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Factors associated with osteonecrosis of the jaw among bisphosponate users

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Abstract

Background—Bisphosphonates are medications that impact bone reformation by inhibiting osteoclast function. Osteonecrosis of the jaw has been reported among patients receiving these medications. It is unclear if the risk factors associated with osteonecrosis of the jaw among cancer patients taking bisphosphonates are also possible risk factors among patients receiving these medications for other indications.

Methods—A systematic review search strategy was used to identify cases of osteonecrosis of the jaw among patients taking bisphosphonates for an indication other than cancer to identify potential contributing factors. Data were analyzed according to previous models to develop a more expanded model that may explain possible mechanisms for the development of osteonecrosis of the jaw among patients without cancer.

Results—Ninety-nine cases of osteonecrosis of the jaw were identified among patients who were prescribed a bisphosphonate for an indication other than cancer. These cases included 85 osteoporosis patients, 10 patients with Paget's disease, two patients with rheumatoid arthritis, one patient with diabetes and one patient with maxillary fibrous dysplasia. The mean age was 69.4 years, 87.3% were female, and 87.6% were receiving oral, but not intravenous, bisphosphonates. Of the 63 patients reporting dental care information, 88.9% had a dental procedure prior to the onset of osteonecrosis of the jaw. Of all cases providing medical information, 71% were taking at least one medication that affects bone turnover in addition to the bisphosphonate, and 81.6% reported additional underlying health conditions.

Conclusions—The case details suggest a multiplicity of factors associated with this condition and provide the foundation for a model outlining the potential mechanism for the development of osteonecrosis of the jaw among patients taking bisphosphonates for an indication other than cancer.

Keywords

bisphosphonates; osteonecrosis of the jaw; osteoporosis; Paget's diesase

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Introduction

Bisphosphonates impact bone reformation by the inhibition of osteoclast function and are currently used to treat hypercalcemia of malignancy, bone metastases, Paget's disease, and osteoporosis. However, widespread use of bisphosphonates has been curbed by reports of osteonecrosis of the jaw among both cancer and osteoporotic patients receiving these medications. Although direct causation has not been established, the associated risk has been deemed sufficient for the U.S. Food and Drug Administration (FDA) and drug manufacturers to include risk of osteonecrosis of the jaw in bisphosphonate package insert materials.

Osteonecrosis of the hip, knee, jaw or other bones affects approximately 20,000 people per year.[1,2] Osteonecrosis of the jaw has been reported as a rare complication of bone disorders and phosphorus exposure since the 1830s;[3] however, many incident cases may have been underreported over the years until it was noticed that osteonecrosis of the jaw was occurring among some patients receiving bisphosphonates.[4]

Hundreds of cases of osteonecrosis of the jaw have been reported to national adverse event reporting systems. Approximately 94% of reported cases among bisphosphonate users have occurred among cancer patients who receive the more potent intravenous bisphosphonate formulations.[5] Incidence estimates of osteonecrosis of the jaw vary considerably, from 1 in 1,260 to less than 1 in 100,000 osteoporosis patients.[6, 7] Among those undergoing dental procedures, incidence may range from 1 in 296 to 1 in 1,130.[6, 7] Recent prevalence studies show that approximately 10–50% of cases of osteonecrosis of the jaw occur among bisphosphonate users, while 50–90% of cases occurred in the absence of these medications.[8, 9]

Equivalent rates of osteonecrosis of the jaw were shown among the bisphosphonate-treated as compared to the control population in a randomized zoledronate trial of 3,889 osteoporosis patients.[10] The potential preventive effects of bisphosphonates are important; therefore, we have the responsibility to fully understand the attribution of side effects such as osteonecrosis of the jaw so that the risk to benefit ratio can be accurately represented to patients without cancer as well as to cancer patients. This knowledge will help to identify appropriate candidates for preventive care who stand to receive the most benefit with the least risk based on the presence or absence of risk factors for osteonecrosis of the jaw.

