

# The Nature and Frequency of Bisphosphonate-Associated Osteonecrosis of the Jaws in Dental Implant Patients: A South Australian Case Series

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**Purpose:** To determine the number of bisphosphonate-associated cases of dental implant failure in South Australia.

**Materials and Methods:** All general and specialist dentists who place dental implants in South Australia were contacted and asked to provide information on the total number of implants placed over the decade to December 2007. Cases of bisphosphonate-associated implant failure were identified.

**Results:** All 46 practitioners involved in implant placement and the management of bisphosphonate-associated osteonecrosis of the jaws in South Australia were identified. Approximately 28,000 implants had been placed in 16,000 patients. We identified 7 cases of oral bisphosphonate-associated implant failure, with 3 cases of failure of osseointegration and 4 cases of successful implants losing integration after being placed on oral bisphosphonates. There were 5 women and 2 men, and the mean age was 65.7 years (range, 49-75 years). Only 1 was medically compromised, with steroids and diabetes. No cases of implant failure in intravenous bisphosphonate cases were identified. On the basis of the assumption that 5% of the patients were taking an oral bisphosphonate, 1 in 114 (0.89%) had implant failure.

**Conclusion:** In patients taking oral bisphosphonates, a failure to integrate or subsequent loss of integration may occur when oral bisphosphonates are started after successful implant placement. The rate of failure is low, at less than 1%.

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*J Oral Maxillofac Surg* 68:337-343, 2010

There is controversy as to whether it is safe to place implants in patients taking bisphosphonates for bone diseases. On the one hand, case reports of patients taking bisphosphonates who either had implants that failed to integrate or had integrated implants that subsequently failed have been reported.<sup>1-3</sup> Conversely, studies with moderate numbers of consecutively placed implants in patients taking oral bisphosphonates, albeit for relatively short periods of time, have

reported that no problems developed.<sup>4,5</sup> This issue of bisphosphonate-associated implant failure is clearly not a simple matter but is a complex inter-relation with the bisphosphonates and their effects on the jaws interacting with implant integration and the maintenance of integration mechanisms.

Bisphosphonates have been widely prescribed over the last decade for a range of bone diseases, mainly intravenously for bone cancers and orally for osteo-

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0278-2391/10/6802-0017\$36.00/0

doi:10.1016/j.joms.2009.09.037

porosis.<sup>6</sup> The initial data on their effectiveness and safety were impressive, with studies involving a minimum of 20 million patient-years not showing any jaw-related problems. However, in 2003 a number of reports appeared in the United States<sup>7-9</sup> and Australia<sup>10</sup> of osteonecrosis of the jaws (ONJ) in patients mainly taking intravenous bisphosphonates. The Australian report, however, concerned patients who had been taking oral bisphosphonates for long periods of time.<sup>10</sup> Bisphosphonate-associated ONJ is defined as an area of exposed bone of more than 8 weeks' duration in a patient taking a bisphosphonate for bone disease. Exclusions include the presence of malignancy at the site of the jaw bone exposure and patients who have had radiotherapy to the jaws. Bisphosphonate-associated ONJ may range from a painless prolonged healing to a seriously painful and debilitating condition that lasts for many years without resolution. Treatment is difficult, and conventional surgical treatment for microorganism osteomyelitis of the jaws or osteoradionecrosis of the jaws fails in cases of bisphosphonate-associated ONJ. Indeed, surgical curettage usually makes ONJ worse. Successful strategies include cessation of the bisphosphonate with symptomatic treatment with mouth rinses and antibiotics as indicated, and this may resolve the condition over many months or years.<sup>11</sup>

Bisphosphonate-associated ONJ has been extensively investigated since 2003, with considerable progress having been made on its nature, frequency, and management. Although it is still controversial as to precisely how the bisphosphonates work, generally it is accepted that they prevent osteoclast action, with consequent cessation of osteoblast activity, so that the bone turnover is markedly reduced or ceased; there are also reductions in angiogenesis.<sup>11-13</sup> In the long bones and spine these actions have the desired effect of progressively increasing the density of osteoporotic bone back toward a more normal structure. With bony malignancy, the bisphosphonates prevent progressive bone resorption, thus reducing extension of the bony metastasis and decreasing pain.

