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SUPPLEMENT ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

The effect of antiresorptive drugs on implant therapy: Systematic review and meta-analysis

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Abstract

Objectives: A considerable portion of the adult population has received and/or is receiving treatment with antiresorptive drugs (ARDs). It is thus relevant to assess possible side effects of ARD intake in connection to various aspects of implant therapy. The aim of this study was to answer the focused question "In patients with systemic intake of ARDs, what is the outcome and complication rate of implant therapy including associated bone grafting procedures comparing to patients without systemic intake of ARDs?"

Materials and Methods: Original studies fulfilled predefined inclusion criteria (e.g., case series, cohort studies, case–control studies, and controlled and/or randomized controlled clinical trials; retro- or prospective design; and ≥10 patients with systemic intake of ARDs). Various patient-, medication-, and intervention-related parameters [i.e., implant loss, grafting procedure complication/failure, peri-implant marginal bone levels/loss, medication-related osteonecrosis of the jaws (MRONJ), and peri-implantitis] were extracted, and meta-analyses and quality assessment were performed.

Results: Twenty-four studies with bisphosphonate (BP) intake (mainly low dose for osteoporosis treatment) and seven studies on hormone replacement therapy (HRT), including ≥10 patients, and controls not taking the medication were identified. Furthermore, seven studies on MRONJ associated with implants were included. Meta-analyses based on four studies reporting on patient level and eight studies reporting on implant level showed no significant differences in terms of implant loss between patients on BPs (mainly low dose for osteoporosis treatment) and controls. Furthermore, low-dose BP intake did not compromise peri-implant marginal bone levels. Based on two studies, no negative effect of HRT was observed on the implant level, while HRT appeared to exert a marginally significant negative effect regarding implant survival on the patient level and regarding peri-implant marginal bone levels. Based on six studies reporting single-patient data, MRONJ in patients on BP for osteoporosis appeared in 70% of the cases >36 months after start of drug intake, while in patients with cancer, MRONJ appeared in 64% of the cases ≤36 months after first BP intake.

Conclusion: Low-dose oral BP intake for osteoporosis treatment, in general, does not compromise implant therapy, that is, patients on ARDs do not lose more implants nor get more implant-related complications/failures comparing to implant patients without BP intake. There is almost no information available on the possible effect on implant therapy of high-dose BPs or other widely used ARDs (e.g., denosumab), or on the success or safety of bone grafting procedures. Patients with high-dose ARD intake for management of malignancies, patients on oral BP over a longer period of time, and patients with comorbidities should be considered as high-risk patients for MRONJ.

KEYWORDS
antiresorptive drugs, bisphosphonates, dental implants, hormone replacement therapy, medication-related osteonecrosis of the jaws, systematic review

1 | INTRODUCTION

Drugs counteracting bone resorption, coined antiresorptive drugs (ARDs), interfere with bone metabolism with the aim to decrease abnormal bone remodeling and/or increased bone resorption. ARDs, despite differences in their mechanisms of action, in general, decrease bone remodeling and resorption by inhibiting differentiation and normal function of osteoclasts (OCLs), and/or increase their apoptosis (Baron, Ferrari, & Russell, 2011). ARDs are thus most commonly/primarily used in the treatment of osteoporosis and primary and metastatic skeletal malignancies, to prevent events such as fractures, and limit pain and metastatic spread; ARDs are also used in less frequent diseases such as Paget's disease of the bone and osteogenesis imperfecta.

The most widely known ARDs are the bisphosphonates (BPs), a group of drugs introduced >30 years ago. Currently used nitrogen-containing BPs (e.g., alendronate, risedronate, ibandronate, pamidronate, and zoledronate) bind readily to hydroxylapatite and are deposited into the bone. They exert antiresorptive action by inhibiting OCL progenitor development and disturbing OCL function (i.e., recruitment, adhesion, and activity), while also reducing OCL lifespan; a direct inhibiting effect on osteoblasts has also been suggested (Baron et al., 2011; Stepan, Alenfeld, Boivin, Feyen, & Lakatos, 2003). The administration route influences skeletal uptake of BPs and thus indirectly the dose; specifically, intravenously (iv) administered BPs (e.g., pamidronate and zoledronate) are bound in very large quantities and are used mainly in the management of malignancies and Paget's disease of bone, and only in rather limited extent for osteoporosis treatment, while orally administered BPs (e.g., alendronate and risedronate) are bound in significantly smaller quantities (<1% of orally administered BPs is absorbed from the gastrointestinal tract) and are predominantly used in the treatment of osteoporosis and rarely, in some types of cancers, for the prevention of secondary osteoporosis. Relatively recently, another treatment option for osteoporosis has been oral administration of strontium ranelate (SrR), which—although the exact mechanisms of action are not completely understood—seems to interfere with bone metabolism by decreasing OCL progenitor differentiation and OCL activity, and increasing their apoptosis, while it also increases osteoblast (OB) progenitor differentiation and OB activity and survival (Bonnelye, Chabadel, Saltel, & Jurdic, 2008; Buehler, Chappuis, Saffar, Tsouderos, & Vignery, 2001). Currently, SrR use appears to be gradually abandoned, because it has been suspected of having a higher risk of adverse cardiovascular events (European Medicines Agency, 2013), although a very recent study did not confirm this (Martín-Merino et al., 2018).

Treatment of osteopenia and osteoporosis has also been pursued by targeting estrogen deficiency, which is a major cause for these conditions during menopause. Estrogen deficiency upregulates several cytokines, including receptor activator of nuclear factor kappa B ligand (RANKL), while it downregulates others, including osteoprotegerin (OPG). Thus, hormone replacement therapy (HRT) with direct estrogen supplementation exerts its antiresorptive effect predominantly through regulating RANKL production by the OB and thereby influencing OCL. Additionally, estrogen has a direct effect on OCL precursors by reducing their responsiveness to RANKL and also on OB by stimulating their proliferation and reducing their apoptosis (Stepan et al., 2003). HRT with estrogen is currently prescribed in rather limited extent, mostly for the management of climacteric symptoms, due to the risk of adverse cardiovascular events (Wong et al., 2017). A somehow similar treatment approach is the administration of selective estrogen receptors modulators (SERMs; e.g., raloxifene and bazedoxifene), which are drugs acting on the estrogen receptor and having a selective estrogenic effect on bone tissue, or by administering calcitonin that binds to its OCL receptor and interferes with normal cell function, including secretion of proteolytic enzymes (Carter & Schipani, 2006).

More recently, a new generation of "biological" ARDs has been introduced based on monoclonal antibodies targeting various mechanisms relevant to bone remodeling. The most widely used is denosumab (Reginster et al., 2014), which is a fully humanized antibody of

RANKL. Denosumab exerts its antiresorptive effect by blocking the binding of RANKL to RANK, and thus interfering with OCL differentiation, and, in contrast to BPs, does not bind to bone. Denosumab is administered subcutaneously (sc) and in various intervals depending on its treatment purpose (i.e., for osteoporosis or malignancies) (Reginster et al., 2014). Recent market analyses estimated about >40% of current osteoporosis treatments are with denosumab (Global Osteoporosis Market & Drugs Analysis 2010–2015, 2011). Similar approaches regard the use of cathepsin K (CatK) inhibitor (odanacatib) and c-Src kinase inhibitor (saracatinib) or the use of an antisclerostin monoclonal antibody (romosozumab).

In perspective, current estimates indicate that about 15% of the population >50 years of age in the European Union (EU) has osteoporosis; this translates into ca. 23.5 million women and 6.0 million men in the year 2015 and, when considering demographic trends, into ca. 27.5 million women and 7.0 million men in the year 2025 (Hernlund et al., 2013). Despite the fact that consumption may vary significantly among countries/regions, due to differences in prescription rates depending on the regulatory framework and/or treatment uptake, as well as the appearance of newer ARDs (e.g., denosumab), BPs appear still the most prevalent drugs for osteoporosis treatment within the EU. In this context, even if patients with osteoporosis are currently not treated with BPs, the majority has most likely received BPs in the past; based on market shares (Hernlund et al., 2013), it was estimated that oral BPs covered about 70% of osteoporosis treatment in 2010. Thus, as a considerable number of patients attending a dental clinic are suffering from osteoporosis, and a major portion of them has received and/or is receiving treatment with ARDs, it is important to consider possible side effects; specifically, dentoalveolar procedures, including dental implant and bone augmentation therapies, might be affected by drugs interfering with bone remodeling. In particular, a specific side effect of ARDs associated with dentoalveolar procedures is osteonecrosis of the jaws; this condition, recognized already for more than a decade ago regarding BPs, is characterized by exposed bone or bone that can be probed through an intra- or extraoral fistula in the maxillofacial region and that has persisted for >8 weeks. Currently, the condition is termed "medication-related osteonecrosis of the jaws" (MRONJ), to reflect the fact that similar lesions can be associated with several ARDs and not exclusively with BPs.

Various available reviews on this topic generally agree that still relatively little information is available in regard to possible effects of ARDs on relevant aspects of implant therapy, such as implant failure rate, marginal bone loss, and MRONJ development. Further, there is no comprehensive review regarding the possible effect of ARDs on the failure of grafting procedures and/or on peri-implantitis. Thus, the aim of the current review was to systematically assess the literature and perform a meta-analysis when possible, to answer the following focused question: "In patients with systemic intake of ARDs, what is the outcome of implant therapy in terms of rates of implant loss, failure of grafting procedures, peri-implant marginal bone levels/loss, MRONJ, and/or peri-implantitis compared to patients without systemic intake of ARDs?"

2 | MATERIAL AND METHODS

2.1 | Protocol and eligibility criteria

The present systematic review was performed following the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA; Liberati et al., 2009; Moher, Liberati, Tetzlaff, & Altman, 2009). The literature was systematically searched for original studies fulfilling the following inclusion criteria: (a) English or German language; (b) case series, cohort studies, case–control studies, and controlled and/or randomized controlled clinical trials (CTs/RCTs); (c) retro- or prospective design; (d) ≥10 patients with systemic intake of ARDs; (e) clearly reported relevant clinical data (please see data extraction section); and (f) full text available. Studies were excluded if (a) not meeting all inclusion criteria; or (b) local application of ARDs.

2.2 | Information sources and literature search

Electronic search was performed in Medline (PubMed), EMBASE (Ovid), and CENTRAL (Ovid)—last search 05/09/2017 and no date restriction used, using relevant search terms (see Appendix 1). Additionally, screening of the reference lists of previous reviews and included full texts and forward search via Science Citation Index of included papers were conducted.

2.3 | Data collection and extraction

Two authors (KB, AS) independently checked title, abstract, and finally full text on the predefined eligibility criteria. Studies with abstracts with unclear methodology were included in full-text assessment to avoid exclusion of potentially relevant articles. One author (KB) repeated the literature search. In case of ambiguity, consensus through discussion was achieved regarding the final selection of studies to be included.

From the included studies, one author (KB) extracted twice the following data when available: (a) study design; (b) no. of cases (i.e., patients with ARD intake) and—when available—controls (i.e., subjects without ARD intake), implants, and grafting procedures; (c) patient characteristics (i.e., systemic diseases/comorbidities, other relevant medication intake, age, gender, and smoking status); (d) indication for ARD intake, type, and administration details; (e) implant follow-up time; (f) reported outcome parameters (i.e., implant loss, grafting procedure complication/failure, peri-implant marginal bone levels/loss, MRONJ, and peri-implantitis); and (g) MRONJ details (i.e., localization, attributable triggering factor, and time between medication intake or triggering factor and MRONJ development).

2.4 | Synthesis of results—Statistics

Implant loss was defined as the primary outcome parameter; failure of the grafting procedure (i.e., additional need for grafting or precluding implant installation), marginal bone loss, MRONJ, and peri-implantitis were defined as secondary outcome parameters.

Random-effects meta-analyses, separately for each ARD type, were implemented to calculate from the included cohort and case–control studies pooled estimates at the patient and/or implant level. All statistical analyses were performed using Stata (StataCorp LLC, USA).

2.5 | Quality assessment

2.5.1 | Newcastle-Ottawa-Scale

Two authors (KB and AS) independently evaluated the methodological and reporting quality of the included studies applying Newcastle-Ottawa-Scale (NOS; Wells et al., 2016), however, with some of the original items modified/adapted to fit the research question herein as follows: (1) selection: (a) selection of controls/nonexposed cohort was awarded with a star, if the controls have been derived from the same office and (b) the item "outcome of interest was not present at start of study" for cohort studies was discarded, as the outcome of interest to include studies in the present review was "implant loss"; (2) comparability: smoking status and/or any augmentation procedure were judged as the most relevant parameters; and (3) exposure: (a) regarding adequate length of follow-up, if ARD intake started prior to implant installation, then for long-term outcomes (e.g., late implant loss), ≥5 years was required, while ≤1 year after prosthetic restoration was accepted for short-term outcomes (e.g., early implant loss); if implant installation occurred before ARD intake, then ≥3 years follow-up since start of intake was required; (b) the item "nonresponse rate" was not judged for case–control studies if the data were based on medical records only; and (c) the item "adequacy of follow-up of cohorts" was not judged for retrospective or cross-sectional cohort studies. Thus, studies could herein achieve a maximum of 8 or 9 stars; for reasons of comparability, a percentage of awarded stars out of the possible maximum number of stars for each specific study was calculated. Further, the percentage of positive scored studies for each specific item was calculated. In case of ambiguity, consensus through discussion was achieved.

2.5.2 | Basic reporting items in Drugs and Implants

A purpose-made tool containing a list of items considered as necessary for meaningful reporting of ARD studies in oral implantology was constructed, and studies were assessed for quality of reporting. Three dimensions were defined (a) subject-, (b) medication-, and (c) intervention-related; the various items in each dimension were adapted to each specific ARD group (Appendix 2). Reporting of the various items was judged separately for each cohort of cases and controls, as well as for the cohorts of cases and controls presenting with a complication/event (i.e., implant loss, grafting procedure complication/failure, peri-implant marginal bone levels/loss, MRONJ, and peri-implantitis). The frequency of reported items per study/cohort as percentage of the total number of items, as well as the percentage of positive scored studies/cohorts for each specific item, was calculated.