Although osteonecrosis of the jaw is known to occur to some in both patients who have received bisphosphonates as well as those who have never been exposed to these medications,[10, 11] it is unclear which patients may be at greatest risk. Recent oral surgery, tooth extraction, denture use, and poor oral hygiene are factors that have been implicated in osteonecrosis of the jaw among patients taking bisphosphonates.[12–14] Other risk factors for osteonecrosis of the jaw have been proposed and may include diabetes, co-morbid conditions, and steroid use.[15, 16]

Osteonecrosis in general has been associated with a wide variety of factors including advanced age, arthritis, chronic inactivity, corticosteroids, estrogen, female sex, hemodialysis, thrombophilic disorders, hyperlipidemia, hypertension, infection, and many other disorders.[13,17,18] Published models of the possible contributing factors for osteonecrosis of the jaw have focused on issues related to bisphosphonate use in cancer populations, but may be useful to guide the exploration of potential contributing factors in patients taking bisphosphonates for indications other than cancer as well.[13, 19]

This study was designed to identify cases of osteonecrosis of the jaw in patients taking bisphosphonates for an indication other than cancer to identify potential contributing factors that may be unique to this population. Data were collected using a systematic review strategy to obtain information related to previous models of osteonecrosis of the jaw among cancer

patients (Figure 1) and prior suggested risk factors.[13, 17, 18] The goal was to develop a model that may explain possible mechanisms for the development of osteonecrosis of the jaw in patients with no history of cancer who receive bisphosphonates.

Methods

A systemic review was conducted to identify cases of osteonecrosis of the jaw among individuals receiving bisphosphonates for an indication other than cancer. The search included articles published from January 1996 through October 2007. Prior reviews[16, 20–22] were used to identify cases that may have been published prior to 1996. The MedLine search strategy included any of the following terms: bisphosphonate, risedronate, ibandronate, alendronate, pamidronate, etidronate, etidronic acid, clodronate, clodronic acid, tiludronate, zoledronate, or zoledronic acid. These terms then were combined with the expanded terms osteonecrosis or jaw. A second MedLine search was performed in which each bisphosphonate term was utilized with a category term for clinical trials. Each clinical trial was reviewed to assess the reported adverse events for indications of osteonecrosis of the jaw among study participants without cancer.

Articles were excluded if they were letters, case reports or reviews exclusively related to a cancer population, the abstract specifically stated there were no cases of osteonecrosis of the jaw, the article focused only on treatment or diagnosis, or if the article did not reference specific cases of osteonecrosis of the jaw. Articles published in languages other than English were translated by MultiLingual Solutions, Inc. (Rockville, MD). Citations from the obtained articles were also reviewed. Data regarding patient age, gender, diagnoses, concomitant medications, dose and duration of bisphosphonate use, and dental procedures were abstracted. To be eligible, a published case must have explicitly stated the diagnosis of osteonecrosis in the jaw. All citations were reviewed to identify potential case duplication. Authors of published articles were contacted to attempt to obtain unpublished clinical information to obtain complete data for this study. Potential factors for the development of the proposed model of risk factors were restricted to those characteristics in at least 40% of cases.

