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Meta-Analysis
Dental Implants

Dental implants in patients with osteoporosis: a systematic review with meta-analysis

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Abstract. There is currently no consensus regarding the survival rate of osseointegrated implants in patients with osteoporosis. A systematic review with meta-analysis was performed to evaluate the survival rate of implants in such patients. The PubMed/MEDLINE, Web of Science, Cochrane Library, and SciELO databases were used to identify articles published up to September 2016. The systematic review was performed in accordance with PRISMA/PICO requirements and the risk of bias was assessed (Australian National Health and Medical Research Council scale). The relative risk (RR) of implant failure and mean marginal bone loss were analyzed within a 95% confidence interval (CI). Fifteen studies involving 8859 patients and 29,798 implants were included. The main outcome of the meta-analysis indicated that there was no difference in implant survival rate between patients with and without osteoporosis, either at the implant level (RR 1.39, 95% CI 0.93–2.08; $P = 0.11$) or at the patient level (RR 0.98, 95% CI 0.50–1.89; $P = 0.94$). However, the meta-analysis for the secondary outcome revealed a significant difference in marginal bone loss around implants between patients with and without osteoporosis (0.18 mm, 95% CI 0.05–0.30, $P = 0.005$). Data heterogeneity was low. An increase in peri-implant bone loss was observed in the osteoporosis group. Randomized and controlled clinical studies should be conducted to analyze possible biases.

Key words: marginal bone loss; dental implants; meta-analysis; osteoporosis; review; survival rate.

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Osteoporosis is considered a very common skeletal disease and is characterized by low bone density in human bone tissues[1,2]. Imbalances in bone remodelling cause a constant decrease in bone volume and quantity[3], and osteoporosis affects many individuals, mainly older women, worldwide[4–10]. The International Osteoporosis Foundation estimates that osteoporosis affects more than 200 million individuals worldwide, possibly reaching 300 million[2]. In osteoporosis, defective bone formation leads to a deterioration in the microstructure of trabecular bone and increases in cortical porosity, bone fragility, and the possibility of fracture. For this reason, the disease is of significance in implantology[7,11]. Two types of primary osteoporosis are known: postmenopausal and senile[12]. Postmenopausal osteoporosis results from the acceleration of bone loss due to low levels of oestrogen, whereas senile osteoporosis occurs at an older age and is associated with a reduction in bone mass[7,13,14].

Dental implant therapy for totally or partially edentulous patients is known to

be a highly effective treatment for the recovery of proper chewing function. However, some implants may be lost early as a result of biological risk factors, e.g. osteoporosis[13]. An impairment of systemic bone metabolism may be a risk factor affecting osseointegration and its maintenance. Little is known about the interactions between osteoporosis conditions and implant survival[15,16], and it is not known whether osteoporosis increases implant failure rates. However, there is evidence indicating that implants installed in low-density bone tissues (type IV bone) present a higher failure risk[17,18].

The literature indicates that osteoporosis may affect the maxilla[7]. Yet, no definitive conclusions have been drawn about the effect of osteoporosis on the maxillary bone tissue, while progress has been made towards improving the osseointegration process, e.g., by using implants with treated surfaces[14,19], implants with a greater length and diameter, and implant platforms, which results in lower peri-implant bone resorption[20].

There is no consensus about whether osteoporosis impairs rehabilitation treatments with dental implants[7,11]. Various studies have indicated that complications may occur in relation to dental implants installed in patients with osteoporosis[7,19,21]. Clinical studies have indicated a higher probability of implant failure in patients with osteoporosis ($P < 0.05$)[21], and osteopenia or osteoporosis ($P = 0.02$)[22]. There have also been reports indicating an association between osteoporosis and the risk of bone loss in the implant area[23]. However, this is controversial, as a number of studies have indicated that the rate of implant loss is no higher in patients with osteoporosis ($P > 0.05$,[24] $P = 0.661$[25]), and neither is there a higher association with peri-implantitis[3,26] or peri-implant bone loss.

A previous systematic review with meta-analysis indicated that osteoporosis has no direct effect on implant loss[27]. Additionally, the authors of that review suggested that data from osteoporosis studies should be analyzed carefully and that further studies should be conducted. Since then, the results of new clinical studies have been published[2,9,22,25,28–30]. Further studies defining implant indications are also needed for osteoporosis patients[5]. In this regard, Gaetti-Jardim et al. have reported that osteoporosis is not a definitive contraindication for dental implants, but that a proper treatment plan with modification of the implant geometry and the use of large-diameter implants with treated surfaces are required to ensure treatment predictability[13]. The effect of osteoporosis in rehabilitation treatment remains controversial, and it is necessary to analyze implant-related bone loss in particular, given the increase in occurrence of osteoporosis[31]. Another study has emphasized that existing data are heterogeneous and that there is little evidence of an association between osteoporosis and implant failure[32], and others have recommended new clinical studies[33].

The literature remains deficient in indication protocols for dental implants in patients with osteoporosis. Measuring survival and success rates for implants, as well as determining the best implant surface roughness, surgical technique, and occlusal load, are important conditions for the predictability of rehabilitation treatment.

The first null hypothesis of the present study, in accordance with the PICO question, was that implants (interventions) in patients with osteoporosis (patients) would have the same survival rate (outcome) as in patients without osteoporosis (control). The second null hypothesis was that implants in patients with osteoporosis would present a similar peri-implant bone loss as in patients without osteoporosis.

Materials and methods

Standardized criteria and study type

This systematic review was designed according to the Cochrane criteria (*Cochrane Handbook for Systematic Reviews of Interventions*, version 5.1.0) for elaborating a systematic review and meta-analysis[34]. Furthermore, the PRISMA criteria (Preferred Reporting Items for Systematic Reviews and Meta-analyses) were adopted[35], and recently published systematic review models were used[20,36,37].

This systematic review has been registered in the PROSPERO database (CRD42016037193).

Eligibility criteria

The analysis was performed using the PICO index: (1) population: patients who required oral rehabilitation treatment; (2) intervention: osseointegrated implant installation; (3) comparison: patients with osteoporosis vs. patients with no systemic changes in bone metabolism; (4) outcome: main implant and bone loss evaluation results for patients with osteoporosis.

Studies published up to September 2016 were selected used the following inclusion criteria: (1) English language; (2) clinical monitoring studies with at least 6 months of follow-up, including retrospective studies, prospective studies, and controlled and randomized clinical trials. Clinical case studies were excluded from the sample and only studies with a minimum of five patients were considered. Adults with osseointegrated implants were considered for these studies.

Exclusion criteria encompassed studies performed in vitro, animal studies, non-controlled clinical cases, studies with incomplete data, or those unsuitable for data collection.

Search strategy

The PubMed/MEDLINE, Web of Science, Cochrane Library, and SciELO databases were used to identify articles published up until September 2016. Boolean operators based on medical subject headings MeSH/PubMed were ''Dental Implants'' and ''Osteoporosis''. For PubMed, the search was: ''(''osteoporosis, postmenopausal'[MeSH Terms] OR (''osteoporosis''[All Fields] AND ''postmenopausal''[All Fields]) OR ''postmenopausal osteoporosis''[All Fields] OR ''osteoporosis''[All Fields] OR ''osteoporosis''[MeSH Terms]) AND (''dental implants''[MeSH Terms] OR (''dental''[All Fields] AND ''implants''[All Fields]) OR ''dental implants''[All Fields])''.

