of exposure, and way of administration strictly related to the type of patient (cancer or not) are involved in the development and progression of osteonecrosis.

Therefore, the aim of the present systematic review was to assess the scientific literature concerning the implants placement in antiresorptive agent users and the related risk of implants failure and ONJ development.

MATERIALS AND METHODS

Literature search

A search of electronic databases including MEDLINE/PubMed, Scopus, Scholar, and the Cochrane Database of Systematic Reviews was undertaken using a combination of keywords: "BRONJ," "ONJ," "ARONJ," "dental implant" and "oral bisphosphonate(s)," "antiresorptive osteoporosis" and "dental implant," "antiresorptive osteoporosis" and "dental," "antiresorptive" and "dental," and "osteoporosis" and "dental implant." Papers were selected if the abstract included the term "oral or dental implant" in conjunction with "oral bisphosphonate(s)" and with "osteonecrosis of the jaws." The following terms: "risedronate," "etidronate," "clodronate," "tiludronate," "alendronate," "ibandronate," "denosumab," "sunitinib," and "bevacizumab" were also searched in conjunction with "dental implant."

Literature search was completed by a hand search, exploring the references cited in all identified publications. No language exclusion criteria were applied; all levels of evidence were considered.

Eligibility criteria

The inclusion criteria for studies selection were as follows: (1) papers published from January 2003 until December 2014, (2) human studies without age limitation, (3) oral or systemic administration of bisphosphonates or antiresorptive agents during or after dental implant placement, and (4) oral rehabilitation with at least 1 dental implant in both jaws per patient.

The exclusion criteria for studies selection were: (1) case reports, case series with <10 patients; (2) studies with <1-year follow-up; and (3) animal studies.

PICO question

Participants

Participants were of any age in treatment with oral or systemic antiresorptive drugs.

Intervention

Implant placement during or before antiresorptive therapy.

Comparison

The comparison included implant success and implant failure after placement in patients in therapy with antiresorptive drugs.

Outcome

The outcome was risk of implant failure or development of osteonecrosis.

Validity assessment

Titles and abstracts retrieved from electronic search were screened separately by 2 examiners (R. G. and L. S.). The full text from all papers suitable for inclusion was obtained. Subsequently, all selected papers were independently assessed by both reviewers. Disagreements were solved by discussion among the reviewers. Finally, an evidence table was redacted with the included papers.

RESULTS

After matching results from 2 separated literature searches and removing duplicates, 277 articles were considered suitable for inclusion in the study. After title reading, 58 articles were eligible for abstract reading. Thirty articles were selected for full text reading and a final 10 articles were included in the study (Figure 1). Among selected papers, 7¹¹⁻¹⁷ were retrospective, 2^{18,19} were cross-sectional, and only 1 study was prospective²⁰ (Figure 1 and Table 1).

Participants

A total of 17 237 patients in BP therapy were enrolled in the included studies. Age and gender distribution are reported in Table 2. The majority of study population was female since oral antiresorptive drugs were mostly administered in postmenopausal women for the treatment of osteoporosis. The most