3 | RESULTS

3.1 | Study selection

Appendix 3 presents the flowchart of the literature search. Out of 4,093 originally identified studies, 3,815 were excluded based on the title and 221 based on the abstract. Three records from forward search via the Science Citation Index and no records from reference lists of previous reviews or later included full texts were additionally identified; thus, 60 articles were selected for full-text review. Twenty-four articles were excluded for various reasons (Appendix 4); finally, 36 articles were included. The included studies were grouped into "studies on BP intake" (n = 24; Table 1) (Al-Sabbagh, Robinson, Romanos, & Thomas, 2015; Al-Sabbagh, Thomas, Bhavsar, & De Leeuw, 2015; Bell & Bell, 2008; Bell, Diehl, Bell, & Bell, 2011; Famili, Quigley, & Mosher, 2011; Fugazzotto, Lightfoot, Jaffin, & Kumar, 2007; Goss, Bartold, Sambrook, & Hawker, 2010; Grant, Amenedo, Freeman, & Kraut, 2008; Jeffcoat, 2006; Kasai, Pogrel, & Hossaini, 2009; Khoury & Hidajat, 2016; Koka, Babu, & Norell, 2010; Martin et al., 2010; Memon, Weltman, & Katancik, 2012; Mozzati et al., 2015; Shabestari et al., 2010; Siebert, Jurkovic, Statelova, & Strecha, 2015; Suvarna et al., 2016; Tallarico, Canullo, Xhanari, & Meloni, 2016; Wagenberg & Froum, 2006; Wagenberg, Froum, & Eckert, 2013; Yajima, Munakata, Fuchigami, Sanda, & Kasugai, 2017; Yip, Borrell, Cho, Francisco, & Tarnow, 2012; Zahid, Wang, & Cohen, 2011), "studies on HRT intake" (n = 7; Table 2) (August, Chung, Chang, & Glowacki, 2001; Koka et al., 2010; Koszuta, Grafka, Koszuta, Łopucki, & Szymańska, 2015; Minsk & Polson, 1998; Moy, Medina, Shetty, & Aghaloo, 2005; de Souza et al., 2013; Yip et al., 2012), and "studies on MRONJ associated with implants" (n = 7; Table 3) (Giovannacci et al., 2016; Holzinger et al., 2014; Jacobsen et al., 2013; Kwon et al., 2014; Lazarovici et al., 2010; Pogrel & Ruggiero, 2017; Troeltzsch et al., 2016). Two studies (Koka et al., 2010; Yip et al., 2012) contributed with data on both BP and HRT intake, while two studies (Wagenberg & Froum, 2006; Wagenberg et al., 2013) are based on the same study population. No studies reporting on SERMs, calcitonin, denosumab, SrR, c-Src, CatK, and sclerostin inhibitors, fulfilling the inclusion criteria, were identified.

3.2 | Study characteristics

Tables 1–3 present general and more detailed characteristics on (a) study design; (b) no. of cases and controls, implants, and grafting procedures; (c) patients' characteristics (i.e., relevant systemic diseases/comorbidities or medication intake, age, gender, and smoking status); (d) indication for type and administration details of ARD; (e) implant follow-up time; (f) reported outcome parameters (i.e., implant loss, grafting procedure complication/failure, peri-implant marginal bone levels/loss, MRONJ, and peri-implantitis); and (g) MRONJ details of included studies. Table 4 presents a summary of studies reporting exact figures (numbers) on the above-mentioned outcome parameters.

TABLE 1 Characteristics of included studies reporting on the effect of BP intake on implant loss, grafting procedure complication/failure, peri-implant marginal bone levels/loss, MRONJ, and peri-implantitis

Study	Study design	Patient level—number of cases/controls a: Implants b: Grafting	Site level—number of implants/grafting procedures in cases/controls a: Implants b: Grafting	a: Systemic disease b: Age range/mean c: Gender m/f (%) d: Smokers (%)	a: Type of BP b: Indication for intake c: Admin. route d: Intake range/mean (years)	a: BP intake prior to/after implant installation b: Implant follow-up range/mean (years)	Outcome parameters	Outcome	Additional information
Jeffcoat (2006)	Prospective Case–control study Clinical data	a: 25/25 b: NR	a: 102/108 b: NR	a: Osteoporosis (*Cases:* 25; *Controls:* 25) b: NR (Postmenopausal) c: 0/100 d: 4	a: ALN, RSN b: Osteoporosis c: Oral d: 1–4/3	a: Prior b: At least 3	Implant success Marginal bone loss Incidence of MRONJ	*Cases:* 100% *Controls:* 99.2% Maximum 2 mm 0	–
Wagenberg and Froum (2006)	Retrospective Cohort study Medical records	a: 24/867 b: NR/121+ unspecified number	a: NR/1925 b: NR/161+ unspecified number	a: NR b: 14–94/58 c: 43/57 d: ca. 17	a: ALN b: Osteoporosis c: NR d: NR	a: NR b: 1–16/6 (post restoration)	Implant loss	*Cases:* 0 *Controls:* 71 implants lost in 68 patients 6 implants failed to meet success criteria 96% survival rate	–
Fugazzotto et al. (2007)	Retrospective Case series Medical records	a: 61/0 b: 22 (at sites with immediate implant installation) /0	a: 169/0 b: 39 (at sites with immediate implant installation) /0	a: NR (excluded: uncontrolled diabetes, immune diseases, or other contraindicating systemic conditions) b: 51–83/NR c: 0/100 d: NR	a: ALN (51), RSN (10) (35 or 70 mg/week) b: NR c: Oral d: 1–5/3.3	a: Prior b: 1–2	Implant success Incidence of MRONJ	100% 0	Immediate implant installation (PL: 22, IL: 39) and implant installation into healed sites (nonsubmerged; PL: 39, IL: 130)
Bell and Bell (2008)	Cross-sectional Case series Clinical data and medical records	a: 42/0 b: 30/0	a: 100/0 b: 68/0	a: Osteoporosis(42) b: NR c: 5/95 d: NR	a: ALN (34), RSN (6), IBN (2) b: Osteoporosis c: Oral d: 0.5–11/NR	a: Prior (34 continuous intakes at time point of surgery) b: 0.3–7.4/3.1	Implant loss Bone graft failure PD & BoP Height of the ridge/vertical bone loss Incidence of MRONJ	5 (PL & IL) 95% success rate (PL & IL) All 5 lost implants successfully replaced 1 sinus lift failed PD unchanged since baseline No BoP 1 patient: 2 mm loss 0	*Case #1:* f, BP since 6 months, nonsmoker, no bone grafting, loss after 3 months *Case #2:* f, BP since 3 years, smoker, socket bone grafting, loss after 2 months *Case #3:*f, BP since 2 years, nonsmoker, sinus lift, loss after 5 months *Case #4:*f, BP since 5 years, nonsmoker, sinus lift, limited implant stability at time of placement, loss after 3 weeks *Case #5:*f, BP since 3 years, nonsmoker, sinus lift, loss after 2 months 3 losses in the posterior MX, 1 loss in MX lateral incisor (immediate implant installation), and 1 loss in MN cuspid (overdenture during healing)

(Continues)

TABLE 1 (Continued)

Study	Study design	Patient level—number of cases/controls a: Implants b: Grafting	Site level—number of implants/grafting procedures in cases/controls a: Implants b: Grafting	a: Systemic disease b: Age range/mean c: Gender m/f (%) d: Smokers (%)	a: Type of BP b: Indication for intake c: Admin. route d: Intake range/mean (years)	a: BP intake prior to/after implant installation b: Implant follow-up range/mean (years)	Outcome parameters	Outcome	Additional information
Grant et al. (2008)	Cross-sectional Cohort study Questionnaire and partly clinical data	a: 115/343 b: 32/NR	a: 468/1450 b: 32/NR	a: NR b: >40/NR c: 0/100 d: NR *Cases:* a: Diabetes (2), Prednisolone intake (3) b: NR/67.4 c: 0/100 d: NR	a: Prior: ALN (66), RSN (21), IBN (2) After: NR b: NR c: Oral d: NR/3.2	a: Prior (33 > 3 years, 56 < 3 years) and after (26) b: NR	Implant success	*Cases:* 2 losses (IL and PL; both due to nonosseointegration, one successfully replaced) *Controls:*14 losses	*Case #1:* MX premolar, BP since >3 years but not anymore at time point of surgery or thereafter *Case #2:* MN molar, BP since >4 years
							Incidence of MRONJ	0	
Kasai et al. (2009)	Retrospective Case–control study Medical records	a: 11/40 b: NR	a: 35/161 b: NR	a: Osteoporosis (*Cases:* 11, *Controls:* 4) (excluded: uncontrolled diabetes, rheumatic disease under corticoid medication) b: > 36/NR; *Cases:* 52–73 c: 0/100 d: 0	a: ALN b: Osteoporosis c: Oral d: At least 3/NR	a: Prior b: *Cases:* 5.3–12.2/7	Implant loss/success	*Cases:* 5 losses in 3 patients/85.7% success rate *Controls:* 7 losses/95.7% success rate	*Case #1:* 2 losses in the anterior MX (lack of integration) *Case #2:* 2 losses in posterior MN (after 33 months) *Case #3:* 1 loss in the anterior MX (after 11 months)
							Incidence of MRONJ	0	
Goss et al. (2010)	Retrospective Cohort study Questionnaire among dentists and medical records	a: 5%/ca. 16 000 b: NR-	a: NR/ca. 28 000 b: NR	a: NR b: NR c: NR d: NR *Cases with a loss:* a: Osteoporosis (6), osteoporosis & diabetes + steroid intake (1) b: 49–75/65.7 c: 29/71 d: NR	a: NR b: NR c: NR d: NR *Cases with a loss:* a: ALN (4), RSN (2), ALN&RSN (1) b: Osteoporosis c: Oral d: 3–10/5.2 (3), 0.25 (1), 5 (2), 5.2 (1)	a: NR b: NR *Cases with a loss:* a, b: 3 losses due to nonosseointegration (BP intake prior to implant installation); 6 losses after successful integration for 1.5–20 years (BP intake after implant installation)	Implant loss	7 (PL) and 9 (IL) Failure rate 0.89% (PL) –	m (2)/f (5), mean age: 65.7 (range: 49–75); 1 with steroids and diabetes
							Incidence of MRONJ	Among the 7 patients with an implant loss, 5 have been reported with localized to extensive ONJ	
Koka et al. (2010)	Retrospective Case–control study (?) Medical records and interview	a: 55/82 b: NR	a: 121/166 b: NR	*Cases:* a: Diabetes (10), HRT (estrogen; 31), steroids (5) b: 50–93/71 c: 0/100 d: 4 *Controls:* a: Diabetes (8), HRT (estrogen; 48), steroids (5) b: 50–89/66 c: 0/100 d: 11	a: NR b: Osteoporosis (32), Osteopenia (18), or not specified (5) c: NR d: <3 (16), 3–5 (20), >5 (19) /NR	a: Prior b: NR	Implant loss	*Cases:* 1 loss/99.2% success rate (IL) *Controls:* 3 losses in 2 patients/98.2% success rate (IL)	Case (1): 82 years, nonsmoker, additional HRT, osteoporosis, ALN (70 mg/week) for 6 years Controls (2): 65/76 years, 1 smoker, both HRT
							Incidence of MRONJ	0	

(Continues)

TABLE 1 (Continued)

Study	Study design	Patient level—number of cases/controls a: Implants b: Grafting	Site level—number of implants/grafting procedures in cases/controls a: Implants b: Grafting	a: Systemic disease b: Age range/mean c: Gender m/f (%) d: Smokers (%)	a: Type of BP b: Indication for intake c: Admin. route d: Intake range/mean (years)	a: BP intake prior to/after implant installation b: Implant follow-up range/mean (years)	Outcome parameters	Outcome	Additional information
Martin et al. (2010)	Cross-sectional Case series Questionnaire and partly medical records	a: 589/0 b: NR/0	a: NR/0 b: NR/0	a: NR b: NR c: NR d: NR *Patients with implant losses:* a: Steroids (1), no diabetes b: NR/70 c: 0/100 d: 2 current, 3 former smokers (*n*)	a: ALN (95%), RSN, IBN b: *Patients with implant losses:* Osteoporosis or osteoporotic fracture prevention c: Oral d: >1/NR	a: Prior and after b: NR	Implant loss Incidence of MRONJ	16 (PL) 26 (IL) 4 weeks to 11 years after installation Early losses: 8 PL/8 IL Late losses: 10 PL/18 IL *(2 patients had both early and late losses)* Immediate (1) and delayed (15) placement 0 (among the implant losses) 1 patient (smoker; 4 losses in the anterior MN 4 years after placement; implants placed 5 months after beginning of ALN treatment): osteomyelitis and extensive bone necrosis surrounding the implants	Patients with losses: all ALN due to osteoporosis for 3–69 months prior (12) and after (4) implant installation, smokers (2), former smokers (3), and steroids (1) MX (8 PL/12 IL): 3 anterior, 9 posterior MN (9 PL/14 IL): 5 anterior, 9 posterior
Shabestari et al. (2010)	Cross-sectional Case series Clinical data	a: 21/0 b: 5/0	a: 46/0 b: NR/0	a: Excluded: diabetes, immune deficiency b: 42–79/53 c: 0/100 d: NR	a: ALN (35–70 mg/week) b: Osteoporosis c: Oral d: 1.7/NR	a: Prior (7) and after (14) b: 4.2/0.6–8.1	Implant loss Incidence of peri-implantitis	0 0 6.3% showed 3 exposed threads	–
Bell et al. (2011)	Retrospective Cohort study Medical records	a: in total: 655 b: NR/reported but without specific numbers	a: 24/898 b: NR/reported but without specific numbers	a: NR b: NR/ca. 59 c: Ca. 42/58 d: Ca. 13	a: NR b: NR c: NR d: NR	a: NR b: 0.25–7.75/1.6	Implant loss	*Cases:* 0 *Controls:*15 (after 1–10 months)	–

(Continues)

TABLE 1 (Continued)