Results

The initial MedLine search strategy resulted in 6,132 articles that included a bisphosphonate term. This number was reduced to 199 when the expanded terms osteonecrosis and jaw were required. The article abstracts were reviewed, and 37 articles were obtained for review. An additional 42 articles were identified within the citations of articles reviewed. Several of the full case reports[23–25] were preceded by brief commentaries,[26–28] thus only the more recent report of those cases was included to avoid duplication. Cases that were reported in more than one publication were limited to the more recent or most detailed publication. The clinical trials search resulted in 72 zoledronate, 286 alendronate, 217 pamidronate, 57 ibandronate, 107 clodronate, 13 tiludronate, 215 etidronate, and 77 risedronate clinical trials. The results of the review process are presented in Figure 1. Of the included articles, one in Hebrew,[29] one in French,[30] and one article in German[31] were translated to English. The 30 articles identified in this systematic review discussed 99 cases of osteonecrosis of the jaw among patients without cancer who had been treated with bisphosphonates (85 osteoporosis patients, 10 patients with Paget's disease, and four patients with other diseases). The mean age was 69.4 years, 87.3% were female, and 87.6% were receiving oral, but not intravenous, bisphosphonates. Of the 63 patients reporting dental care information, 88.9% had a dental procedure prior to the onset of osteonecrosis of the jaw. Of the cases reporting concomitant medication use, 71% were taking at least one medication that affects bone turnover in addition to the bisphosphonate, and 80.6% had additional underlying medical conditions. A summary of the identified articles is presented in Table 1, and a summary of individual cases in Table 2

Osteoporosis

Eighty-five osteoporotic patients using bisphosphonates were identified who had been diagnosed with osteonecrosis of the jaw. The mean age was 68.7 years (standard deviation 9.4) and 90.6% were female. The majority of these patients (96.5%) were receiving oral bisphosphonates. Sixty-three (74.1%) were taking oral alendronate, six (7.1%) were taking oral risedronate, two (2.4%) were receiving intravenous pamidronate, and four patients were receiving dual bisphosphonate therapy: oral alendronate plus intravenous zoledronate (n=1, 1.2%); aledronate plus risedronate (n=2, 2.4%); and pamidronate plus zoledronate (n=1, 1.2%). An additional ten patients (11.8%) did not provide individual-level data, but included nine patients who were taking oral alendronate alone or alendronate plus clodronate.

Of the 53 (62.4%) cases with dental information, 49 (92.5%) had a dental procedure prior to the onset of osteonecrosis of the jaw. Twenty-four cases (28.2%) provided information on concomitant medication use. Of these, 17 (70.8%) were taking between one and five medications, in addition to a bisphosphonate, that are known to affect bone turnover (Table 3). The most common medications included steroids (n=10, 41.7%), diuretics (n=4, 16.7%), statins (n=4, 16.7%) and calcium channel blockers (n=3, 12.5%). Three of the osteoporosis cases had associated Therapeutic Goods Association adverse event reports that indicated incorrect dosing or a drug prescribing error had occurred with the bisphosphonate prescribed. Among cases providing clinical information, 26.3% reported poor oral health or other underlying oral conditions (e.g. periodontis, gingivitis), 21.1% had rheumatoid arthritis or lupus, and 15.8% had diabetes or impaired glucose function.

Paget's Disease

Ten patients with Paget's disease who experienced osteonecrosis of the jaw while receiving bisphosphonates were identified. The mean age of Paget's disease patients with osteonecrosis of the jaw was 77.5 years (standard deviation 5.6). Of cases reporting gender, 50% were male and 50% were female. Four patients (40.0%) were taking oral alendronate, four patients were taking pamidronate (40.0%), and two patients were taking combination therapy: alendronate plus risedronate (n=1, 10.0%); and alendronate plus pamidronate (n=1, 10.0%). Four out of six patients (67%) had a dental procedure prior to the onset of osteonecrosis of the jaw. Five out of 10 cases (50%) included concomitant medication use, four of these cases (80%) reported use of between one and three concomitant drugs that affect bone turnover (Table 3). One of the Paget's disease cases[32] had an associated Therapeutic Goods Association report that indicated incorrect dosing or a drug prescribing error had occurred with the bisphosphonate prescribed. Of those reporting concomitant medications or medical conditions, 50% (n=4) had additional health issues. These included one patient with diabetes and hypercholesterolemia, two patients with hypertension, one with hypercholesterolemia, and one patient who had problems with thyroid function. Each of these patients also had a dental procedure preceding the onset of osteonecrosis of the jaw. One patient that did not have a prior dental procedure also did not report concomitant medication use; therefore, the relationship of osteonecrosis of the jaw to other factors for this patient could not be explored.

