

# Is oral bisphosphonate therapy a risk factor for implant failure?

Johan Hartshorne<sup>1</sup>

**A critical appraisal of a systematic review:** Ata-Ali J, Ata-Ali F, Peñarrocha-Oltra D, Galindo-Moreno P. What is the impact of bisphosphonate therapy upon dental implant survival? A systematic review and meta-analysis *Clinical Oral Implants Research* 2014 doi: 10.1111/clr.12526

Article accepted: 22 October 2014

Article first published online: 19 November 2014

(Origin of research –Valencia University Medical and Dental School, Valencia, Spain and Department of Oral Surgery and Implant Dentistry, University of Granada, Granada, Spain)

## Summary

**Systematic review conclusion:** The present study suggests that dental implant placement in patients receiving bisphosphonates (BP's) does not reduce the dental implant success rate. However, such patients are not without complications, and risk evaluation therefore must be established on an individual basis, as one of the most serious though infrequent complications of BP therapy is osteonecrosis of the jaw.

**Critical appraisal conclusion:** This meta-analysis indicates that exposure to oral BP's for less than 3 years may not be a risk factor for implant failure. However, the studies included in the review are mostly retrospective studies, with several limitations including bias, small sample sizes and variability amongst subjects, interventions and outcome measurement. Therefore, the clinical significance and implications of the results of this review should be interpreted with caution due to the low level of the evidence and lack of controlling and analyzing important confounding factors such as patient's age, smoking habits, poor oral hygiene, periodontal disease, dental trauma, diabetes, and obesity, that is known to influence the incidence of bisphosphonate related osteonecrosis of the jaws (BRONJ) and implant failures.

**Implications for clinical practice:** It is prudent to apply appropriate clinical judgment in all patients who are on oral BP therapy when implant placement or any other dento-alveolar surgical procedure is contemplated. A preventive approach aimed at optimizing oral health and mitigating factors such as smoking, periodontal disease, diabetes, history of cancer and cortico-steroid use that increase the risk of BRONJ or implant failure should be followed in patients using oral BP's. Patients treated with oral BP's must be given a full disclosure of risk of BRONJ and the possibility of implant loss over the long-term. It is also essential for patients receiving dental implants that are on oral BP therapy to comply with a regular recall schedule. Placing implants in patients receiving IV therapy is contraindicated at this stage of time.

## Clinical question

*What is the impact of bisphosphonate therapy upon dental implant survival?*

## Review methods

### Methodology

This study followed the *Preferred Reporting Items for Systematic Reviews and Meta-analysis* (PRISMA) guidelines.<sup>1</sup> Two reviewers independently assessed the

<sup>1</sup> Johan Hartshorne B.Sc., B.Ch.D., M.Ch.D, M.P.A. Ph.D. (Stell), FFPH.RCP (UK), Visiting Professor, Department of Periodontics and Oral Medicine, University of Pretoria, Pretoria, South Africa.

E-mail: jhartshorne@kanonberg.co.za

methodological quality of the studies using the Newcastle-Ottawa scale (NOS).<sup>2</sup> Discrepancies in the score were resolved through discussion by the reviewers.

### Search strategy and study selection

The investigators did an electronic search of the PubMed (Medline) database up until February 22, 2014. Two examiners read the titles and abstracts with no blinding carried out regarding names of authors, journals, or publication date. The references of the selected articles were reviewed to identify additional studies not found in the initial literature search. The authors also conducted a manual search of dental implant-related journals. No restrictions were placed on the year or language of publication.

### Eligibility and exclusion criteria

To be included in this review studies had to meet the following eligibility criteria: (i) subjects with a history of systemic bisphosphonates (BP) therapy (via the oral and/or intravenous route) and receiving at least one dental implant before or after BP administration; (ii) prospective or retrospective studies and case series; and (iii) studies specifying implant success rate (osseointegration).

Studies failing to specify the implant success rate, in vitro or animal studies, case reports and studies lacking a control group were excluded. The reviewers independently assessed all the articles selected from the search according to the eligibility criteria. Disagreements between the reviewing authors were resolved by consensus.