Study	Study design	Patient level—number of cases/controls a: Implants b: Grafting	Site level—number of implants/grafting procedures in cases/controls a: Implants b: Grafting	a: Systemic disease b: Age range/mean c: Gender m/f (%) d: Smokers (%)	a: Type of BP b: Indication for intake c: Admin. route d: Intake range/mean (years)	a: BP intake prior to/after implant installation b: Implant follow-up range/mean (years)	Outcome parameters	Outcome	Additional information
Famili et al. (2011)	Retrospective Cohort study Medical records	a: 22/98 b: NR	a: 75/272 b: NR	a: Osteoporosis (*Cases:* 22, *Controls:* 5), osteoarthritis (1) b: >50/NR c: 0/100 d: NR	a: ALN (15), RSN (4), IBN(1), ALN and IBN (2) b: Osteoporosis c: Oral d: 0.5–1 (6), 1–5 (9), >5 (5), unknown (2) /NR	a: NR b: NR	Implant loss Incidence of MRONJ	*Cases:* 1 at second-stage surgery (PL and IL; successfully replaced) *Cases:* 98.7% success rate (IL) 0	–
Zahid et al. (2011)	Retrospective Cohort study Medical records	a: 26/274 b: NR	a: 51/610 b: in total 173	a: Osteoporosis (8% of the study population) b: 17–87/56 c: 37/63 d: 9	a: ALN, IBN b: Osteoporosis c: NR d: 0.5–16 (11 not available) /NR	a: Prior b: 0.17–6.5/2.17	Implant loss Marginal bone loss Incidence of MRONJ	19 in total (success rate 97.1%) 3 implants in cases [success rate: 94.1% (IL) /88.5% (PL)] In total: 71 implants with "1–8 thread exposure" *Cases:* 13 implants with "thread exposure" out of 51 OR 3.3 with BP use 0	*Losses in total:* anterior (2), posterior (17) *Losses in cases: Case #1:* 72 years, f, 1st MN-molar, ALN (70 mg per week for unknown period), loss after 7 weeks, successful replaced *Case #2:* 75 years, f, MN canine, IBN (150 mg per month for unknown period), loss after 8 weeks, successful replaced *Case #3:* 75 years, f, immediate implant at 2nd MX-premolar, ALN since 4 years, no initial stability, loss after 4 weeks, not replaced
Memon et al. (2012)	Retrospective Case–control study Medical records	a: 100/100 b: NR	a: 153/132 b: ca.44 /ca. 44	*Cases:* a: Diabetes (3) b: 46–91/66 c: 0/100 d: 3 *Controls:* a: Diabetes (4) b: 47–90/63 c: 0/100 d: 5	a: ALN (72) RSN (23), IBN (5) b: Osteoporosis c: Oral d: <1 (20), 1–3 (19), >3 (15), unspecified (46) / NR	a: Prior b: Until stage-two surgery 4–6 months	Early implant loss/ Implant success Marginal bone level*(assessed in a fraction of the study population 4–6 months post-op at second-stage surgery)*	*Cases:* 10 losses (IL) /93.5% success rate *Controls:* 6 losses (IL) /95.5% success rate *Cases: 0.87 mm Controls: 0.92 mm* No difference between groups No effect of BP type and duration intake No effect of implant location	Implant losses: ALN (6), RSN (1), and IBN (3)
Wagenberg et al. (2013)	Retrospective Cohort study Medical records	a: NR/541 b: NR/121 + unspecified number	a: 35/1151 b: NR/161 + unspecified number	a: NR b: 12–88/59 c: 43/57 d: ca. 15	a: ALN b: Osteoporosis c: NR d: NR	a: NR b: 1–22/10	Marginal bone loss	*Cases:* 0.61 mm *Controls:* 0.53 mm Overall: 0.52 mm, <1.5 mm in 90% (IL), >3 mm in 2.5% (IL)	No significant effect of BP intake

(Continues)

TABLE 1 (Continued)

Study	Study design	Patient level—number of cases/controls a: Implants b: Grafting	Site level—number of implants/grafting procedures in cases/controls a: Implants b: Grafting	a: Systemic disease b: Age range/mean c: Gender m/f (%) d: Smokers (%)	a: Type of BP b: Indication for intake c: Admin. route d: Intake range/mean (years)	a: BP intake prior to/after implant installation b: Implant follow-up range/mean (years)	Outcome parameters	Outcome	Additional information
Yip et al. (2012)	Retrospective Case–control study Medical records	a: 20/317 b: NR	a: in total 1181 b: NR	a: HRT (36), diabetes (20), thyroid disorders, cardiovascular diseases b: ≥40/57 c: 0/100 d: 15	a: ALN, RSN b: Osteoporosis c: Oral d: NR	a: NR b: 0.3–11.9/6	Implant loss	OR 2.7 of BP use for implant loss Cases were more likely oral BP users (9.7%) than controls (4.0%; $p = 0.04$)	No significant interaction between BP use and implant location Stratified analyses: association between BP use and implant loss was stronger and significant in MX (adjusted OR 2.6; 95% CI 1.4–5.0), while of less magnitude and nonsignificant in MN (adjusted OR 1.4; 95% CI 0.5– 3.7)
Al-Sabbagh, Thomas, et al. (2015)	Cross-sectional Cohort study Interview	a: 39/376 b: NR	a: in total: 963 b: NR	a: Osteoporosis (*Cases:* 39, *Controls:* 20), diabetes (43) b: NR/59.4 c: 42/58 d: 11.1	a: NR b: Osteoporosis c: NR d: NR	a: NR b: NR/6	Implant success	84.9% success (PL) No effect of BP (PL) 89.4% success (IL) No use of BP (OR 9.22; 95% CI, 1.849, 45.975) associated with poor implant outcome (IL) *Cases:* 35 (89.7%) success, 4 (10.3%) failure (PL) *Controls:*318 (84.6%) success, 58 (15.4%) failure (PL)	–
							Implant loss	10 (2.4%; PL) 25 (2.6%; IL)	
							Incidence of MRONJ	0	
Al-Sabbagh, Robinson, et al. (2015)	Cross-sectional Cohort study Interview	a: 20/183 b: NR	a: 46/469 b: NR	a: Osteoporosis (*Cases:* 20, *Controls:* 9) b: 21–90/55.5 c: 41/59 d: *Cases:* 0	a: NR b: Osteoporosis c: Oral d: ≥3	a: NR b: 0.84–10/7.05	Implant failure	0	–
							Incidence of MRONJ	0	

(Continues)

TABLE 1 (Continued)

Study	Study design	Patient level—number of cases/controls a: Implants b: Grafting	Site level—number of implants/grafting procedures in cases/controls a: Implants b: Grafting	a: Systemic disease b: Age range/mean c: Gender m/f (%) d: Smokers (%)	a: Type of BP b: Indication for intake c: Admin. route d: Intake range/mean (years)	a: BP intake prior to/after implant installation b: Implant follow-up range/mean (years)	Outcome parameters	Outcome	Additional information
Mozzati et al. (2015)	Retrospective Case series Medical records	a: 235/0 b: NR/0	a: 1267/0 b: 54/0	a: Diabetes (21), Corticosteroids (24) b: 48–79/61 c: 0/100 d: 22	a: ALN (141), RSN (45), IBN (68) b: Osteoporosis c: Oral d: 0.6–7.3/3.4	a: Prior b: Minimum 2, up to 10	Implant loss Incidence of MRONJ	- 16 IL/15 PL Success rate: 98.7% (IL) /93.2% (PL) All lost 1–3 months after surgery All successfully replaced 0	*Implant losses:* 51–77 years old, smokers (9), 3 diabetes (3), corticosteroids (3), ALN (6), RSN (5), IBN (4), BP intake 2–82 months, MX anterior (3) / posterior (9), MN anterior (2)/ posterior (2), immediate loading (1),sinus lift (7), and immediate placement (9) Significant risk factors: RSN, diabetes, corticosteroids, and smoking
Siebert et al. (2015)	Prospective Case–control study (?) Clinical data	a: 12/12 b: NR	a: 60/60 b: NR	a: None (excluded: steroids) b: >54 c: 0/100 d: 0	a: ZLN (5 mg once per year) b: Osteoporosis c: iv d: 2–3	a: Prior b: 1	Implant survival Incidence of MRONJ	100% 0	All implants immediate implant installation in the anterior MN
Khoury & Hidajat (2016)	Retrospective Case series Medical records	a: 15/0 b: 15/0	a: 71/0 b: 61/0	a: Osteoporosis (15) b: 55–72/NR c: 0/100 d: 0	a: Oral: ALN, RSN, IBN, CLN iv: IBN b: Osteoporosis c: Oral and iv d: 0.25–10/NR	a: Prior b: 3–6	Implant loss Marginal bone loss Incidence of MRONJ Outcome grafting	- 1 (immediately loaded; after 5 months), successfully replaced No major bone loss No peri-implantitis 0 Incomplete healing of the grafted bone and necessity of regrafting during implant installation (2) Limited soft tissue necrosis after implant installation (2) Uneventful healing at donor sites	Implants inserted simultaneously (28) or 3 months after augmentation (43), second-stage surgeries after 3 months and prosthetic restorations after 4–8 weeks

(Continues)

TABLE 1 (Continued)

Study	Study design	Patient level—number of cases/controls a: Implants b: Grafting	Site level—number of implants/grafting procedures in cases/controls a: Implants b: Grafting	a: Systemic disease b: Age range/mean c: Gender m/f (%) d: Smokers (%)	a: Type of BP b: Indication for intake c: Admin. route d: Intake range/mean (years)	a: BP intake prior to/after implant installation b: Implant follow-up range/mean (years)	Outcome parameters	Outcome	Additional information
Suvarna et al. (2016)	Retrospective Case series Medical records	a: 112/0 b: 55/0	a: 140/0 b: 82/0	a: NR b: NR c: 30/82 d: NR	a: ALN (40), RSN (10), IBN (8) b: NR c: NR d: NR	a: Prior b: Minimum of 3	Implant loss Marginal bone loss Incidence of MRONJ	10 (IL and PL) Success rate 92.9% 3 losses within 1 month, 2 losses within 2 months, 2 losses within 6 months, and 3 losses within 3 weeks 0 0	Implant losses: 8 in f (3 patients: smokers, bone grafting; 2 patients: BP since 1 year, nonsmokers, sinus lift; 3 patients: BP since 3 years, smokers, sinus lift), 2 in m (BP since 5 months, nonsmokers, no bone grafting), 70% in posterior MX
Tallarico et al. (2016)	Prospective Case series Clinical data	a: 32/0 b: NR/0	a: 98/0 b: NR/0	a: NR b: 46–80/65 c: 0/100 d: no "heavy smokers (>10 cigarettes/day)"	a: ALN (70 mg per week) b: Osteoporosis c: Oral d: >3/NR	a: Prior (at least 3 years, but drug holidays for 6 months before and 4–6 months after implant installation) b: 3–6/4	Implant survival Marginal bone loss	1 implant loss 99% survival rate after 3 years mean: 1.35 mm (after 3 years)	Implant loss occurred before prosthetic restoration and in MX
Yajima et al. (2017)	Retrospective Cohort study Medical records (?)	a: 11/14 b: NR	a: 25/28 b: NR	a: Osteoporosis (*Cases:* 11, *Controls:* 14) (excluded: steroids and diabetes) Controls: 8 SERM and 6 PTH intake b: *Cases:* >60 /70; *Controls:* >60 /67 c: 0/100 d: 0	a: ALN b: Osteoporosis c: Oral d: 1–3 (5), >3 (6)	a: Prior b: *Cases:* 3.2; *Controls:*5.2	Implant loss Incidence of MRONJ	*Cases:* 3 (IL & PL) within 1 year Controls: 0 0	*Case #1:* 68 years, f, molar (MN), BP since 1 year *Case #2:* 67 years, f, premolar (MN), BP since 4 years *Case #3:* 75 years, f, molar (MN), BP since 5 years

Notes. , retrospective case series; , cross-sectional case series; , prospective case series; , retrospective cohort study; , cross-sectional cohort study; , prospective cohort study; , retrospective case–control study; , cross-sectional case–control study; , prospective case–control study.

ALN, alendronate; BoP, bleeding on probing; BP, bisphosphonate; CLN, clodronate; CI, confidence interval; f, female; HRT, hormone replacement therapy; IBN, ibandronate; IL, implant level; iv, intravenous; m, male; MN, mandible; MRONJ, medication-related osteonecrosis of the jaw; MX, maxilla; NR, not reported; OR, odds ratio; PD, probing pocket depth; PL, patient level; PTH, parathyroid hormone; RSN, risedronate; SERM, selective estrogen receptor modulator; ZLN, zoledronate.

Inconsistencies in the numbers among the columns in this table are due to inconsistencies in the original papers.