A manual search of the following implantology journals was also performed by the researchers: *Clinical Implant Dentistry and Related Research*, *Clinical Oral Implants Research*, *European Journal of Oral Implantology*, *Implant Dentistry*, *International Journal of Oral and Maxillofacial Implants*, *International Journal of Oral and Maxillofacial Surgery*, *International Journal of Periodontics and Restorative Dentistry*, *International Journal of Prosthodontics*, *Journal of Clinical Periodontology*, *Journal of Dental Research*, *Journal of Oral Implantology*, *Journal of Oral and Maxillofacial Surgery*, *Journal of Oral Rehabilitation*, *Journal of Periodontal Research*, *Journal of Periodontology*, and *Journal of Prosthetic Dentistry*.

Data collection

The article selection and data collection were performed by two previously calibrated reviewers (FCFLM and JFSJr); consensus meetings were scheduled in the case of discrepancies. Titles and summaries were evaluated and an agreement test for the selected articles was performed for both databases using a kappa test (PubMed 0.8, 1.0, Web of Science 1.0,

Cochrane 1.0, SciELO 1.0), in order to reduce article selection bias. Two further reviewers (BGL and GAHK) participated in the article selection and assisted in data collection and database search verification. Weekly meetings to determine agreement on the article sample selection were scheduled (November 2015 to September 2016).

Data extracted

Data extracted from each study were analyzed and sorted, and the following standardized information was obtained: author, year of publication, study country of origin, number of patients, number of implants and sites, implant type, implant length and diameter, oral rehabilitation installation time, peri-implant bone loss rate, survival rate of implants in each situation analyzed, follow-up time of each study, study type, and drugs administered for the treatment of osteoporosis. Data were collected using a standardized form.

Evaluation of study quality and risk of bias

Clinical studies were evaluated for their methodological structure, sample size, and sample calculations. For the sample type evaluation, the level of evidence bias scale was adopted as proposed by the Australian National Health and Medical Research Council (NHMRC)[38]. Each clinical study design type was assessed and only studies with control groups were included in the systematic review, in accordance with the PRISMA and PICO criteria[35].

Summary of measurements used and statistical analysis

Quantitative data were collected from articles and tabulated for the analysis of the relative risk (RR) with the associated 95% confidence interval (CI), as well as the weight contribution of each study for meta-analysis calculation purposes. Dichotomous data were analyzed using the RR and 95% CI. Continuous data were analyzed using the mean difference (MD) and 95% CI. For the identification of the standard deviation (SD) through the standard error of the mean, the formula $SD = SE \times \sqrt{N}$ was used, according to the Cochrane recommendation[34]. *P*-values of <0.05 were considered significant for all analyses. Review Manager (RevMan) version 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014) was used for the meta-analysis and to draw the graphs.

Outcomes

The primary outcome was the osseointegrated implant survival rate in patients with osteoporosis, as compared to that in patients without osteoporosis. The secondary outcome was the peri-implant bone loss rate for osseointegrated implants in patients with osteoporosis, as compared to that in patients without osteoporosis.

Quantitative data risk of bias

The fixed-effects model was to be used whenever no significant statistical difference was found, and the random-effects model was to be adopted whenever a significant statistical difference was found (high heterogeneity among tests). Heterogeneity was considered significant at $P < 0.1$. Heterogeneity was evaluated using the χ^2 test and the I^2 value; I^2 values above 75 (range 0–100) were considered to indicate significant heterogeneity[20,39–41].

Additional analysis

Sensitivity tests for subgroups and the outcome 'implant survival rate' at the patient level were performed in order to avoid potential heterogeneity[40].

Results

The database search led to the identification of a total of 582 articles (Web of Science, PubMed, SciELO, and Cochrane databases), from which 30 eligible studies were identified following the application of the inclusion criteria. The titles and abstracts of these papers were investigated thoroughly. After this detailed analysis, 15 articles were considered for the qualitative analysis and 13 for the quantitative analysis (Fig. 1). The studies that were excluded at this stage did not meet the required inclusion criteria on study design, sample size, or analysis method. A total of 8859 patients and 29,798 implants were included in the 15 selected studies. The average age of the patients in the nine studies reporting this adequately was 63.03 years. It was not possible to ascertain an accurate age for the remaining six studies[1,8,21,42–44].

Experimental design

Five of the 15 studies were retrospective[16,21,25,42,45], five were prospective[1,23,24,30,43], one was a cohort type/multi-centre study[2], two were case − control studies[8,9], one was a cohort type/prospective study[44], and one was a cross-sectional study[3]. The main data are presented in Table 1.

Of all of the studies analyzed, one was considered multi-centre, involving three different countries[2]. By geographic distribution, nine studies were performed in Europe[1–3,21,23–25,42,45], four in North America[8,9,16,44], one in South America[43], and one in Asia[30].

Patient selection

Some studies did not specify how patients with or without osteoporosis were categorized[21,25,44,45] and some did not indicate whether the patient's records were analyzed thoroughly through surveys or from electronic information[9,24,42]. Bone densitometry was used in some studies to categorize the patients with osteoporosis[1–3,8,16,30,43]. The World Health Organization (WHO) recommended scale (T-score) was used: osteoporosis = T-score ≤ -2.5 standard deviations; normal = T-score ≥ -1 standard deviation[43], with the lumbar spine (L1–L4) and femoral neck considered[43]. One study used a maxilla bone mineral density analysis[23].

Some studies considered patients with other systemic diseases or bad habits[1,16,21,24,25,42,44], whereas others were more specific and did not select patients with other chronic diseases[8] or bad habits, those using immunosuppressive drugs and bisphosphonates, and those with poor dental hygiene habits, a history of radiotherapy[1,43,45], or decompensated diabetes[30,45]. One study considered patients who used annual infusions of 5 mg zoledronic acid[1].

