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ORIGINAL ARTICLE

Antiresorptive therapy and dental implant survival: an up to 20-year retrospective cohort study in women

Yu-Chi Cheng[1] · Rolf Ewers[2] · Katherine Morgan[3] · Muneki Hirayama[3] · Laura Murcko[3] · John Morgan[3] · Edmara T. P. Bergamo[4] · Estevam A. Bonfante[4]

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Abstract

Objectives To investigate the effects of antiresorptive treatment on the survival of plateau-root form dental implants.

Materials and methods Patients undergoing antiresorptive therapy via oral or intravenous administration as well as patients not undergoing antiresorptive therapy and healthy control patients were included in this retrospective cohort study. In total, 1472 implants placed in 631 postmenopausal patients (M: 66.42 ± 9.10 years old), who were followed for a period of up to 20 years (8.78 ± 5.68 years). Kaplan–Meier survival analysis was performed, and univariate and multivariate Cox regression, clustered by each patient, was used to evaluate and study factors affecting the survival of their implants.

Results Implants placed in patients undergoing oral antiresorptive treatment presented significantly higher survival rates, than implants placed in the osteoporosis/osteopenia control cohort (p value < 0.001), and similar survival rates, when compared to healthy controls (p value = 0.03). Additionally, clustered univariate and multivariate Cox regression analysis also revealed higher implant survival when oral antiresorptive drugs (p value = 0.01 and 0.007, respectively) were used, and lower implant survival in the presence of untreated osteoporosis/osteopenia (p value = 0.002 and 0.005, respectively). Overall, the 20-year implant survival in osteoporotic patients undergoing antiresorptive therapy was 94%. For the failed implants, newly replaced implants in patients under antiresorptive treatment presented a 10-year survival of 89%.

Conclusions Long-term plateau-root form implant survival in osteoporotic patients taking oral antiresorptives was similar to a healthy population and significantly higher than the untreated controls.

Clinical relevance These results suggest that plateau-root form implants provide a robust solution for treating tooth loss in patients, who are undergoing antiresorptive therapy.

Keywords Osteoporosis · Antiresorptives · Implants · Clinical trials · Dental biology

Introduction

Dental implant therapy is a common and effective treatment method for patients with tooth loss that improves the patients' oral health-related quality of life [1]. High success rates of dental implant therapy have been reported, especially in individuals with healthy bone metabolism [2]. However, some patients planning to receive dental implants or those who have them in function also suffer from age-related medical conditions such as osteoporosis [3–5]. In these patients, it is unclear whether some medications targeted to balance bone metabolism, such as antiresorptive therapies for treating osteoporosis, may affect the survival of implant-supported reconstructions [6].

Osteoporosis has been defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures [7]. This condition is estimated to affect 200 million women worldwide [8], coinciding with postmenopausal-related estrogen deficiency, which is associated with bone resorption due to predominant

✉ Edmara T. P. Bergamo
edmaratatiely@gmail.com

1 Department of Biology, Massachusetts Institute of Technology, Cambridge, MA, USA

2 University Hospital for Cranio-Maxillofacial and Oral Surgery and CMF Institute Vienna, Vienna, Austria

3 Implant Dentistry Centre, Boston, MA, USA

4 Department of Prosthodontics and Periodontology, University of Sao Paulo – Bauru School of Dentistry, 9-75 Octavio Pinheiro Brizola, Bauru, SP 17012-901, Brazil

increase of osteoclastic activity [9]. On the other hand, senile osteoporosis, which affects both men and women after age 70, is due to a predominant decrease in osteoblastic activity [10]. The increased susceptibility to fractures in osteoporosis, chiefly at the vertebrae (spine), hips, and wrists, represents a significant cause of disability and healthcare costs [11], which makes it a public health concern. Osteoporosis results in 1.5 million fractures per year in the USA alone, chiefly in postmenopausal women [12], with an overall economic burden of US $17.9 billion [13].

The treatment of osteoporosis is commonly targeted at reducing bone resorption with orally or intravenously administered antiresorptive drugs with acceptable risk–benefit, and at decreasing the fracture risks by interventions in nutrition and lifestyle [14]. Both bisphosphonates and denosumab reduce osteoclastic activity, each with its own mechanism of action. Bisphosphonates bind to the bone mineral, preventing the resorption of bone by osteoclasts and triggering osteoclast apoptosis. Denosumab is a monoclonal antibody that precludes the binding of the RANKL with its receptor. RANKL, short for receptor activator of nuclear factor-κB ligand, is a cytokine that is essential for the formation, function, and survival of osteoclasts [15].

Cases of implant failure and osteonecrosis have been reported in patients treated with antiresorptive drugs, while undergoing implant therapy. This condition is referred to as medication-related osteonecrosis of the jaw (ONJ) and is defined as exposed bone in the maxillofacial region that does not heal within 8 weeks [16]. However, even though evidence has pointed to antiresorptive drugs as the cause of ONJ, there is still no consensus regarding whether antiresorptive medication is a contraindication to implant therapy. A multicenter study in women with osteoporosis/osteopenia, who started antiresorptive medication only after implant placement and abutment surgery showed that 1-year survival rates of implants were similar to a control group [17]. A 3-year retrospective evaluation of dental implants placed in breast cancer patients prior to intravenous bisphosphonate administration showed that intravenous bisphosphonates were not a risk factor for the development of ONJ [18]. In contrast, an average follow-up of 85 months of antiresorptive drug administration in patients with successfully osseointegrated implants showed a significantly reduced implant survival rate, where pre-existing marginal bone loss, diabetes, type of final prosthesis, and the interval between implant placement and initiation of medication therapy were reported as risk factors, that were correlated with implant loss in antiresorptive-treated patients [19]. In a study where patients had implants before or after starting antiresorptive drug therapy, an increased risk for developing ONJ was also reported in both cohorts [20]. Another study specifically identified dental implant treatment during or after bisphosphonate administration as a risk factor for developing ONJ [21]. While ONJ can be successfully treated with surgery [22], especially in patients with osteoporosis or multiple myeloma [23], prevention of the condition is still of paramount importance [24].

In addition to the individual studies mentioned above, some available systematic reviews also present differing perspectives regarding implant survival prior, during or after antiresorptive therapy as well as the occurrence of ONJ. The placement of implants in patients taking oral bisphosphonates for less than 5 years was considered safe, with low occurrence of ONJ and no influence on short-term (1–4 years) implant survival compared to untreated controls [25]. In another systematic review, antiresorptive therapy was considered a risk factor for the development of implant failure and ONJ, despite the high risk of bias and heterogeneity of studies [26]. It has been reported that although low-dose oral bisphosphonate intake for osteoporosis treatment did not affect implant therapy, no information was available regarding high-dose bisphosphonate use or the widely used monoclonal antibody denosumab [27]. Lastly, a recent review paper concluded that even though the existing level of evidence associating ONJ with implant treatment in patients undergoing antiresorptive therapy remains low, antiresorptive therapy should still be considered as a risk factor for implant therapy [28].