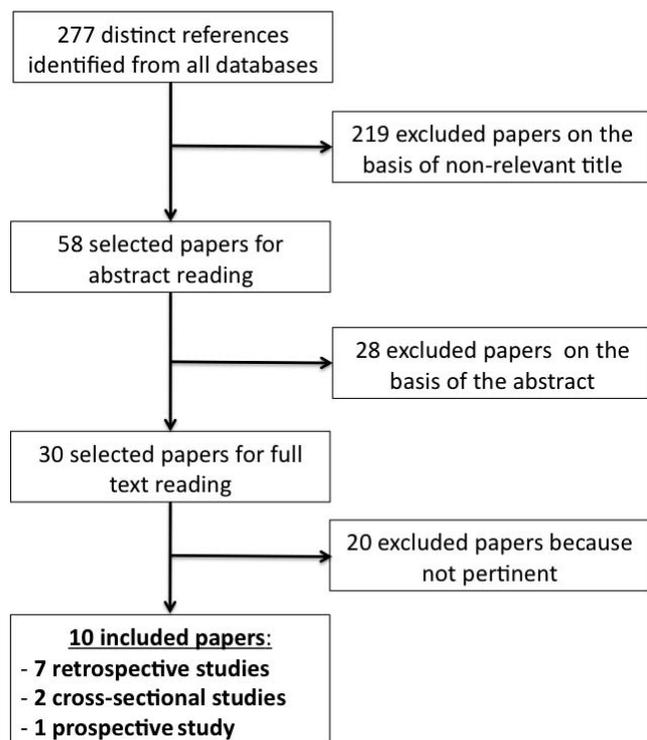


FIGURE 1. Flow chart during search of studies. According to the inclusion criteria for the selection, a total of 10 papers were included and reviewed. The final selected studies were 7 retrospective, 2 cross-sectional, and 1 prospective.

investigated molecules were alendronate, risedronate, and orally-administered ibandronate.

Intervention

A total of 30 070 dental implants were placed in the included studies; however, in 2 studies^{18,19} the precise number of evaluated implants was not specified (Table 2). Regarding time range between oral antiresorptive drug exposure and dental implant placement, differences were reported by several authors,^{11–20} according to Table 2, patients were treated with antiresorptive agents prior to implants placement in a time range between 10 weeks to more than 11 years. In addition, 3 studies^{12,13,15} reported that some subjects were treated with antiresorptive drugs even after implant surgery, however, without specifying the timing of postimplant therapy (Table 2).

Outcome

Positive effects of antiresorptive agents

Several authors^{11,12,14–16,20} agreed on considering as safe the use of oral bisphosphonates prior or after dental implant surgery (Table 3). Particularly, Bell and Bell¹¹ reported a 95% success rate (5/100 implants failed in 5/100 female patients) without evidence of exposed bone or development of ONJ, and Grant et al¹³ showed that implant success rates in antiresorptive drugs users and nonusers were comparable. In the study of Jeffcoat,²⁰ 25 women were rehabilitated with 102 dental implants and 25 BP users women with 108 implants. Success

rates were 100% and 99.2% for the 2 groups respectively, without any occurrence of ONJ. Similarly, Koka et al¹⁶ demonstrated an implant survival rate in BP users and BP nonusers of 99.17% and 98.19%, respectively. In addition, Shabestari et al¹⁵ demonstrated that antiresorptive therapy before (7 patients) or after (14 patients) implant placement had no statistically significant influence on peri-implant probing depth, bleeding on probing, and thread exposure. Even Zahid et al¹⁴ showed high implant success rates, 94.11% and 88.46% for the implant-based and subject-based analyses respectively, in patients treated with oral BPs.

Negative effects of antiresorptive agents

Although good clinical results were reported, Zahid et al¹⁴ noted a relationship between BPs and alveolar bone loss around osseointegrated implants, with 13 implants out of 51 exhibiting thread exposure. Moreover, Goss et al¹² and Grant et al¹³ reported dental implant failure also when oral bisphosphonate administration started after dental implant surgery. Goss et al¹² described a relatively low but real risk, ~1%, when dental implants were placed in patients taking oral bisphosphonates, and Yip et al¹⁷ indicated that women with implant failure (163/490 dental implants) had increased probability of reporting a history of oral bisphosphonates use (9.65%) than controls (4.04%). In the same way, Lazarovici et al¹⁸ showed that the 27 patients included in their study who had developed ONJ after dental implant placement had taken orally administered (41%) or intravenous (59%) bisphosphonates. ONJ occurred in 77.8% of the patients in mean 16.2 months after surgery; moreover, 6 patients developed ONJ 6 months after surgery. Particularly in patients treated with alendronate, zoledronic acid, and pamidronate, ONJ developed after mean periods of 68, 16.4, and 50.2 months, respectively.¹⁸ Martin et al¹⁹ reported 26 implant failures in 16 patients out of 589 patients who had treatment with BPs. Early failures (<1 year after implant placement) were registered for 8 implants, whereas late failures (>1 year after implants placement) were demonstrated in 18 implants. In 2 patients both early and late failures were reported.

All data are reported in Table 3, where follow-up period of dental implants is also shown.