Surgical phase

Some studies required at least 7 mm of bone tissue height for implant installation[21,24,30,42]. Another study considered only patients with a minimum height of 13 mm and thickness of 4 mm[43]. Some studies highlighted that antibiotic therapy was used in cases with evident pre-existing infections or as prophylaxis[2,21,24,42]. One study considered the administration of 2 g intravenous amoxicillin and 200 mg clavulanic acid at 1 h prior to surgery[45]. Another study considered the administration of antibiotic therapy using 1 g amoxicillin + clavulanic acid twice a day for 6 days, initiated 24 h prior to surgery[1]. One study described the administration of postoperative antibiotic therapy (875 mg amoxicillin and 125 mg clavulanic acid, twice a day for 5 days), painkillers (600 mg ibuprofen, not exceeding the dai-

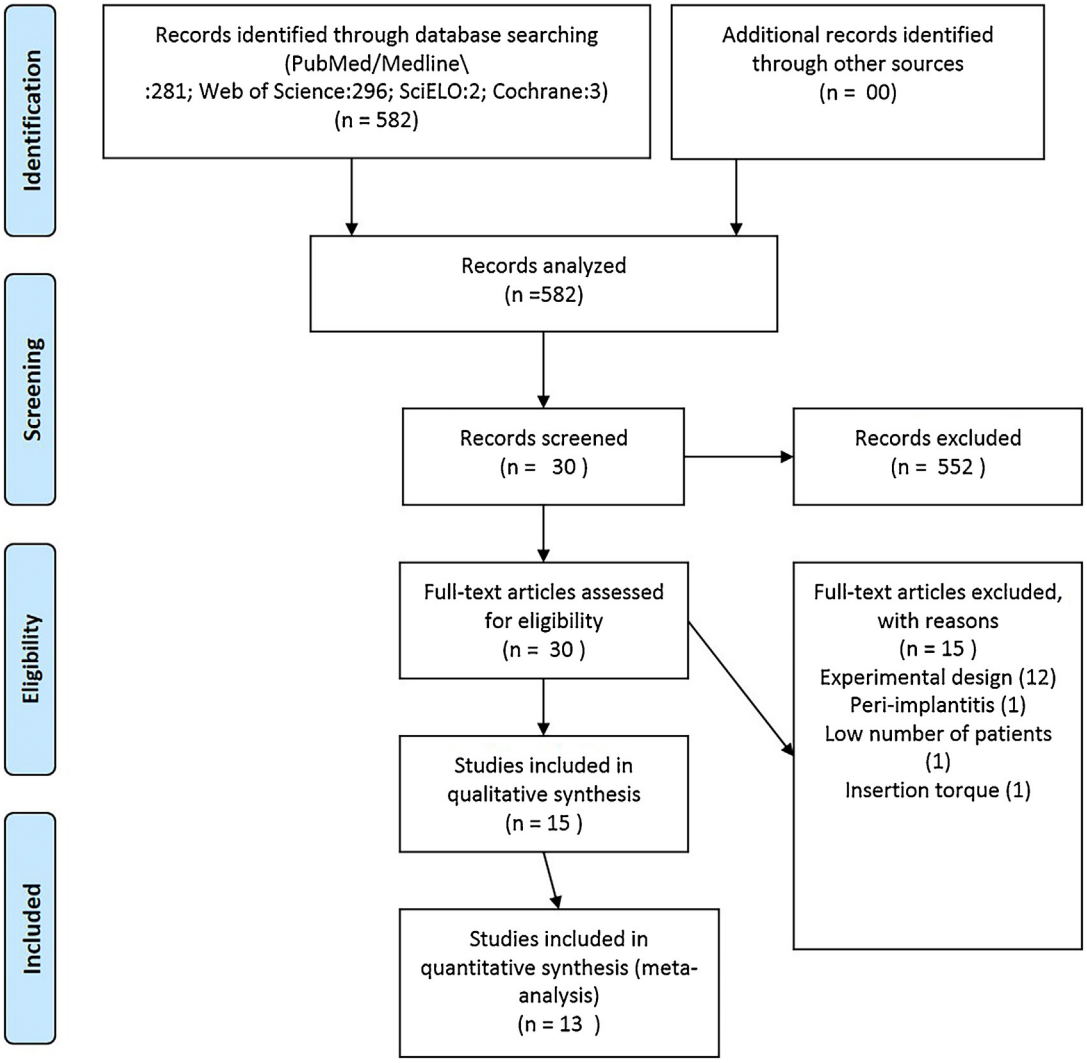

Fig. 1. Diagram showing the selection of articles for the systematic review.

ly human dose), and 0.1% chlorhexidine rinses for 2 weeks[45]; chlorhexidine rinses were also considered in another study[2]. Of note, Alsaadi et al. did not identify a significant prevention of early implant failure with the use of antibiotics ($P = 1.00$; Fisher's exact test)[24].

One study reported that all implants should present a 30 N clamping force or even $\geq$30 N[8], and another study indicated that in order to perform immediate loading, an insertion torque of $\geq$30 N was planned for the dental implants[45].

Patients

The studies evaluated included a total of 8859 patients. These patients were monitored for 0.75–22 years[1,2,21], with a mean of 5.85 years and a median of 6 years for all studies included in the review.

Amorim et al. (2007) evaluated the mandibular cortex morphology using panoramic radiographs, indicating that a normal cortex was present in five patients with osteoporosis and a moderately to severely resorbed cortex in 14 patients[43]. However, no significant difference was seen between the cortices of healthy control patients and patients with moderate or severe erosion ($P = 0.1053$). Mandibular trabecular bone analysis from panoramic radiographs also did not present a significant difference between the high- and low-density trabecular bone groups ($P = 0.3406$). However, the authors indicated that there was a significant difference between the mandibular cortical indexes (moderate/severe vs. normal cortex) and femoral neck bone density, and there was evidence of higher femoral neck bone density in patients with a normal mandibular cortex ($P < 0.021$). In relation to this, a retrospective study that analyzed the bone mineral density (T-score) did not find an association with the dental implant survival rate ($P = 0.25$)[16].

A case–control study with a mean follow-up period of 7.05 years reported the administration of oral bisphosphonates for 3 years or more in 20 patients with osteoporosis, in whom 46 implants were installed[9]. The authors indicated that patients did not develop osteonecrosis due to the use of bisphosphonates. Another controlled clinical study considered three patients who were treated for osteoporosis: two were treated with oral bisphosphonates and one was treated using calcitonin spray; no implant failures were identified within this group[8].

A prospective study with a mean follow-up period of 6.9 years reported the loss of one implant in a patient with osteopenia; however, the patient contin-

Table 1. Studies included in the systematic review.