Other conditions

Four additional cases of osteonecrosis of the jaw were identified among women taking bisphosphonates for conditions other than osteoporosis or Paget's disease. The mean age was 65.8 years (standard deviation 9.6). Two patients were receiving oral alendronate (50%) and two were receiving intravenous zoledronate (50%). Three patients (75%) had a dental procedure prior to the onset of osteonecrosis of the jaw. The patient without a prior dental procedure had a known history of bony disease in her jaw (maxillary fibrous dysplasia). Two cases were identified in patients treated for rheumatoid arthritis, and one case was in a patient

with diabetes. All cases (n=2) reporting medication use were taking medications that affect bone turnover (Table 3).

Summary of potential contributing factors

Similar to the cancer population, dental procedures were the most common risk factor, which was associated with 88.9% of all non-cancer cases of osteonecrosis of the jaw among bisphosphonate users.(Table 3) Dental procedures were most common among osteoporosis patients (92.5%) and less common among Paget's disease patients (67%) prior to onset of osteonecrosis of the jaw. Osteoporosis patients also demonstrated a longer duration of bisphosphonate use (93.3% more than 1 year of use) compared with Paget's disease (60% more than 1 year of use) or other patients (33.3% more than 1 year of use). The majority of patients also had underlying medical conditions (81.3%) and reported concomitant use of medications that affect bone turnover (70.9%). The most common concomitant medical condition included hypertension, hyperlipidemia or hypercholesterolemia (22.6%). However, patients with osteoporosis were most likely to have periodontal disease or other oral conditions (26.3%), whereas Paget's disease patients were most likely to have hypertension or hypercholesterolemia (75%), and other patients had a variety of conditions (rheumatoid arthritis, diabetes or other oral conditions). Among those taking medications that affect bone turnover (Table 4), the most commonly used medication affecting bone metabolism included steroids (52.2%). All other medications were used by 20% or less of patients. A model of risk factors, representing reported factors present in more than 40% of the osteoporosis and Paget's disease patients in this study population, is presented in Figure 3.

Discussion

As a result of this search, 99 cases of osteonecrosis of the jaw among patients receiving bisphosphonates for an indication other than cancer were identified in the published medical literature. The increase in published cases of osteonecrosis of the jaw between 2002 and 2007 is likely related to a combination of patient, disease, and concomitant medication factors, as well as awareness in the medical field,[33] as nitrogen-containing bisphosphonates were used for nearly 10 years prior to the first published case of osteonecrosis of the jaw. In this study, there was a predominance of oral bisphosphonate use, as would be expected for patients treated for osteoporosis or Paget's disease.

There appears to be a consistent association of osteonecrosis of the jaw with invasive dental procedures (e.g. tooth extraction, oral surgery) among patients without cancer, similar to the cancer population. In addition to bisphosphonate use, many of these patients reported taking additional medications that impact bone metabolism, which may have resulted in an additive effect on bone turnover. The concomitant medications may be suggestive of the extent of the underlying disease, which may independently increase risk of osteonecrosis of the jaw (e.g. multiple medications may suggest reduced mobility and subsequent loss of bone mass or may suggest advanced bone disease).

A number of identified cases provide no published or unpublished clinical information about patient health or medication use. There were too little data available to include the other diseases in the risk model. Additionally, cases reported from adverse event reports, which are not comprehensive medical reports, lack patient-level clinical details. However, data from the cases with associated clinical information suggest that those individuals experiencing osteonecrosis of the jaw appear to have multiple contributing factors, primarily co-existing conditions (either implied by the multiple medications or explicitly stated), contraindicated medication use or medication error, and invasive dental procedures prior to the onset of osteonecrosis of the jaw. There were only two published spontaneous case of osteonecrosis of the jaw reported among all osteoporosis patients to date--one in a patient receiving steroid

therapy, the other in a patient with controlled hypertension but no steroid use (complete medication information was not reported). Although common among bisphosphonate users diagnosed with osteonecrosis of the jaw, concomitant medication use of additional agents that impact bone turnover appear to be less frequent among osteoporosis patients (69.6%) and other patients (67%) than among those with Paget's disease (80%), and additional underlying medical conditions were more prevalent among osteoporosis (90.0%) and other patients (100%) than among patients with Paget's disease (50%). This suggests that there may be differences among these populations and the risk factors may need to be addressed separately depending on the underlying condition for which the bisphosphonate is prescribed.