### Outcome measures and data extraction and synthesis

Implant success rate was the primary outcomes measured. Appropriate statistical tests were conducted to determine inter-study heterogeneity and publication bias. A random-effects model was used for the meta-analysis. The odds ratio (OR) with 95% confidence intervals (95% CI) was used to estimate the average intervention effect across studies. The number needed to harm (NNH) or number of implants that must be exposed to the administration of BP to cause a single implant failure, was also calculated.

### Main results

A total of 14 studies were included in the qualitative analysis of the systematic review. Of these, 8 studies were included in the meta-analysis (quantitative analysis). Two were prospective and 6 retrospective studies. Four studies were rated as having a low and four a high methodological quality.

The data set for the meta-analysis consisted of a total of 386

cases (1090 dental implants) (subjects exposed to BP) and 902 controls (3472 dental implants) (subjects not exposed to BP). Twenty-six of the 1090 implants among those exposed to BP failed (2.38%) as opposed to the 76 of the 3472 implants in those subjects not exposed to BP (2.19%). The statistical tests indicated that the studies were homogenous and that there was no evidence of publication bias.

The estimated average OR across the studies was 1.43 ( $P = 0.156$ ). This indicates that there is not enough evidence that BP's have a negative impact on implant survival. The number of dental implants that must be exposed to BP's to cause a single implant failure (NNH) was calculated at 509 dental implants. No cases of BRONJ were reported in the studies included in the meta-analysis.

### Conclusion

The study suggests that dental implant placement in patients receiving oral BP's does not reduce the dental implant success rate.

*The authors received no financial support and declared that there was no potential conflict of interest with respect to the authorship and/or publication of this review.*

### Commentary

#### Background and importance

Oral BP's are now a ubiquitous medication seen daily in practice for the purpose of treating osteoporosis in at-risk populations. Intravenous (IV) BP's are primarily used in the treatment and management of cancer-related conditions, including skeletal related events associated with bone metastases from breast cancer, prostate cancer, lung cancer, multiple myeloma, and hypercalcemia of malignancy.<sup>3</sup> Patients on oral BP's are likely to be otherwise healthy women undergoing preventive therapy for osteoporosis. On the other hand, patients receiving IV BP's for treating metastatic cancer manifest important medical co-morbidity factors such as immunodeficiency, anemia, and bleeding disorders, and concomitant multiple drug effects of chemotherapy, or corticosteroid use. The IV BP's are much more potent than the oral BP's since they include nitrogen in the molecule (i.e. zoledronate), that inhibit tumor proliferation and angiogenesis.<sup>4,5</sup>

Both oral and IV BP's bond with bone and inhibit osteoclastic bone resorption. In normal bone homeostasis, osteoclastic resorption is tightly linked to osteoblastic bone deposition and both functions are essential for healing of bone. Prolonged use of BP's may suppress bone turnover to the point that micro damage persists and accumulates.<sup>6</sup> The result is hypo dynamic bone with decreased biomechanical

competence. It is hypothesized that BP's at high doses and extended duration may affect bone remodeling by blocking osteoclasts and thus impair the bone-repairing (healing) process, which may have detrimental effects on osseointegration and long-term implant survival. An important distinction between oral and IV BP's is that oral BP's simply suppresses osteoclast function whilst IV BP's induce an apoptosis of osteoclasts that may prevent the recovery of bone metabolism after withdrawal. It is plausible that compromised blood supply, cellular metabolism, oxygenation, and immune response likely play an important role as co-factors in the osseointegration process as well as the initiation and outcome of BRONJ and therefore the survival of dental implants.

