Implant Placement in Patients with Oral Bisphosphonate Therapy: A Case Series

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ABSTRACT

Background: Although the effect of bisphosphonates on dental implant osseointegration is not clear, dental implant failures attributable to oral bisphosphonate therapy have been reported in patients with osteoporosis.

Purpose: The aim of this study was to evaluate implant survival in patients with a history of bisphosphonate therapy in a retrospective survey.

Materials and Methods: A total of 46 ITI implants placed in 21 osteoporotic patients (females; average age 53 years, range 42–79 years) were evaluated with regard to probing depth, mobility, thread exposure, and bleeding on probing. All patients were under oral bisphosphonate therapy.

Results: None of implants showed mobility and all patients could be considered free from peri-implantitis. Time of bisphosphonate therapy before and after implant insertion showed no statistically significant influence on PD, BOP, and TE. Likewise, implant location, prosthetic type, and opposing dentition had no statistically significant influence on the clinical and radiological parameters of implants.

Conclusion: Within the limitations of this study, it could be concluded that neither being on oral bisphosphonate treatment before implant placement nor starting bisphosphonate therapy after implant installation might jeopardize the successful osseointegration and clinical and radiographic condition of the implants.

KEY WORDS: bisphosphonate, case series, implant, survival

INTRODUCTION

Osteoporosis is the most common disease of bone metabolism encountered in implant patients, and almost one-third of patients over age 60 are affected.[1] Dental professionals involved in implant therapy will increasingly manage patients who are currently or potentially at risk for osteoporosis. Extended healing time is recommended for these patients.[1] These patients would roughly be anyone who has experienced a drop in bone marrow density of 10% greater than what is normal. In 1994, the World Health Organization defined osteoporosis as a bone mineral density level more than 2.5 standard deviations below the mean of normal, young women.[2] Currently, there are four approved treatments for postmenopausal osteoporosis: (1) estrogen replacement therapy, (2) selective estrogen receptor modulators, (3) calcitonin, and (4) bisphosphonates.[3] Medical treatment with bisphosphonate drugs, potent antiresorptive agents, also has become standard practice

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TABLE 1 Oral Bisphosphonates

Generic Name	Chemical Formula	Brand Name	Primary Indication
Clodronate	$CH_4Cl_2O_6P_2$	Bonefos	Hypercalcemia of malignancy
Ibandronate	$C_9H_{22}O_7NP_2Na$	Boniva Bondronat	Osteoporosis
Risedronate	$C_7H_{10}NO_7P_2Na$	Actonel	Osteoporosis
Tiludronate	$C_7H_7ClNa_2O_6P_2S$	Skelid	Paget's Disease
Alendronate	$C_4H_{12}NNaO_7P_2 .3H_2O$	Fosamax	Osteoporosis
Etidronate	$C_2H_6Na_2O_7P_2$	Didronel	Paget's Disease

in benign and malignant diseases involving bone resorption, such as bone lesions of multiple myeloma, metastatic bone diseases, and osteoporosis.[4,5]

Bisphosphonates are traditionally divided into nitrogen-containing (N-) and non-nitrogen-containing (non-N-) categories.[6] Nitrogen-containing bisphosphonates, such as Zolendronate, are potent inhibitors of osteoclastic bone resorption through inhibition of synthesis of farnesyl pyrophosphate, a key enzyme in the mevalonate pathway.[7] Potent bisphosphonates are delivered intravenously and are indicated to stabilize metastatic cancer (primarily breast and prostate) deposits in bone and to treat the bone resorption defects of multiple myeloma and correct severe hypercalcemia. These are Pamidronate and Zoledronate.[8] In patients with osteoporosis, oral bisphosphonates are prescribed and include Clodronate (Bonefos; Aventis, NJ, USA), Ibandronate (Boniva; Roche, Nutley, NJ, USA), Risedronate (Actonel; Proctor and Gamble Pharmaceuticals, Cincinnati, OH, USA), Tiludronate (Skelid; Sanofi-Synthe Lab Inc., New York, NY, USA), and Alendronate (Fosamax; Merck Co., West Point, PA, USA) (Table 1). Because bisphosphonates are not metabolized, these concentrations are maintained within bone for long periods of time.[9] This ability to affect systemic bone remodeling raises natural questions about the drug's influence on dental implant osseointegration. Therefore, implant therapy in patients with osteoporosis may be more challenging when bisphosphonate therapy is also coupled with the process of osseointegration.[10]