Author	Study type	Country	Bias scale	Patients, *n*	Age, years (mean)	Follow-up, years	Implants, *n*	Length × width minimum (mm)	Implant system[a]	Surface	Rehabilitation	Difference osteoporosis vs. control (*P*-value)
Alsaadi et al.[21] (2007)	RS	Belgium	III-3	2004	NR	22	6946	7 × 3.75	Nobel Biocare (Brånemark)	Machined: 6316 TiUnite: 630	NR	Yes ($P = 0.001$)
Alsaadi et al.[42] (2008)	RS	Belgium	III-3	412	NR	2	1514	<10 × 3.3	Nobel Biocare (Brånemark)	Machined: 1316 TiUnite: 198	NR	No ($P = 0.11$)
Alsaadi et al.[24] (2008)	PS	Belgium	III-2	283	56.2	2	720	7 × 3.3	Nobel Biocare (Brånemark)	Mk III, TiUnite	NR	No ($P = 1.00$)
Al-Sabbagh et al.[9] (2015)	CC	USA	III-2	203	55.5	7.05	515	NR	Straumann	Sandblasted and acid-etched	Overdenture (122), single (393)	No
Amorim et al.[43] (2007)	PS	Brazil	III-2	39	≥55	0.75	82	NR	INP (Conus)	NR	Total and partial	No
Busenlechner et al.[25] (2014)	RS, cohort	Austria	III-2	4316	58.6	8	13,147	<10 and <3.75	Nobel Biocare (Brånemark), Astra Tech, Dentsply, Biomet 3i	NR	Total, partial, and single	No ($P = 0.661$)
Chow et al.[30] (2016)	PS	China	III-2	63	76.7	6.9	158	3.75 wide	Nobel Biocare (Brånemark, Mk III)	NR	Overdenture	No
Dvorak et al.[3] (2011)	CS	Austria	III-2	177	63 ± 9	6 ± 4	828	NR	Nobel Biocare (Brånemark)	Turned, TiUnite, rough surface	NR	No ($P = 0.74$)
Famili and Zavoral[8] (2015)	CC	USA	III-2	30[b]	50–80	2	31	10 × 3.5	Nobel Biocare (Nobel Replace Tapered Groovy)	NR	NR	No
Farino et al.[44] (2010)	Cohort	USA	III-2	116	NR	7.05	248	NR	NR	NR	Overdenture	No
Holahan et al.[16] (2008)	RS	USA	III-2	746	63.4	10	3224[c]	NR	NR	Machined Ti, anodized Ti, sandblasted, large-grit, acid-etched Ti, and plasma-sprayed Ti	NR	No ($P = 0.76$)
Niedermaier et al.[45] (2017)	RS	Germany	III-2	380	61.9	7	2081	8 × 3.5	Nobel Biocare/ Biomet 3i	NR	Total	Yes ($P = 0.002$)
Siebert et al.[1] (2015)	PS	Slovakia	III-2	24	≥54	1	120	16 × 3.7	Impladent (STI Bio)	Bio surface	NR	No
Temmerman et al.[2] (2017)	Multi-centre	Belgium, Sweden, Germany	III-2	48	67	1	148[d]	NR	Nobel Biocare (Brånemark)	NR	Fixed	No ($P = 0.430$)
von Wowern and Gotfredsen[23] (2001)	PS	Denmark	III-2	18	65	5	36	NR	Astra Tech (OsseoSpeed)	NR	Overdenture	No

RS, retrospective study; PS, prospective study; CC, case–control study; CS, cross-sectional study; NR, not reported; Ti, titanium.

[a] Astra Tech AB, Mölndal, Sweden; Biomet 3i, West Palm Beach, FL, USA; Dentsply, Mannheim, Germany; Dentsply Implants, Mölndal, Sweden (OsseoSpeed); Impladent, Lasak, Prague, Czech Republic; INP, Sao Paulo, Brazil (Conus); Nobel Biocare, Gothenburg, Sweden (Brånemark System); Nobel Biocare, Yorba Linda, CA, USA (Nobel Replace Tapered Groovy); Straumann, Basel, Switzerland.

[b] One patient dropped out during treatment.

[c] In the study by Holahan et al., 3224 dental implants were placed in total in all study patients. Bone mineral density scores were available for 646 implants in 192 patients (94 with no osteopenia or osteoporosis, 57 with osteopenia, and 41 with osteoporosis).

[d] After 1 year of follow-up, 136 implants were reassessed.

ued to use cigarettes, even after orientation[30]. In fact, active use of cigarettes during the implant installation period was associated with more implant failures in another study ($P = 0.016$)[16], and the authors indicated that patients who smoke are more likely to present with failure of osseointegrated implants, independent of the diagnosis of osteoporosis. In contrast, another study reported that the use of cigarettes did not influence osseointegrated implant failure[45].

Implant analysis

The total number of implants considered in the 15 studies was 29,798. The smallest diameter used was 3.3 mm[24,42], and the shortest implant length was 7 mm[21,24]. However, information on the length and diameter was not given in some studies[2,3,9,16,23,43,44]. Machined and treated surfaces were specified by some studies[1,3,9,16,21,24,42] and others did not specify the surface roughness[2,8,23,25,30,43–45]. Thirteen studies specified the commercial brand of the implants used, whereas two did not[16,44]. One study described that patients were monitored by oral hygiene professionals at least once on a quarterly basis[23].

Regarding rehabilitation, one study considered immediate loading[45] and eight studies considered fixed (single unit or complete) and overdenture prostheses[2,9,23,25,30,43–45].

Two of the 15 studies indicated significantly more implant losses or failures in patients with osteoporosis[21,45]. Alsaadi et al.[21] (2007) evaluated 2004 patients who received 6946 implants, but did not clarify how many patients had osteoporosis and how many did not. However, the authors indicated that there was a significant trend for implant failure with an osteoporosis factor in 1757 patients and 5759 implants (odds ratio 2.88, 95% CI 1.51–5.48; $P = 0.001$). Furthermore, the authors also indicated a higher failure index for implants placed in type IV bone tissue (soft, reduced cortical bone tissue) when compared to type II (odds ratio 3.05, 95% CI 1.73 − 5.38; $P < 0.001$). Niedermaier et al.[45] (2017) analyzed 380 patients, seven of whom had osteoporosis, and reported a 94.1% survival rate, with a significant difference when compared to control group patients ($P = 0.002$). The authors also indicated that implant failures in patients with osteoporosis occurred in the oral bisphosphonate-treated group.

Positive implant failure data were presented by Temmerman et al., who reported implant survival rates of 98.4% and 100% for patients with osteoporosis and control group patients, respectively[2]. The failures occurred after prosthetic abutment installation due to non-integration of the implants with the bone tissue.

One retrospective study included 4316 patients and reported a 94.4% implant survival rate in osteoporosis patients who were monitored for 8 years; however, there was no significant difference in the survival rate in this group as compared to the control group ($P = 0.661$)[25]. The authors highlighted that the failure rate was 2% higher in the maxilla of patients with osteoporosis as compared to the mandible[25].

On the other hand, six studies indicated that there was no statistically significant difference in the failure of osseointegrated implants among patients with and without osteoporosis[2,3,16,24,25,42]. It is worth noting that Alsaadi et al. indicated that more implant losses were identified in the posterior region of the maxilla than in the anterior region ($P = 0.04$)[42].

Amorim et al. also reported a histomorphometric evaluation of bone tissue removed for osseointegrated implant installation and identified less osteoid and more resorption surfaces in osteoporosis patients, with no significant difference as compared to the control group[43].

Dvorak et al. did not observe a significant association of peri-implantitis with osteoporosis ($P = 0.75$, osteopenia; $P = 0.59$, osteoporosis)[3]. In a prospective study, Siebert et al. did not observe a significant difference in crestal bone loss in patients with osteoporosis when compared to a control group who received immediate implants[1]. The authors highlighted that implants with treated surfaces were used in the groups analyzed[1]. However, Wowern and Gotfredsen identified higher marginal bone loss in the osteoporosis group (bone mineral content (BMC) z-scores below −2) as compared to the control group ($P < 0.01$)[23].

Regarding resonance frequency analysis, a clinical study considering comparisons among patients indicated that implant stability values (Osstell AB, Gothenburg, Sweden) were significantly higher in the control group than in the osteoporosis group ($P = 0.049$).