In a 2014 position paper, the American Association of Oral and Maxillofacial Surgeons recognized that patients treated with antiresorptive drugs for cancer and osteoporosis are at risk for ONJ, albeit with limited evidence [29]. While most studies agree that patients taking high doses of bisphosphonates are at risk for osteonecrosis of the jaw, some studies have failed to show negative effects on implants from low-dose bisphosphonate treatment, yet still advised caution due to the severity of possible ONJ symptoms [30–32]. The 2021 Oral Reconstruction Foundation (ORF) Consensus Report suggested that bone grafting could not be recommended, while undergoing under antiresorptive therapy. Moreover, the report concluded that low-dose bisphosphonate treatment for osteoporosis did not affect short-term implant survival but could lead to ONJ. No information was presented regarding low dose denosumab intake and implant survival [33].

Given the conflicting literature on the interactions between antiresorptive drugs and dental implant therapy, there is a need for clinical studies investigating the robustness of individual implant systems in antiresorptive-treated patients. The need is heightened by the prevalence of osteoporosis combined with the need or presence of implant therapy, as well as the lack of long-term (more than 5-year follow-up) studies where multiple antiresorptive therapies were used [34, 35]. The plateau-root form implant, which integrates via a unique bone-healing mechanism, is a promising candidate. This study aimed to retrospectively evaluate the

up to 20-year survival of plateau-root form dental implants in postmenopausal and senile osteoporotic patients with or without antiresorptive therapy, as well as identify covariates that influence implant survival.

Patients and methods

Study population

Under approval of an Institutional Review Board (NEIRB# 14–338, 2014), this retrospective cohort study was designed according to the Declaration of Helsinki and the Good Clinical Practice guidelines, as well as STROBE guidelines. The study population consisted of two cohorts of osteoporotic female patients aged 45–90 years old, one under antiresorptive treatment and the other untreated, and one cohort of non-osteopenic female age-matched controls, all had received dental implants (Bicon LLC, Boston, USA) at the Implant Dentistry Centre in Boston, USA, between the years 2000 and 2021. Most patients with conditions that warrant antibiotic prophylaxis, such as rheumatic fever, mitral valve prolapse, and artificial joints, were pre-medicated with antibiotics prior to implant surgery. In the oral antiresorptive, antiresorptive injection, untreated osteoporosis control, and general population control cohorts, there were 82, 2, 141, and 50 patients who required antibiotic prophylaxis, respectively. The surgical treatments procedures were designed by the clinicians following the manufacturer's recommendations. A software database (Dentrix, version 17.3.548, Henry Schein One) built over several years was created with patient information; thus, the current data were collected from the patient database, where the appropriate checks were set to restrict sample characteristics and avoid bias. The oral antiresorptive cohort consisted of patients taking bisphosphonates orally (Fosamax, Actonel, Boniva). The injectable antiresorptive cohort consisted of patients receiving bisphosphonates (Reclast, Zoledronate) intravenously or denosumab (Prolia) subcutaneously. The osteoporosis/osteopenia control cohort consisted of patients diagnosed with osteoporosis and osteopenia but had not been treated with antiresorptive therapy. The general population control cohort consisted of non-osteopenic individuals sampled from patients, who presented for implant therapy. The osteoporosis/osteopenia and general population control cohorts were sampled from 752 and 8225 implants, respectively, by stratified sampling, that controlled for patient gender and age at the time of implant placement. Since many patients received more than one implant, the number of patients were fewer than the number of implants. The osteoporosis/osteopenia and general population control cohorts had 311 and 3175 patients, respectively. One patient, whose implants had been removed per patient's request, without displaying any sign of osteonecrosis, bone loss, non-integration, or periimplantitis, was excluded from the study.

To assess the effects of antiresorptive treatment on implant survival, four patient cohorts were retrospectively sampled based on antiresorptive treatment status at the time of implant placement or during subsequent follow-ups. The oral antiresorptive cohort included 105 patients with 338 implants total; the injectable antiresorptive cohort included 19 patients with 79 implants. In the injectable antiresorptive cohort, 13 patients with 50 implants were treated with bisphosphonates, while 6 patients with 29 implants were treated with denosumab. The number of implants was greater than the number of patients in each cohort because many patients received more than one implant. Both cohorts consisted of patients, who were either undergoing antiresorptive therapy at the time of implant treatment or were undergoing said therapy during subsequent follow-ups. The osteoporosis/osteopenia control cohort included 199 patients with 640 implants; and the general population control cohort included 371 patients with 415 implants.

Due to the retrospective nature of the study, the cohorts were validated for even distribution of study parameters between cohorts. Patient ages ranged from 45 to 90 years old at time of implant placement (Fig. 1, M: 66.42 years old, SD: ± 9.10 years old), and the difference between cohorts was within 3 years. Nine hundred forty-eight implants were placed when the patients were under 70 years of age, while 524 implants were placed in patients over 70 years of age. One thousand three hundred two implants had a hydroxyapatite (HA) coating (Integra-CP^{TM}, Bicon LLC, Boston, USA), while 170 implants had a sandblasted and acid-etched surface

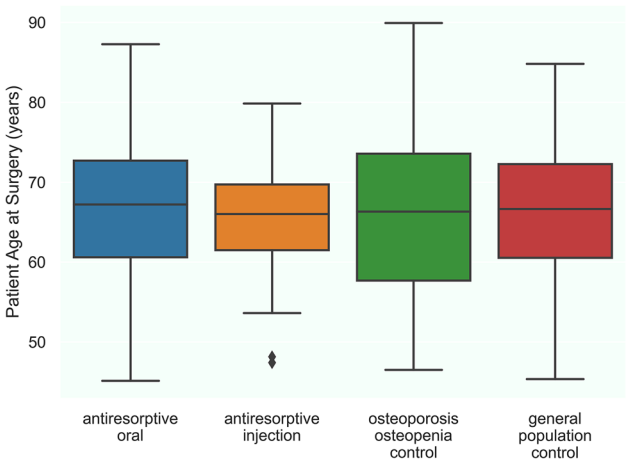

Fig. 1 Age distributions of patients among cohorts. Box plot describing the quartile ranges of patient age at surgery in years, plotted for each cohort studied. All four cohorts displayed similar age distributions. Number of patients in the oral antiresorptive cohort, the antiresorptive injection cohort, the osteoporosis/osteopenia control cohort, and the general population control cohort: 105, 19, 199, and 371 patients, respectively

