BISPHOSPHONATE AND IMPLANT DENTISTRY – IS IT SAFE?

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ABSTRACT

Bisphosphonates are a group of drugs that are commonly used to alter bone metabolism in order to prevent bone loss in diseases such as osteoporosis and bone cancers. Unfortunately, the use of bisphosphonates has been associated with bisphosphonate-related osteonecrosis of the jaws. The debate as to whether it is wise to consider implant therapy in patients being treated with bisphosphonate therapy remains a grey area. This review will present the latest evidence and guidelines available on bisphosphonates and their possible effects on implant dentistry. The risk factors, co-morbidities, clinical presentation and findings from various imaging modalities for bisphosphonate-related osteonecrosis of the jaws are highlighted. The management of patients being treated with bisphosphonates, in whom dental implants might be considered or have already been placed, will also be discussed. Finally, the areas requiring future research are considered.

KEY WORDS
Bisphosphonate, Bone, Osteonecrosis, Implant, Osteoblast, Osteoclast, Telopeptide

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Introduction

Dental implants are a popular way to solve the problem of missing teeth due to their wide availability and success. Numerous studies have shown implants to be a predictable way to replace teeth. A review by Simonis *et al*. found the long-term implant cumulative survival rate, up to 16 years, to be 83%.[1,2]

Certain systemic disorders have been found to be a contraindication for dental implant placement, patients on bisphosphonates being one of them.[3-5] Bisphosphonates can treat a number of ailments affecting bone metabolism, hence research has centred on their beneficial effects as well as their adverse ones in periodontal and implant therapy. These drugs can be applied systemically or locally to the actual surface of the implants or implant-surrounding bone.

Bisphosphonates are bone-seeking agents with potent osteoclast disruptive properties. They gained popularity a couple of decades ago as a viable alternative to hormone replacement therapy for osteoporosis. Bisphosphonates are presently commonly prescribed for the prevention as well as the treatment of an array of malignant and non-malignant conditions affecting bone metabolism.[6]

Implant therapy and bisphosphonate

Bisphosphonate and osseointegration

Since osseointegration relies heavily on bone turnover and the behaviour of osteoblasts and osteoclasts, it follows that the action of bisphosphonate on this process could have an effect on the initial phase, thus preventing osseointegration, or even at the later stage by delaying healing, and there could be a loss of integration.

Bisphosphonate-related osteonecrosis of the jaws

Bisphosphonate-related osteonecrosis of the jaws (often abbreviated to BRONJ or BONJ) was defined in 2006 as exposed necrotic bone that has persisted for more than eight weeks, appearing in the jaws of patients treated by systemic intravenous or oral bisphosphonate, who had not received radiation in the head and neck area (Figure 1).[7]

Figure 1: The clinical appearance of the exposed necrotic bone. In this case, the potential risk factor was the extraction of the lower left first molar

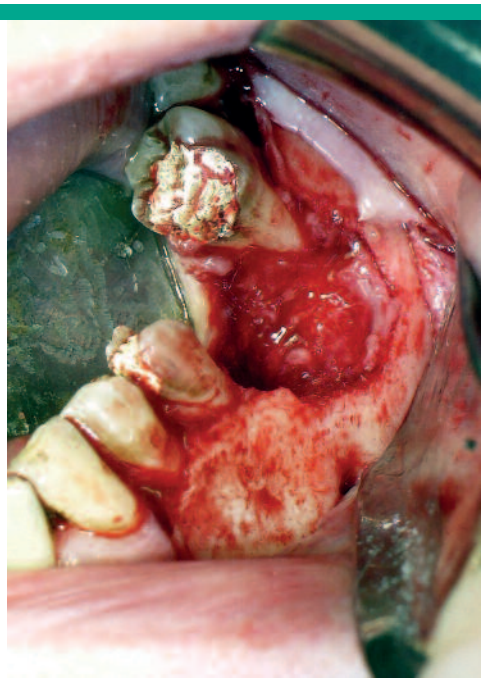

Figure 2: The socket in Figure 1 post curettage

Although the exact pathologic processes which culminate in osteonecrosis in the jaws remain elusive, it is generally accepted that there is disruption of the osteoblast-osteoclast homeostatic cycle.[8-10] The anti-angiogenic activity, which the bisphosphonates are thought to have on the endothelial cells,[11] may also play a role.

