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Research Article

Dental Implants in Osteoporotic Patients Taking Oral Bisphophonates: A Literature Review

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Abstract

Objective: Osteoporosis is a systemic disorder characterized by generalized decrease in bone mineral density that can eventually result in fragility fracture. Bisphosphonates have been used in the treatment of osteoporosis for many years in order to inhibit bone resorption. Unfortunately, the use of bisphosphonates has been found to be associated with several adverse events in patients where dental pathologies were present. For this reason, an increased attention has been recommended in those patients where bisphosphonates have been assumed and where dental therapies are mandatory. The aim of this article is to focus on the aspects of implant therapy in patients under bisphosphonates treatment and to produce a bibliographic review of dental implants placed in osteoporotic/osteopenic patients under treatment with oral bisphosphonates.

Materials and Methods: The literature review was performed on PUBMED, MEDLINE using as search terms: oral bisphosphonates, dental implants, osteoporosis/osteopenia, osteonecrosis of the jaws (ONJ).

Conclusions: In conclusion the analysis of the studies shows that the therapy with oral bisphosphonates does not affect osteointegration of dental implants and in most cases determines a low risk of ONJ.

Keywords: Oral bisphosphonates; Dental implants; Osteoporosis/osteopenia; Osteonecrosis of the jaws (ONJ)

Introduction

Osteoporosis is a systemic skeletal disorder characterized by skeletal fragility, and macro/micro-architectural modifications [1]. Osteoporosis is one of the most common chronic diseases referred in 1/3 postmenopausal women and 1/5, men over the age of 50 years (European Parliament Osteoporosis Interest Group and EU Osteoporosis Consultation Panel 2004) [2]. For example in Europe, the USA and Japan, osteoporosis is estimated to affect 75 million people [3] ; currently, it is estimated that over 200 million people worldwide suffer from this disease, and the incidence of osteoporosis increases exponentially after the age of 50 [4] . In fact one third of women and one-fifth of men over 50 had experienced osteoporotic fractures [5,6]. The risk of hip, forearm and vertebrae fracture is approximately 40% the same as the risk of cardiovascular disease [6]. According to some authors, 40% of women [7,8] or 50% of women over 50 [9] and up to 29% of men may sustain an osteoporotic fracture. A higher prevalence of fragility fractures has been described in white populations [10], especially in non Hispanic-Caucasians [11]; lower rates have been found among black populations [10]. In Europe, the Scandinavian countries have the highest prevalence of fragility fractures [12]. Although it is widely recognized that low bone mass is not the only determinant of bone fragility, the strength of the skeleton is influenced by other bone tissue properties, collectively named "bone quality" [13,14]. The mean change of bone remodelling pattern in osteoporosis patients resulted in perforation of trabecular plates and loss of cancellous trabecular elements with consequent bone mineral density. Established risk factors for osteoporosis include older age; female gender; post-menopause; Caucasian or Asian race; a low body mass index; cigarette use; alcoholism; inadequate calcium and vitamin D intakes; physical inactivity; taking medications such as glucocorticoids and anticonvulsants; and anorexia nervosa [15,16].

The current medications approved for osteoporosis include calcium, vitamin D, bisphosphonates, parathyroid hormone, selective estrogen, receptor modulators, calcitonin, hormone therapy, denosumab and strontium ranelate [17]. Bisphosphonates 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 on the increase. These drugs are commonly prescribed to stabilize bone loss caused by osteoporosis in millions of postmenopausal women [18]. The term "bisphosphonates" is derived from the base of the drug, namely two phosphate (PO3) groups covalently linked to a central carbon. The carbon atom confers resistance to hydrolysis and allows two R side-chains to attach. The short side chain, R1 influences the chemical properties, whereas the long side chain R2 determines the mode of action and the strength of bisphosphonates. Bisphophonates inhibit osteoclasts by two mechanisms, depending on whether the R2 side chain contains nitrogen side groups. Bisphosphonates can be divided into two groups:

- The **nonaminobisphophonates** (etidronate, clodronate and tiludronate) lack a nitrogen in their side chains and are able to inactivate nonhydrolyzable ATP analogs that interfere with osteoclast activity and so induces apoptosis.