An increasing amount of reports is being published, suggesting a relationship between the use of bisphosphonates and the development of osteonecrosis of the jaw.[11,12] In 2004, Ruggiero and colleagues[9] reported 63 cases of osteonecrosis of the jaw related to bisphosphonate therapy. Fifty-six of the patients had received intravenous bisphosphonates for at least 6 months as part of cancer therapy, seven of whom were undergoing long-term oral bisphosphonate therapy for osteoporosis. Oral treatments in these patients at risk of osteonecrosis are aimed at eliminating infections and the need for invasive dental procedures in the near future; so preventive therapy should be aggressive and should include tooth removal, periodontal surgery, root canal treatment, tooth decay control, dental restorations, and prosthesis, if needed.[8] Although the effect of bisphosphonates on dental implant osseointegration is not clear, dental implant failures attributable to oral bisphosphonate therapy have been reported in patients with osteoporosis.[13] There is one case report of dental implant failure associated with bisphosphonate use.[13] Marx and colleagues suggested that these patients are not candidates for dental implants because of the risk elements involved.[8] Despite these reports, Wang and colleagues recently have reported successful implant treatment in a patient treated more than 10 years with oral bisphosphonates.[10] The short- and long-term effects of bisphosphonates on dental implant osseointegration need to be established for those patients receiving the more potent bisphosphonates such as Pamidronate and Zolendronic acid.[14] The effect of osteoporosis in animal models on endosseous implant integration has been investigated recently by multiple centers.[15–17] In light of these findings, clinicians should be aware of the potential for implant failure and delayed wound healing, especially in patients receiving intravenous bisphosphonates for malignant disease.[14]

The purpose of this case series study was to report the successful implant treatments in patients submitted to long-term treatment with oral bisphosphonates owing to postmenopausal osteoporosis.

MATERIALS AND METHODS

From several implant centers in Tehran, Iran, 21 patients (treated with 46 implants) with a history of oral bisphosphonate therapy who had received dental implants between 1998 and 2006 and had provided written informed consent were asked to participate in this study. The mean age of the women was 53 years (range 42–79 years) and past medical history in all patients included postmenopausal osteoporosis, which necessitated bisphosphonate therapy. The patients were selected for this survey, treated weekly with oral bisphosphonates (Fosamax, 35–70 mg qwk) at least 2 months continuously. The mean duration of oral bisphosphonate therapy was 20.5 months. Fourteen patients started oral bisphosphonate therapy after implant surgery and subsequent healing. The remaining seven patients started bisphosphonate therapy before implant placement. In addition to the bisphosphonate therapy, all patients received calcium and vitamin D supplements for osteoporosis. The study protocol had been approved by the local ethical committee. One or more of the following conditions would have resulted in exclusion from the study: immune deficiency, a diabetic condition, head or neck radiation therapy, or anticoagulation therapy. All patients had received one or more implants on average 4.2 years prior to the study appointment (range 0.6–8.1 years). All implants (ITI, Strauman AG, Waldenburg, Switzerland) had been placed according to a transgingival unloaded healing protocol and were loaded approximately 3 to 5 months after placement. Augmentation had been necessary for implant bed preparation in five patients. Location of the implants, type of the restoration, and opposing dentition were recorded. Twelve individuals had fixed implant-supported prosthesis, and the remaining 9 individuals wore removable implant-supported prosthesis. A single calibrated examiner clinically evaluated the implants. Clinical parameters included bleeding on probing (BoP), probing depth (PD), mobility, and thread exposure (TE). These were recorded along with a conventional oral hygiene assessment and functional checkup in each patient. Probing of peri-implant pocket was carried out at four sites per implant (mesial, distal, buccal, and lingual), and the mean value was used in calculations. BoP scores were recorded dichotomously (present = 1, absent = 0). Changes in marginal bone were evaluated by measuring TE using periapical radiographs. Two sets of radiographs, one obtained after implant placement (baseline) and the other obtained during the research period (follow up), were compared to determine osseous changes. The unit of analysis was the implant itself. Months of bisphosphonate therapy before and after implant placement were recorded for each implant. The statistical analysis was performed by using statistical software (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p < .05$.