(Integra-TI™, Bicon LLC, Boston, USA). Bone graft material (SynthoGraft™, Bicon LLC, Boston, USA) was used with 285 implants. Implant diameters ranged from 3.0 to 6.0 mm; implant lengths ranged from 5.0 to 11.0 mm; and implant well size ranged from 2.0 to 3.0 mm. Implants placed in all areas of the mouth were analyzed. Lastly, systemic risk factors, including diabetes, smoking, and the use of glucocorticoids were analyzed. The distributions of these categorical variables were analyzed for homogeneity using a chi-squared test (Table 1). For all covariates except glucocorticoid use ($p=0.02$), there is insufficient evidence of uneven distribution across cohorts ($p>0.1$). Demographic information (average and standard deviation) of the aforementioned variables is presented in Table 1 and Supplementary Table 1.

Data collection

The following covariates were collected for each implant: the date of implant placement; age of the patient at said date; gender of the patient; implant surface treatment; use of bone graft material; diameter, length, and well size (diameter of the locking taper bore) of the implant; and the area in the mouth where the implant was placed. Systemic factors, including diabetes, smoking, and the use of glucocorticoids were also included. If the implant had been explanted, the explant date was recorded. Prosthesis type, including single crown, fixed dental prosthesis, or overdenture, was also recorded.

In the case of implant removal, the surrounding bone and tissue were visually inspected and probed for signs of ONJ, which was staged according to the American Association of Oral and Maxillofacial Surgeons' (AAOMS) 2014 staging system [29]. Patient charts and radiographs were examined to determine the cause of implant removal.

Statistical analysis

Statistical analysis was performed using the lifelines 0.26.0 software library in Python. Chi-squared tests were used to validate the random distribution of patient age and implant parameters in the cohorts by comparing the cohorts ($n=338$, 79, 640 implants) with the general population control ($n=415$ implants). The primary outcome of the study was computed by Kaplan–Meier survival analysis, which compared implant and prosthesis survival between cohorts. Pairwise log-rank tests were then used to assess the significance of differences between cohorts ($n=338$, 79, 640, 415). Univariate and multivariate Cox regressions, clustered by patient with the robust variance estimator to adjust for multiple implants being placed in the same patient, were performed on all implants to regress the aforementioned covariates to implant survival outcomes ($n=1472$). To explore in detail the covariates that drive implant and prosthesis survival, univariate and multivariate Cox regressions were then performed on each individual cohort, and for an aggregate cohort comprised of all osteoporosis/osteopenia patients, whether or not they were receiving antiresorptive therapy ($n=1057$). Descriptive statistics were presented as a function of mean (M) and standard deviation (SD).

Results

Having established the even distribution of patients among cohorts, Kaplan–Meier (K-M) survival analysis was used to compare the differences in implant survival between antiresorptive-treated and control cohorts. The analysis revealed that the survival of implants placed in patients taking oral antiresorptive medications, as well as those placed in the non-osteoporotic general population, were both significantly

Table 1 Validation statistics for the equivalence between patient cohorts

Covariate	Range of equivalence (within the described range)	*p* value		
		Oral antiresorptive vs. general population ($n=753$)	Injectable antiresorptive vs. general population ($n=494$)	Osteoporosis/osteopenia vs. general population ($n=1055$)
Age	± 3 years	< 0.001	0.009	< 0.001
Implant surface	± 20%	< 0.001	0.006	< 0.001
Use of bone graft	± 10%	0.009	0.05	< 0.001
Implant diameter	± 0.3 mm	< 0.001	0.005	< 0.001
Implant length	± 1 mm	< 0.001	0.003	< 0.001
Implant well size	± 0.2 mm	< 0.001	0.002	< 0.001
Area in mouth	± 10%	0.001	0.03	< 0.001
Diabetes	± 10%	< 0.001	0.02	< 0.001
Smoking	± 15%	< 0.001	< 0.001	< 0.001
Glucocorticoid use	± 15%	< 0.001	< 0.001	< 0.001

better than those in the osteoporosis/osteopenia control (p value = 0.0005 and 0.03, respectively). The K-M survival curve of implants placed in patients injected with bisphosphonates lay between the oral antiresorptive cohort and the general population control, yet there is not enough statistical significance to declare a difference from the osteoporosis/osteopenia control (Fig. 2).

To justify the sampling of the injectable antiresorptive cohort, a separate K-M survival analysis was conducted to compare implant survival between the two types of injected antiresorptive drugs—bisphosphonates (13 patients with 50 implants) and denosumab (6 patients with 29 implants). The results indicate that the two survival curves were not different in any significant way (log-rank test statistic = 0.01, p value = 0.93) (Supplementary Fig. 1). Thus, injectable bisphosphonates and the monoclonal antibody denosumab can be considered as one cohort and analyzed as such.

Univariate and multivariate Cox regression, clustered by each patient, was used to assess the effect of patient age at time of surgery, implant surface, bone graft material usage, implant diameter, length, and well size, the area of implant placement, and antiresorptive treatment on implant survival (Tables 2 and 3). Univariate analysis showed that improved implant survival was correlated with the prosthesis being a single crown (z-value = −4.43, p value < 0.001), longer implant length (z-value = −3.79, p value < 0.001), and oral antiresorptive treatment (z-value = −2.99, p value = 0.03), while the worse prognosis was correlated with bone graft material usage (z-value = 2.68, p value = 0.007) and untreated osteoporosis or osteopenia (z-value = 3.40, p value < 0.001). Multivariate analysis confirmed all four findings: the improved survival for crown prostheses (z-value = −4.49, p value < 0.001), longer implants (z-value = −4.06, p value < 0.001) and oral antiresorptive intake (z-value = −3.24, p value = 0.001), as well as the correlation with the worse prognosis of untreated osteoporosis or osteopenia (z-value = 3.41, p value = 0.001) and bone graft material use (z-value = 1.97, p value = 0.05.) Additionally, multivariate analysis also revealed that implants in the posterior mandible presented higher survival (z-value = −2.32, p value = 0.02). Overall, the beneficial effect of oral antiresorptive treatment as well as the deleterious effect of untreated osteoporosis/osteopenia was confirmed via Cox regression.