DISCUSSION

Major risks of ONJ development were definitely related to the use of antiresorptive agents and invasive dental procedures.^{3,4} Indeed, cancer patients undergoing intravenous antiresorptive therapy and also dentoalveolar procedures had a 5- to 21-fold increased risk of ONJ development than the same population who did not undergo dentoalveolar surgery,⁴ whereas oral use of antiresorptive agents seems to have a lower grade risk of ONJ.^{2,9,21}

Tooth extraction was a common predisposing event for ONJ occurrence, mainly in cancer subjects in treatment with antiresorptive drugs.²² Particularly, Saad et al²³ reported a previous history of tooth extraction for 61.8% of cancer patients who developed ONJ. According to the latest position paper of AAOMS,⁹ the current estimate for the risk of ONJ among

TABLE 1

Studies included in the present systematic review. A brief description of the type of the study, type of medication, and main results are provided for each paper.

| Study | Type | Antiresorptive Drugs | Results |
|--------------------------------|------------------------------|--|---|
| Bell et al ¹¹ | Retrospective | Oral alendronate, risedronate, and ibandronate | 95% success rate. There was no evidence of exposed bone or ONJ in any of these patients. |
| Goss et al ¹² | Retrospective, case series | Oral and IV BPs | There is a small risk of additional implant failure for patients taking bisphosphonates, <1%, but devastating to the patient. No development of ONJ was reported. |
| Grant et al ¹³ | Retrospective | Oral alendronate, risedronate, and ibandronate | Two implants failed; however, implant success rate was comparable for BP users and BP nonusers. No evidence of BRONJ was reported. |
| Jeffcoat ²⁰ | Parallel controlled study | Oral alendronate and risendronate | 100% implant success in BP users vs 99.2% implant success in BP nonusers. No ONJ evidence. Oral BPs seemed to be protective against ONJ. |
| Zahid et al ¹⁴ | Retrospective radiographic | Oral BPs | No statistically significant relationship between BPs and implant failure (3/51) were recorded; positive correlation was demonstrated between BPs and alveolar bone loss around the osseointegrated implants. No evidence of ONJ. |
| Lazarovici et al ¹⁸ | Prospective, cross sectional | Oral alendronate; IV zoledronic acid and pamidronate, both alone or together | Development of BRONJ associated with dental implants was a late complication and was not usually related to the oral surgery. |
| Martin et al ¹⁹ | Cohort | Oral BPs | Few patients reported implant failures (16/589). There were more late than early failures; moreover, slightly higher proportion of failures in the mandible vs the maxilla. |
| Shabestari et al ¹⁵ | Retrospective, case series | Oral alendronate | Patients did not show pathologic, clinical, and radiographic findings of ONJ around dental implants. |
| Koka et al ¹⁶ | Retrospective | Oral BPs | BPs group showed an implant survival rate of 99.17%; non-BP group showed a survival rate of 98.19% without any statistical difference. |
| Yip et al ¹⁷ | Retrospective, case control | Oral BPs | Women with implant failure had increased odds (2.69) of reporting a history of oral bisphosphonate use compared with those without implant failure. |

*IV, intravenous.

patients exposed to oral bisphosphonates following tooth extraction is 0.5%; however, this risk increased with the presence of comorbidities and protracted exposure to anti-resorptive medications. On the other hand, the correlation between dentoalveolar procedures and risk of ONJ development among patients in treatment with antiresorptive agents is still unknown. Indeed, results of the present systematic review corroborated the absence of univocal data.

This review had included 10 studies (7 retrospective, 2 cross-sectional, 1 prospective), which evaluate the risk of implant failures and ONJ development in patients treated with antiresorptive agents. Even the occurrence of ONJ was reported in just 2 studies,^{12,18} incidence of related implant failure seems to be more common, and represents a real side effect of bone resorption inhibition therapy.^{13,14,17,19} On the other hand, 6 studies out of 10^{11,13-16,20} considered as not dangerous the use of oral antiresorptive drugs prior to or after dental implant surgery. Particularly, Jeffcoat²⁰ and Koka et al¹⁶ reported that use of oral BPs should be classified as safe, showing implant survival rates of 100% and 99.17%, respectively, with better results than BP nonusers (survival rates of 99.2% and 98.19%, respectively). In addition, Koka et al¹⁶ concluded that implant survival in postmenopausal BP users was similar to that observed in postmenopausal women with no history of

antiresorptive therapy and without any sign of ONJ occurrence and need of predictable “drug holiday.” Moreover, Bell and Bell¹¹ reported that dental implant placement and oral bone grafting appeared to be safe and successful procedures in patients taking oral BPs for osteoporosis.