Methodological quality and risk analysis

Some studies used blinded operators[30] or independent researchers[2,3] for each patient's radiographic analysis. One study referred to the use of a blinded examiner for bone densitometry examinations[8]. Another study randomized the sample by rehabilitation criteria, using a bar or ball-retained implant prosthesis[23]. An important limitation of this review is the absence of randomized controlled clinical trials and the retrospective design used in some studies[16,21,25,42,45]. However, some studies presented details about the reasons for withdrawal and exclusion of patients or implants[45].

The NHMRC level of evidence scale was used to assess study quality (additional levels of evidence and grades for recommendations for developers of guidelines). As randomized controlled trials were not included and several studies were retrospective, the scores were low (evidence level III). However, it is important to highlight that the studies presented a comparison between patients with and without osteoporosis; thus, it was possible to establish a direct association when comparing survival rates at the implant level (Table 2) in 10 studies, and at the patient level in six studies (Table 3).

A cross-sectional study with 6 years of follow-up ($n = 177$: 46 patients with osteoporosis, 16 with osteopenia, and 115 in the control group) considered a sample size calculation after analysis of the results indicated that for a 30% prevalence of patients with osteoporosis, the sample size should be 200 patients with osteoporosis and 200 healthy patients[3]. This analysis is important, since a number of studies did not find a significant difference ($P \geq 0.05$), and did not present a sample size calculation or power analysis.

Meta-analysis

Primary outcome—survival rate at the implant level

The implant survival rate in patients with osteoporosis was analyzed and calculated in 10 studies, since these studies presented data on implants in patients with and without osteoporosis (Table 2). These 10 studies were included in a meta-analysis and were evaluated using a fixed-effects model: 702 implants were installed in patients with osteoporosis, with 33 failures (4.70% failure rate), and 4114 implants were installed in healthy patients, with 147 failures (3.57% failure rate). There was no significant difference in the group comparison osteoporosis vs. control: RR 1.39, 95% CI 0.93 − 2.08; $P = 0.11$. The χ^2 test for heterogeneity result was 7.22 ($P = 0.41$, $I^2 = 3\%$) (Fig. 2). This analysis considered a total of 217 patients with osteoporosis and 890 patients in the control group, as described in Table 2.

Table 2. Analysis of the survival rate at the implant level.

Study	Patients		Failure		Healthy group		Osteoporosis group		Primary outcome Osteoporosis vs. control
	Healthy	Osteoporosis	Total	Number of failures (total)	Failure rate	Number of failures (total)	Failure rate	Number of failures (total)	
Alsaadi et?al.[42]	393	19	6.67%	101 (1514)	6.36%	92 (1446)	13.24%	9 (68)	No, $P = 0.11$
Alsaadi et?al.[24]	NC	NC	1.94%	14 (720)	2.03%	14 (691)	0%	0 (29)	No, $P = 1.00$
Amorim et?al.[43]	20	19	1.22%	1 (82)	0%	0 (43)	2.56%	1 (39)	No
Famili and Zavoral[8]	10	19	3.33%	1 (30)	10%	1 (10)	0%	0 (20)	No
Farino et?al.[44]	100	16	1.61%	4 (248)	1.92%	4 (208)	0%	0 (40)	No
Holahan et?al.[16]	94	98	5.73%	37 (646)	5.56%	17 (306)	5.88%	20 (340)	No, $P = 0.76$
Niedermaier et?al.[45,a]	222	7	1.64%	21 (1279)	1.53%	19 (1245)	5.88%	2 (34)	Yes, $P = 0.002$
Siebert et?al.[1]	12	12	0%	0 (120)	0%	0 (60)	0%	0 (60)	No
Temmerman et?al.[2]	28	20	0.71%	1 (141)	0%	0 (83)	1.72%	1 (58)	No, $P = 0.430$
von Wowern and Gotfredsen[23]	11	7	0%	0 (36)	0%	0 (22)	0%	0 (14)	No
Total	890	217	3.74%	180 (4816)	3.57%	147 (4114)	4.70%	33 (702)	No (9); Yes (1)

NC, not clear.

[a] In the study by Niedermaier et?al., the osteoporosis group was compared to 222 patients with a medical status of healthy ($n = 1245$ implants).

Table 3. Analysis of the survival rate at the patient level.

Study	Patients		Failure		Healthy group		Osteoporosis group		Primary outcome Osteoporosis vs. control
	Healthy	Osteoporosis	Total	Number of failures (total)	Failure rate	Number of failures (total)	Failure rate	Number of failures (total)	
Al-Sabbagh et al.[9]	174	29	0%	0 (203)	0%	0 (174)	0%	0 (29)	No
Chow et al.[30]	10	53[a]	3.17%	2 (63)	10%	1 (10)	1.89%	1 (53)	No
Dvorak et al.[3]	115	62[b]	13.56%	24 (177)	13.04%	15 (115)	14.52%	9 (62)	No, $P = 0.74$
Famili and Zavoral[8]	10	19	3.45%	1 (29)	10%	1 (10)	0%	0 (19)	No
Temmerman et al.[2]	28	20[c]	2.08%	1 (48)	0%	0 (28)	5.56%	1 (18)	No, $P = 0.417$
von Wowern and Gotfredsen[23]	11	7	0%	0 (18)	0%	0 (11)	0%	0 (7)	No
Total	348	190	5.20%	28 (538)	4.89%	17 (348)	5.85%	11 (188)	No (6)

[a] In the study by Chow et al., patients with osteoporosis were considered those with osteopenia, osteoporosis, and severe osteoporosis.
[b] In the study by Dvorak et al., patients with osteoporosis and osteopenia were compared to the control group.
[c] In the study by Temmerman et al., two patients with osteoporosis died.

Primary outcome—survival rate at the patient level

In the analysis considering the total number of patients with osteoporosis vs. the control group who had failure of osseointegrated implants, it was found that 11 of 188 patients with osteoporosis presented implant failure (5.85% failure rate) and that 17 of 348 patients in the control group presented implant failure (4.89% failure rate). There was no significant difference between the osteoporosis and control groups, with RR 0.98, 95% CI 0.50 – 1.89; $P = 0.94$. The χ^2 test for heterogeneity result was 3.58 ($P = 0.31$, $I^2 = 16\%$) (Fig. 3). A total of 538 patients were considered in this analysis, as described in Table 3.