To explore in detail the covariates that influence implant survival in each cohort, clustered univariate and multivariate Cox regressions were performed on each cohort separately. Cox regression failed to converge due to low variance in the oral and injectable antiresorptive treatment cohorts. Thus, an aggregate cohort was compiled from all patients with osteoporosis/osteopenia, regardless of whether they received antiresorptive therapy. Additionally, glucocorticoid use was not analyzed due to the covariate's high collinearity with implant survival outcomes. Both univariate and multivariate Cox regressions revealed that implant length (z-value = −5.01 and −4.74, p value < 0.001), crown prostheses (z-value = −3.31 and −3.22, p value = 0.001), and bone graft usage (z-value = 2.92 and 2.13, p value = 0.003 and 0.03) were significant covariates affecting survival specifically in osteoporosis/osteopenia patients, with longer implants and crown prostheses being correlated with higher survival and bone graft usage with lower survival.

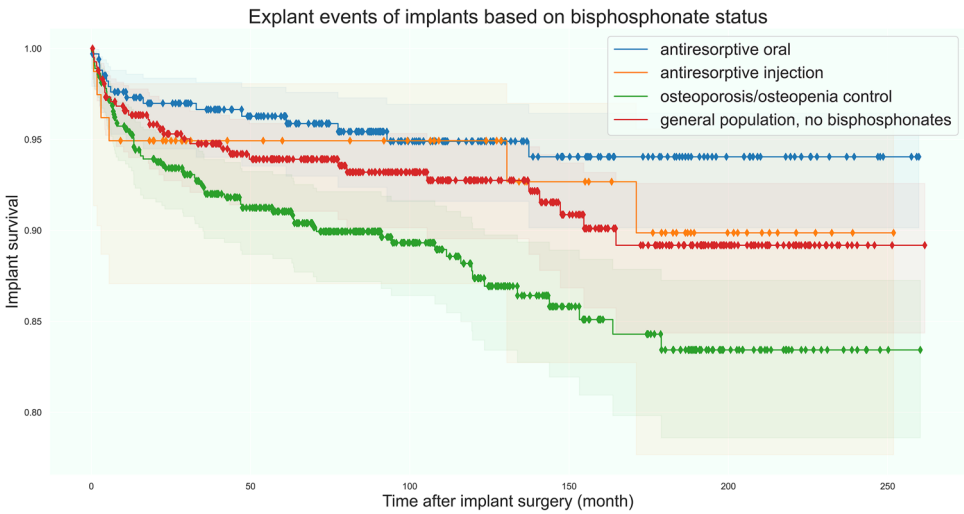

Fig. 2 Kaplan–Meier survival of implants grouped into cohorts by antiresorptive treatment. Kaplan–Meier survival curve plotting the implant survival probability against the time after implant surgery for each cohort. Implants in the oral antiresorptive cohort presented significantly higher survival rates compared to those in the untreated osteoporosis/osteopenia control cohort, and similar survival rates compared to the healthy control. Implants in the intravenous antiresorptive cohort presented similar survival rates to both control cohorts. Shaded regions represent 95% confidence intervals

Table 2 Results of univariate Cox regression on implant survival

Covariate	Coefficient	Lower 95% CI	Upper 95% CI	*z*	*p*
Prosthesis—crown	−0.79541	−1.14699	−0.44383	−4.43416	9.24E−06
Implant length	−2.24002	-3.39826	-1.08178	-3.79054	0.00015
Oral antiresorptives	−1.0863	−1.79909	−0.37351	−2.98701	0.002817
HA surface coating	−0.91288	−1.86081	0.035057	−1.88748	0.059096
Implant in posterior mandible	−0.44142	−0.96884	0.085995	−1.64039	0.100923
Glucocorticoid use	−1.76562	−4.43144	0.900199	−1.29812	0.194246
General population	−0.41618	−1.05436	0.221989	−1.27819	0.201183
Smoking	−0.68593	−2.24169	0.869833	−0.86414	0.387511
Injected antiresorptives	−0.43139	−1.87361	1.010829	−0.58625	0.557704
Implant diameter	−0.5845	−2.62383	1.454822	−0.56176	0.574282
Prosthesis—fixed dental prostheses	−0.09069	−0.68855	0.507161	−0.29732	0.766219
Patient age at surgery	−0.20373	−2.80589	2.398434	−0.15345	0.878044
Implant in anterior mandible	0.031466	−1.15046	1.213395	0.052179	0.958386
Implant well size	0.161121	−0.76438	1.086621	0.341212	0.732944
Implant in anterior maxilla	0.213002	−0.42011	0.846114	0.659403	0.509637
Prosthesis—overdenture	0.368396	−0.60049	1.337287	0.745227	0.456134
Implant in posterior maxilla	0.193252	−0.27792	0.664421	0.803886	0.421463
Prosthesis—treatment pending	0.273192	−0.26477	0.811158	0.995317	0.319582
Diabetes	0.790937	−0.0636	1.645476	1.814088	0.069664
Bone graft material used	0.820852	0.221382	1.420321	2.683773	0.00728
Osteoporosis/osteopenianot treated with antiresorptives	1.033474	0.438404	1.628545	3.403922	0.000664

Table 3 Results of multivariate Cox regression on implant survival

Covariate	Coefficient	Lower 95% CI	Upper 95% CI	*z*	*p*
Prosthesis—crown	−0.40532	−0.58223	−0.2284	−4.49035	7.11E−06
Implant length	−0.79008	−1.17181	−0.40836	−4.05666	4.98E−05
Oral antiresorptives	−0.30112	−0.48321	−0.11903	−3.24123	0.00119
Implant in posterior mandible	−0.19442	−0.35884	−0.03	−2.31751	0.020476
Prosthesis—fixed dental prostheses	−0.1916	−0.41799	0.03479	−1.65877	0.097162
General population	−0.14488	−0.32848	0.038721	−1.54661	0.121957
Implant diameter	−0.40051	−0.98724	0.18622	−1.3379	0.180929
HA surface coating	−0.37873	−0.94046	0.183001	−1.32145	0.186352
Prosthesis—treatment pending	−0.12629	−0.33166	0.079079	−1.20528	0.228097
Glucocorticoid use	−0.29705	−0.86456	0.270469	−1.02588	0.304949
Patient age at surgery	−0.25983	−1.2007	0.681039	−0.54126	0.588328
Smoking	−0.08853	−0.47359	0.296539	−0.4506	0.652279
Injected antiresorptives	−0.04981	−0.5304	0.430794	−0.20311	0.839045
Implant in anterior mandible	0.046967	−0.3116	0.405532	0.256726	0.79739
Prosthesis—overdenture	0.116599	−0.44429	0.677484	0.407445	0.683681
Implant well size	0.096199	−0.16241	0.354807	0.729078	0.465954
Implant in posterior maxilla	0.059432	−0.08916	0.208023	0.783934	0.433079
Implant in anterior maxilla	0.138335	−0.11524	0.391913	1.069221	0.28497
Diabetes	0.427008	−0.16011	1.014124	1.425476	0.15402
Bone graft material used	0.356928	0.002565	0.71129	1.974154	0.048364
Osteoporosis/osteopenia not treated with antiresorptives	0.362065	0.154249	0.569881	3.414729	0.000638

Additionally, univariate analysis identified hydroxyapatite implant surface coatings as a covariate that is correlated

to increased survival (z-value = −2.51, p value = 0.01) (Tables 4 and 5).

