Original Article

Influence of Oral Bisphosphonate on Dental Implant: A Review

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Abstract

Background: Bisphosphonates (BPs) are medications employed widely in the management of metabolic bone diseases. Dental implants are new therapy for replacement of missing teeth depend on the osseointegration process. There is a considerable debate on the effect of oral BPs on the osseointegration process and subsequently on the success rate of dental implant and development of BRNOJ. **Objectives:** The aim of this study was to revise literatures on the effect of oral (BPs) on the success rate of dental implants and the development of BPs-related osteonecrosis of the jaws. **Materials and Methods:** PubMed, google scholar, Scopus database, and manual search were performed to find out articles on the effect of oral BPs on dental implant outcome and development of BRNOJ. **Results:** twelve articles were found six retrospective studies, one prospective studies, two case control studies and one case series discussing the effect of oral BPs on success rate of dental implant and development of BRNOJ. **Conclusion:** the majority of patients were osteoporotic females and treated with oral BPs. Oral BPs have little, if any, influence on success rate of dental implant and there is no conclusive evidence on BRNOJ-related oral BPs in implanted patients. Patients on BPs and received implant therapy should be cautioned on developing BRNOJ and followed-up for long time period.

Keywords: BRNUJ, dental implant, oral bisphosphonate, osseointegration

Introduction

Bisphosphonates (BPs) are medications employed widely in the management of metabolic bone diseases like osteoporosis, Paget's diseases and other conditions associated with bone-lytic tumors, multiple myeloma and hypercalcemia.[1] The chemical structure of these compounds includes the replacement of oxygen atoms with those of carbon, which is similar to the naturally occurring inorganic pyrophosphate. These compounds targeted specifically bone due to a high affinity to calcium phosphate and not-completely metabolized.[2] The exact mechanism of action of such compounds are still vague, but they are known to inhibit osteoclastic activity and their differentiation from precursors, to stimulate apoptosis of osteoclasts and to change angiogenesis.[3] Due to a potential bond with bone minerals (hydroxyapatite), these compounds accumulate and remain for long time in bone and circulation after stop taking the drugs.[4] Hence, as bisphosphonates are slowly released from bone minerals, their action to suppress bone turnover continue even after cessation of therapy.[5]

One of the serious side effects of these compounds is the avascular bone necrosis of the maxilla and the mandible. By definition BP-related bone necrosis is the current or previous treatment with BPs that exposes the upper and lower jaws to the oral cavity and does not cure within 2 months of identification by oral health staff and the patient does not have a history of radiotherapy in the maxillofacial region.[6] The eight weeks period is the timetable for healing of the most surgical and infectious sites even in the presence of complications such as post-operative infection, chemotherapy, or systemic illnesses.[7] Osteonecrosis is usually affecting the upper and lower jaws due to the rapid remodeling rate of alveolar ridge and their exposure to the external environment through teeth.[8]

Dental implant is a device used to replace single or multiple missing teeth. The success rate of dental implant depends

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on the osseointegration process. This process is defined as the direct attachment between living bone and the implant surface with the capacity of bearing functional load.[9] One of the factors that influencing osseointegration process is the bone density and structure which are strongly correlated with the success rate of dental implant.

Studies revealed that BPs improve bone density around dental implants and subsequently osseointegration process.[10,11] In theory, this action could be explained by decreasing osteoblastic bone resorption and subsequent reduction in bone remodeling. However, it has been shown that people taking BPs could experience a bad prognosis of dental treatment, particularly after surgery of dental implants.[12]

The skeletal uptake of these medications could be influenced by the route of administration. It has been found that orally administered BPs are poorly absorbed and represent less than 1% of bioavailability, whereas the intravenous are totally bioavailable.[13] Therefore, the hazard of developing bone necrosis is highly attributed to I.V administration.[14] However, the incidence of BRONJ associated with oral BPs have been increased in time.[15] The most common Oral BPs that employed nowadays are alendronate, risedronate, etidronate, tiludronate.[16] Though, some BPs can be administered by oral and intra-venous routes.

The aim of this review was to investigate the literature that considered patients who received oral BPs and treated with dental implants before or after BPs therapy. These articles compared between healthy persons and those who submitted for BPs administration and the outcome of dental implants was based on failure of dental implants or the development of BP- associated osteonecrosis of the jaws (BRNOJ).