Secondary outcome

It was possible to compare the rate of peri-implant bone loss in patients with osteoporosis with that in controls in three studies[2,23,30]. A total of 129

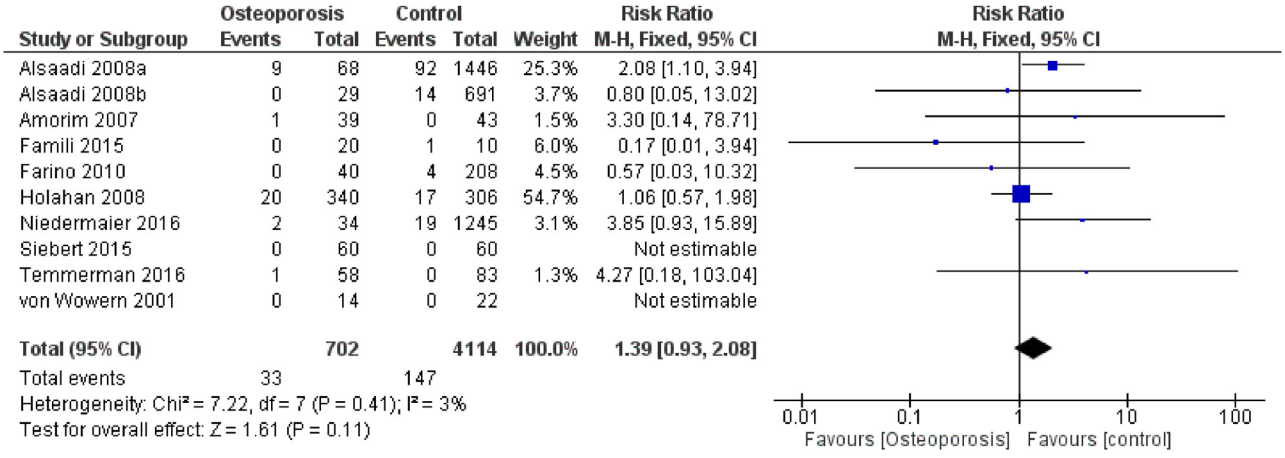

Fig. 2. Meta-analysis forest plot for the comparison of implants placed in patients with osteoporosis vs. the control group for the outcome 'implant failure' at the implant level.

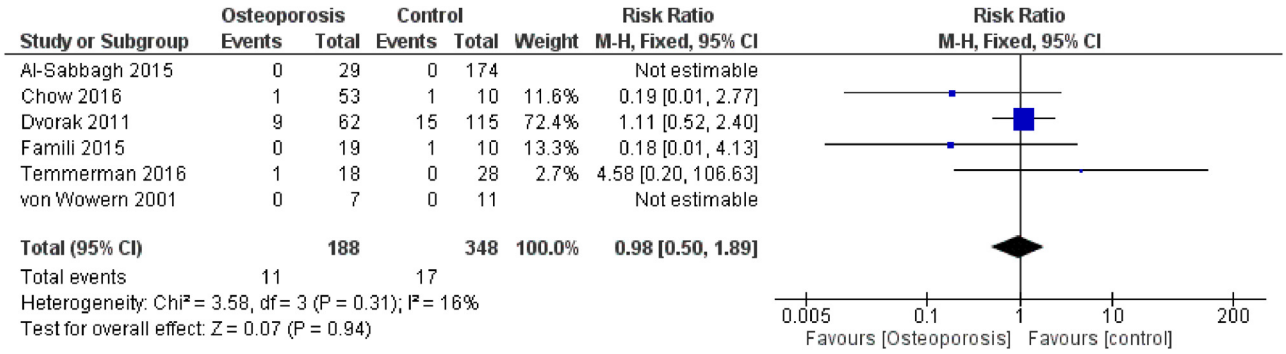

Fig. 3. Meta-analysis forest plot for the comparison of implants placed in patients with osteoporosis vs. the control group for the outcome 'implant failure' at the patient level.

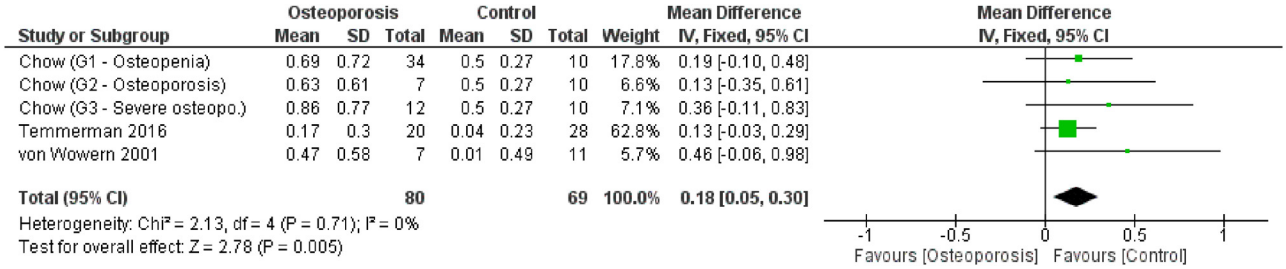

Fig. 4. Meta-analysis forest plot for the comparison of implants placed in patients with osteoporosis vs. the control group for the outcome 'marginal bone loss' (mm).

patients were analyzed; 80 had osteoporosis and 49 belonged to the control group. In the meta-analysis of these three studies, including five subgroups, a significant difference in bone loss was found for the osteoporosis group when compared to the control group: a 0.18-mm average difference (95% CI 0.05 – 0.30; $P = 0.005$) (Fig. 4). The χ^2 test for heterogeneity result was 2.13 ($P = 0.71$, $I^2 = 0\%$).

Implant survival analysis

Implant loss was identified in five studies through an implant survival rate analysis in patients with osteoporosis[2,16,42,43,45]. The highest failure rate in these studies was 13% and the lowest was 1.7% (mean 5.6%, median 5%) (Fig. 5).

An implant survival rate of 96.46% in patients with osteoporosis was calculated using a survival curve analysis[1,2,8,23,24,42–45], as described in Fig. 6 and Table 4.

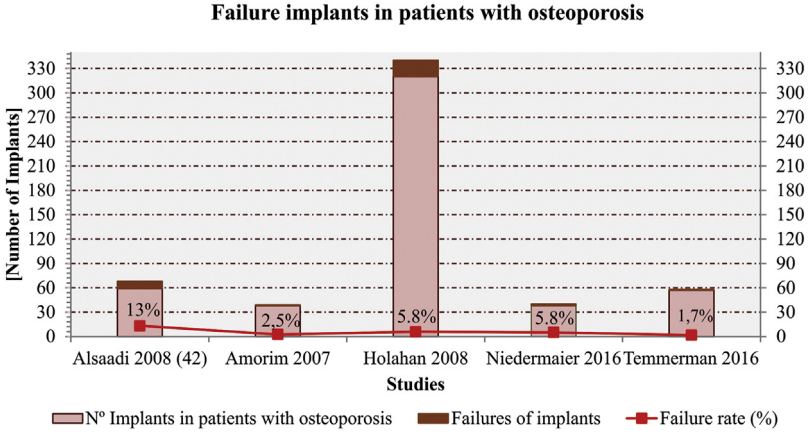

Fig. 5. Number of implants in patients with osteoporosis at each follow-up interval according to implant failure for the five selected studies.

A total of 368 implants were considered for this analysis, with 13 implants failing during a period varying from 0 to 7 years.

Risk of bias in the studies

Heterogeneity was considered low for the failure outcome at the implant level ($\chi^2 = 7.22$, $P = 0.41$; $I^2 = 3\%$) and at the patient level ($\chi^2 = 3.58$, $P = 0.31$; $I^2 = 16\%$), and for comparisons of marginal bone loss between implants in patients with osteoporosis vs. controls ($\chi^2 = 2.13$, $P = 0.71$; $I^2 = 0\%$), thus the fixed-effects model was adopted (inverse variance for marginal bone loss and Mantel–Haenszel

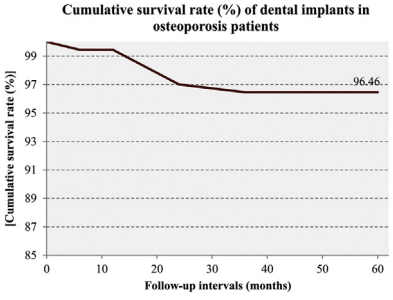

Fig. 6. Cumulative survival rate (%) of dental implants in the nine studies selected.