Bisphosphonates have similar effects on the jaw bones, but given that the bone turnover of the alveolus is up to 10 times greater than that of the long bones, there is a more marked reduction in bone turnover.<sup>11,13</sup> There are also differences in the nature of jaw osteoclasts as compared with the long bones, and lastly, the jaw bones are covered by a thin layer of mucoperiosteum from the bacterially infested oral cavity.<sup>11,13</sup> When simple oral wounds such as extractions occur, bacteria can freely enter into the socket and the bone is unable to react, thus triggering ONJ, which always commences at the alveolus.<sup>11,13</sup>

In a large Australian study, the frequency of ONJ occurring after extractions was estimated at 1 in 296

to 1 in 1,130 extractions in patients taking oral bisphosphonates.<sup>14</sup> The rate of ONJ is much higher in patients receiving intravenous bisphosphonates and has been calculated as occurring in 1 of every 11 to 15 extractions. The original data for this study have subsequently been externally audited and confirmed.<sup>14</sup> Similar results have been subsequently shown in other studies.<sup>15,16</sup>

Dental implants have revolutionized the management of tooth loss, and they have been shown to have a high rate of success when technically correctly implanted into the jaws.<sup>17,18</sup> Although the success rate varies with the position in the jaws and whether ancillary procedures are performed, the success rate is generally 95% or better. The successful integration of an implant to the jaw bones involves 3 phases, the first being osteoconduction, which relies on the recruitment and migration of osteogenic cells to the implant surface. The second healing phase is the formation of new bone at the junction between the pre-existing bone and the implant. These 2 healing phases, osteoconduction and new bone formation, result in contact osteogenesis against the implant surface. There is a third healing phase of bone remodeling, which essentially involves renewal of the bone and its contact to the implant surface.<sup>19</sup> Given that bisphosphonates significantly reduce bone turnover, it is not surprising that a patient taking bisphosphonates may have a problem with integration occurring in the first phase or, if the implants are already successfully integrated, then there can be a marked delay in bone healing and thus the potential for loss of integration to occur. Accordingly, from this brief review, it is apparent that for some patients whose alveolus is affected by bisphosphonates, implants will either fail to integrate or subsequently lose integration.

The main difficulty with studies on this issue is obtaining a large enough prospective sample to determine the rate of failure. Statistically, if an adverse event occurs at a rate of 1 in 100 and one requires a statistical level of significance of  $P = .05$ , then a very substantial number is required, over 10,000 patients, in each arm of the study to obtain statistical significance. Studies of this size are not possible in a single center. However, in a population sense the low risk will result in a large number of cases because the number of individuals taking bisphosphonates is high. In Australia approximately 5% of the population is taking bisphosphonates. An alternative strategy to prospective studies is to retrospectively review a large number of implant cases and determine the number with bisphosphonate-associated failure. This requires the ability to capture all of the patients involved in a defined location so that one can reliably determine risk. South Australia has a number of unique features that make such a study possible. Al-

though the state is large, 2.4 times the size of Texas, the population is small, at 1.6 million persons.<sup>20</sup> Seventy-five percent of the population resides within 20 km of the central business district of the state capital of Adelaide.<sup>20</sup> All major health centers, including all the dental specialists, are in Adelaide. The dental profession is cohesive and has a strong tradition of continuing education. The nearest other metropolitan centers of dental specialists are Melbourne, which is 605 km to the east, and Perth, which is 2,134 km to the west. The smaller regional towns either lack specialists or have visiting specialists from the metropolitan centers.

The aim of this study is to determine the total number of implants placed in South Australia and to determine the number of bisphosphonate-associated failed implant cases; by this means, the frequency of the adverse event can be reliably calculated.

## Materials and Methods

A postal questionnaire was sent to all of the oral and maxillofacial surgeons, periodontists, prosthodontists, and general dental practitioners with large implant placement practices in South Australia. The questionnaire consisted of a cover letter describing the nature and purpose of the study and requested information on the total number of implants placed, in particular over the last decade or longer if known by the participants. They were also asked to provide details on any potential cases of bisphosphonate-associated implant problems. The study was also discussed at local specialist meetings.

The questionnaire was followed up by direct personal contact, and the case records of the potential bisphosphonate-associated implant problems were reviewed. The identified patients were also interviewed and data were obtained from their general dental and medical practitioners as required.

The data were recorded on a standalone personal computer, and appropriate statistical calculations made. The study had the ethical approval of our institution.

## Results

Forty-six dental practitioners were identified as placing more than 50 implants per year in South Australia and/or were likely to see and treat patients with bisphosphonate-associated ONJ. All fully cooperated with the study, and there were no exclusions. Six of the implantologists had been placing implants for over 2 decades, but most had been active mainly in the last decade. Records range from standalone full implant databases to the patients' general records.