In contrast, neither implant length nor bone graft material use were significantly correlated with implant survival in the general population (Tables 6 and 7). In this cohort, significant covariates included crown prostheses (z-value = −3.21 and −3.40, p value = 0.001 and 0.001, respectively); implant placement in the posterior mandible (z-value = −1.95 and −2.21, p value = 0.05 and 0.03, respectively); and diabetes (z-value = 4.38 and p value < 0.001 and p value = 0.003, respectively). In both univariate and multivariate analyses, crown prostheses and placement in the posterior mandible were correlated with improved survival, while the presence of diabetes was correlated with worsened survival. Overall, implant length, bone graft material use, and other parameters were found to be correlated with implant survival in osteoporotic/osteopenic patients and not in non-osteopenic controls, while diabetes was correlated with implant survival in non-osteopenic controls but not in osteoporotic/osteopenic patients.

After exploring the covariates that may influence implant prognosis, the prevalence, pathology, and treatment of implant failure was examined in detail for patients under antiresorptive therapy. Over a period of 250 months, the survival probability of implants in patients under oral antiresorptive therapy was 94% (CI: 90–96%), with 16 failed implants. For patients receiving injectable antiresorptive

Table 4 Results of univariate Cox regression on implant survival in osteoporotic and osteopenic patients

Covariate	Coefficient	Lower 95% CI	Upper 95% CI	z	p
Implant length	−3.15808	−4.39301	−1.92315	−5.0122	5.38E−07
Prosthesis—crown	−0.71164	−1.13253	−0.29075	−3.31389	0.00092
HA surface coating	−1.12641	−2.00429	−0.24853	−2.51484	0.011909
Implant in posterior mandible	−0.37389	−0.93372	0.185938	−1.30899	0.190537
Smoking	−0.90328	−2.77346	0.966909	−0.94664	0.343823
Implant diameter	−0.67727	−3.01161	1.657067	−0.56865	0.569591
Patient age at surgery	−0.54532	−3.54802	2.457392	−0.35595	0.721881
Prosthesis—fixed dental prostheses	−0.09799	−0.72757	0.531584	−0.30507	0.760314
Implant in anterior mandible	−0.07728	−1.56075	1.406198	−0.1021	0.918679
Diabetes	0.004898	−1.27115	1.280943	0.007524	0.993997
Implant in anterior maxilla	0.038691	−0.72463	0.802015	0.099346	0.920864
Implant well size	0.237047	−0.87175	1.34584	0.419017	0.675204
Prosthesis—treatment pending	0.209805	−0.42527	0.844883	0.647494	0.517312
Prosthesis—overdenture	0.494584	−0.54875	1.537919	0.929104	0.352835
Implant in posterior maxilla	0.35265	−0.18494	0.890234	1.285714	0.198543
Bone graft material used	0.992343	0.326299	1.658387	2.920164	0.003498

Table 5 Results of multivariate Cox regression on implant survival in osteoporotic and osteopenic patients

Covariate	Coefficient	Lower 95% CI	Upper 95% CI	z	p
Implant length	−1.22213	−1.7269	−0.71735	−4.74528	2.08E−06
Prosthesis—crown	−0.36421	−0.58593	−0.14249	−3.21949	0.001284
Implant diameter	−0.61177	−1.33552	0.111984	−1.65671	0.097579
HA surface coating	−0.4773	−1.085	0.1304	−1.5394	0.123707
Implant in posterior mandible	−0.15265	−0.35635	0.051044	−1.46882	0.141881
Prosthesis—treatment pending	−0.16982	−0.40494	0.065301	−1.41561	0.15689
Prosthesis—fixed dental prostheses	−0.18494	−0.45589	0.086011	−1.33779	0.180965
Patient age at surgery	−0.50533	−1.68131	0.670662	−0.8422	0.399674
Smoking	−0.20915	−0.79093	0.372631	−0.70461	0.481053
Implant in anterior mandible	0.00153	−0.44067	0.443732	0.006782	0.994589
Diabetes	0.005617	−0.59355	0.604788	0.018373	0.985341
Prosthesis—overdenture	0.153788	−0.59722	0.904792	0.401354	0.68816
Implant well size	0.081416	−0.21539	0.378219	0.537641	0.590825
Implant in anterior maxilla	0.089885	−0.21037	0.390145	0.586733	0.557383
Implant in posterior maxilla	0.093165	−0.05986	0.246187	1.193297	0.232753
Bone graft material used	0.451444	0.036802	0.866087	2.133922	0.032849

Table 6 Results of univariate Cox regression on implant survival in the general population

Covariate	Coefficient	Lower 95% CI	Upper 95% CI	*z*	*p*
Prosthesis—crown	−1.0248	−1.65031	−0.39929	−3.21111	0.001322
Implant in posterior mandible	−1.07626	−2.15976	0.007235	−1.94688	0.05155
Implant in posterior maxilla	−0.22606	−1.17484	0.722719	−0.46699	0.640506
Prosthesis—fixed dental prostheses	−0.35254	−1.97852	1.273433	−0.42496	0.670866
Implant diameter	−0.04885	−2.74544	2.647733	−0.03551	0.971675
Smoking	0.02355	−1.75017	1.797272	0.026023	0.979239
Implant well size	0.047355	−1.25148	1.346186	0.071459	0.943032
Implant length	0.090264	−1.33686	1.517391	0.123965	0.901343
Prosthesis—overdenture	0.229661	−1.34496	1.804277	0.285865	0.774982
Implant in anterior mandible	0.312366	−0.81478	1.439509	0.543166	0.587016
Bone graft material used	0.476335	−0.7636	1.71627	0.752943	0.451484
Prosthesis—treatment pending	0.482921	−0.47341	1.439252	0.989729	0.322306
Patient age at surgery	1.409878	−1.31862	4.138373	1.012759	0.311175
HA surface coating	1.528616	−0.56381	3.621041	1.431848	0.152187
Implant in anterior maxilla	0.724181	−0.22594	1.674307	1.493875	0.135208
Diabetes	1.908801	1.053799	2.763804	4.37564	1.21E−05