TABLE 2 Characteristics of included studies reporting on the effect of HRT intake on implant loss, grafting procedure complication/failure, peri-implant marginal bone levels/loss, MRONJ, and peri-implantitis

Study	Study design	Patient level—number of cases/controls a: Implants b: Grafting	Site level—number of implants/grafting procedures in cases/controls a: Implants b: Grafting	a: Systemic disease b: Age range/mean c: Gender m/f (%) d: Smokers (%)	a: HRT product details (content, dosage) b: Indication for HRT intake c: Administration route d: Duration range/mean (years)	a: HRT intake prior to/after implant installation b: Implant follow-up range/mean (years)	Outcome parameters	Outcome	Additional information
Minsk and Polson (1998)	Retrospective Cohort study Medical records	a: 25/91 b: NR	a: 71/379 b: NR	a: Excluded: steroids, metabolic disorders b: 51–91/NR c: 0/100 d: *Cases:* 22 implants; *Controls:* 104 implants	a: NR b: NR c: NR d: NR	a: Prior b: NR	Implant loss	*Cases:* 8 (11.3%; IL) *Controls:* 28 (7.4%; IL) Only early failures	Smoking appeared to significantly increase the failure rate among cases
August et al. (2001)	Retrospective Cohort study Medical records	a: 75/168 b: 0	a: 241/570 b: 0	a: Excluded: concurrent illness, metabolic bone disease, BP, or raloxifene intake b: *Cases:*33–79; *Controls:* 50–96 c: 0/100 d: 0	a: Estrogen b: Osteoporosis c: NR d: NR	a: Prior b: Until implant exposure	Implant loss	*Cases:* 22 (9.1%; IL) *Controls:* 66 (11.6%; IL)	—
Moy et al. (2005)	Retrospective Cohort study Medical records	a: 161/304 b: NR	a: NR b: NR	a: NR b: 12–94/NR c: 41/59 d: NR	a: Estrogen b: NR c: NR d: NR	a: Prior b: Up to 20	Implant loss	*Cases:* 44 (27.3%; PL) *Controls:* 49 (16.1%; PL) HRT: RR 2.55 for implant failure (compared to healthy patients)	-
Koka et al. (2010)	Retrospective Case–control study (?) Medical records& interview	a: 79/58 b: NR	a: in total 287 b: NR	a: Diabetes (18), steroids (10), osteoporosis (32), osteopenia (18), and BP (55) of all participants b: 50–93/NR c: 0/100 d: 7	a: Estrogen b: Osteoporosis c: NR d: NR	a: Prior b: NR	Implant loss	*Cases:* 4 implants in 3 patients *Controls:* 0	*Case #1:* 82 years old, nonsmoker, BP intake since 6 years *Case #2:* 76 years old, nonsmoker *Case #3:* 65 years old, smoker

(Continues)

TABLE 2 (Continued)

Study	Study design	Patient level—number of cases/controls a: Implants b: Grafting	Site level—number of implants/grafting procedures in cases/controls a: Implants b: Grafting	a: Systemic disease b: Age range/mean c: Gender m/f (%) d: Smokers (%)	a: HRT product details (content, dosage) b: Indication for HRT intake c: Administration route d: Duration range/mean (years)	a: HRT intake prior to/after implant installation b: Implant follow-up range/mean (years)	Outcome parameters	Outcome	Additional information
de Souza et al. (2013)	Retrospective Cohort study Medical records	a: 13/180 b: 0	a: 61/661 b: 0	a: Osteoporosis (6), Diabetes (5) of all participants b: NR/50.3 c: 35/65 d: 8.3	a: NR b: NR c: NR d: NR	a: Prior b: 1–8.75/NR	Marginal bone loss (≥2 mm)	*Cases:* 26 (42.6%; IL) *Controls:* 189 (28.6%; IL)	—
Yip et al. (2012)	Retrospective Case–control study Medical records	a: 36/301 b: NR	a: in total 1181 b: NR	a: BP (20), diabetes (20), thyroid disorders, cardiovascular diseases b: ≥40/57 c: 0/100 d: 15	a: NR b: NR c: NR d: NR	a: NR b: 0.3–11.9/6	Implant loss	No significant different distribution between cases and controls	—
Koszuta et al. (2015)	Prospective Cohort study Clinical data	a: 20/51 b: NR	a: NR b: NR	a: NR b: NR c: 0/100 d: NR	a: Low doses of estrogens b: NR c: NR d: NR/2.6	a: Prior b: NR/0.5	Implant success rate Marginal bone level	*Cases:* 75% (PL) *Controls:* 92.9% (PL) Average: cases 25%, controls 15% Range: cases 17.5–100%, controls 10–20% Significant correlation between bone loss and HRT	—

Notes. , retrospective case series; , cross-sectional case series; , prospective case series; , retrospective cohort study; , cross-sectional cohort study; , prospective cohort study; , retrospective case–control study; , cross-sectional case–control study; , prospective case–control study.
BP, bisphosphonate; f, female; HRT, hormone replacement therapy; IL, implant level; m, male; NR, not reported; PL, patient level.
Inconsistencies in the numbers among the columns in this table are due to inconsistencies in the original papers.

TABLE 3 Characteristics of the included studies reporting on features of medication-related osteonecrosis of the jaw associated with implant and/or augmentation procedures

Study	Number of patients(number of implants)	a: Age range/ mean (years) b: Gender m/ f(n) c: Smokers (n)	Comorbidities and/or other relevant medication intake reported (yes/ no)	MRONJ localization	a: Indication, type, dosage and administration route b: Intake prior to/after surgery	Intake time and timeframe between various time points	Triggering factor
Lazarovici et al. (2010)	27	a: NR/70 b: 7/20 c: 2	Yes	Posterior MN (15), anterior MN (5), posterior MX (4), anterior MX (3)	a: Oral for osteoporosis (11)—ALN 70 mg/week or 10 mg/day (11) iv for malignant disease (16)—ZLN 4 mg every 3–4 weeks (7), PMN 90 mg every 3–4 weeks (5), PMN 90 mg every 3–4 weeks + ZLN 4 mg every 3–4 weeks (4) b: prior and after	BP-MRONJ: ALN (68 months), ZLN (16.4 months), PMN (50.2 months), PMN + ZLN (53 months) I-MRONJ: within 6 months (6), mean 16.2 months (BP prior to I)	Implant surgery (6), implant presence/ spontaneous (21)
	Group 1—BP prior to I 23				a: ALN (10), ZLN (5), PMN (5), PMN + ZLN (3) b: prior	BP-I: 0–108 months I-MRONJ: 0–53 months BP-MRONJ: 10–115 months	
	Group 2—BP after I 4				a: ALN (1), ZLN (2), PMN + ZLN (1) b: after	I-BP: 22–125 months BP-MRONJ: 1–156 months	
Jacobsen et al. (2013)	12 + 2 with metastasis or infiltration of malignant underlying disease (23 implants)	a: NR b: 3/11 c: NR	No	4 MX, 8 MN sites [posterior MN (5), posterior MX (4), anterior MN (3)] 1 in combination with a sinus lift (2 patients with metastasis/ infiltration NR)	a: Osteoporosis (5)—ALN oral (2), PMN (1), IBN iv (1), ALN + PMN (1) iv for malignant diseases (9)—ZLN (8), PMN + ZLN (1) b: NR	BP-MRONJ: 38 months for 7 patients with malignant disease, 50 months for 5 patients with osteoporosis I-MRONJ: 20.9 months (17 months for 7 patients with malignant disease, 25.6 months for 5 patients with osteoporosis) (2 patients with metastasis/ infiltration: NR)	Not specified

(Continues)

TABLE 3 (Continued)

Study	Number of patients(number of implants)	a: Age range/ mean (years) b: Gender m/ f(n) c: Smokers (n)	Comorbidities and/or other relevant medication intake reported (yes/ no)	MRONJ localization	a: Indication, type, dosage and administration route b: Intake prior to/after surgery	Intake time and timeframe between various time points	Triggering factor
Holzinger et al. (2014)	13 (47 implants)	a: 52–79/65.7 b: 0/13 c: 7	Yes	12 patients in MN, 1 patient in MX	a: ZLN 4 mg/month iv (7), ALN 70 mg/ week oral (3), PMN 90 mg/month oral (2), IBN 3 mg every 3 months iv (1); Osteoporosis (5), malignant diseases (8) b: prior and after	30 implants lost after 0–210/50.8 months (10 lacked osseointegration)	Not specified
	Group 1—I prior to BP 3 (8 implants)				a: iv (3) b: after	BP intake: 23–41/32 months I-BP: 57–193/115 months BP-MRONJ: 14–23/18 months I-MRONJ: 80–210/133 months	
	Group 2—BP started and stopped prior to I 3 (19 implants)				a: oral (2), iv (1) b: prior	BP intake: 65–122/93 months BP-MRONJ: 6–108/57 months BP-I: 48–119/83 months I-MRONJ: 0–66/33 months	
	Group 3—BP prior and continued after I 7 (20 implants)				a: iv b: prior	BP intake: 39–243/88 months BP-MRONJ: 18–223/77 months BP-I: 0–187/50 months I-MRONJ: 6–73/32 months	
Kwon et al. (2014)	Group 1—BP prior to I 16	a: 42–85 b: 2/14 c: NR	Yes	Posterior MN (9), posterior MX (6), anterior MN (1)	a: Oral for osteoporosis (13)—ALN (6), RSN (3), ALN + RSN (2), ALN + IBN (1), ALN + RSN + IBN (1); iv for osteoporosis (2)—IBN (1), PMN (1); iv for malignant disease (1)—ZLN b: prior	BP intake: 12–120/60.5 months BP-I: 6–108 months I-MRONJ: 3–82 months	Implant surgery (3), implant explantation (4), and unknown (9)
	Group 2—BP after I 3	a: 67–73 b: 0/3 c: NR	Yes	Posterior MX (2), posterior MN (1)	a: Oral for osteoporosis (3)—ALN (2), RSN (1) b: after	I-BP: 6–108 months BP-MRONJ: 13–27 months	Implant explantation (1), unknown (2)

(Continues)

TABLE 3 (Continued)

Study	Number of patients(number of implants)	a: Age range/ mean (years) b: Gender m/ f(n) c: Smokers (n)	Comorbidities and/or other relevant medication intake reported (yes/ no)	MRONJ localization	a: Indication, type, dosage and administration route b: Intake prior to/after surgery	Intake time and timeframe between various time points	Triggering factor
Giovannacci et al. (2016)	Group 1—implant surgery as trigger 6 (17 implants)	a: 61–74/65.2 b: 0/6 c: 2	Yes	4 sites in 3 patients in MX, 4 sites in 3 patients in MN *additionally: MRONJ wo implants (1), implants wo MRONJ (3 patients/5 implants)*	a: Oral for osteoporosis (5)—ALN (3), IBN (1), IBN + ALN (1); iv for breast cancer (1)—IBN + ZLN b: prior	BP intake: 36–131/83.7 months I-MRONJ: 2–10 months	Implant surgery
	Group 2—implant presence as trigger 9 (35 implants)	a: 45-83/63.4 b: 4/5 c: 0	Yes	5 sites in 4 patients in MX, 7 sites in 7 patients in MN *additionally: MRONJ wo implants (2), implants wo MRONJ (4 patients/13 implants)*	a: Oral for osteoporosis (1)—ALN iv for malignant disease (8)—ZLN (6), ZLN + PMN (1), PMN (1) b: NR	BP intake: 15–60/27.8 months I-MRONJ: 1–15 years	Implant presence
Troeltzsch et al. (2016)	19 (61 implants)	—	No	—	a: Osteoporosis, malignant disease b: After (55 implants), prior (6 implants)	I-BP: 23.8 months (55) BP prior to I: 2 implants did not osseointegrate, 4 healed uneventful I-MRONJ: 45.4 months BP-MRONJ: 32 months	Not specified
	Peri-implant MRONJ: 15	a: NR/66.3 b: 9/6 c: NR		MN (13), MX (2)	a: Osteoporosis (3), malignant disease (iv; 12)	BP intake: 32.3 months	
	MRONJ involving teeth & implants: 4	a: NR/63.5 b: 1/3 c: NR		MN (1), MX (3)	a: Malignant disease (iv; 4)	BP intake: 35.7 months	
Pogrel and Ruggiero (2017)	11	a: NR b: 0/11 c: NR	Yes	MN (9), MX (2)	a: ALN (8), ZLN (1), denosumab (2) for osteoporosis or metastatic bone disease b: After	I-BP: "number of years" BP-MRONJ: 2–13/4.8 years	Implant presence (11)

Notes. , retrospective case series; , cross-sectional case series; , prospective case series; , retrospective cohort study; , cross-sectional cohort study; , prospective cohort study; , retrospective case–control study; , cross-sectional case–control study; , prospective case–control study.

ALN, alendronate; BP, bisphosphonate; f, female; IBN, ibandronate; I, implant installation; iv, intravenous; m, male; MN, mandible; MX, maxilla; MRONJ, medication-related osteonecrosis of the jaw; NR, not reported; PMN, pamidronate; RSN, risedronate; wo, without; ZLN, zoledronate.

Inconsistencies in the numbers among the columns in this table are due to inconsistencies in the original papers.

TABLE 4 Summary of studies reporting exact figures on one or more of the evaluated outcome parameters (i.e., implant loss, grafting procedure complication/failure, peri-implant marginal bone levels/loss, MRONJ, and peri-implantitis)

Studies on BP intake								
Event	**Level**	**No. of studies**	**Administration route (NR/oral/iv/oral&iv)**	**Cases**	**Controls**	**Event (cases)**	**Event (controls)**	**Additional information**
Implant loss	PL	12	3/7/1/1	1218	1,144	49	71	
Implant loss	IL	15	4/9/1/1	2849	3,946	54	60	
Grafting complication	IL	6	1/4/0/2	336	0	3	0	Cases required regrafting and/or presented with limited soft tissue necrosis after implant installation (n = 2); sinus-lift failure (n = 1)
MRONJ (assoc. with implants)	PL	16	4/10/1/1	1390	—	1 (?)	—	Case did not meet the AAOMS criteria for MRONJ
MRONJ (assoc. with grafting sites)[a]	IL	6	1/4/0/1	336	—	0	—	

Studies on HRT intake							
Event	**Level**	**No. of studies**	**Cases**	**Controls**	**Event (cases)**	**Event (controls)**	**Additional information**
Implant loss	PL	2	240	362	47	49	
Implant loss	IL	2	312	949	30	94	

Notes. AAOMS, American Association of Oral and Maxillofacial Surgeons; BP, bisphosphonate; HRT, hormone replacement therapy; IL, implant/site level; iv, intravenous; MRONJ, medication-related osteonecrosis of the jaw; NR, not reported; PL, patient level.

[a]Includes studies, which did not specifically report on MRONJ for grafting sites, but MRONJ was not reported for the whole study sample.

TABLE 5 Methodological and reporting quality assessment of case–control studies

	BP-associated studies						HRT-associated studies	
	Jeffcoat (2006)	Kasai et al. (2009)	Koka et al. (2010)	Memon et al. (2012)	Siebert et al. (2015)	Overall %	Koka (2010)	Overall %
Selection (4)								
Adequate case definition (1)	*				*	40		0
Representativeness of the cases (1)		*	*	*		60	*	100
Selection of controls (1)		*	*	*		60	*	100
Definition of controls (1)	*	*	*	*	*	100	*	100
Comparability (2)								
Comparability based on design or analysis (2)	*	*	*	**	*	60	*	100
Exposure (3)								
Ascertainment of exposure—cases (1)	*		*		*	60	*	100
Ascertainment of nonexposure—controls (1)	*	*	*	*	*	100	*	100
Nonresponse rate (1)	*	x		x	*	67		0
Overall %	67	63	67	75	67		67	

Notes. x, the data are based on medical records, which does not allow to judge "nonresponse rate"; BP, bisphosphonate; HRT, hormone replacement therapy.