The latter cases were cross checked against implant purchases and fee records.

The total number of implants placed was approximately 28,000 implants in 16,000 patients. The number of implants was informally confirmed as being consistent with industry records from implant suppliers to South Australia.

Initially, 12 patients were identified as having bisphosphonate-associated problems, but 5 were excluded after investigation because either they were duplicates or they were not taking a bisphosphonate in the relevant period. Seven cases of bisphosphonate-associated implant failure were identified; these are described in Table 1 and Figures 1, 2, and 3. There were 5 women and 2 men, and the mean was 65.7 years (range, 49-75 years). One was immunocompromised, with steroids and diabetes, but the others were healthy with only minor medical comorbidities. Three were taking bisphosphonates at the time of implant placement, although this had not been either known or considered significant by the implantologists. In these 3 the implants failed to integrate; it was only at this point that the significance of the bisphosphonate was appreciated by the implantologist in 1 case. In the other 2, the patients first noted the connection. One heard a radio interview about bisphosphonate-associated implant problems, and another realized the significance of her medication when she was discussing her problems with a friend who had a health background.

Four patients had successfully integrated implants placed before they were diagnosed as having osteoporosis. They were medically prescribed an oral bisphosphonate, and some of their implants subsequently lost integration and failed. In the case of the immunocompromised patient, who was a medical practitioner, he self-diagnosed the cause of the problem. The failure occurred within 12 weeks of when the patient began taking the bisphosphonate, when the implant fell out. However, he had had minor problems with the implant before the commencement of the bisphosphonate. The others were slow, progressive failures, and it took some time for the true nature of the problem to be determined. None of the medical practitioners who prescribed the bisphosphonates were aware that the patients had implants or that there potentially may have been a problem. When the implant showed problems, 6 of the patients underwent attempts by the implantologist to salvage the implant by surgery and antibiotics. Two had aggressive bone grafting procedures. All of the attempts at salvage failed and indeed hastened the loss of the implants.

Three patients had been taking alendronate for over 3 years, with a mean of 5.2 years (range, 3-10 years), and one who was immunocompromised had

**Table 1. DETAILS OF BISPHOSPHONATE-ASSOCIATED CASES OF DENTAL IMPLANT FAILURE**

Patient	Age (yr)/gender	Medical Status	Bone Disease	Bisphosphonate	Total No. of Implants	No. of Failed Implants	Reason for Failure	Treatment	Outcome
Failed to integrate 1 (Fig 1)	49/F	Fit	Osteoporosis	Alendronate for 5 yr	1 sinus lift, partially integrated, bone graft	1 (left first maxillary molar), oronasal fistula	ONJ on 1 surface, integrated on other 3 surfaces	Implant eventually removed	Pain and recurrent infection for 3 yr, resolved at present; had successful placement of 2 implants subsequently
2	70/F	Fit	Osteoporosis	Risedronate for 5 yr	5	1 (right maxillary lateral incisor)	Failed to integrate	Removed	12/12 healed
3 (Fig 2)	62/F	Fit	Osteoporosis	Risedronate for >6 yr	1 delayed healing implants	1 (left mandibular central incisor)	Failed to integrate, localized ONJ	Removed	12/12 healed
Integrated 4 (Fig 3)	66/F	Fit	Osteoporosis fractures	Alendronate for 3 yr	8 in maxilla and mandible	2 (left mandibular second premolar and molar), left mandible lost integration	Extensive ONJ	Two attempts at surgery with antibiotic cover	Pain for 3 yr, resolved at present
5	75/F	Fit	Osteoporosis	Risedronate for 10 wk, previously alendronate	1 crown lost after integration for 20 yr	1 (left mandibular third molar) loose, removed, and did not heal	Localized ONJ, localized sequestrum	One attempt at surgical salvation	Healed over 3 mo
6	68/M	Diabetes, taking steroids	Osteoporosis fractures	Alendronate for 12 wk	1 integrated for 15 yr	1 (left mandibular second premolar)	ONJ, implant fell out	NI	Healed over 3 mo
7	70/M	Fit	Osteoporosis fractures	Alendronate for 10 yr	2	2 (left mandibular canine and right mandibular canine)	Implants fell out	Removed	Healed slowly, bisphosphonate stopped, and 5 further implants were placed and integrated

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**FIGURE 1.** Computed tomography scan in case 1. A hydroxyapatite-coated implant was placed in the left maxillary first molar site with sinus lift and autogenous bone. It failed to integrate at the buccal site with oronasal communication. It was integrated on the palatal side. Two attempts at surgical salvage made the situation worse.