Bisphosphonate related osteonecrosis of the jaw (BRONJ) is an adverse effect of BP therapy and distinguished from other delayed healing conditions by the presence of the following three characteristics: current or previous treatment with a BP; exposed bone in the maxillofacial region that has persisted for more than 8 weeks; and no history of radiation therapy to the jaws.<sup>3</sup> Increasing age, smoking, periodontal disease, osteoporosis, obesity, diabetes and chemotherapy are important risk and co-morbidity factors in the development of BRONJ.<sup>7</sup>

In patients taking lower dose oral BP's for osteoporosis, the risk of ONJ is recognized to be extremely low (1 in 10,000 to 1 in 100,000 patients), compared to 1-2% of cancer patients receiving higher doses of nitrogen containing IV BP's.<sup>7</sup> Patients receiving IV BP's with BRONJ represent 94% of all published cases.<sup>8</sup> Although the association between BP use and osteonecrosis is established, the extent to which BRONJ is attributable to the use of oral BP's is by no means clear as it is with IV BP's. To date there is no study that has shown a cause-effect relationship between oral BP exposure and BRONJ or implant failure. Currently, controversy still exists in the placement of dental implants in patients using BP's.

The effect of long-term oral BP use on implant osseointegration remains unclear.

### Are the results valid?

The qualitative analysis of this systematic review was not considered in the critical appraisal because it contained three studies that had no controls. Only the meta-analysis was subjected to critical appraisal. Most of the studies included in this review were retrospective studies.<sup>9,10,11,12,13,14</sup> The number of studies as well as the sample sizes were too small to answer the question of interest thus leading to imprecision

of the point estimates and reducing our confidence in the estimate of the effect of BP exposure on implant failure.

The individual studies varied regarding: subjects' age included in the population of interest (BP users) and controls (non- BP users); the intervention (type of BP used – oral vs. IV BP), duration of treatment, period of BP therapy prior to implant placement and BP discontinuation prior to surgery); outcome (end point outcome 'implant failure' not objectively defined); as well as co-founders (i.e. smoking, diabetes, periodontal disease, concomitant bone grafting, and antibiotic prophylaxis). All studies, except one,<sup>15</sup> were exposed to oral BP's. The follow-up period (median = 3 years) was inadequate to answer the question of interest.

No studies have yet indicated a causal relationship between BP therapy and implant failure. Various other confounding variables may be causally associated with implant failure (i.e. periodontal disease, diabetes, obesity, smoking and use of corticosteroids) or non-causally or causally associated with BP exposure (i.e. dosage, period of medication, and discontinuation of BP). The studies included in the meta-analysis are inadequate and too small to address the confounding factors, and to produce "adjusted" OR's by means of stratification and multiple regression techniques. The question of interest in this review is not focussed and would have been more appropriate if stated as: "What is the impact of oral BP therapy upon dental implant survival rate as compared to subjects who do not receive BP therapy?"

Overall, the high level of variability, high risk of bias, lack of controlling confounding factors, and lack of precision and consistency between individual studies resulted in poor quality of evidence and therefore does not lend support to the validity of the results.

### What were the key findings?

The pooled estimate of effect for the OR was 1.43 indicating that exposure to BP's is associated with higher odds of implant failure. The OR was however statistically non-significant and clinically insignificant. The study-specific point estimates of the outcome effect (OR) varied considerably between studies thus indicating inconsistency. Three studies favoured lower odds of implant failure,<sup>10,12,16</sup> one study impartial (exposure to BP does not affect the odds of implant failure),<sup>15</sup> and four studies<sup>9,11,13,14</sup> favoured higher odds of implant failure due to exposure to BP's. Thus, given the large difference between point estimates indicating inconsistency, the more we should question the decision to pool results across studies.

All the studies presented large confidence intervals thus also

indicating a lack of precision. This could be ascribed to the small number of studies and sample sizes. Widely separated CIs flag the presence of important variability in the results. The reviewers failed to try and explain between-study variability in the results by examining the differences in subjects, BP intervention, end-point outcome measurement, and methodology.

Only one individual study<sup>11</sup> had a confidence interval not overlapping the Null value (OR = 1) thus indicating that there was a statistical significance.

The results of other individual studies included in the meta-analysis can also be considered as clinically insignificant due to small sample sizes. The odds for implant failure are likely to increase over time due to various risk and co-morbidity factors.