- The **aminobisphosphonates** (pamidronate, alendronate, ibandronate, risendronate and zoledronate) with nitrogen containing side groups, have four activities: inactivation of ATP; inhibition of

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farnesyldiphosphonate synthase resulting in cytoskeletal disruption, dysregolation of intracellular transport and inhibition of cell proliferation; reduction of osteoclast recruitment; and induction of osteoblast to produce an osteoclast-inhibiting factor. It is estimated that in 2010 there were approximately 700,000 prescriptions of bisphosphonates per week.

Bisphophonates are available in oral doses (daily, weekly, monthly and quarterly) and in intravenous yearly doses [17]. There are differences between bisphophonates administered intravenously and those taken orally.

Intravenous bisphosphonates

Intravenous bisphosphonates are antiresorptive medications used to manage cancer-related conditions including hypercalcemia of malignancy, skeletal-related events (SRE) associated with bone metastases in the context of solid tumors such as breast cancer, prostate cancer and lung cancers, and for the management of lytic lesions in the setting of multiple myeloma [19,20] While the potential for bisphosphonates to improve cancer-specific survival remains controversial, these medications have had a significant positive effect on the quality of life for patients with advanced cancer involving the skeleton.

Oral bisphosphonates

Oral bisphosphonates are approved for treatment of osteoporosis and are frequently used to treat osteopenia as well [21]. They are also used for a variety of less common conditions such as Paget's disease of bone, and osteogenesis imperfecta [22,23]. The most common use, however, is for osteopenia and osteoporosis [24,25].

An increase in life expectancy of the world population has been observed [26,27]. Like osteoporosis, in this context, the edentulism affects the elderly population around the world (from 11% to 44%) [28]; US data show that the number of edentulous patients in 2020 will be around 38 million people [29]. The use of dental implants constitutes a well-documented treatment-modality [30] and represents an alternative to rehabilitate these patient aesthetically and functionally and present high predictability. Success becomes more predictable when adequate local and systemic conditions are present to provide bone healing during the osteointegration process [31,32]. Since the increase of life is accompanied inexorably with the greatest chance of having bone diseases, frequently in clinical practice we might treat osteoporotic subjects with dental implants. As written above most osteoporotic patients are taking oral bisphosphonates such as alendronate, risendronate or ibandronate. Bisphosphonates treatment was first identified by Marx in 2003 as a possible contributor to osteonecrosis of the jaw, a serious dental-medical complication that is seen among individuals undergoing invasive dental procedures such as extraction and implant placement [33]. Oral surgical procedures, including dental implant placements are known to be the most relevant risk factors for the ONJ development in cancer patients taking intravenous bisphosphonates; the majority of ONJ cases reported in the scientific literature after dental implants placement and oral surgery such as dental extraction include patients receiving intravenous bisphosphonates for bone metastases and multiple myeloma [34]. Furthermore, with the introduction of nBPs, namely zoledronate (zoledronic acid), which has a powerful bone resorption inhibitor, the incidence of complications associated with intra-venous BPs has grown [35,36]. The incidence of BRONJ after dental extractions range from 1% to 11% in breast cancer patients, 3% to 17% in multiple myeloma patients, and 3% to 18% in prostate cancer patients [37,38]. Kühl, et al. selected 23 studies and reported an incidence of BRONJ equal to 0-11.5% in therapies up to one year and 0-27.5% in therapies lasting from 1 to 4 years with the use of zoledronate [36]. The current guidelines contraindicate the use of dental implants in cancer patients taking intravenous bisphosphonates [39]. Mínguez-Serra, *et al.* [40] suggested the avoidance of dental implant procedures in patients that have been receiving intravenous BPs. This is in accordance with several studies where it has been shown that the combined use of oral and intravenous BP, have determined cases of osteonecrosis [41-43].

The estimated incidence of orally administered bisphosphonates related osteonecrosis of the jaws for patient treated with weekly alendronate is 0.01 to 0.04% [44]; furthermore, when administered intravenously, bisphosphonate loads bone and accumulates in bone 142.8 times faster than when administered orally [45]. For this reason, dental implant placement is not contraindicated in patients taking oral bisphosphonates, but oral surgical procedures are considered the major risk factor of development of ONJ in patients under therapy with this drugs [46]. The aim of this article is to produce a bibliographic review of dental implants placed in osteoporotic/osteopenic patients under treatment with oral bisphosphonates.

Materials and Methods

According to our aim, a literature review was performed on PUBMED, MED-LINE using as search terms: oral bisphosphonates, dental implants, osteoporosis/osteopenia, osteonecrosis of the jaws. Our research discovered 166 papers of which these only 22, following the inclusion and esclusion criteria, were eligible for our literature review.