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been taking alendronate for only 12 weeks. Two had been taking risedronate for 5 years each. One had been taking risedronate for 10 weeks but previously had been taking alendronate for approximately 5 years, with a gap to when the risedronate was started. No patients were receiving intravenous bisphosphonates.

The calculated rate of implant failure in the whole group is 1 in 2,286 patients (0.04%). On the basis of the assumption that 5% of the population was taking bisphosphonates, the calculated rate of implant fail-

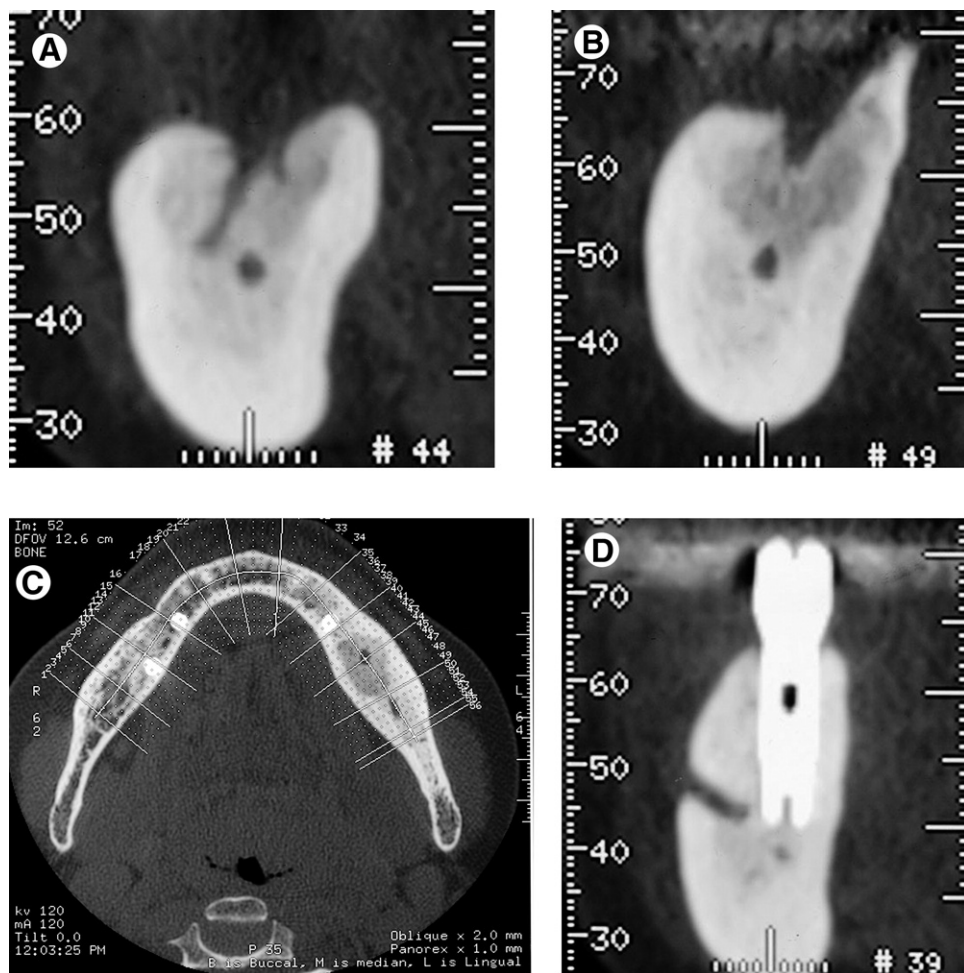


**FIGURE 2.** Computed tomography scan in case 3. A titanium implant was placed in the left mandibular first incisor site. It failed to integrate and was painful. One attempt at surgery made the situation worse. The implant was removed with light finger pressure.

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**FIGURE 3.** A, Computed tomography scan in case 4, with previously integrated implant in the left mandibular second premolar site. It was removed with light pressure. Imaging showed the implant defect and surrounding ONJ. B, Previously integrated implant in the left mandibular second molar site, which was removed with light pressure. Imaging showed the implant defect and surrounding ONJ, which was continuous with the left mandibular second premolar site. C, Extent of ONJ in left mandible. D, Implant in the left mandibular first premolar site. It was mobile but attached. The dense surrounding bone should be noted. The implant unloaded, with borderline integration.