Materials and Methods

Articles on the use of oral BPs and their effect on dental implants outcome have been collected from October 15, 2020 to June, 2021. An electronic PubMed, google scholar, Scopus database and manual search were performed to collect articles and case series relevant to this review. The key words or terms used for searching the articles and case series include bisphosphonate, dental implant, oral bisphosphonate, osteonecrosis, implant failure, bone density. The inclusion criteria include original articles, studies using adult patients, articles discussed the use of oral BPs accompanied with dental implant treatment (before or after), articles published in English language. The exclusion criteria involve studies using patients under the age of 17 years and more than 92 years old, *in vitro* animal studies, systemic reviews, a sample size of less than 12 patients, studies conducted before 2005 and studies using IV BPs.

The articles were analyzed according to the type of study, number of cases/control, sex distribution, number of implants/control, age of patients, type of drug, duration of treatment, reason for treatment, implant success rate (clinically and radiographically) /control, and follow-up period.

Ethical consideration

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 111 (including the number and the date in 13/08/2020) to get this approval.

Results

Twelve original articles were chosen to carry out a review on the influence of oral BPs on outcomes of dental implant treatment. The included articles were chosen according to the inclusion and exclusion criteria of this study.

There are seven articles include retrospective studies, one prospective study, two case controlled studies and two a case series. Meta-analysis was not performed as the number of articles was low and there are variation in the implant procedure (bone graft or sinus lift) and implant numbers inserted in the upper and lower jaws. The evaluation was determined according to the outcome of implant surgery in patients under medical treatment of oral BPs and those of healthy patients. Dental implant outcomes were evaluated clinically and radiographically according to the reviewed articles and included implant failure, success rate and development of BRONJ. Details of each study are depicted in [Table 1].

Discussion

Some research indicated that oral BPs have no effect on dental implant treatment and there is no clear evidence correlates between the development of BRONJ and implant procedures.[17,18] However, others stated that these drugs could be the reason behind implant failure and the evolution of BRONJ.[19] Therefore, there is still a considerable debate on the impact of oral BPs on the dental implant therapy and the development of bone necrosis.

The majority of patients included in this review were osteoporotic females with age range 40–91 years old. Females are more submitted for oral BPs therapy after cessation of menstruation and to a greater rate of breast tumor and osteoporosis.[20] It has been shown that age, sex and early menopause among the risk factors of osteoporosis[21] and these factors are similar to those

Table 1: Summery of the studies involved in the review

N	References	Type of study	Average Age or range (years)	Sex	cases/ control	Implants no.-BPs users/ control	Reason of treatment	Duration of treatment	success rate %	Follow-up
1	Demarosi *et al*, 2010[2]	A prospective study	56 - 86 years	F=19/ M=2	21	38	Osteoporosis	6 – 144 months	95%	6 - 24 months
2	Bell and Bell, 2007[26]	A Retrospective Study	NA	F=40/ M=2	42	101	Osteoporosis	6 months - 11years	95%	4 months- 7 years.
3	Kwon *et al*, 2014[22]	A Retrospective analysis	42-85 years	F=17/ M=2	19	?	Osteoporosis & Multipl-myeloma	11-82 months	23 failures-19 cases BRNOJ	24-months
4	Memon *et al*, 2012[31]	A retrospective study	46-91 years	F=200	100/100	153/132	osteoporosis	NA	143/126 implants	NA
5	Zahid *et al*, 2011[27]	Retrospective radiographic study	17-87 mean age 56 years	F=227/ M=135	26/274	51/610	osteoporosis	NA	48/594 implants	26-months
6	Shabestari *et al*, 2010[28]	A case series	average age 53 years	all females	21	64	osteoporosis	20.5-months	100%	51.6-months
7	Fugazzotto *et al*, 2007[29]	Retrospective study	51-83	all females	61	169	osteoporosis	mean period of 3.3 years (range, 1 to 5 years)	100%	12-24 months
8	Jeffcoat, 2006[21]	Case control study	30 - 79	M=162 F= 173	335	?	osteoporosis	NA	100%	36-months
9	Yajima *et al*, 2017[32]	Retrospective cohort study	>60	F=25	11/14	25/28	osteoporosis	NA	89.9%/-100%	3.2+-1.3years/5.2+-1.2years
10	Goss *et al*, 2010[30]	A case series	65.7	NA	16.000	28.000	Osteoporosis	3-10 years	Failure rate (0.89%) BRNOJ	NA
11	Lazarovici *et al*, 2010[23]	A Retrospective study	70	M=7 F=20	27	NA	Osteoporosis Multiple myeloma Breast cancer	115 months	BRNOJ (11) 41%	3-43 months
12	Yip *et al*,. 2012[33]	Case control study	>40 years	F=337	114/223	490/691	osteoporosis	NA	66.7%	6.03 years mean