The main theories or hypotheses include excessive reduction of bone turnover, infection, impaired angiogenesis and/or toxicity to soft tissues.

Diagnosis requires clinical and radiological findings, histological analysis and blood tests.[9]

The majority of BRONJ cases occur in association with long-term bisphosphonate therapy (three to five years), so it is thought that it is time and dose dependent.[12,13]

Dentoalveolar surgery including extractions, dental implant placement, periapical surgery and periodontal surgery involving osseous injury may be considered as potential risk factors for BRONJ (Figures 1 and 2). Other risk factors should be considered, such as oral infection, poor oral hygiene, local anatomy (lingual and palatal tori) and concomitant oral diseases (oral cancer) or steroid therapy.[14]

The epidemiology of BRONJ is difficult to ascertain, although intravenous bisphosphonates are much more commonly associated with osteonecrosis of the jaws.[15] Fresco et al.[16] observed in their review that more women, especially those over 55 years of age, suffered from osteonecrosis. The intravenous high potency drugs pamidronate and zolendronate most commonly showed a correlation with the occurrence of osteonecrosis, 94% of BRONJ patients have been administered either or both these drugs.[6] The incidence of intravenous bisphosphonate-related BRONJ is estimated at around 3–11%.[5] Looking at individual bisphosphonates, zoledronate showed an incidence of BRONJ of 9.4–10%, whereas in pamidronate patients this incidence was 4–14.3%.[9-17]

Orally administered alendronate, ibandronate, and risedronate, were also shown to be associated with osteonecrosis, although this was less common.[9,18] Estimates for orally administered bisphosphonate vary from 1 in 10,000 to less than 1 in 100,000 persons per year's exposure,[7] but this may be an underestimation due to poor reportage of cases. Additionally, in 2007, the Advisory Task Force on BRONJ[7] estimated the incidence of orally-administered bisphosphonate BRONJ cases in the range of 0.01–0.04%.

Oral bisphosphonate and implant surgery

Madrid and Sanz[19] carried out a systematic review in 2009, to study what impact bisphosphonates had on implant therapy. Unfortunately, due to limited quality, inconsistent outcome

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variables and heterogeneity of the studies retrieved by their search, a meta-analysis was not viable. The studies were all regarding oral bisphosphonate. They also searched current guidelines and recommendations.

Case reports[5,20] have shown implant failure in oral bisphosphonate patients.

Regarding the guidelines/ recommendations, all are based on very low evidence, and general agreement is as follows[21]:
Dental implants are contraindicated in cancer patients taking intravenous bisphosphonate. Dental implants are not contraindicated in non-cancer patients under oral bisphosphonate (usually for osteoporosis).[21]
(Carefully consider alternative treatment modality.)

A recent review[22] found that compared to other invasive potential BRONJ-inducing procedures, there was a low occurrence of BRONJ in patients undergoing implant therapy.

Rationale for drug holidays

Due to the persistence of bisphosphonate for years after withdrawal, the effect of bisphosphonate and BRONJ risk can be present well beyond treatment duration, hence stopping the drug prior to any procedures associated with risk of BRONJ may be fruitless, especially if intravenous bisphosphonate has been used.[23]

Nevertheless, the American Association of Oral and Maxillofacial Surgeons (AAOMS)[24] has attempted to divide oral bisphosphonate patients into two risk groups: low (<3 years) and high risk (>3 years or <3 years but concurrent corticosteroid treatment).

