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
drug-related risk factors, particularly, intravenous (IV) administration in the treatment of multiple myeloma and bone metastases, exposes a risk of ONJ development 100 times higher than oral administration for treatment of osteopenia, osteoporosis, and Paget’s disease. 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. Although dentoalveolar surgery performed on patients receiving oral antiresorptive treatment seems not to be contraindicated, the presence of comorbidities, such as diabetes, use of glucocorticoids, use of antiangiogenic drugs, and time of exposure >4 years, should be taken into account, 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.

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, 218,19 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
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, 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; 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 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 agreed on considering as safe the use of oral bisphosphonates prior or after dental implant surgery (Table 3). Particularly, Bell and Bell 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 al. reported that implant success rates in antiresorptive agents users and nonusers were comparable. In the study of Jeffcoat, 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 al demonstrated an implant survival rate in BP users and BP nonusers of 99.17% and 98.19%, respectively. In addition, Shabestari et al 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 al 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 al noted a relationship between BPs and alveolar bone loss around osseointegrated implants, with 13 implants out of 51 exhibiting thread exposure. Moreover, Goss et al and Grant et al reported dental implant failure also when oral bisphosphonate administration started after dental implant surgery. Goss et al described a relatively low but real risk, ~1%, when dental implants were placed in patients taking oral bisphosphonates, and Yip et al 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 al 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. Martin et al 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. 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, whereas oral use of antiresorptive agents seems to have a lower grade risk of ONJ.

Tooth extraction was a common predisposing event for ONJ occurrence, mainly in cancer subjects in treatment with antiresorptive drugs. Particularly, Saad et al reported a previous history of tooth extraction for 61.8% of cancer patients who developed ONJ. According to the latest position paper of AAOMS, the current estimate for the risk of ONJ among...
patients exposed to oral bisphosphonates following tooth extraction is 0.5%; however, this risk increased with the presence of comorbidities and protracted exposure to antiresorptive 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. Moreover, results of the present systematic review were corroborated 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 $21^{15}$ to $16,000^{12}$ patients and from 10 weeks$^{12}$ 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.

### 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.

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

*IV, intravenous.
without specifying the onset and the duration, and in another 3 studies\textsuperscript{14,16,17} the period of antiresorptive drug exposure is completely missing. Moreover, the number of implants varies from 46\textsuperscript{15} to 28 000\textsuperscript{12} 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,\textsuperscript{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.\textsuperscript{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,\textsuperscript{7} proposed the existence of a major infectious component in the development of osteonecrosis due to bone resorption inhibitors therapy; indeed, bacterial invasion by \textit{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,\textsuperscript{8} supporting the hypothesis that inflammation crucially influenced the disease pathogenesis. Furthermore, inhibition of angiogenesis might play a key role in ONJ pathophysiology,\textsuperscript{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\textsuperscript{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.

<table>
<thead>
<tr>
<th>Study</th>
<th>Positive Effect of Antiresorptive Drugs on Dental Implants</th>
<th>Negative Effect of Antiresorptive Drugs on Dental Implants</th>
<th>Follow-Up Of Dental Implants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell et al11</td>
<td>95% implant success rate without evidence of exposed bone or ONJ development.</td>
<td>na</td>
<td>4–89 months</td>
</tr>
<tr>
<td>Goss et al12</td>
<td>Small risk of additional implant failure for patients taking BPs.</td>
<td>Real risk (1%) of developing ONJ for patients taking BPs.</td>
<td>Implants placed between 1997 and 2007</td>
</tr>
<tr>
<td>Grant et al13</td>
<td>Implant success rates in antiresorptive drug users and non-users were comparable.</td>
<td>Dental implant failure can occur also when oral BPs administration started after dental implant surgery.</td>
<td>48 months</td>
</tr>
<tr>
<td>Jeffcoat20</td>
<td>100% implant success in BPs users. No ONJ evidence.</td>
<td>na</td>
<td>36 months</td>
</tr>
<tr>
<td>Zahid et al14</td>
<td>High implant success rates (94.11% and 88.46% for the implant-based and subject-based analyses, respectively) in patients treated with oral BPs.</td>
<td>Positive correlation was demonstrated between BPs and alveolar bone loss around the osseointegrated implants and thread exposure.</td>
<td>Implants placed between 1997 and 2008</td>
</tr>
<tr>
<td>Lazarovici et al18</td>
<td>na</td>
<td>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.</td>
<td>Implants placed between 2003 and 2009</td>
</tr>
<tr>
<td>Martin et al19</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Koka et al16</td>
<td>na</td>
<td>Patients with implant failure (163/490) had increased probability of reporting a history of oral bisphosphonates use (9.65%).</td>
<td>1 to 31 months</td>
</tr>
<tr>
<td>Yip et al17</td>
<td>na</td>
<td>na</td>
<td>Implants placed between 1997 and 2004</td>
</tr>
</tbody>
</table>

*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

REFERENCES

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