Table 7 Results of multivariate Cox regression on implant survival in the general population

Covariate	Coefficient	Lower 95% CI	Upper 95% CI	*z*	*p*
Prosthesis—crown	−0.45699	−0.72047	−0.19352	−3.39958	0.000675
Implant in posterior maxilla	−0.27836	−0.52568	−0.03104	−2.20596	0.027387
Prosthesis—fixed dental prostheses	−0.24688	−0.71758	0.223817	−1.028	0.303948
Implant in posterior maxilla	−0.07497	−0.38071	0.230767	−0.48062	0.63079
Prosthesis—overdenture	−0.07445	−0.82944	0.680534	−0.19329	0.846736
Prosthesis—treatment pending	−0.01608	−0.32359	0.291435	−0.10246	0.918391
Smoker	0.005337	−0.69773	0.708401	0.014879	0.988129
Implant diameter	0.108702	−0.74004	0.957442	0.251022	0.801797
Implant length	0.080896	−0.47238	0.634172	0.286574	0.774439
Implant in anterior mandible	0.119168	−0.39687	0.635209	0.45261	0.650829
Bone graft material used	0.118623	−0.37031	0.607561	0.475516	0.634419
Implant well size	0.147612	−0.35122	0.646444	0.579982	0.561927
Patient age at surgery	0.435337	−0.50741	1.378085	0.90506	0.365434
Implant in anterior maxilla	0.298236	−0.11259	0.70906	1.422831	0.154785
HA surface coating	0.250883	−0.02168	0.523449	1.804041	0.071225
Diabetes	1.095359	0.353685	1.837034	2.894617	0.003796

treatment, the implant survival rate was 90% (CI: 78–97%), with 6 failed implants, that were not censored. In contrast, the overall 250-month survival of implants in the osteoporosis/osteopenia control group, and in the general population was 84% (CI: 79–88%) and 89% (CI: 85–92%), respectively.

The pathologies of these failed implants were evaluated by examining the patients' charts. A review of the 22 failed implants in 19 patients under antiresorptive therapy revealed that only 1 patient exhibited signs of ONJ at stage 1 (exposed necrotic bone or fistulae in patients, who were asymptomatic and had no evidence of infection). The stage 1 ONJ in said patient, who was receiving denosumab therapy, accounted for 3 failed implants. The remaining 19 implants in 18 patients displayed no clinical evidence of necrotic bone (stage 0 ONJ). None of the patients exhibited stage 2 or 3 ONJ. Careful examination of patient charts and radiographs revealed that out of the 19 non-ONJ implants, 11 were removed due to non-integration upon uncovering, while 8 were later removed due to periimplantitis. The low prevalence of ONJ indicates that ONJ is not a major concern in antiresorptive-treated patients receiving the implants studied.

Among those 22 cases of failed implants in patients under antiresorptive treatment, 12 were retreated with implant placement, while still undergoing antiresorptive medication. Of those 12 implants, only one implant was explanted, and the overall K-M survival lies around 89% (Fig. 3).

One case of a successful replacement implant use is demonstrated in Fig. 4. The first implant was extracted 15 months after insertion due to peri-implantitis, as evident from the bone loss in the peri-implant region (Fig. 4a–c). Osteonecrosis was not observed. Upon placement of the implant, the peri-implant bone level increased (Fig. 4d, e). The replacement implant functioned for more than 120 months and is still in function at the time of this writing.

Discussion

To assess the efficacy of plateau-root form implants in treating antiresorptive-treated patients, this study investigated the difference in implant survival between patients

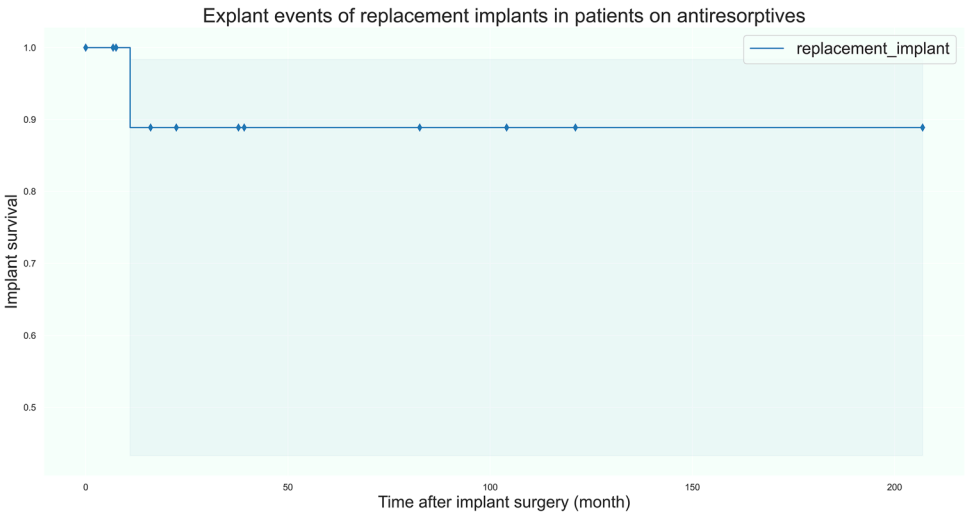

Fig. 3 Kaplan–Meier survival of replaced implants for cases of failed implants in patients undergoing antiresorptive treatment. Kaplan–Meier survival curve plotting the implant survival probability against the time after implant surgery for replacement implants. Shaded regions represent 95% confidence intervals