3.2.1 | Studies on BP intake (*n* = 24)

Eight case series, 10 cohort studies, and six case–control studies reporting on BP intake were included. About 2/3 of the studies were retrospective, six were cross-sectional (Al-Sabbagh, Robinson, et al., 2015; Al-Sabbagh, Thomas, et al., 2015; Bell & Bell, 2008; Grant et al., 2008; Martin et al., 2010; Shabestari et al., 2010), and most were based only on information in the medical/dental patient journals; only three prospective studies (Jeffcoat, 2006; Siebert et al., 2015; Tallarico et al., 2016) were identified. Among studies, cases (i.e., patients with BP intake) with implants ranged from 11 to approximately 800, while the implant number ranged from 24 to 1267 implants; controls (i.e., patients without BP intake) with implants ranged from 12 to approximately 16,000, and the implant number ranged from 28 to approximately 28,000 implants. Two (Bell et al., 2011; Wagenberg et al., 2013) and five studies (Al-Sabbagh, Robinson, et al., 2015; Goss et al., 2010; Martin et al., 2010; Wagenberg & Froum, 2006; Yip et al., 2012), respectively, did not report separately numbers of cases and controls on the patient or implant level. Studies report on an observation period ranging from 0.3 to 16 years after implant installation/restoration.

In six studies (Bell & Bell, 2008; Fugazzotto et al., 2007; Grant et al., 2008; Khoury & Hidajat, 2016; Shabestari et al., 2010; Suvarna et al., 2016) providing some—often nonspecific—information on grafting procedures in cases, the range of patients was 5–55 and the range of grafting sites 32–82. Five studies (Bell et al., 2011; Memon et al., 2012; Wagenberg & Froum, 2006; Wagenberg et al., 2013; Zahid et al., 2011) provided only approximate information/figures regarding grafting procedures in controls. Three studies (Memon et al., 2012; Tallarico et al., 2016; Wagenberg et al., 2013) reported exact figures of peri-implant marginal bone loss/levels, while information on peri-implantitis was rarely provided.

Collectively, some type of information was provided regarding implant success, failure, or loss in 23 studies, regarding grafting procedures in 11 studies, regarding MRONJ in 17 studies, and regarding peri-implantitis in nine studies (Table 1). More detailed single-patient data on ARD type and indication for intake, as well as the duration of intake until MRONJ, were possible to extract from two studies (Al-Sabbagh, Robinson, et al., 2015; Goss et al., 2010; Martin et al., 2010; Wagenberg & Froum, 2006; Yip et al., 2012) (six patients).

3.2.2 | Studies on HRT intake (*n* = 7)

Five cohort studies and two case–control studies reporting on HRT intake were included. All studies, but one prospective study (Koszuta et al., 2015), were retrospectively based on medical/dental records. Among studies, cases (i.e., patients with HRT intake) with implants ranged from 13 to 161, while the implant number ranged from 24

TABLE 6 Methodological and reporting quality assessment of cohort studies

	BP-associated studies											HRT-associated studies					
	Wagenberg and Froum (2006)	Grant et al. (2008)	Goss et al. (2010)	Bell et al. (2011)	Famili et al. (2011)	Zahid et al. (2011)	Wagenberg et al. (2013)	Al-Sabbagh, Robinson, et al. (2015)	Al-Sabbagh, Thomas, et al. (2015)	Yajima et al. (2017)	Overall %	Minsk (1998)	August (2001)	Moy (2005)	Souza (2013)	Koszuta (2015)	Overall %
Selection (3)																	
Representativeness of the exposed cohort (1)					*	*		*	*	*	50	*	*	*	*	*	100
Selection of the nonexposed cohort (1)	*	*		*	*	*	*	*	*	*	90	*	*	*	*	*	100
Ascertainment of exposure (1)	*			*			*	*	*		50		*	*	*	*	80
Comparability (2)																	
Comparability based on design or analysis (2)						*		*		*	15	*	**		*		40
Outcome (3)																	
Assessment of outcome (1)	*		*	*	*	*	*				60	*	*	*	*	*	100
Follow-up long enough for outcomes to occur (1)											0						0
Adequacy of follow-up of cohorts (1)	x	x	x	x	x	x	x	x	x	x	-	x	x	x	x	*	100
Overall %	43	14	14	43	43	57	43	57	43	43		57	86	57	71	63	

Notes. x, the data are based on retrospective or cross-sectional assessment, which does not allow to judge "adequacy of follow-up of cohorts"; BP, bisphosphonate; HRT, hormone replacement therapy.

to 61 implants; controls (i.e., patients without HRT intake) with implants ranged from 51 to 304, and the implant number ranged from 379 to 661; however, four studies (Koka et al., 2010; Koszuta et al., 2015; Moy et al., 2005; Yip et al., 2012) did not report exact implant numbers. Studies report on an observation period ranging from 0.3 to 20 years after implant installation/restoration.

Two studies (August et al., 2001; de Souza et al., 2013) specifically excluded grafted sites, while the remaining studies did not provide any information on any possible grafting procedures. Collectively, some type of information was provided regarding implant success and/or loss in six studies, and on marginal bone loss in two studies (Table 2).

3.2.3 | Studies on MRONJ associated with implants (*n* = 7)

Among seven case series studies, reporting on MRONJ associated with implants, cases ranged from 11 to 27 patients (116 in total) and the implant number ranged from 8 to 61 implants. More detailed single-patient data on ARD type and indication for intake, as well as the duration of intake until MRONJ, were possible to extract from four studies (68 patients) (Giovannacci et al., 2016; Holzinger et al., 2014; Jacobsen et al., 2013; Kwon et al., 2014; Lazarovici et al., 2010; Pogrel & Ruggiero, 2017; Troeltzsch et al., 2016).

3.3 | Quality assessment

3.3.1 | Newcastle-Ottawa-Scale

Tables 5 and 6 present the methodological and reporting quality assessment, based on the modified NOS, of the included case–control and cohort studies regarding both BPs and HRT, respectively. Case–control and cohort studies received from 5 to 6 (i.e., 63%–75%) and from 1 to 6 (i.e., 14%–86%) stars, respectively. The percentage of positive scored studies per item ranged for BP case–control studies from 40% to 100% and for cohort studies from 0% to 90%, respectively; the corresponding values for HRT studies ranged from 0% to 100% irrespective study type. One study (Yip et al., 2012) was excluded from the quality assessment due to its study design not allowing comparison of cases with ARD intake versus controls; specifically, the study compared patients with implant losses with patients with no losses.

3.3.2 | Basic reporting items in Drugs and Implants

Tables 7–9 present assessment of BP, HRT, and MRONJ studies in terms of quality of reporting on the defined basic items. Large variation was observed regarding the percentage of positive scored items among BP studies for both cases and controls, with or without complications (i.e., 0%–88%). Additionally, the percentage of positive scored items among the various cohorts of cases and controls, with or without a complication/event, was in general low; for example, the percentage of positive scored items in the cohort of cases with and without complications was ≤50% in 71% and 41% of the studies, respectively. Only five (i.e., gender, indication for BP intake, BP type, BP administration route, and time point of first BP intake) of 16 items were reported adequately in >50% of the studies. For example, in about 30% of the studies, the indication and/or administration route for BP intake was not clearly/precisely reported, while only 50% of the studies provided some information regarding smoking habits. Information on other relevant systemic diseases (e.g., diabetes) or medication intake (e.g., corticosteroids) was provided in only ca. 35% of the studies. Further, about 30% of the studies did not report whether implants were placed before or after BP intake, while 70% of the studies did not include information on whether implants were placed in augmented or pristine bone.

Similarly, large variation was observed regarding the percentage of positive scored items among HRT studies for both cases and controls, with or without complications (i.e., 0%–78%). Further, the percentage of positive scored items among the various cohorts of cases and controls, with or without a complication/event, was in general low; for example, the percentage of positive scored items in the cohort of cases, with and without complications, was ≤50% in 86% and 71% of the studies, respectively. Only three (i.e., gender, product details, and time point of first HRT intake) of 15 items were reported adequately in >50% of the studies. For example, only about 30% of the studies provided some information regarding smoking habits, other relevant systemic diseases or medication intake, or whether implants were placed in augmented or pristine bone.

Slightly better reporting, comparing to BP and HRT studies, was observed in the MRONJ studies regarding the patient- and medication-related items, but there was also lack of relevant information on intervention-related items. The percentage of positive scored items ranged among studies from 0% to 100%. Further, in three of seven studies, the percentage of positive scored items was ≤50%, while nine of 16 items were reported adequately in >50% of the studies.

3.4 | Summary of results

3.4.1 | Studies on BP intake

In the majority of studies, oral BP was prescribed for osteoporosis treatment; only two studies (Khoury & Hidajat, 2016; Siebert et al., 2015) reported iv administration of BP, but no study reported BP administration related to malignancies. In general, no significant differences were observed regarding implant loss between cases and controls, and implant success rate ranged for cases from 85.7% to 100%, which was similar to the 84.6% to 100% of the controls; however, the success criteria used in the various studies were rather different and/or questionable. In two studies, conflicting results regarding implant loss were presented, with one study (Yip et al., 2012) reporting an odds ratio (OR) of 2.7 for BP intake compared with controls, while the other study (Al-Sabbagh, Robinson, et al., 2015) reported an OR of 9.2 for controls (i.e., controls had a higher risk for

TABLE 7 Frequency of basic reporting items among studies reporting on the effect of bisphosphonate intake on implant and/or grafting procedure outcome and incidence of medication-related osteonecrosis of the jaw

		Patient-related						Medication-related	
		Age (range and mean)	Gender	Smoking	Indication for medication intake (e.g., osteoporosis and cancer)	Comorbidities (e.g., diabetes)	Other relevant medications (e.g., steroids)	Type	Dosage
Jeffcoat (2006)[a]									
I	Cohort—BP intake	–	+	+	+	–	–	+	–
II	Cohort—Non-BP intake	–	+	+	x	–	–	x	x
IV	Individ. with complications (Non-BP cohort)	–	+	–	x	–	–	x	x
Wagenberg and Froum (2006)[a]									
I	Cohort – BP intake	–	–	–	+	–	–	+	–
II	Cohort – Non-BP intake	–	–	–	x	–	–	x	x
IV	Individ. with complications (Non-BP cohort)	–	+	+	x	–	–	x	x
Fugazzotto et al. (2007)[a,b]									
I	Cohort—BP intake	–	+	–	–	+	–	+	+
Bell and Bell (2008)[b]									
I	Cohort—BP intake	–	+	–	+	–	–	+	–
III	Individ. with complications (BP cohort)	–	+	+	+	–	–	–	–
Grant et al. (2008)									
I	Cohort—BP intake	+	+	–	–	+	+	+	–
II	Cohort—Non-BP intake	–	+	–	x	–	–	x	x
III	Individ. with complications (BP cohort)	–	+	–	–	–	–	–	–
IV	Individ. with complications (Non-BP cohort)	–	+	–	x	–	–	x	x
Kasai et al. (2009)									
I	Cohort—BP intake	–	+	+	+	–	–	+	–
II	Cohort—Non-BP intake	–	+	+	x	–	–	x	x
III	Individ. with complications (BP cohort)	–	+	+	+	–	–	+	–
IV	Individ. with complications (Non-BP cohort)	–	+	+	x	–	–	x	x
Goss et al. (2010)									
I	Cohort—BP intake	–	–	–	–	–	–	–	–
II	Cohort—Non-BP intake	–	–	–	x	–	–	x	x
III	Individ. with complications (BP cohort)	+	+	–	+	+	+	+	–
IV	Individ. with complications (Non-BP cohort)	–	–	–	x	–	–	x	x
Koka et al. (2010)									
I	Cohort—BP intake	+	+	+	+	+	+	–	–
II	Cohort—Non-BP intake	+	+	+	x	+	+	x	x
III	Individ. with complications (BP cohort)	+	+	+	+	+	+	+	+
IV	Individ. with complications (Non-BP cohort)	+	+	+	x	+	+	x	x
Martin et al. (2010)[b]									
I	Cohort—BP intake	–	–	–	–	–	–	+	–

				Intervention-related				
Administration route (e.g., oral, iv, and both)	First intake prior to/ after surgery	Medication intake time (range and mean) until end of study (cohort level) or complication (individual level)	Drug holiday at surgery (i.e., yes/no, duration)	Implant—region	Augmentation/ pristine	Perioperative medication (e.g., antibiotics)	Follow-up period until end of study (cohort level) or complication (individual level)	Overall %
+	+	+	–	–	–	–	+	50
x	x	x	x	–	–	–	+	33
x	x	x	x	–	–	–	+	22
–	–	–	–	–	–	+	–	19
x	x	x	x	–	–	+	–	11
x	x	x	x	+	–	+	–	44
+	+	+	–	–	+	+	–	56
+	+	–	–	–	+	–	+	44
+	+	+	–	+	+	–	+	56
+	+	–	–	–	+	–	–	50
x	x	x	x	–	–	–	–	11
+	+	+	–	+	+	–	+	44
x	x	x	x	–	–	–	–	11
+	+	–	–	–	–	+	+	50
x	x	x	x	–	–	+	–	33
+	+	–	–	+	–	+	+	56
x	x	x	x	–	–	+	–	33
–	–	–	–	–	–	–	–	0
x	x	x	x	–	–	–	–	0
+	+	+	–	+	+	–	–	69
x	x	x	x	–	–	–	–	0
–	+	–	+	–	–	–	–	50
x	x	x	x	–	–	–	–	56
+	+	+	+	–	–	–	–	75
x	x	x	x	–	–	–	–	56
+	+	–	–	–	–	–	–	19

(Continues)

TABLE 7 (Continued)