RESULTS

Table 2 shows BoP, PD, and TE of implants according to location, prosthesis type, and TE measurements, and, in all groups, there was no significant difference ($p < .05$) between bisphosphonate-treated patients either pre or post implant insertion. None of the implants showed mobility. There was no TE in 29.66% of all kind of all prosthetic options, while 6.3% showed three exposed threads. These all show that all patients could be considered free from peri-implantitis. Time of bisphosphonate therapy before and after implant insertion showed no statistically significant influence on PD, BoP, and TE ($p > .05$). Likewise, implant location, prosthetic type, and opposing dentition had no statistically significant influence on implant for the clinical and radiological parameters ($p > .05$) (see Tables 2 and 3).

DISCUSSION

Bisphosphonate drugs have now been in use for more than 10 years, and the number of patients who have used them or continue to use them is increasing. These drugs are commonly prescribed to stabilize bone loss caused by osteoporosis in millions of postmenopausal women. The strategy in the treatment of osteoporosis is to inhibit the resorption of trabecular bone by osteoclasts and hence preserve its density.[8] Although elective surgery within the jaws, such as removal of third molar or tori, periodontal surgery, or placement of dental implants, has been strongly discouraged in the literature, while delivering bisphosphonate therapy,[8] the results of this study showed that implant therapy could be a different entity. Despite the widespread use of oral bisphosphonates, a review of the literature found only one case of dental implant failure associated specifically with nonnitrogen oral bisphosphonate use. A case report from 1995 suggested that failure of five implants was caused by bisphosphonate therapy.[18] The possible suggestion is that all patients in our study had oral

TABLE 2 Distribution of Implants according to Evaluated Parameters and Months of BP Therapy

	Years of BPs Therapy after Implant Insertion					Month of BPs Therapy before Implant Insertion			
	0–1	1–2	2–3	3–4	4–5	0–9	9–18	18–27	27–36
	Implant Numbers								
Prosthesis type									
Over denture	6	4	4	4	4	6	6	6	4
Single	4	3	2	1	0	4	2	1	3
FPD	2	2	2	6	2	10	0	2	2
Implant position									
Ant. Man	2	5	1	5	4	7	2	3	5
Ant. Max	7	1	5	2	0	5	5	4	1
Pos. Man	2	3	0	2	2	5	1	0	3
Pos. Max	1	0	2	2	0	3	0	2	0
Opposing dentition									
Natural	5	4	6	3	1	11	4	0	4
Fixed	3	1	2	4	3	5	2	3	3
Removable	4	4	0	4	2	4	2	6	2
BoP = 0	7	7	5	9	4	15	6	6	5
BoP = 1	5	2	3	2	2	5	2	3	4
TE = 0	5	5	2	5	2	8	3	5	3
TE = 1	4	2	3	4	2	6	3	3	3
TE = 2	2	0	3	2	2	4	1	1	3
TE = 3	1	2	0	0	0	2	1	0	0
	3	3	2	0	0	4	2	1	1
PD = 2	4	3	1	4	3	6	2	5	2
PD = 3	2	0	4	4	1	3	2	2	4
PD = 4	2	1	1	3	2	5	1	1	2
PD = 5	1	2	0	0	0	2	1	0	0

BoP = bleeding on probing; BP = bisphosphonate; FPD = fixed partial denture; TE = thread exposure; PD = pocket depth.