The inclusion parameters were:

- Studies concerning humans.
- Papers where dental implants were inserted in patients taking bisphosphonates orally.
- Papers with patients for the treatment of osteoporosis/osteopenia.
- We selected for our literature review both case series and case reports.

The esclusion paramaters were:

- Animal studies.
- Papers where dental implants were inserted in patients taking bisphosphonates intravenously.
- Papers with patients for the treatment of malignant hypercalcemia, skeletal complications suffered by patients with Paget's disease or myeloma and for the treatment of bone metastasis derived from various cancers.

Results

Following the inclusion and esclusion criteria, 22 papers were eligible for our literature review; we preferred to perform a literature

Table 1: Published studies of oral bisphosphonates and implant placement.

Author (year)	N.patients	N. implants	Failure	ONJ	Survival rate
[47]	25	102	0	No	100%
[48]	61	169	0	No	100%
[49]	115	468	2	No	99,6%
[50]	41	101	5	No	95%
[51]	11	35	5	No	86,7%
[52]	55	121	1	No	99,1%
[53]	21	46	0	No	100%
[54]	22	75	1	No	98,7%
[55]	26	56	3	No	94,1%
[56]	100	153	10	No	93,5%
[57]	235	1267	16	No	98,7%
[58]	32	98	1	No	98%

review rather than a systematic review or meta-analysis because there were many variables in the studies that we have carefully selected, represented by the number of selected patients, the number of implants placed, the follow-up period and finally the type of drug taken by patients. In the selected studies, the main complication was represented by the osteonecrosis of the jaws (ONJ); in fact we have divided the studies into two tables. The first contains all studies where there has not been this kind of complication, in the second, where it is manifested.

Discussion

As reported before bisphosphonates treatment (oral and intravenous) was identified as a possible contributor to ONJ, especially after oral surgical procedures, including dental implant placement; however, the incidence of BRONJ (bisphosphonates related osteonecrosis of the jaws) seems to be low in patients treated with oral bisphophonates. For example, in 2007, Fugazzotto, et al. published the outcome of 169 implants placed in 61 patients treated with oral bisphosphonates during an average period of 3.3 years, showed no cases of BRONJ during follow-up (12-24 months), and no implant was lost. He reported a case of bone exposure of the torus around a post-extraction implant, that closed spontaneously after four weeks [48]. Grant, et al. described a case- series of 468 implants placed in 115 patients, of which 89 took bisphosphonates orally prior to implant surgery and 33 of them for more than three years. No cases of BRONJ appeared and there were only two implants that failed to osteointegrate but of these, one patient had taken oral bisphosphonates for four years preceding surgery [49]. A large survey of 46 dentists in South Australia gathered information on about 28, 000 implants in 16, 000 patients over a 10-year period. The estimated prevalence of BRONJ in patients treated with oral bisphosphonates was 0.89% [70]. Furthermore, recent studies used oral bisphosphonates to assess the osteointegration of dental implants; some authors reported that clodronate could be useful in the maintenance of primary stability [71-73]. Zuffetti, et al. administred a 3% clodronate solution mixed with a surfactant (Tween-20) at a 1:3 ratio both at the implant surface and at the implant site, reporting that oral BPs may positively affect implant survival in the preloading and postloading phases in partially and fully edentulous patients [74].

Table 2: Published cases of ONJ after dental implant placement in patient taking oral bisphosphonates.
*The type of oral bisphosphonate is not specified by the authors.

Author (year)	Disease	Drug	Duration	N.implants
[59]	Osteoporosis	Risedronate	2.5 yr	10
[60]	Osteoporosis	Alendronate	10 yr	3
[61]	Osteoporosis	Alendronate	5,5 yr	2
[62]	Osteoporosis Osteoporosis	Alendronate Alendronate	NA NA	NA NA
[63]	Osteoporosis	OralBp*	NA	NA
[64]	Osteoporosis	Alendronate	5 yr	6
[65]	Osteoporosis	Alendronate	5 yr	2
[66]	Osteoporosis	Alendronate	9 yr	1
[67]	Osteoporosis	Alendronate	6,6 yr	1
[68] [69]	Osteoporosis Osteoporosis Osteoarthritis-Osteoporosis Polymialgya rheumatica	Risedronate Alendronate Ibandronate Risedronate	2,5 yr AVG 3,7 yr AVG 2,8yr 4 yr	1 12