Table 4. Life-table survival analysis showing the cumulative survival rate of implants in patients with osteoporosis for the nine selected studies.

Study follow-up intervals, months	Number of implants in each interval (Osteoporosis patients)	Number of failures in each interval (Osteoporosis patients)	Survival rate within each interval (%)	Cumulative survival rate (%)
0	368	0	100	100
0–6	368	2	99.45	99.45
7–12	366	0	100	99.45
13–24	366	9	97.54	97.01
25–36	357	2	99.43	96.46
37–48	355	0	100	96.46
49–72	355	0	100	96.46

for implant failure, 95% confidence interval).

Funnel plots showed evident symmetry in the difference in means in the studies analyzed (Figs 7–9).

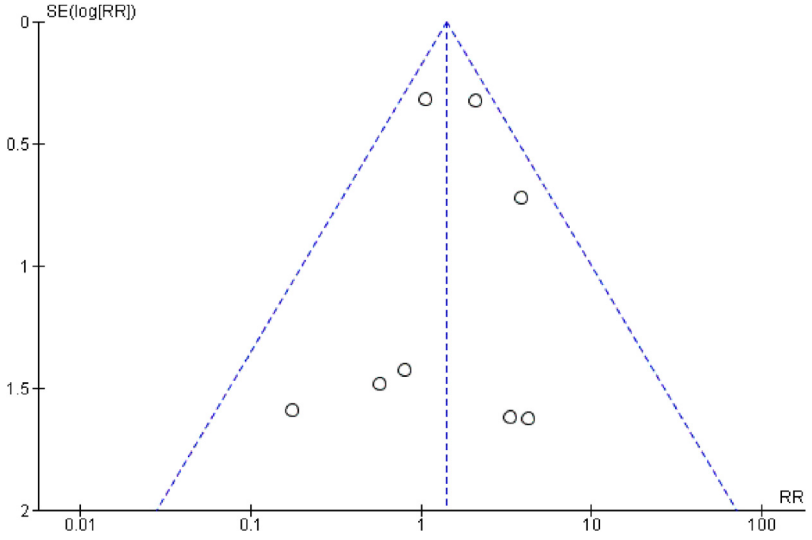

Fig. 7. Funnel plot for the assessment of publication bias for the primary outcome 'implant failure' at the implant level.

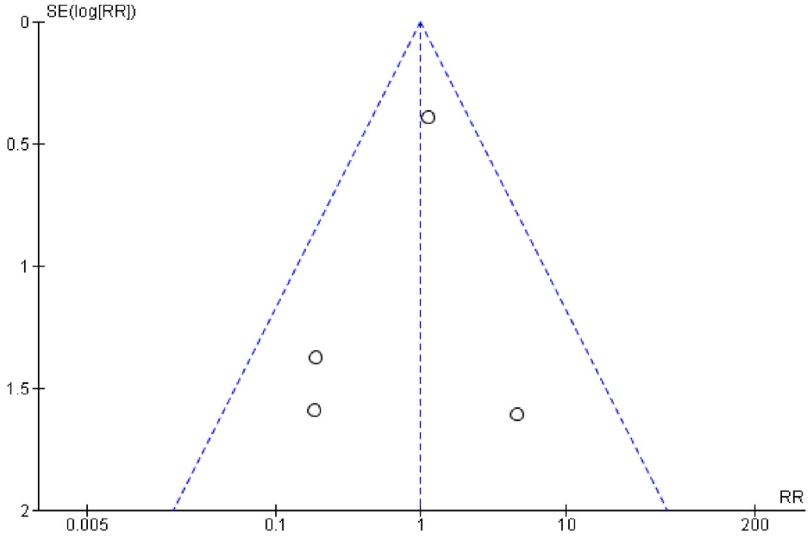

Fig. 8. Funnel plot for the assessment of publication bias for the primary outcome 'implant failure' at the patient level.

Discussion

The first null hypothesis proposed for the survival rate of dental implants was accepted. In fact, the implant survival rate in bone tissue with osteoporosis installations was similar to that of the control group at the implant level ($P = 0.11$) and at the patient level ($P = 0.94$).

Two clinical studies indicated significantly higher osseointegrated implant loss in patients with osteoporosis than in control subjects[21,45]. Alsaadi et al. reported a positive association between osseointegrated implant failure and osteoporosis and also reported higher rates of implant failure in patients who smoke, have Crohn's disease, short and wide implants, implants placed in the posterior region, and lower bone quality[21]. However, it was not possible to determine the total number of patients with osteoporosis, as well as the exact number of implant failures in patients with osteoporosis. The retrospective study by Niedermaier et al. also indicated a higher implant failure rate in osteoporosis patients who were followed up for 7 years[45]; however, that study considered only seven such patients. The authors highlighted that two implant failures occurred in a patient treated with oral bisphosphonates. The association between implant failure and the use of bisphosphonates remains controversial. Al-Sabbagh et al. monitored patients with osteoporosis and the use of bisphosphonates for 7 years and did not find an increased implant failure rate in these patients[9].

Another retrospective clinical study conducted by Alsaadi et al. did not find any significant difference in implant failure rate between patients with and without osteoporosis ($P = 0.11$)[42]; however, there was a trend towards implant failure in the osteoporosis group (13.24%) as compared to the control group (6.36%) (Fig. 5). Some studies observed difficulty in isolating a systemic factor (osteoporosis) in patients of advanced age, since other diseases could also be associated, e.g. diabetes. This should be considered in future clinical studies[46]. Recently, another clinical study, which was not included in this review[22], indicated a higher rate of osseointegrated implant failure in patients

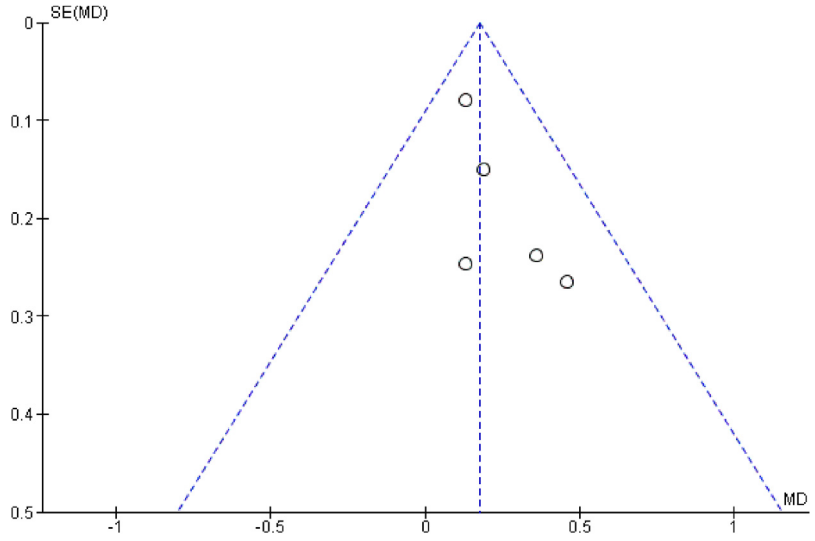

Fig. 9. Funnel plot for the assessment of publication bias for the secondary outcome 'marginal bone loss'.

with osteoporosis or osteopenia ($P = 0.022$).