The number needed to harm (NNH) was calculated at 509 dental implants (81 dental implants – 95% CI lower limit). NNH is a clinically useful measure of the effort required [*number of implants that must be exposed to a risk factor (BP)*] to cause a single adverse outcome (implant failure) which otherwise would not have occurred with an intervention. For NNH, large numbers are good, because they mean that adverse events (implant failures) are rare. Small values for NNH are bad, because they mean adverse events are common. Although NNH is powerful instrument for interpreting prognostic or risk effects, they also have important limitations. First, an NNH is generally expressed as a single number, which is known as its point estimate. As with all experimental measurements, however, the true value of the NNT can be higher or lower than the point estimate determined through clinical studies. The 95% CI of the NNH are useful in this regard because they provide an indication that, 19 times out of 20, the true value of the NNH falls within the specified range (81 to 509) therefore includes the possibility of more implant failures. Such a point estimate may still have clinical importance as a benchmark until further data permit the determination of a finite CI, but clinical decisions must take this large degree of uncertainty into account. Secondly, the NNH for BP exposure in an individual patient depends not only on the nature of the treatment (oral vs. IV BP's) but also on the risk at baseline (that is, the probability at baseline that the patient being considered will experience the outcome of interest). Therefore, risk of implant failure may not be the same for all patients (i.e. bone quality, dental trauma, poor oral hygiene, smoking, periodontal disease, diabetes). In this review the limited number of studies does not allow for the NNH to be adjusted to compensate for patient's risk at baseline.

No cases of BRONJ were reported in the studies included in the meta-analysis.

### How are the results of this review applicable in clinical practice?

Good quality clinical trials with well defined end point outcomes of treatment and long-term follow-up data are not yet available to support evidence-based clinical recommendations for placing implants in patients treated with BP's. To facilitate clinical decision-making the following published guidelines are proposed.<sup>3</sup> Placing implants is not contraindicated in patients that are on oral BP therapy provided that the following principles are followed: (a) if the patient has been treated with oral BP's for less than 3 years and has no clinical risks, dental implants can be placed without altering the conventional surgical treatment; (b) if the patient has been treated with oral BP's for less than 3 years and is treated jointly with corticosteroids the prescribing provider should be contacted to consider discontinuation of the oral BP for at 3 months before implant placement, if systemic conditions permit. BP must not restarted until the bone has completely healed; (c) if the patient has taken oral BP for more than 3 years with or without corticosteroid medication, the prescribing provider should be contacted to consider discontinuation of the oral BP for 3 months before implant placement, if systemic conditions permit. The BP should not be restarted until bone has completely healed; (d) dental implants are contraindicated in patients being treated with intravenous bisphosphonates.

All patients treated with BP's must (be adequately informed of the small risk of compromised bone healing) given a full explanation of the risks of BRONJ and the possibility of implant loss over the long-term for continuing to take BP's, and informed consent must be obtained before placing dental implants. Such patients should also comply with a regular recall schedule. If systemic conditions permit, modification or cessation of oral BP therapy should be done in consultation with the treating physician and the patient.<sup>3</sup>

Clinical judgment is always essential, in patients who may require extensive invasive oral surgery, as well as those with multiple risk factors for ONJ (i.e. drug related factors: BP potency, route of administration and duration of therapy; and local and systemic factors: (poor oral hygiene, smoking, periodontal disease, glucocorticoid treatment, diabetes, immune deficiencies, obesity and history of cancer.)

### Clinical Resolution

Clinicians placing implants are especially anxious to avoid the risk of BRONJ and implant failure in their patients. Current available evidence indicates that patients using oral BP therapy are not a risk factor for implant failure.

Avoidance of unnecessary invasive dental procedures,

optimizing oral health, and mitigating cofactors identified as contributing to BRONJ and implant failure remain key factors in reducing the risk BRONJ and increasing dental implant survival rate. Sound recommendations determined from strong clinical research designs, over a longer period (5 – 10 years), are still lacking for patients taking oral BP's to enable the development of optimal care strategies for our patients.