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ure for patients taking oral bisphosphonates is 1 in 114 (0.89%). This is higher than the rate for dental extractions.<sup>14</sup>

## Discussion

The study shows that there is a risk of failure of implants related to oral bisphosphonates. This may occur either when there is a failure to integrate when implants are placed in patients taking oral bisphosphonates or when there are existing integrated implants and the patient subsequently prescribed begins taking oral bisphosphonate for osteoporosis. The risk is relatively low, less than 1%, but is devastating to the patient. The study also helps explain the dichotomy between the few reported cases of bisphosphonate-associated implant failure and prospective studies that have not shown evidence of problems.<sup>4,5</sup> This highlights the difficulty of developing a study of sufficient power when the frequency of the problem developing is low. However, there are large numbers of patients in our aging population having both osteoporosis and implant placement for tooth loss. Implant loss and ONJ are devastating to the individual.

There was full cooperation from all implantologists in South Australia with the study to capture the required data. The numbers were independently cross checked by contact with the involved practitioners, and the numbers of implants placed were informally confirmed as being consistent with industry sales. Any patient with a bisphosphonate-associated implant problem was identified and the details authenticated by discussion with the patient and his or her various medical and dental practitioners.

As a group, the patients were all orally conscious, one was a medical practitioner, one was the sister of a dentist, and all had had successful occupations. All had invested considerable time and finance in their general oral and implant state of health. All were aggrieved with the implant failure and in particular were concerned that neither the dental nor medical practitioner had warned them that potentially there was a problem.

The main weakness of the study is that the number of patients who had implants and were taking bisphosphonates was not precisely known; thus the Australian community figure of 5% was used.<sup>14</sup> Given that the target population for implant placement is

older, wealthy, and more oral and general health conscious, the figure of 5% is probably an underestimation because the key group taking oral bisphosphonate is also older and health conscious. Currently, in our practices, the percentage of patients taking bisphosphonates presenting for possible implant treatment is higher than 5%. On informed-consent discussions with the patient, the percentage decreases for those who actually proceed to having implant placement. Strategies, besides considering the oral bisphosphonate as an absolute contraindication, include having the patient re-evaluated medically as to the need for the bisphosphonate treatment or whether he or she can be managed alternatively.<sup>21</sup> The serum beta cross laps test measures bone turnover and is a predictor of the risk of decreased bone turnover and ONJ.<sup>22</sup> It is independent of the other risk factors, such as age, medical compromise, and duration of bisphosphonate dosage. If the patient continues to take a bisphosphonate, then the dosage could be adjusted so that the bone turnover is kept around 200 pg/mL and both the patient's osteoporosis is being controlled and osseointegration is not being interfered with. This, however, has not been shown in a prospective clinical trial. In this study 2 patients had serum beta cross laps testing at the time of implant failure (patients 3 and 4). Both had values of less than 100 pg/mL, which indicates little or no bone turnover.

The main problematic group is patients who have successfully integrated implants but in whom osteoporosis then develops, who have not consulted with their implantologists, and are prescribed oral bisphosphonates by their medical practitioner. If the medical practitioners remember to enquire as to whether the patient is dentally healthy, then reasonably the patients could respond in the affirmative. Given that the main difficulty is making medical practitioners even consider the patient's oral health, it is currently probably unrealistic to make them ask about the presence or absence of dental implants.<sup>23</sup>

The conclusion of this study is that there is a small risk of additional implant failure for patients taking bisphosphonates, over and above the other factors involved in dental implant failure. The treating implantologist should give the patient complete information on the risks before implant placement. This study provides guidance on the magnitude of the risk. When implants either fail to integrate or lose their integration, the medical history of the patient needs to be taken again and in particular the history of bisphosphonate use checked. This should be done before attempts at salvage, because conventional salvage techniques are likely to fail in patients taking bisphosphonates. Consideration should be given to changing the management of the patient's osteoporo-

sis. If, with appropriate medical advice, it is possible to cease the bisphosphonate and change the strategy, then future implants are not contraindicated. Once a bisphosphonate has been eliminated from the system to an appropriate clinical level and bone turnover has returned to a reasonably normal rate, then it is possible to consider placing further implants. This strategy was followed for 2 patients (patients 1 and 7) in this study.

Overall, given the low rate of failure of less than 1% and given that the general failure rate for implants is on the order of 5%, osteoporosis being treated with oral bisphosphonates is a relative rather than absolute contraindication to implant placement.

### Acknowledgments

The authors acknowledge the statistical advice of Dr Toby Hughes, Statistician, The University of Adelaide, and the partial financial support of the Australia & New Zealand Association of Oral and Maxillofacial Surgeons Research and Education Fund.

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