It is important to highlight that patients included in the studies in this review were appropriately selected, and that patients with uncontrolled diabetes and severe bone loss were excluded[30]. Thus, clinical studies with properly selected samples must be performed, accounting for other systemic conditions.

Hormone therapy was considered in the review. Alsaadi et al. indicated a higher implant failure rate in women aged 50 years or older who were receiving hormone therapy; however, the implant failure rate was not higher in patients with osteoporosis (100% survival rate)[24]. Another clinical study did not find an increase in the implant failure rate in patients taking hormone therapy[47].

Systemic osteoporosis is frequently associated with oral or intravenous bisphosphonate treatment to improve bone mineral density[2]. In this context, a 2-year clinical study indicated that patients who have received bisphosphonate treatment for a period of 5 years or less may be candidates for implant installation[8]; however, the authors recommended that studies with larger sample sizes and longer follow-up periods should be performed for patients receiving oral bisphosphonate treatment. Furthermore, a 1-year prospective study did not find any effect of the use of intravenous bisphosphonates on patients with osteoporosis or any association with osseointegrated implant failure[1]. The effects of oral bisphosphonates on the implant survival rate were not analyzed in this review, as some studies did not indicate the type of treatment or excluded patients undergoing oral bisphosphonate treatment[2].

The majority of the studies included in this review reported the use of implants with treated surfaces, except for two studies that included implants with machined surfaces[21,42]. Further research is necessary to define the best implant surface profile for patients with osteoporosis[16]. This is an important factor, since a recent biomechanical study showed that implants with treated surfaces may enhance the dissipation of bone tissue tension[48], and that implants placed in low-density bone tissue (type IV) may experience increased tension as compared to other bone types[49]. In fact, finite element analysis indicated that simulated osteoporotic bone tissue may extend the area with concentrated tension[50]. Further studies should be designed to define the best geometry and surface roughness for dissipating tension in these patients.

In terms of the diagnosis of osteoporosis, some studies used the WHO recommendations for diagnosis, based on bone mineral density measurements through X-ray absorptiometry, indicating a diagnosis of osteoporosis for patients who present a bone density level of 2.5 SD below that of a young population[42,51].

The second null hypothesis proposed for marginal peri-implant bone loss was rejected ($P = 0.005$). In fact, implants in patients with osteoporosis presented a higher marginal bone loss when compared to implants placed in control patients. This suggests that peri-implant bone loss in patients with osteoporosis may be more severe than in patients without osteoporosis. However, it should be noted that the bone loss was limited, which may have resulted from the quality of oral hygiene practiced by these patients and the functional stimulus caused by the dental implants[23]. Furthermore, it is important to highlight that only three studies were considered for this analysis[2,23,30], and although two of these were recent (2016), additional randomized controlled clinical studies are necessary to evaluate this variable fully. Another clinical study, which lacked a control group, considered that peri-implant bone loss was similar (mean 0.60 mm) to the results of a meta-analysis (osteoporosis group mean 0.56 mm) during the first year of function[52]. These parameters were therefore normal when considering the expected pattern of peri-implant bone loss during the first year of function[53].

An analysis of the peri-implant condition is crucial to implant longevity and success. Dvorak et al. indicated that 23.9% of the osteoporosis patients developed peri-implantitis and stated the need for an appropriate rehabilitation plan[3]. In fact, a number of reports recommended that patients return for monitoring of oral hygiene adequacy, as well as to exclude factors that may be related to bone loss in patients with osteoporosis[23]. Gay et al. demonstrated that at least yearly professional maintenance may prevent implant failure in 90% of cases, independent of risk factors such as age, race, sex, diabetes, and osteoporosis[15].

Amorim et al. showed an association between lower peripheral bone mass in the femoral bone tissue and the presence of erosions in the mandibular cortical bone, indicating more frequent involvement of the mandibular cortical bone in patients with osteoporosis, which may indicate an association with peri-implant bone loss[43]. Furthermore, the authors indicated an association of more bone tissue erosion with a greater presence of osteoid surface and resorption. They also recommended designing better epidemiological studies, including a larger patient sample and a longer follow-up period.

Another important aspect is the implant insertion torque of implants in osteoporosis patients[54]. Clinical studies have recommended the use of higher insertion torque for lower bone density installations, such as in patients with osteoporosis. Primary stability is important for osseointegration. A clinical study that measured the implant stability through resonance frequency analysis (ISQ, implant stability quotient) found a lower value for implants in patients with osteoporosis (mean ISQ 65.8), when compared to the control group

(mean ISQ 69.2)[2]. Similar results were recently obtained by Merheb et al., who performed a primary stability analysis using resonance frequency and indicated that primary stability was lower in patients in the osteoporosis group (mean ISQ 63.3) than in the osteopenia group (mean ISQ 65.3) and the control group (mean ISQ 66.7)[55].

In a recent systematic review and meta-analysis, Santiago Junior et al. identified less marginal bone loss for platform-switching implants when compared to implants with a regular platform (control group)[20]. Thus, such implants might be indicated for patients who present more fragile bone tissue due to systemic conditions. Controlled clinical studies should be conducted to determine the implant geometries that may result in less peri-implant bone loss.

Patient satisfaction was analyzed in one clinical study[44], which found that osteoporosis was associated with treatment dissatisfaction in terms of function and appearance; however, the authors recommended that studies including a larger number of patients with osteoporosis and other diseases should be conducted in order to obtain a correlation between success and survival.

The main limitations of this systematic review are related to the absence of randomized controlled clinical studies[22] and the small sample sizes in some of the clinical studies[56]. Different implant types, surfaces, lengths/diameters, and rehabilitation types were used (Table 1), and different drugs were administered. These variables should be standardized in future randomized controlled trials. Finally, only studies meeting the PICO criteria were considered for the statistical analysis, i.e., those that presented a control group ($n = 13$). Therefore, randomized controlled clinical studies should be performed in the near future to analyze implant survival rates and periodontal parameters in patients with systemic osteoporosis.

In conclusion, implants placed in patients with systemic osteoporosis did not present higher failure rates than those placed in patients without osteoporosis. Based on three studies included in the systematic review[2,23,30], implants placed in patients with osteoporosis presented greater marginal bone loss than those placed in control group subjects. Nevertheless, the values are within clinical parameters, and furthermore this is an outcome that should be analyzed with caution. Accordingly, appropriately designed randomized controlled clinical trials presenting a sample size calculation are needed to analyze this matter further.

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Competing interests

None.

Ethical approval

Not required.

Patient consent

Not required.

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