Nevertheless, we must also consider the cases of implant failure and BRONJ in patients under treatment with oral bisphosphonates. For example Wang, et al. showed a case of BRONJ in one of the five mandibular implants in a patient who had taken alendronate orally for a period of more than ten years [70]. Similarly Marx, et al. reported two cases of osteonecrosis resulting from implant surgery in patients who had taken bisphosphonates orally over periods of more than three years [61]. Bedogni, et al. in 2010 published a case report where a case of necrotic bone was underlined around an implant two years after the surgery in a patient of 63 years treated with a 70 mg of alendronate weekly for about seven years [66]; but it is important to emphasize that in all cases presented the patients are taking the drug for a period exceed three years. In fact, interestingly a systematic review conducted by Kumar, et al. reported that the implant survival rates ranged between 95% and 100% in the case of bisphosphonates users and 96.5% to 99.2% in the non-users; concluding that short term bisphopshonate therapy does not increase or decrease the survival rate of dental implants in bisphosphonates users as compared to non-users [75]. In fact, several retrospective studies above cited did not find a relationship between the long term use of oral bisphosphonates and implant failure or occurrence of ONJ, but the cases above reported suggest that all the patients reported ONJ taking medications for a period exceeding four years [33,59,61,65-67]. Essentially, for patients receiving oral bisphosphonates therapy to manage osteoporosis, the prevalence of ONJ increases over time from near 0 at baseline to 0.21% after four or more years of bisphosphonate exposure . The median duration of bisphosphonate exposure for patients with ONJ and ONJ-like features was 4.4 years. For patients without ONJ, the median exposure to oral bisphosphonates was 3.5 years [76,77]. The American Association of Oral and Maxillofacial Surgeons recommendations for implant placement are [78]. For individuals who have taken an oral bisphosphonate for less than four years and have no clinical risk factors, no alteration or delay in the planned surgery is necessary.

It is suggested that if dental implants are placed, informed consent should be provided related to possible long-term implant failure and

the low risk of developing osteonecrosis of the jaws if the patient continues to take an antiresorptive agent. These concerns are based on recent animal studies that have demonstrated impaired long-term implant healing [79].

For patients who have taken an oral bisphosphonate for less than four years and have also taken corticosteroids or antiangiogenic medications concomitantly, the prescribing provider should be contacted to consider discontinuation of the oral bisphosphonate (drug holiday) for at least two months prior to oral surgery, if systemic conditions permit. The antiresorptive should not be restarted until osseous healing has occurred.

For those patients who have taken an oral bisphosphonate for more than four years with or without any concomitant medical therapy, the prescribing provider should be contacted to consider discontinuation of the antiresorptive for two months prior to oral surgery, if systemic conditions permit. The bisphosphonate should not be restarted until osseous healing has occurred.

In addition, patients with periodontal disease and dental abscesses are also at higher risk. Migliorati's study indicated that 84% of patients with BRONJ are affected also by periodontal disease [80]. Marx, et al. recommended a blood test, the serum C-terminal telopeptide test (CTX) on an empty stomach, in order to evaluate the risk of ONJ in patients who have been administered bisphophonates for longer than three years. Values obtained that are greater than 150 pg/mL permit any kind of surgery to be performed at minimum risk and without the need to suspend medication. When values lower than 150 pg/mL are obtained, then medication should cease for a period of between four and six months or an alternative treatment option involving other types of prosthesis should be sought [61]. However, the American Dental Association and others, indicate that the collagen type 1 cross-linked telopeptide may be of questionable value and is not based on strong clinical evidence [81,82], as indicated in the paper by Flichy Fernandez, et al. in which BRONJ was observed in a patient with normal values of serum CTX [67]. Furthermore even Bagan do not find a direct correlation between the level of CTX and the number and the dimension of area of BRONJ (but in case of bisphosphonates taken intravenously) [83]. Therefore the use of systemic markers of bone turnover as a measure of BRONJ risk is not recommended although the research in this area is continuing [84,85].

Conclusion

In conclusion, the analysis of the studies show that treatment with oral bisphosphonates does not affect osseointegration of dental implants and in most cases determine a low risk of BRONJ. However, more studies of dental implant placement in osteoporotic patients taking bisphosphonates orally need to establish risk assessment of this procedure in these kind patients.

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