However, though the risk of implant failures was considered relatively low, ~1%,¹² it is really devastating for the patients. For this reason, Yip et al¹⁷ suggested the discontinuation of oral BPs therapy prior to dentoalveolar surgery, demonstrating that oral BP use was 2.69 times higher in patients who presented implant failures compared with the patients for whom the implants did not fail. Probably, ONJ development should be considered as a late complication^{18,19} of implant therapy; however, these data are not yet supported by the scientific literature, where few reports lacking of details are available. Also the present systematic review has many limits due to the heterogeneity of the included papers and the high risk of bias. The majority of the selected studies (7/10) are retrospective with inclusion/exclusion criteria different from each other. Even the sample size and the exposure to drugs are extremely varied ranging from 21¹⁵ to 16 000¹² patients and from 10 weeks¹² to more than 11 years,¹¹ respectively. In addition, 3 studies^{12,13,15} reported that the bone resorption inhibition therapy was administered also after implant surgery,

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TABLE 2

Patients, implants, and drug exposure reported in the papers included in the systematic review

| Study | Total Number of Participants | M:F | Mean Age | Total Number of Implants | Antiresorptive Exposure |
|--------------------------------|-------------------------------|--------------|----------------------------------|-----------------------------------|---|
| Bell et al ¹¹ | 42 patients | na | na | 101 implants | 6 months to 11 years prior to implant surgery. |
| Goss et al ¹² | 16 000 patients | na | 49–75 years | 28 000 implants | 10 weeks to more than 5 years. |
| Grant et al ¹³ | 115 patients | 100% female | 40 years | 468 implants | Mean exposure of 38 months. Twenty-six patients started oral bisphosphonate therapy after implant surgery. The remaining 89 patients started bisphosphonate therapy before implant placement. |
| Jeffcoat ²⁰ | 50 patients (25 BP users) | 100% female | 50 years | 210 implants (102 in BP users) | Mean exposure of 3 years. |
| Zahid et al ¹⁴ | 300 patients (26 BP users) | 135:227 | 56 years (range: 17–87 years) | 661 implants (51 in BP users) | na |
| Lazarovici et al ¹⁸ | 27 patients | 7:20 | 70 years | na | Mean exposure of 16.2 months before implant placement. |
| Martin et al ¹⁹ | 589 patients | na | 70.2 years | na | Mean exposure of 38 (range: 3–69) months. |
| Shabestari et al ¹⁵ | 21 patients | 100 % female | 53 years, (range 42–79 y) | 46 implants | Mean exposure of 20.5 months (7 patients started BP therapy before implant placement; 14 patients started BP therapy after implant surgery). |
| Koka et al ¹⁶ | 137 patients (55 BP users) | 100% female | 71 years | 287 implants (121 in BP users) | na |
| Yip et al ¹⁷ | 337 patients | 100% female | >40 years | 1181 implants | na |

*na, not available.

without specifying the onset and the duration, and in another 3 studies^{14,16,17} the period of antiresorptive drug exposure is completely missing. Moreover, the number of implants varies from 46¹⁵ to 28 000¹² with a widely heterogeneous follow-up period (Table 3) and criteria of implant success. Additional risk factors such as comorbidities, periodontal status, implant type and position, and differences in the type of drugs taken, definitely contribute to the lack of univocal data. According to a recent literature review,²¹ there is a paucity of data regarding the development of ONJ resulting from implant therapy in patients treated with antiresorptive agents; however, authors included just 4 studies in their review and concluded that the placement of dental implants should be considered a safe procedure in patients taking oral BPs for <5 years.²¹