Further research is required to answer questions such as: Do dental implants and other implant related surgical procedures increase the risk of BRONJ in patients using oral BP's? Do patients on oral BP's have an enhanced or diminished capacity for osseointegration? Do surgical technique influence the outcome of implant related surgical procedures in patients using oral BP's. The risk of BRONJ associated with long-term use (> 3 years) of oral BP's requires continued analysis and research as well as the effect of oral BP's on soft tissue and bone healing. As more data become available and a better level of evidence is obtained, these strategies can be updated and modified as necessary.

### Disclosure and Disclaimer

Dr Johan Hartshorne is trained in clinical epidemiology, biostatistics, research methodology and critical appraisal of research evidence. This critical appraisal is not intended to, and do not, express, imply or summarize standards of care, but rather provide a concise reference point for dentists to aid in understanding and applying research evidence from referenced early view or pre-published articles in top ranking scientific publications and to facilitate clinically sound decisions as guided by their clinical judgement and by patient needs.

### References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, Prisma Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Ann Int Med* 2009; 151:264-269.
2. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M,

et al. The Newcastle– Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses. 2000. Available from: [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Accessed on August 27, 2014.

3. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B. American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate –Related Osteonecrosis of the jaws – 2009 Update. *J Oral Maxillofac Surg* 2009; 67 (Suppl 1): 2-12.

4. Heymann D, Ory B, Gouin F, Green JR, Rédini F. Bisphosphonates: new therapeutic agents for the treatment of bone tumors. *Trends Mol Med* 2004; 10: 337-343.

5. Wood J, Bonjean K, Ruetz S, Bellacène A, Devy L, Foidart JM, et al. Novel anti-angiogenic effects of the bisphosphonate compound zoledronic acid. *J Pharmacol Exp Ther* 2002; 302: 1055-1061.

6. Mashiba T, Mori S, Burr DB, Komatsubara S, Cao Y, Manabe T et al. The effects of suppressed bone remodelling by bisphosphonates on micro damage accumulation and degree of mineralization in the cortical bone of dog rib. *J Bone Miner Res* 2005; 23 (Suppl): 36-42.

7. International Task Force on Osteonecrosis of the Jaw. Diagnosis and management of osteonecrosis of the jaw: A systematic review and international consensus. *J Bone Mineral Res* 2015; 30(1): 1-197.

8. Woo S-B, Hellstein JW, Kalmar JR. Systematic review: Bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 2006; 144: 753-761.

9. Bell BM, Bell RE. Oral bisphosphonates and dental implants: A retrospective study. *J Oral Maxillofac Surg* 2008; 66(5): 1022-1024.

10. Grant BT, Amenedo C, Freeman K, Kraut RA. Outcomes of placing dental implants in patients taking oral bisphosphonates: a review of 115 cases. *J Oral Maxillofac Surg* 2008; 66(2): 223-230.

11. Kasai T, Pogrel MA, Hossaini M. The prognosis for dental implants placed in patients taking oral bisphosphonates. *J Calif Dent Assoc* 2009; 37(1): 39-42.

12. Koka S, Babu NM, Norell A. Survival of dental implants in post-menopausal bisphosphonate users. *J Prosthodont Res* 2010; 54: 108-111.

13. Zahid TM, Wang BY, Cohen RE. Influence of bisphosphonates on alveolar bone loss around osseointegrated implants. *J Oral Implantol* 2011; 37: 335-346.

14. Memon S, Weltman RL, Katancik JA. Oral bisphosphonates: early endosseous dental implant success and crestal bone changes. A retrospective study. *Int J Oral Maxillofac Impl* 2012; 27: 1216-1222.

15. Siebert T, Jurkovic R, Stelova D, Strecha J. Immediate implant placement in a patient with osteoporosis undergoing patient using bisphosphonate therapy: 1- year preliminary prospective study. *J Oral Implantol* (Epub ahead of print) Manuscript number: AAID-JOI-D-13-00063R1

16. Jeffcoat MK. Safety of oral bisphosphonates: controlled studies on alveolar bone. *Int J Oral Maxillofac Impl* 2006; 21(3): 349-353.