		Patient-related						Medication-related	
		Age (range and mean)	Gender	Smoking	Indication for medication intake (e.g., osteoporosis and cancer)	Comorbidities (e.g., diabetes)	Other relevant medications (e.g., steroids)	Type	Dosage
III	Individ. with complications (BP cohort)	–	+	+	+	+	+	+	+
Shabestari et al. (2010)[a,b]									
I	Cohort—BP intake	+	+	–	+	+	–	+	+
Bell et al. (2011)[a]									
I	Cohort—BP intake	–	–	–	–	–	–	–	–
II	Cohort—Non-BP intake	–	–	–	x	–	–	x	x
IV	Individ. with complications (Non-BP cohort)	–	–	+	x	+	–	x	x
Famili et al. (2011)									
I	Cohort—BP intake	–	+	–	+	–	–	+	–
II	Cohort—Non-BP intake	–	+	–	x	–	–	x	x
III	Individ. with complications (BP cohort)	–	+	–	+	–	–	–	–
IV	Individ. with complications (Non-BP cohort)	–	+	–	x	–	–	x	x
Zahid et al. (2011)									
I	Cohort—BP intake	–	+	+	+	–	–	+	–
II	Cohort—Non-BP intake	–	–	–	x	–	–	x	x
III	Individ. with complications (BP cohort)	+	+	–	+	–	–	+	+
IV	Individ. with complications (Non-BP cohort)	–	–	–	x	–	–	x	x
Memon et al. (2012)									
I	Cohort—BP intake	+	+	+	+	+	–	+	–
II	Cohort—Non-BP intake	+	+	+	x	+	–	x	x
III	Individ. with complications (BP cohort)	–	+	–	+	–	–	+	–
IV	Individ. with complications (Non-BP cohort)	–	+	–	x	–	–	x	x
Wagenberg et al. (2013)									
I	Cohort—BP intake	–	–	–	+	–	–	+	–
II	Cohort—Non-BP intake	–	–	–	x	–	–	x	x
III	Individ. with complications (BP cohort)	–	–	–	+	–	–	+	–
IV	Individ. with complications (Non-BP cohort)	–	–	–	x	–	–	x	x
Yip et al. (2012)									
I	Cohort—BP intake	–	+	–	+	–	–	+	–
II	Cohort—Non-BP intake	–	+	–	x	–	–	x	x
III	Individ. with complications (BP cohort)	–	+	–	+	–	–	–	–
IV	Individ. with complications (Non-BP cohort)	–	+	–	x	–	–	x	x

				Intervention-related				
Administration route (e.g., oral, iv, and both)	First intake prior to/ after surgery	Medication intake time (range and mean) until end of study (cohort level) or complication (individual level)	Drug holiday at surgery (i.e., yes/no, duration)	Implant—region	Augmentation/ pristine	Perioperative medication (e.g., antibiotics)	Follow-up period until end of study (cohort level) or complication (individual level)	Overall %
+	+	+	–	+	–	–	–	69
+	+	–	–	+	+	–	+	69
–	–	–	–	–	–	+	–	6
x	x	x	x	–	–	+	–	11
x	x	x	x	+	–	+	+	56
+	–	–	–	–	–	–	–	25
x	x	x	x	–	–	–	–	11
+	+	–	–	–	–	–	+	31
x	x	x	x	–	–	–	–	11
–	+	–	–	+	–	+	+	50
x	x	x	x	–	–	+	–	11
–	+	–	–	+	–	+	+	56
x	x	x	x	–	–	+	–	11
+	+	–	–	+	–	–	+	63
x	x	x	x	+	–	–	+	67
+	+	–	–	–	–	–	+	38
x	x	x	x	–	–	–	+	22
–	–	–	–	–	–	+	–	19
x	x	x	x	–	–	+	–	11
–	–	–	–	–	–	+	–	19
x	x	x	x	–	–	+	–	11
+	–	–	–	–	–	–	–	25
x	x	x	x	–	–	–	–	11
+	–	–	–	–	–	–	–	19
x	x	x	x	–	–	–	–	11

(Continues)

TABLE 7 (Continued)

		Patient-related						Medication-related	
		Age (range and mean)	Gender	Smoking	Indication for medication intake (e.g., osteoporosis and cancer)	Comorbidities (e.g., diabetes)	Other relevant medications (e.g., steroids)	Type	Dosage
Al-Sabbagh, Thomas, et al. (2015)									
I	Cohort—BP intake	–	–	–	–	–	–	–	–
II	Cohort—Non-BP intake	–	–	–	x	–	–	x	x
III	Individ. with complications (BP cohort)	–	–	–	–	–	–	–	–
IV	Individ. with complications (Non-BP cohort)	–	–	–	x	–	–	x	x
Al-Sabbagh, Robinson, et al. (2015)[a]									
I	Cohort—BP intake	–	+	+	+	–	–	–	–
II	Cohort—Non-BP intake	–	+	–	x	–	–	x	x
Mozzati et al. (2015)[b]									
I	Cohort—BP intake	+	+	+	+	+	+	+	–
III	Individ. with complications (BP cohort)	+	+	+	+	+	+	+	–
Siebert et al. (2015)[a]									
I	Cohort—BP intake	–	+	+	+	+	+	+	+
II	Cohort—Non-BP intake	–	+	+	x	+	+	x	x
Khoury & Hidajat (2016)[b]									
I	Cohort—BP intake	–	+	+	+	+	+	+	+
III	Individ. with complications (BP cohort)	–	+	+	+	+	+	+	+
Suvarna et al. (2016)[b]									
I	Cohort—BP intake	–	+	–	–	–	–	+	–
III	Individ. with complications (BP cohort)	–	+	+	–	–	–	–	–
Tallarico et al. (2016)[b]									
I	Cohort—BP intake	+	+	+	+	–	–	+	+
III	Individ. with complications (BP cohort)	–	+	+	+	–	–	+	+
Yajima et al. (2017)[a]									
I	Cohort—BP intake	–	+	+	+	+	+	+	–
II	Cohort—Non-BP intake	+	+	+	x	+	+	x	x
III	Individ. with complications (BP cohort)	+	+	+	+	+	+	+	–
Overall %									
I	Cohort—BP intake	25	75	46	71	38	25	79	21
II	Cohort—Non-BP intake	19	63	38	–	25	19	–	–
III	Individ. with complications (BP cohort)	29	88	47	82	35	35	65	29
IV	Individ. with complications (Non-BP cohort)	8	62	31	–	15	8	–	–

Notes. x, does not apply to this group; BP, bisphosphonate; iv, intravenous.

[a]No major complication in either the BP or non-BP group or in both—individual report not possible. [b]Case series—only patients with BP intake.

				Intervention-related				
Administration route (e.g., oral, iv, and both)	First intake prior to/ after surgery	Medication intake time (range and mean) until end of study (cohort level) or complication (individual level)	Drug holiday at surgery (i.e., yes/no, duration)	Implant—region	Augmentation/ pristine	Perioperative medication (e.g., antibiotics)	Follow-up period until end of study (cohort level) or complication (individual level)	Overall %
–	–	–	–	–	–	–	–	0
x	x	x	x	–	–	–	–	0
–	–	–	–	–	–	–	–	0
x	x	x	x	–	–	–	–	0
+	–	–	–	–	–	–	–	25
x	x	x	x	–	–	–	–	11
+	+	+	–	–	+	+	–	75
+	+	+	–	+	+	+	+	88
+	+	–	–	+	–	+	+	75
x	x	x	x	+	–	+	+	78
+	+	+	–	+	+	+	-	81
+	+	+	–	+	+	+	+	88
–	+	–	–	–	+	–	-	25
–	+	–	–	–	+	–	+	31
+	+	–	+	–	–	+	+	69
+	+	–	+	–	–	+	+	63
+	+	–	–	–	–	–	+	50
x	x	x	x	–	–	–	+	67
+	+	+	–	+	–	–	–	69
67	67	17	8	21	29	42	33	
–	–	–	–	13	0	38	25	
77	82	47	12	53	35	35	59	
–	–	–	–	15	0	38	23	

TABLE 8 Frequency of basic reporting items among studies reporting on the effect of hormone replacement therapy on implant and/or grafting procedure outcome

		Patient-related						Medication-related	
		Age (range and mean)	Gender	Smoking	Indication for medication intake (e.g., osteoporosis and cancer)	Comorbidities (e.g., diabetes)	Other relevant medications (e.g., steroids)	Product details (i.e., content and/or dosage)	Administration route (i.e., oral or transdermal)
Minsk and Polson (1998)									
I	Cohort—HRT intake	–	+	+	–	+	+	–	–
II	Cohort—Non-HRT intake	–	+	+	x	+	+	x	x
III	Individ. with complications (HRT cohort)	–	+	+	–	+	+	–	–
IV	Individ. with complications (Non-HRT cohort)	–	+	+	x	+	+	x	x
August et al. (2001)									
I	Cohort—HRT intake	+	+	+	+	+	+	+	–
II	Cohort—Non-HRT intake	+	+	+	x	+	+	x	x
III	Individ. with complications (HRT cohort)	–	+	+	+	+	+	+	–
IV	Individ. with complications (Non-HRT cohort)	–	+	+	x	+	+	x	x
Moy et al. (2005)									
I	Cohort—HRT intake	–	–	–	–	–	–	+	–
II	Cohort—Non-HRT intake	–	–	–	x	–	–	x	x
III	Individ. with complications (HRT cohort)	–	–	–	–	–	–	+	–
IV	Individ. with complications (Non-HRT cohort)	–	–	–	x	–	–	x	x
Koka et al. (2010)[a]									
I	Cohort—HRT intake	–	+	–	+	–	–	+	–
II	Cohort—Non-HRT intake	–	+	–	x	–	–	x	x
III	Individ. with complications (HRT cohort)	+	+	+	+	+	+	+	–
de Souza et al. (2013)									
I	Cohort—HRT intake	–	–	–	–	–	–	–	–
II	Cohort—Non-HRT intake	–	–	–	x	–	–	x	x
III	Individ. with complications (HRT cohort)	–	–	–	–	–	–	–	–
IV	Individ. with complications (Non-HRT cohort)	–	–	–	x	–	–	x	x
Yip et al. (2012)									
I	Cohort—HRT intake	–	+	–	–	–	–	–	–
II	Cohort—Non-HRT intake	–	+	–	x	–	–	x	x
III	Individ. with complications (HRT cohort)	–	+	–	–	–	–	–	–
IV	Individ. with complications (Non-HRT cohort)	–	+	–	x	–	–	x	x
Koszuta et al. (2015)									
I	Cohort—HRT intake	–	+	–	–	–	–	+	–

			Intervention-related				
First intake prior to/ after surgery	Medication intake time (range and mean) until end of study (cohort level) or complication (individual level)	Drug holiday at surgery (i.e., yes/no, duration)	Implant—region	Augmentation/ pristine	Peri-operative medication (e.g., antibiotics)	Follow-up period until end of study (cohort level) or complication (individual level)	Overall %
+	–	–	–	–	–	–	33
x	x	x	–	–	–	–	44
+	–	–	–	–	–	+	40
x	x	x	–	–	–	+	56
+	–	–	–	+	–	+	67
x	x	x	–	+	–	+	78
+	–	–	–	+	–	+	60
x	x	x	–	+	–	+	67
+	–	–	–	–	–	–	13
x	x	x	–	–	–	–	0
+	–	–	–	–	–	–	13
x	x	x	–	–	–	–	0
+	–	–	–	–	–	–	27
x	x	x	–	–	–	–	11
+	–	–	–	–	–	–	53
+	–	–	–	+	–	–	13
x	x	x	–	+	–	–	11
+	–	–	–	+	–	–	13
x	x	x	–	+	–	–	11
–	–	–	–	–	–	–	7
x	x	x	–	–	–	–	11
–	–	–	–	–	–	–	7
x	x	x	–	–	–	–	11
+	–	–	–	–	–	+	27

(Continues)

TABLE 8 (Continued)

		Patient-related						Medication-related	
		Age (range and mean)	Gender	Smoking	Indication for medication intake (e.g., osteoporosis and cancer)	Comorbidities (e.g., diabetes)	Other relevant medications (e.g., steroids)	Product details (i.e., content and/or dosage)	Administration route (i.e., oral or transdermal)
II	Cohort—Non-HRT intake	–	+	–	x	–	–	x	x
III	Individ. with complications (HRT cohort)	–	+	–	–	–	–	+	–
IV	Individ. with complications (Non-HRT cohort)	–	+	–	x	–	–	x	x
Overall %									
I	Cohort—HRT intake	14	71	29	29	29	29	57	0
II	Cohort—Non-HRT intake	14	71	29	–	29	29	–	–
III	Individ. with complications (HRT cohort)	14	71	43	29	43	43	57	0
IV	Individ. with complications (Non-HRT cohort)	0	83	33	–	33	33	–	–

Notes. x, does not apply to this group; HRT, hormone replacement therapy; iv, intravenous.
[a]No major complication in either the HRT or non-HRT group or in both—individual report not possible.

TABLE 9 Frequency of basic reporting items among studies reporting on medication-related osteonecrosis of the jaw associated with implant and/or augmentation procedures

	Patient-related						Medication-related		
III Individuals with relevant medication intake and complications	Age (range and mean)	Gender	Smoking	Indication for medication intake (e.g., osteoporosis and cancer)	Comorbidities (e.g., diabetes)	Other relevant medications (e.g., steroids)	Type	Dosage	Administration route (e.g., oral, iv, and both)
Lazarovici et al. (2010)	–	+	+	+	+	+	+	+	+
Jacobsen et al. (2013)	–	+	–	+	–	–	+	–	+
Holzinger et al. (2014)	+	+	+	+	+	–	+	+	+
Kwon et al. (2014)	+	+	–	+	+	+	+	–	+
Giovannacci et al. (2016)	+	+	+	+	+	+	+	–	+
Troeltzsch et al. (2016)	–	+	–	+	–	–	–	–	+
Pogrel and Ruggiero (2017)	–	+	–	+	–	+	+	–	–
Overall %	43	100	43	100	57	57	86	29	86

implant loss than cases). More implant losses occurred in the posterior maxilla and mostly after a short time from installation. In general, no relevant differences are described between cases and controls in the various studies regarding peri-implant marginal bone loss/levels, except for one study (Zahid et al., 2011), where an OR of was reported 3.3 for "thread exposure" in cases compared with controls.

Several studies reported no MRONJ in association with implants or with grafting procedures. Further, in one study (Goss et al., 2010) reporting on ca. 16,000 patients, only five cases with MRONJ in association with an implant were observed, while in another study including ca. 600 patients (Martin et al., 2010), one case with implant-related osteonecrosis was reported. However, information on both

			Intervention-related				
First intake prior to/after surgery	Medication intake time (range and mean) until end of study (cohort level) or complication (individual level)	Drug holiday at surgery (i.e., yes/no, duration)	Implant—region	Augmentation/pristine	Peri-operative medication (e.g., antibiotics)	Follow-up period until end of study (cohort level) or complication (individual level)	Overall %
x	x	x	–	–	–	+	22
+	–	–	–	–	–	+	27
x	x	x	–	–	–	+	22
86	0	0	0	29	0	29	
–	–	–	0	29	0	29	
86	0	0	0	29	0	43	
–	–	–	0	33	0	50	

			Intervention-related				
First intake prior to/after surgery	Medication intake time (range and mean) until complication/MRONJ	Drug holiday at surgery (i.e., yes/no, duration)	Implant/MRONJ—region	Augmentation/pristine	Perioperative medication (e.g., antibiotics)	Follow-up period (range and mean) until complication/MRONJ	Overall %
+	+	–	+	–	–	+	75
–	–	–	+	+	–	–	38
+	+	+	–	–	–	+	75
+	+	–	+	–	–	+	69
+	–	–	–	–	–	–	56
+	–	–	–	–	–	+	31
+	+	–	–	–	–	–	38
86	57	14	43	14	0	57	

studies seems based only on information in the medical/dental patient journals.