*N/A: not available information.

influence failed bone-implant integration. However, Two studies in this review[22,23] revealed that oral BPs were used for the treatment of osteoporosis, multiple myeloma and breast cancer. Oral BPs prevent bone resorption by inhibiting osteoclasts activity and bone turnover for this reason they employed as a remedy of osteoporosis and other metabolic bone disorders.[24,25] Besides, these medications enhance bone mineral density and subsequently prevent bone fracture due to osteoporosis.[15]

Most studies[2,21,26-29] in this review indicated the success rate of dental implants was ranged between 95–100%. Gross *et al*,[30] found that the failure rate of implant was 0.89% among those taking oral BPs. Others,[31,32] reported early failure of dental implant but there is no significant differences between the control groups and patients on BPs. However, Yip *et al*,[33] stated that implant success rate decreased to 66.7% in-patient taking oral BPs and most of the failures occurred in the maxilla compared with those in the mandible. Oral BPs might be beneficial for successful osseointegration, as they improve bone mineral density around dental implant.[10,11] However, such medications may affect negatively implant stability even in the absence of BRONJ, as BPs increase the amount of cancellous bone and decrease that of cortical bone.[32] Moreover, these drugs inhibit bone remodeling which is essential for healing process after surgical trauma of implant insertion.[15]

Only two studies[22,23] in this review reported the development of BRNOJ-related oral BPs in implanted patients. Kwon *et al*,[22] in their prospective study reported 19 cases of BRNOJ after implant insertion. In fact, only 3 cases out of 19 of BRONJ were regarded as BRNOJ-associated dental implants, as oral BPs were administered after implant surgery and the lesion was diagnosed 13–27 months after BPs initiation. Lazarovici *et al*,[23] identified 11 out of 27 cases of BRNOJ-associated oral BPs developed after implant surgery. Apparently, these studies revealed that bone necrosis occurred after long

course treatment of oral BPs. However, it is difficult to draw a definitive conclusion based on two studies to blame oral BPs for the establishment of BRNOJ due to implant surgery. Besides, these studies did not mention information on other drugs taken by the patients, precise doses of oral BPs and the exact time of the follow-up stage. It has been stated that the development of BRNOJ is not only associated with type, dose and duration of BPs administration, but also there are other factors such as systemic diseases, genetic factors, anatomical position,[15] smoking, corticosteroid intake and periodontal diseases.[34]

In order to explain the pathogenesis of BRNOJ-associated oral BPs due to implant surgery, Yarum and his co-workers[35] suggested that surgical trauma associated with implant insertion combined with the possible inhibition of bone remodeling may cause the development of BRONJ. In addition to that, these drugs inhibit proliferation of keratinocyte in the oral mucosa and soft tissue injury during implant placement may increase the risk of BRNOJ.[15] Jacobson *et al*,[36] stated that the presence of implant itself may contribute to the development of BRNOJ and not only the implant surgery.

It is mandatory that patients under medical treatment of oral BPs and seek dental implant therapy should be cautioned on the possibility of developing BRNOJ. Particularly, those suffering from osteoporosis, as these medications may improve bone mineral density but increase the possibility of bone necrosis. Furthermore, those patients who received implant therapy and on oral BPs should be followed-up for long time period.

Conclusion

The majority of patients treated with oral BPs were females and suffering from osteoporosis. Oral BPs exert little, if any, influence on success rate of dental implants. It is difficult to draw a definitive conclusion on BRNOJ-related Oral BPs in implanted patients. Patients under medical treatment of BPs should be cautioned on the possibility of developing BRONJ as a results of implant placement and should be followed-up for long time period.

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Conflicts of interest

There are no conflicts of interest.

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