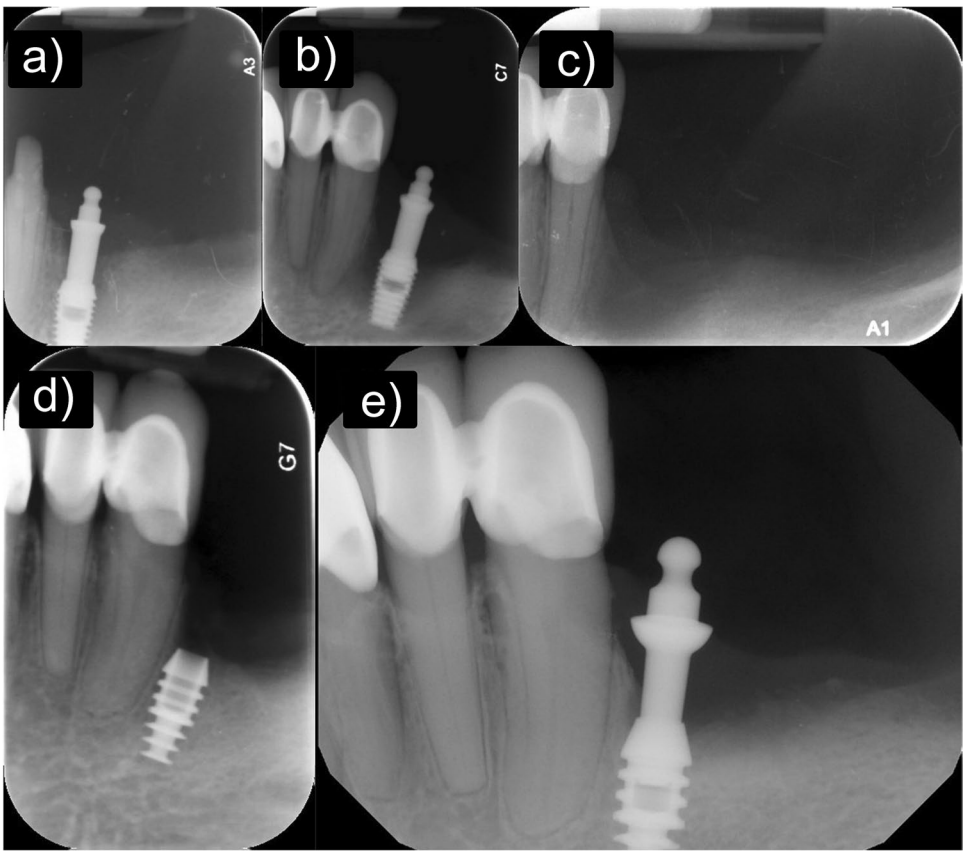

Fig. 4 Radiographic evidence of replacement implant efficacy. **A** a radiograph of the original implant 3 months after placement; **B** a radiograph of the implant one year after loading, showing radiolucency characteristic of periimplantitis; **C** a radiograph of the site two months after implant removal; **D** radiograph of the replacement implant, placed 20 months after implant removal; **E** radiograph of the replacement implant and dense, radiopaque surrounding bone, 7 years after placement

taking oral and injectable antiresorptive treatments, patients with untreated osteoporosis and osteopenia, and healthy female patients in the general population. The main outcome studied was implant and prosthesis survival, which was followed for up to 250 months. Chi-square tests failed to show any significant difference in the distribution of implant parameters across cohorts except for glucocorticoid use, making it unlikely that biased sampling was driving any differences in survival, especially since studies have shown that glucocorticoid use was not associated with increased risk of dental implant failure [36, 37]. K-M survival analysis, which was used as a model for analyzing dental implant survival in accordance with prior research [38], revealed that patients under antiresorptive treatment have an overall high rate of implant survival. The 20-year implant survival probability was 93% for those with oral administration and 90% for injections. Remarkably, implants placed in those patients presented significantly higher survival rates compared to the untreated osteoporosis/osteopenia control group (84%), at a rate comparable to the general population control (89%). On the other hand, untreated osteoporosis and use of bone graft material were associated with significantly lower survival rates compared to the general population and to osteoporosis patients under antiresorptive medication. The improved survival of implants in oral antiresorptive-treated patients over the control population suggests that oral antiresorptive administration, not only seems to mitigate the detrimental effects of osteoporosis but may also contributes positively towards implant survival for the implant system studied.

A separate K-M survival analysis revealed that for the small number of patients (13 for bisphosphonate injections, 6 for denosumab) studied, there was no significant difference in implant survival rates between patients treated with two different types of antiresorptive injections. This supports previous observations that denosumab affects dental implants similarly to bisphosphonate injections and validates prior research that has discussed denosumab alongside other bisphosphonates [39]. This justifies the grouping of injectable bisphosphonates and monoclonal antibodies together as one cohort and suggests that both treatments allow for similarly high implant survival.

Our study identified several parameters that significantly influenced implant survival: untreated osteoporosis, orally administered antiresorptive drugs, implant length, and single crown prostheses. Cox regression revealed that untreated osteoporosis is detrimental to the survival of the dental implants being studied. It has been a subject of debate whether osteoporosis is a contraindication to implant therapy in general [40], and a recent systematic review pointed out that convenient sampling in studies tends to exclude individuals with systemic diseases such as osteoporosis [41], while another recent review identified a direct but insignificant effect of osteoporosis on implant loss [28]. This study demonstrated that for the evaluated cohort and implant system, the presence of osteoporotic conditions is indeed correlated with significantly lower survival. One recent systematic review and meta-analysis [42] reporting a positive effect of anti-osteoporotic drugs on osseointegration is consistent with our findings, but it was based on preclinical studies. This is in contrast with findings currently available in most systematic reviews and meta-analyses. From earlier to more recent systematic reviews [25, 27, 32, 43, 44], most conclude that low-dose antiresorptive drug intake does not compromise implant therapy; that there is limited information on high-dose of antiresorptive drug (valid to consider those patients undergoing treatment of malignancies as high-risk); and that, in general, information is derived from studies of low quality [27], with heterogeneity that sometimes hinders meta-analysis [44]. One systematic review with meta-analysis based on approximately 30,000 implants concluded that there was no difference observed in implant survival rates between patients with and without osteoporosis [45]. The review received a later commentary [46] that its PICO concepts were incorrect. The intervention/exposure was implant therapy, while it should have been osteoporosis presence or absence. One aspect that seems to be the consensus is that most systematic reviews highlight the need for explaining the risk of ONJ to the patient. Also, despite the different pathophysiology of age-related osteoporosis compared to postmenopausal osteoporosis [47], age was not a factor influencing implant survival of antiresorptive treatment or untreated osteoporosis groups. Both postmenopausal and senile osteoporosis patients experienced high success rates. Furthermore, the detrimental effects of osteoporosis on implant therapy can be ameliorated by several treatments (regular exercise, calcium and vitamin D intake, among others) and antiresorptive treatments [48]. In particular, the oral administration of bisphosphonates as an antiresorptive treatment may positively impact dental implant therapy, as shown by K-M survival analysis. Thus, implant therapy with the implant system currently under investigation is a viable solution for osteoporotic patients.

While osteoporosis was shown to be detrimental to implant survival, treatment of osteoporosis with antiresorptive drugs surprisingly had a beneficial effect on implant survival. The effect is not limited to bisphosphonates—the overall reported rate of ONJ in postmenopausal women with osteoporosis treated with denosumab for up to 10 years had been low, and the risks of ONJ were outweighed by the benefits of bone fracture prevention [39]. The deleterious effect of untreated osteoporosis and osteopenia, as well as the rescuing effect of orally administered bisphosphonate antiresorptive drugs, was further

confirmed in univariate and multivariate clustered Cox regression, firmly establishing those covariates as significant parameters that influence implant survival.