3.4.2 | Studies on HRT intake

Studies on HRT intake reported in general somehow higher implant loss rates in cases (9.1%–27.3%) compared to controls (7.4%–16.1%); one study (Moy et al., 2005) found a relative risk of 2.55 for cases versus controls. One study (Koszuta et al., 2015) reported larger amount of peri-implant marginal bone loss in patients receiving HRT comparing to controls (25% vs. 15% of the implant length, respectively), while another study (de Souza et al., 2013) reported 43% vs. 29% of implants with peri-implant marginal bone loss ≥2 mm at cases versus controls, respectively.

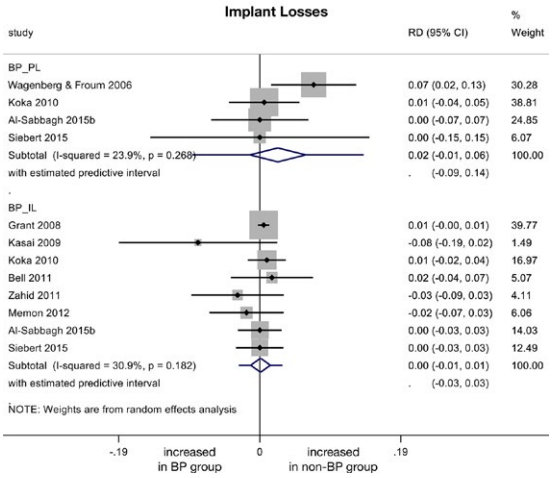

FIGURE 1 Forest plot from random-effects meta-analyses of the included cohort and case–control studies on bisphosphonates presenting pooled estimates at the patient (PL) and implant level (IL)

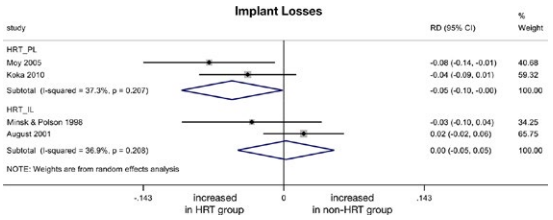

FIGURE 2 Forest plot from random-effects meta-analyses of the included cohort and case–control studies on hormone replacement therapy presenting pooled estimates at the patient (PL) and implant level (IL)

3.4.3 | Studies on MRONJ associated with implants

Medication-related osteonecrosis of the jaws development was associated with BP intake in all identified studies, except for one (Pogrel & Ruggiero, 2017), where in addition to the nine patients on BPs, two patients with denosumab intake were included. The MRONJ lesion was located in the mandible in 84 patients and in 34 patients in the maxilla, and somehow more often in posterior regions of the jaws. In 15 and 5 patients, implant installation or explantation, respectively, was described as the trigger of MRONJ, while in 41 patients, mere implant presence was considered as the trigger. Further, in 11 patients, an obvious reason could not be identified, while three studies (Holzinger et al., 2014; Jacobsen et al., 2013; Troeltzsch et al., 2016) did not report on any possible triggering factor. BP intake was iv in 61 patients and orally in 44 patients, while one study (Pogrel & Ruggiero, 2017) did not specify administration pathway. ARD intake started prior to implant installation in 55 patients and in 21 patients after implant installation, while two studies did not specify intake starting time point (Jacobsen et al., 2013) or did not report on patient level (Troeltzsch et al., 2016). The timeframe between implant installation and occurrence of MRONJ ranged from 0 to 210 months, while the timeframe between first ARD intake and occurrence of MRONJ ranged from 1 to 223 months.

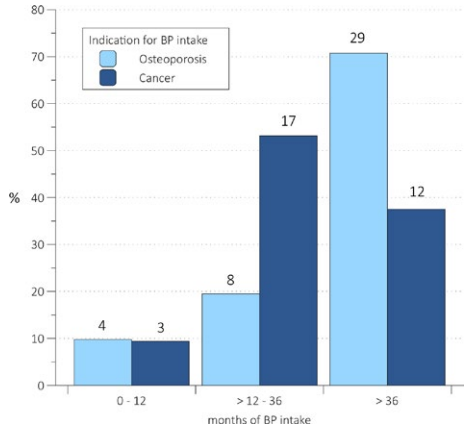

FIGURE 3 Bar chart showing the number of cases of medication-related osteonecrosis of the jaws at different timeframes in patients with low- and high-dose bisphosphonate intake, based on single-patient data reported in six studies

3.5 | Synthesis of results

Meta-analysis was possible for implant loss, on the patient and implant level, for both BP and HRT studies (Figures 1 and 2). Based on four studies reporting on the patient level and eight studies reporting on the implant level, no significant differences were observed in terms of implant loss between cases and controls in BPs studies. In contrast, based on two studies, HRT appeared to exert a marginally significant negative effect regarding implant survival on the patient level; however, based on another two studies, no negative effect of HRT was observed on the implant level.

Based on six studies reporting single-patient data, MRONJ in patients on BP for osteoporosis appeared mainly >36 months after start of drug intake (in 29 of 41 patients; 71%), while in patients with cancer, MRONJ appeared mainly ≤36 months after BP intake (20 out of 32 patients; 64%) (Figure 3).

4 | DISCUSSION

A considerable portion of the adult population (estimated to about 15% for persons ≥ 50 years of age) is suffering from osteoporosis and has received and/or is receiving treatment with ARDs, mainly BPs and denosumab; these drugs are also used for the management of other conditions, such as primary or metastatic malignancies of the bones. ARDs have traditionally been divided according to the route of administration (i.e., oral, sc, and iv). Current understanding, however, is that dose rather than route of administration per se is important; thus, low- and high-dose ARDs can be today administered through all three routes (Table 10). Primarily, low dose is used for osteoporosis treatment, whereas high dose is used in patients with

TABLE 10 List of ARDs currently used for osteoporosis and cancer treatment. Updated February 2018

Trade name	Generic name	Diagnosis	Administration route	Dosing interval	Dose
Fosamax	Alendronate	Osteoporosis	Oral	Weekly	70 mg
Alendronate	Alendronate	Osteoporosis	Oral	Weekly	70 mg
Fosavance	Alendronate + cholecalciferol (vitamin D3)	Osteoporosis	Oral	Weekly	70 mg + 70 μg
Aclasta	Zoledronate	Osteoporosis	iv	Yearly	5 mg
Pamidronate sodium	Pamidronate	Osteoporosis	iv	Yearly	5 mg
Bonviva	Ibandronate	Osteoporosis	iv	Monthly	1 mg/ml
Bonviva	Ibandronate	Osteoporosis	Oral	Monthly	150 mg
Ibamyl	Ibandronate	Osteoporosis	Oral	Monthly	150 mg
Ibandronate "Stada"	Ibandronate	Osteoporosis	Oral	Monthly	150 mg
Ibandronic acid "medical valley"	Ibandronate	Osteoporosis	Oral	Monthly	150 mg
Optinate Septimum	Risedronate	Osteoporosis	Oral	Weekly	35 mg
Risedronate sodium	Risedronate	Osteoporosis	Oral	Weekly	35 mg
Riseostad	Risedronate	Osteoporosis	Oral	Weekly	35 mg
Primadronat	Risedronate	Osteoporosis	Oral	Weekly	35 mg
Prolia	Denosumab	Osteoporosis	sc	6 months	60 mg
Zometa: Zoledronate "Actavis" Zoledronate "SUN" Zoledronate "Hospira"	Zoledronate	Cancer	iv	3–4 weeks	4 mg
Pamifos Pamidronate sodium "Hospira"	Pamidronate	Cancer	iv	3–4 weeks	90 mg
Bonefos	Clodronate	Cancer	Oral	Daily	1,600 mg
Bondronate	Ibandronate	Cancer	iv	3–4 weeks	6 mg
Bondronate	Ibandronate	Cancer	Oral	Daily	50 mg
Xgeva	Denosumab	Cancer	sc	4 weeks	120 mg

Notes. iv, intravenous; sc, subcutaneous injection.

cancer with bone metastases. In this context, it is relevant to assess possible side effects of ARD intake in connection to various aspects of implant therapy, including fixture installation, bone augmentation interventions, and late biological complications.

It is recognized that OCL-mediated bone resorption plays major role during various stages of morphogenesis of dental implant osseointegration and during peri-implant bone homeostasis. For example, during the early weeks postinstallation, extensive bone resorption occurs at the pitches of the thread where the implant is engaged with the bone achieving primary anchorage, that is, at the points of pressure, while OCL also cleanse the bone debris within the peri-implant hard tissue wound (Berglundh, Abrahamsson, Lang, & Lindhe, 2003). Furthermore, OCLs mediate marginal peri-implant bone modeling at later stages of healing to establish the marginal hard tissue seal around the implant and are fundamental for peri-implant bone homeostasis under functional loading (e.g., bone microcrack repair) (Insua, Monje, Wang, & Miron, 2017; Rossi et al., 2014). As ARDs interfere through various mechanisms with bone remodeling, and primarily with OCL function, it is reasonable to consider that these drugs may compromise aspects of implant therapy; for example, more implants might fail to integrate, or larger peri-implant marginal bone loss might occur during modeling or functional loading, or those patients may be prone to peri-implant infections.

Keeping in mind the fact that study design, size, and follow-up time varied considerably among the identified studies, meta-analysis was deemed possible to perform herein regarding implant loss for BPs and HRT, on both the implant and patient level. The results showed that patients on BPs for osteoporosis treatment (i.e., low dose) do not lose a significantly larger number of implants compared with persons not taking such medications, and the number of patients experiencing implant loss is similarly low in those patients compared with those without systemic BP intake. This regards both patients on low-dose BP receiving implants and patients with implants that start to take low-dose BP. These results are in accordance with what reported in other recent systematic reviews on the topic (Ata-Ali, Ata-Ali, Peñarrocha-Oltra, & Galindo-Moreno, 2016; Chrcanovic, Albrektsson, & Wennerberg, 2016; Walter, Al-Nawas, Wolff, Schiegnitz, & Grötz, 2016). In very crude numbers, considering only studies reporting exact figures and irrespective study design, out of a total of 2,894 implants placed in patients on BPs, only 54 were lost versus 60 implants lost out of 3946 implants placed in

patients without BP intake (i.e., 1.9% vs. 1.5%, respectively); this corresponds to 4.0% versus 6.2% of patients, respectively, experiencing implant loss. Similarly, the meta-analysis showed that patients receiving HRT lose a similar number of implants as those not taking such medications; on the patient level, however, it appeared that significantly more HRT patients experienced implant loss compared to the non-HRT group. Nevertheless, both meta-analyses on HRT are based on only two studies each, while one of the two studies reporting on patient level presented an unusually large number of patients with implant loss in both HRT and non-HRT groups (i.e., 27% vs. 16%, respectively) (Moy et al., 2005). In general, it seemed that the majority of reported implant losses in ARD patients occur within short time postinstallation/postloading (i.e., early losses), and somehow more often in the posterior maxilla. Similar numbers and patterns regarding implant losses have previously been reported for the general population (Bryant, 1998; Quirynen, Van Assche, Botticelli, & Berglundh, 2007). In this context, it has to be stressed that there are not much data available to draw conclusions on the success or safety of bone grafting procedures in conjunction with implant installation in patients on ARDs, or on the possible effect of low-dose sc and iv ARD administration on the outcome of implant placement or preexisting implants in patients with osteoporosis.

In the studies included in this review, information about peri-implant marginal bone levels/loss was scarce; only very few studies reporting on BPs for osteoporosis treatment presented exact figures (i.e., distance in mm). In particular, the possible impact of BPs on peri-implant marginal bone modeling was assessed only in one study (Memon et al., 2012). In this study, no difference was noted between implants placed in patients on BPs and those placed in patients without BP intake, 4–6 months after installation at second-stage surgery, with both groups exhibiting peri-implant marginal bone levels that are considered as normal (0.87 vs. 0.92 mm, respectively) (Laurell & Lundgren, 2011). Further, only one study reported on peri-implant bone levels on the long term (Wagenberg et al., 2013), with no differences observed between implants in patients with and without BP intake in terms of peri-implant marginal bone loss 1 to 20 years postloading (i.e., 0.61 vs. 0.53 mm, respectively). Additionally, in 90% of the implants, peri-implant marginal bone loss was <1.5 mm, and the small number of implants (i.e., 2.5%) exhibiting a peri-implant marginal bone loss >3 mm was not specifically associated with BP intake. Obviously, as these two studies evaluated bone levels at distinctly different time points in terms of peri-implant bone biology, that is, second-stage surgery and several years postloading, no meta-analysis was performed herein regarding peri-implant marginal bone levels for BP studies, although technically feasible. In the two studies reporting on marginal bone levels around implants placed in HRT vs. control patients, significantly more bone loss both during the osseointegration phase (Koszuta et al., 2015) and on the long term (de Souza et al., 2013) was observed in the HRT group; however, the studies did not provide precise values in mm.