Another crucial issue that should be fully investigated is the pathophysiology of ONJ occurrence. Recent findings suggested that the use of antiresorptive medications was not the only cause of disease appearance. Schipmann et al,⁷ proposed the existence of a major infectious component in the development of osteonecrosis due to bone resorption inhibitors therapy; indeed, bacterial invasion by *Actinomyces* might be a decisive factor in the etiology of the lesion. Moreover, Major Histocompatibility Complex Class II polymorphisms seem to be a genetic risk factor for the development of ONJ,⁸ supporting the hypothesis that inflammation crucially influenced the disease pathogenesis. Furthermore, inhibition of angiogenesis might play a key role in ONJ pathophysiology,^{24,25} since a decrease of vascularization is always related to bone necrosis. Histologic examination found peri-implant nonvital demineralized bone

with empty osteocyte lacunae, inflammatory cell infiltrate, and few small blood vessels^{26,27} around dental implants involved in osteonecrosis lesions.

The clarification of ONJ pathophysiology is of crucial significance in the prevention and treatment of the disease; moreover, the role of the inflammatory response in the occurrence of osteonecrosis should be deeply investigated; further studies are needed to evaluate the role of chronic BPs and antiresorptive therapy in the long-term implant osseointegration maintenance.

CONCLUSIONS

Within the limitations of the present systematic review, high quality studies are needed to provide an adequate level of evidence regarding the safety of dentoalveolar surgery during or before bone resorption inhibition therapy, and the increase predisposition to ONJ development. Therefore, antiresorptive agent therapy should be considered a risk factor until further evidence is prospectively obtained.

ABBREVIATIONS

AAOMS: American Association of Oral and Maxillofacial Surgeons
 ARM: anti-resorptive medication
 ARONJ: anti-resorptive agent-induced osteonecrosis of the jaws
 BP: bisphosphonates
 BRONJ: bisphosphonate-related osteonecrosis of the jaw

TABLE 3

Summary of the effects of the antiresorptive drugs on dental implant failure and ONJ development. Moreover, follow-up period of dental implants is reported.

| Study | Positive Effect of Antiresorptive Drugs on Dental Implants | Negative Effect of Antiresorptive Drugs on Dental Implants | Follow-Up of Dental Implants |
|---|---|---|---|
| Bell et al ¹¹ | 95% implant success rate without evidence of exposed bone or ONJ development. | na | 4–89 months |
| Goss et al ¹² | Small risk of additional implant failure for patients taking BPs. No development of ONJ was reported. | Real risk (1%) of developing ONJ for patients taking BPs. | Implants placed between 1997 and 2007 |
| Grant et al ¹³ | Implant success rates in antiresorptive drug users and non-users were comparable. No evidence of ONJ was reported. | Dental implant failure can occur also when oral BPs administration started after dental implant surgery. | 48 months |
| Jeffcoat ²⁰ | 100% implant success in BPs users. No ONJ evidence. Oral BPs seemed to be protective against ONJ. | na | 36 months |
| Zahid et al ¹⁴ | High implant success rates (94.11% and 88.46% for the implant-based and subject-based analyses, respectively) in patients treated with oral BPs. No ONJ evidence. | Positive correlation was demonstrated between BPs and alveolar bone loss around the osseointegrated implants and thread exposure. | Implants placed between 1997 and 2008 |
| Lazarovici et al ¹⁸ | na | ONJ occurred in 77.8% of the patients in the mean 16.2 months after surgery; moreover, 6 patients developed ONJ 6 months after surgery. | Implants placed between 2003 and 2009 |
| Martin et al ¹⁹ | na | 16/589 patients reported implant failures. There were more late than early failures. | na |
| Shabestari et al ¹⁵ | No statistically significant influence on peri-implant probing depth, bleeding on probing, and thread exposure. No ONJ evidence. | na | Implants placed between 1998 and 2006. |
| Koka et al ¹⁶ Yip et al ¹⁷ | Implant survival rate in BPs users of 99.17%. na | na Patients with implant failure (163/490) had increased probability of reporting a history of oral bisphosphonates use (9.65%). | 1 to 31 months Implants placed between 1997 and 2004 |

*na, not available.

IV: intravenous

MRONJ: medication-related osteonecrosis of the jaw

ONJ: osteonecrosis of the jaw

RANKL: human monoclonal antibody against nuclear factor-kappa B ligand

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