Additionally, Cox regression identified implant length as a significant covariate that influences implant survival specifically in osteoporotic and osteopenic patients, with longer implant length resulting in significantly higher survival. Previous analyses on the general survival of the same implant system in healthy patients did not identify such a correlation [49], a fact that was confirmed with the control cohort in this study. These findings validated previous research conclusions that for healthy individuals, ultrashort and short implants functioned similarly as well as long implants [50–52]. It is important to note that even though implant length is a newly implicated covariate, which acts specifically on osteoporotic and osteopenic patients, there is still the possibility, as is with any retrospective study, that the correlation is a result of sampling bias. Furthermore, the mechanism behind such a correlation has yet to be elucidated.

Another covariate that was correlated with higher survival was the use of single crown prostheses on the implant compared to long-span fixed dental prostheses and overdentures. This correlation existed across the entire patient population and was observed in separate analyses of patients with and without osteoporosis and osteopenia. This is consistent with previous findings that showed single crowns presenting higher survival in general [53], as well as in patients treated with antiresorptive drugs [19].

On the other hand, the presence of diabetes was correlated with poor implant prognosis only in patients without osteoporosis/osteopenia. This finding is also in agreement with previous literature suggesting that diabetes may directly impair implant osseointegration [54], even though a recent systematic review has failed to show an association between diabetes and implant failure [28]. As data is not available regarding the degree of disease control in patients, the observed correlation is likely driven by diabetic patients, whose disease was poorly controlled. The absence of a similar correlation in osteoporotic/osteopenic patients suggest that osteoporosis or its treatment may interact with the mechanisms by which diabetes interferes with osseointegration, or that the diabetic patients in the osteoporosis cohort happen to have a higher quality of glycemic control. Other systemic factors, including smoking and glucocorticoid use, were not found to be significantly correlated with implant survival. Overall, systemic factors do not significantly affect the survival of the investigated implant in osteoporotic/osteopenic patients.

In this study, implants placed in the antiresorptive-treated osteoporotic patients presented significantly higher survival compared to the control patients, which suggests that antiresorptive treatment was successful in balancing bone remodeling homeostasis. In the past, several strategies have been proposed to increase dental implant stability in osteoporotic bone, including modifications in the implant design [55], in the implant surface [56], using less invasive surgical instrumentation, and complementary medical treatment [57]. The results of this study suggest that for the implant system studied, antiresorptive medication may be an additional factor that improves implant survival in osteoporotic patients. One potential underlying mechanism could be the previously described osseointegration healing pattern of the investigated plateau-root form implant system where the implant's plateau macro-geometry allows for direct bone formation at the implant surface [58–61]. This unique plateau-root form implant macro-design leads to three characteristics. Firstly, the currently investigated implant system exhibited a unique healing pattern in retrieval studies, where bone remodeling evolved to a harversian-like configuration at the healing chambers [62, 63]. Secondly, there was a steady increase in bone to implant contact as well as in bone area fraction occupancy, for implants that were evaluated for up to 18 years [64]. Thirdly, human bone nanomechanical properties at the implant healing chambers presented a significant increase after 5 years in function [65]. Therefore, it cannot be excluded that the cortical-like bone properties observed in the healing chambers may be a factor explaining the improved implant survival when antiresorptive agents are used, as well as acceptable survival rates even in untreated osteoporotic patients. Human retrievals of dental implants in osteoporotic patients are needed to confirm this assumption.

The rare event of an implant failing in patients undergoing antiresorptive treatment can be accounted for by non-integration and periimplantitis. The incidence of ONJ was rare (0.8% of patients), and even when present, only at asymptomatic levels (AAOMS stage 1). Implant failures, including those associated with ONJ, were remedied via the placement of a new implant, which survived at a high rate over a long period of time (10-year K-M survival 89%). The high efficacy of the replacement implant suggests that antiresorptive therapy is not the primary cause of implant failure in patients. Given the consequences of ONJ, clinicians should be aware of ONJ treatment strategies and to inform patients regarding the risks and the need of signed informed consent [66, 67].

As a retrospective cohort study, this study is limited by the inherent disadvantage of retrospective studies: there is the possibility that confounding factors may have not been considered, resulting in bias. Major limitations of this study include the following: unknown dosage of antiresorptive drug intake; unknown duration of antiresorptive drug intake; and unknown disease severity of the osteoporosis. Also, potential differences between the start of antiresorptive drug intake and implant insertion, as well as the duration and dosage of antiresorptive drug administration could not be accounted for, which are limitations of the current study.

Although data about the severity of osteoporosis was not available to us, it cannot be assumed that the control population did not receive anti-resorptive drugs because their osteoporosis was less severe. In fact, a "crisis" on the treatment of osteoporosis has been highlighted in the literature [68], with increasing evidence that many patients, who should unequivocally receive pharmacological treatment for, are either not being prescribed one of several effective available drugs or are simply refusing to take them, mainly because of concerns regarding drug-related side effects [69]. Multivariate Cox regression, which was used in the study to evaluate the effects of various covariates on implant survival, operates on the assumption that possible confounders are equally distributed across different sub cohorts. One such potential confounder—corticosteroid use—was significantly different between sub cohorts. Although corticosteroid use was not associated with implant failure in this study, it is unknown whether the group with higher corticosteroid use has been treated for secondary osteoporosis instead of primary. Even while the distribution of all known covariates analyzed in this study has been verified, there is still a possibility of unknown confounding variables, that are unequally distributed across the study cohorts. Prospective studies with larger sample sizes with control groups are warranted.

Moreover, the study is limited to implants from one manufacturer, without available data to provide adequate comparisons with other implant systems. Therefore, the established benefits of bisphosphonate administration on implant survival may be limited to the implant system under investigation. Also, since it is difficult to distinguish between ONJ and periimplantitis clinically and radiographically, the study is limited by a lack of histopathological examinations on failed implants. For implants that did not fail, this study is limited by a lack of information regarding implant success as opposed to survival. Because of the retrospective design, another limitation was that it was not possible to analyze the time difference between the start of antiresorptive drug intake and the time of implant insertion.

Conclusions

High survival rates for implant-supported restorations were observed in treating patients, who are undergoing treatment with bisphosphonates or other antiresorptive drugs. The use of orally administered antiresorptive drugs is significantly correlated with improved plateau-root form implant survival for the osteoporotic patient.

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Declarations

Ethical approval This retrospective cohort study was approved by an Institutional Review Board (NEIRB# 14-338, 2014).

Informed consent All patients signed an informed consent and authorized the disclosure of their health information.

Conflict of interest The authors declare no competing interests.

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