In this context, reduced peri-implant marginal bone levels may represent a surrogate sign for peri-implantitis. Indeed, in this systematic review, the literature search included terms about peri-implantitis, but only a handful of publications fulfilled the inclusion criteria. In particular, out of 24 and seven studies reporting on BP and HRT intake, respectively, only two studies on patients receiving BPs for osteoporosis treatment reported explicitly assessing peri-implantitis; specifically, the authors stated that there were no cases of peri-implantitis (Khoury & Hidajat, 2016; Shabestari et al., 2010). Nevertheless, in the latter study, a small fraction of the evaluated implants (i.e., 6%) had three threads exposed, and considering the fact that the implants in this study were one-piece tissue level implants, one may question the validity of the findings/reporting in this study. The concern that patients on ARDs may have a higher risk for peri-implantitis should be also seen in light of MRONJ. As mentioned earlier, this condition has been recognized already for more than a decade as a side effect of BPs associated with dentoalveolar procedures, but now it is accepted that similar lesions can occur also in patients receiving other types of ARDs (Aljohani et al., 2017; Boquete-Castro, Gómez-Moreno, Calvo-Guirado, Aguilar-Salvatierra, & Delgado-Ruiz, 2016). The pathogenesis of the condition is not completely understood and seems to be multifactorial, but one mechanism among others is that bone is more vulnerable to infection due to decreased remodeling. Thus, the presence of an implant could in some cases function as a *locus minori resistentiae* for the development of MRONJ; for example, plaque-induced peri-implantitis triggers MRONJ or microcracks develop around the loaded implant, do not repair timely, accumulate, and give rise to necrosis. Most of the articles included in the present systematic review, however, reported no MRONJ in association with implants or grafting procedures. Specifically, in 16 studies on BP intake (mainly low dose for osteoporosis treatment), however, with variable design and follow-up time, only one case of MRONJ of 1,390 inserted implants was reported, while no studies on HRT intake reported on the event MRONJ. On the other hand, in a few publications fulfilling the inclusion criteria of this systematic review (i.e., reporting on ≥ 10 cases), some relevant information on MRONJ in association with implant therapy was provided. About 10% of MRONJ cases occurred during the first year of BP intake, and in some cases, drug intake was prior to implant installation, while in other cases, patients started taking the drugs after implant placement; occasionally, MRONJ appeared within a short timeframe of weeks of drug intake. Mere implant presence was considered as the trigger for MRONJ in about 30% of the patients, while in about 16% of the cases, the lesion was related to implant installation or explantation; in about 10% of the cases, no obvious reason for MRONJ could be identified, while in several of the cases, comorbidities (e.g., corticosteroid intake) were present. Based on single-patient data, MRONJ associated with implants appeared to occur after a shorter period of time in patients with cancer on high-dose ARD intake compared with patients with osteoporosis on low-dose ARD intake. Specifically, the majority of MRONJ cases (71%) in patients on low-dose BP occurred >3 years of drug intake, while MRONJ in patients on high-dose BP appeared mainly <3 years (64% of the cases). In perspective, it is known that the risk of MRONJ generally increases with duration of ARD therapy (Kajizono et al., 2015). These observations are in accordance with

information presented in recent systematic reviews and position papers on MRONJ (Aljohani et al., 2017; Ruggiero et al., 2014; Walter et al., 2016). Thus, the risk for MRONJ development appears to be multifactorial, and in general, high-dose ARD intake for management of malignancies, low-dose oral BP intake over a longer period of time, and presence of comorbidities (e.g., diabetes and corticosteroid intake), as well as procedures involving the mandible, should be considered as risk factors for MRONJ also in regards with implant therapy. In this context, the information provided in the studies included herein was very limited to draw any conclusions regarding the potential benefits of the "drug holiday" concept (i.e., drug intake interruption prior to and/or during implant therapy), which has been recommended in published clinical guidelines (Ruggiero et al., 2014).

In this systematic review, to assess the quality of the included studies, an established tool (NOS) (Wells et al., 2016) and a purpose-made tool (Basic reporting items in Drugs and Implants [BaRIDI]) including a list of basic reporting patient-, medication-, and intervention-related items considered relevant for a better coverage of this specific topic were used. In general, irrespective of the tool used, most of the included studies were of moderate to questionable quality, in terms of design, number of included cases and/or controls, and especially reporting. For example, information on concomitant diseases or other relative interacting medications was reported in only about 35% of the studies. Similarly, in about 30% of the studies, the indication and/or administration route for BP intake was not clearly/precisely reported, while only 50% of the studies provided some information regarding smoking habits. Further, about 30% of the studies did not report whether implants were placed before or after BP intake, and 70% of the studies did not include information on whether implants were placed in augmented or pristine bone. Most likely, all missing information was simply not possible to retrieve, as most of the studies were retrospective, a study design with inherent issues regarding the accuracy and completeness of information.

In perspective, the relatively limited number of studies reporting on aspects of implant therapy in patients on ARDs that could be included herein could simply be explained by the fact that implant therapy is not compromised by ARD intake at an extent that it becomes an obvious problem in every day clinical work, and thus, there is not so much "to write home about". It would otherwise be expected that many more studies—even in the form of case reports fulfilling the inclusion criteria (i.e., reporting on ≥ 10 cases)—would have been published and identified by the current systematic review, at least as it regards the long-standing BPs. On the other hand, lack of studies may reflect the fact that clinicians are aware of the risks in patients with ARD intake and simply are very cautious when treating these patients, including use of antibiotic prophylaxis and antiseptic mouth rinses, or simply refrain from treating them. In this context, the current review used a much wider search term basis compared to previous systematic reviews on this topic (e.g., Ata-Ali et al., 2016; Chrcanovic et al., 2016; Walter et al., 2016), both regarding implant therapy-related terms and ARDs; in particular, the search strategy included terms related to bone augmentation procedures and peri-implant biological complications, as well as ARDs that have either been abandoned or not widely used, among other reasons due to systemic side effects (e.g., HRT and SrR has been associated with an increase in cardiovascular problems), or are still under development (e.g., CatK inhibitor and antisclerostin antibody) in order to obtain a comprehensive view of the field. It appears thus unlikely that a relevant number of significant publications may have been missed.

In conclusion, the results of the present systematic review showed

- Low-dose oral BP intake for osteoporosis treatment, in general, does not compromise implant therapy, that is, these patients do not lose more implants nor get more implant-related complications/failures (i.e., in regard with grafting procedures, peri-implant marginal bone loss, MRONJ, and peri-implantitis), comparing to implant patients without BP intake.
- There is almost no relevant information available on the possible effect on implant therapy of high-dose BPs or other widely used ARDs (e.g., denosumab).
- HRT has no negative effect on the implant level, while it appears to exert a marginally significant negative effect regarding implant survival on the patient level and regarding peri-implant marginal bone levels.
- The available knowledge regarding success or safety of bone grafting procedures in conjunction with implant installation is too limited to draw conclusions.
- The information is derived from studies with generally low quality, in terms of design, number of included cases and/or controls, and especially reporting.
- There are valid reasons to consider as high-risk patients for MRONJ those patients with high-dose ARD intake for management of malignancies, patients on oral BP over a longer period of time, and patients with comorbidities; both implant installation/explantation and implant presence per se may trigger MRONJ.

CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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APPENDIX 1

Information sources and literature search

Electronic search was performed in Medline (PubMed), EMBASE (Ovid), and CENTRAL (Ovid) — last search 05/09/2017, no date restriction. The database Medline (PubMed) was searched with the following keywords: (dental OR oral) AND (implant therapy OR implant treatment OR dental implant OR dental implants OR implant OR implants OR oral implants OR osseointegration OR osseo-integration OR implant loss OR implant failure OR peri-implantitis OR periimplantitis OR peri-implant disease OR periimplant disease OR alveolar ridge augmentation OR bone regeneration OR guided tissue regeneration OR bone grafting OR bone substitutes OR bone augmentation OR bone augmentations OR lateral bone augmentation OR lateral ridge augmentation OR guided bone regeneration OR gbr OR bone graft substitute OR bone graft substitutes OR autogenous bone graft OR autogenous bone grafts OR bone block OR bone blocks OR split ridge osteotomy OR split ridge osteotomies OR ridge expansion OR ridge expansions OR maxillary sinus OR sinus OR augmentation OR elevation OR lift* OR graft*) AND (antiresorptive agent OR antiresorptive agents OR anti-resorptive agent OR anti-resorptive agents OR antiresorptive drug OR antiresorptive drugs OR anti-resorptive drug OR anti-resorptive drugs OR bisphosphonate OR bisphosphonates OR alendronate OR alendronic acid OR ibandronate OR Ibandronic acid OR risedronate OR risedronic acid OR zoledronate OR zoledronic acid OR pamidronate OR pamidronic acid OR etidronate OR etidronic acid OR clodronate OR clodronic acid OR tiludronate OR tiludronic acid OR estrogen OR estrogens OR oestrogen OR oestrogens OR selective estrogen receptor modulator OR selective estrogen receptor modulators OR selective estrogen-receptor modulator OR selective estrogen-receptor modulators OR selective oestrogen receptor modulator OR selective oestrogen receptor modulators OR selective oestrogen-receptor modulator OR selective oestrogen-receptor modulators OR SERM OR SERMs OR raloxifene OR bazedoxifene OR calcitonin OR human monoclonal antibody to receptor activator for nuclear factor kappa B ligand OR human monoclonal antibody to RANKL OR denosumab OR RANK ligand OR RANKL antibody OR saracatinib OR c-src kinase OR c-src inhibitor OR cathepsin K OR cathepsin K inhibitor OR odanacatib OR romosozumab OR sclerostin antibody OR sclerostin inhibitor OR sclerostin OR strontium ranelate OR strontium). For the other two databases, comparable terms were used, but adapted to the specific criteria of the particular database.

APPENDIX 2

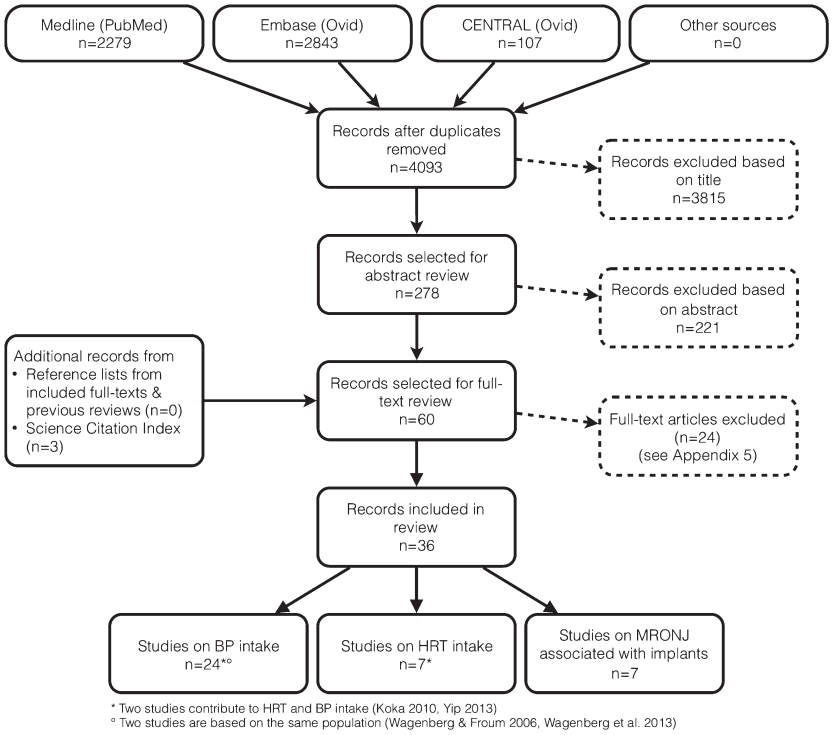
Basic reporting items in Drugs and Implants (BaRIDI)

Patient-related	Age	Range and mean reported yes/no
	Gender	Reported yes/no
	Smoking	Reported yes/no
	Reason for medication intake (e.g., osteoporosis and cancer)	Reported yes/no
	Comorbidities (e.g., diabetes)	Reported yes/no
	Other relevant medications (e.g., steroids)	Reported yes/no
Medication-related	Type[a]	Reported yes/no
	Dosage[a]	Reported yes/no
	Product details (i.e., content and/or dosage)[b]	Reported yes/no
	Administration route (oral, iv, or both for BP and MRONJ studies; oral or transdermal for HRT studies)	Reported yes/no
	First intake prior to/after surgery	Reported yes/no
	Medication intake time until end of study (cohort level) or complication (individual level)	Range and mean reported yes/no
	Drug holiday at surgery (i.e., yes/no, duration)	Reported yes/no
Intervention-related	Implant—region/MRONJ—region	Jaw type and anterior or posterior region reported yes/no
	Augmentation/pristine	Reported yes/no
	Perioperative medication (e.g., antibiotics)	Reported yes/no
	Follow-up period until end of study (cohort level) or complication (individual level)	Range and mean reported yes/no

[a]Relevant for BP and MRONJ studies.
[b]Relevant for HRT studies.
Note. BP, bisphosphonate; HRT, hormone replacement therapy; iv, intravenous; MRONJ, medication-related osteonecrosis of the jaw.

APPENDIX 3

Flowchart of the inclusion process of studies for the systematic review



APPENDIX 4

Reasons for exclusion of 24 full texts

Study (year)	Reason for exclusion
Stvrtecky, Kaufman, and Borgetti, (1995)	Only 9 patients
Marx, Sawatari, Fortin, and Broumand (2005)	Only 4 patients with MRONJ associated with implants
Phillips (2007)	Review
Albandar (2008)	Summary of Grant et al. (2008)
Wynn (2008)	Review
Zuffetti et al. (2009)	Single case report, local BP application
Kos, Kuebler, Luczak, and Engelke (2010)	Only 1 patient with MRONJ associated with implants
Borromeo et al. (2011)	Published study protocol
Akintoye (2012)	Summary of Yip et al. (2012)
Andriani et al. (2012)	Only 3 patients associated with implants
Griffiths (2012)	Only 5 patients with BP intake
Jacobsen, Metzler, Obwegeser, Zemann, and Graetz (2012)	No relevant data on MRONJ patients associated with implants
Leonida, Vescovi, Baldoni, Rossi, and Lauritano (2012)	Only 9 patients
Fleisher et al. (2013)	Only 8 patients with MRONJ associated with implants
Holzinger et al. (2013)	No relevant data on MRONJ patients associated with implants
López-Cedrún et al. (2013)	Only 9 patients
Borromeo et al. (2014)	Only 3 patients associated with implants
Taxel et al. (2014)	Relevant clinical data not reported
Famili and Zavoral (2015)	Only 3 patients with relevant medication intake
Nisi et al. (2015)	Only 9 patients with MRONJ associated with implants
Rugani, Kirnbauer, Acham, Truschnegg, and Jakse (2015)	Single case report
Matsuo et al. (2016)	Only 6 patients
Gurgel et al. (2017)	Patients with BP and/or HRT intake not reported separately
Wagner et al. (2017)	Only 5 patients with BP intake

Note. BP, bisphosphonate; HRT, hormone replacement therapy; MRONJ, medication-related osteonecrosis of the jaw.