bisphosphonate therapy. Osteonecrosis of the jaw probably results from the inability of hypodynamic and hypovascular bone to meet an increased demand for repair and remodeling owing to physiologic stress (mastication), iatrogenic trauma (tooth extraction or denture injury), or tooth infection in an environment that is trauma intense and bacteria laden.[19] Several studies show that effects of bisphosphonates persist for extended periods, and this could explain why osteonecrosis appears after long-term treatment and even in cases in which bisphosphonate treatment was discontinued.[9,19] This study showed that even 4-year oral bisphosphonate therapy did not result in osteonecrosis of the jaws after implant insertion.

There are reports of "spontaneous" exposures and necrosis of the alveolar bone. Most of these bone exposures reported in the literature (approximately 30%) occurred in the lingual surface of the posterior mandible, an area of thin mucosa.[9,20] Although this study showed that, even in posterior mandible, no osteonecrosis occurred, larger sample size would result in more distinct results. The jaws are the only bones in the human body that frequently become exposed into oral cavity and are subject to repeated microtrauma through the presence of teeth that could result in bone exposure.[20] The increased frequency of both osteoporosis implant patients and administration of bisphosphonates therapy within this patient group requires a better understanding by the dental community of how this disease, and specifically drug therapy, affects dental implant placement, healing, and restoration. Clinical trials should be carried out to determine the most acceptable implant treatment protocols for patients who intake bisphosphonate drugs.

TABLE 3 Overview of Clinical-Measured Parameters

	Probing Depth* (PD [SD])	Bleeding on Probing (BoP) (%)		Thread Exposure (%)			
		0	1	0	1	2	3
Over denture	2.6 (1.2)	59.1	40.9	50.0	27.3	13.6	9.1
Single	3.0 (1.2)	70	30	20.0	40.0	30.0	10.0
FPD	2.3 (1.0)	85.7	14.3	42.9	35.7	21.4	.0
p Value	**0.45**	**0.09**			**0.29**		
Ant. man	3.1 (1.1)	58.8	41.2	35.3	35.3	17.6	11.8
Ant. max	2.1 (0.9)	73.3	26.7	53.3	33.3	13.3	.0
Pos. man	2.3 (1.4)	77.8	22.2	44.4	22.2	22.2	11.1
Pos. max	3.2 (0.8)	80	20	20.0	40.0	40.0	.0
p Value	**0.05**	**0.25**			**0.46**		
Natural	2.5 (1.1)	78.9	21.1	52.6	21.1	21.1	5.3
Fixed	2.5 (1.0)	76.9	23.1	23.1	53.8	23.1	.0
Removable	2.9 (1.3)	50	50	42.9	28.6	14.3	14.3
p Value	**0.64**	**0.08**			**0.62**		
p Value (months of BP therapy after implant insertion)	**0.30**	**0.59**			**0.93**		
p Value (months of BP therapy before implant insertion)	**0.83**	**0.21**			**0.94**		

*Mean of four circular sites measured to the nearest millimeter (mesial, distal, buccal, and lingual).
BP = bisphosphonate; FPD = fixed partial denture; PD = pocket depth.

In this retrospective study, the number of patients that could fulfill the inclusion criteria seems to be not enough to extrapolate the results of this study directly to the clinical situation. Other limitation of this study was the inconsistent patient pool, as 14 patients started bisphosphonate therapy after implant installation, and only 7 patients were on bisphosphonate treatment prior to implant placement. However, the results of the study showed that the 14 patients did not have pathologic clinical and radiographic findings of implants, neither did the 7 patients. In conclusion, many issues regarding the pathogenesis of the bisphosphonate-associated osteonecrosis still remain unclear, and, at the moment, not enough data are available to prove a causal link between the use of oral bisphosphonates and osteonecrosis of the jaw. However, enough circumstantial evidence has been published to alert clinicians to be vigilant and to encourage the meticulous reporting of every occurrence of osteonecrosis, a disease with a low prevalence but a potentially high impact.

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