AAOMS have suggested the following protocol:
Drug holiday for three months before, and three months after implant therapy (assuming this is feasible considering the systemic health of the individual) is recommended in high risk patients.[25]

TABLE 1
CTX LEVELS AND INTERPRETATION/ RECOMMENDATIONS FOR PATIENTS TAKING ORAL BISPHOSPHONATE[25]

CTX plasma levels	Interpretation of results
>300 pg/ml	Normal[13]
>150 pg/ml	Minimal BRONJ risk-surgery possible
>150 pg/ml	Minimal BRONJ risk-surgery possible
<150 pg/ml >100 pg/ml	Moderate BRONJ risk-defer surgery and implement drug holiday until CTX>150
<100 pg/ml	High BRONJ risk-defer surgery and implement drug holiday until CTX >150

C-terminal telopeptide (CTX) blood test

Osteoclasts involved in bone resorption cleave this C-terminal telopeptide from the main cross-linked collagen chains. As a result, the blood levels of this peptide is proportional to osteoclastic activity and is a specific marker of bone turnover and therefore healing.[26]

CTX levels will be lower in patients taking bisphosphonates, and the dose and drug therapy duration affects these levels. Conversely, terminating drug therapy will gradually lead to elevated CTX levels. Therefore there is great potential in this area of research and this test may be able

Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. J. Pharmacol. Exp. Ther. 2002;**302**:1055–61.
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to assist practitioners in risk assessment regarding implant placement, as it could give a measure of the response of osteoclasts to bisphosphonate therapy and therefore quantify the risk of BRONJ.[5,13]

Management of patients under bisphosphonate

BRONJ is notoriously difficult to treat, be it caused by oral or intravenous bisphosphonates, because it does not respond predictably to standard surgical treatment. Marx *et al*.[9] have stated that it is not possible to completely prevent BRONJ and it has also been recommended that because of this, all surgical procedures should be completed before commencing with bisphosphonate therapy.[27] But with implants it is very difficult to predict what might happen even if they are placed before bisphosphonate administration, and there is an increasing chance of problems developing with more prolonged use of these drugs, including oral bisphosphonates.

It has not been conclusively decided whether it is wise to place implants prior to the commencement of bisphosphonate therapy, although current evidence, albeit minimal,[28] suggests that BRONJ is less likely in this category compared to implants placed after the start of bisphosphonate therapy.

For oral bisphosphonates, the three-year segregation,[24] although useful, is probably too general and needs to be judged on an individual level, hopefully with the eventual help of the CTX test.

The American Dental Association (ADA) emphasises the importance of regular maintenance in order to prevent peri-implantitis with repeated initial phase therapy when needed, and if no response, surgical revision of soft tissues and possibly modest bone recontouring.

Emergence of new and alternative anti-resorptive drugs

The United States Food and Drug Administration (FDA) approved Denosumab as an anti-resorptive drug in 2013. It is administered subcutaneously or intravenously to treat osteoporosis, bone malignancies or metastases. Receptor activator nuclear factor kappa-B ligand (RANKL) is a protein that acts as the primary signal for bone removal. In bone loss conditions it overwhelms our body's defences against aberrant bone destruction. Denosumab and similar anti-resorptive drugs work by inhibiting RANKL, thus preventing bone resorption and renewal. These drugs should be treated with the same amount of caution as bisphosphonates when considering implant therapy.[29]

Future scope for research

- More specific information to determine time-dose relations for bisphosphonate and the associated newly emerging anti-resorptive medication.
- Standardised criteria for the diagnosis of BRONJ.
- Clarification of risks predisposing to BRONJ development, for example bone replacement grafts prior to implant placement or peri-implantitis.
- More research regarding CTX tests and drug holidays and their efficacies in prevention of BRONJ or implant loss.
- Identification of individual variation on drug response so that a predictable risk assessment might be performed.
- Creation of evidence-based guidelines for dental implant placement in patients being administered anti-resorptive drugs via an easily accessible, user-friendly, centrally reported databases on properly documented BRONJ cases.
- More research relating to long-term effects of oral bisphosphonates on implant failure.

Figures 1 and 2 by kind permission of, and with grateful thanks to, Julian Yates, Professor of Oral and Maxillofacial Surgery and Implantology, School of Dentistry, The University of Manchester.

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