This model-based systemic review suggests that in the majority of cases, the risk of this morbid condition may not be solely attributable to the bisphosphonate. Osteonecrosis of the jaw does not appear to occur in an otherwise healthy patient taking bisphosphonates; multiple factors are likely associated with this condition. Out of all cases, only one (78 year old patient with Paget's disease; 90 mg/month intravenous pamidronate for 18 months) reported no underlying medical conditions, concomitant medication use, or dental procedures. These data suggest that osteonecrosis of the jaw may rather be due to a combination of factors that impact the bone of the jaw that, when combined with a bisphosphonate, increase the risk of osteonecrosis of the jaw. Although more than half of those reporting these medications used steroids, it is unclear if the underlying morbid condition and concomitant medication use work together or independently to increase the risk of osteonecrosis of the jaw among bisphosphonate users. There were a variety of underlying medical conditions in this population, including those previously believed to put patients at increased risk of osteonecrosis. In this review, the prevalence of diabetes and hypertention in the published cases of osteonecrosis of the jaw in this review was is similar to the U.S. prevalence estimates,[35 36] although the extent of disease is unknown. Therefore, it is unclear if the individual underlying medical conditions in this review truly represent individual risk factors.

In a randomized zoledronate clinical trial,[10] one osteoporosis patient receiving placebo and one receiving zoledronic acid experienced osteonecrosis of the jaw, suggesting that incidence may be due in part to the underlying medical condition. Others[4,37] have suggested that osteonecrosis of the jaw in the absence of bisphosphonate use has been in existence for some time, but had been underreported, as there is no mechanism of national or international reporting of adverse events in the absence of the concomitant use of an agent monitored by medication safety and regulatory agencies. Of osteonecrosis of the jaw cases identified in two medical record reviews, between 50 and 90% had never received bisphosphonates.[8,9] A preliminary FDA review found a total of 100 reports of osteonecrosis/necrosis among users of raloxifene, tamoxifen, estrogen, or calcitonin. This represents a small proportion of the total safety reports (0.18%), but suggests that there may be other cases of osteonecrosis of the jaw unrelated to bisphosphonate use that are not being considered.[34]

Further work should determine the frequency of osteonecrosis of the jaw among osteoporosis and Paget's disease patients not taking bisphosphonates. It is important to investigate osteonecrosis of the jaw independent of any particular medication, as it is evident that this condition occurs among users of a variety of other medications and illnesses, and although less commonly, does occur among those with no contraindicated medication use. Future work must address the challenge of separating the drug effects from the underlying effects of the disease it is designed to treat.

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55. Milillo P, Garribba AP, Favia G, Ettorre GC. Jaw osteonecrosis in patients treated with bisphosphonates: MDCT evaluation. La Radiologia Medica 2007;112(4):603–611. [PubMed: 17563854]
56. Dimitrakopoulos I, Magopoulos C, Karakasis D. Bisphosphonate-induced avascular osteonecrosis of the jaws: a clinical report of 11 cases. International Journal of Oral and Maxillofacial Surgery 2006;35 (7):588–593. [PubMed: 16687238]
57. Friedrich RE, Blake FA. Avascular mandibular osteonecrosis in association with bisphosphonate therapy: a report on four patients. Anticancer Research 2007;27(4A):1841–1845. [PubMed: 17649782]
58. Boyd, IW. Therapeutic goods administration, public case detail. Australia: TGA; 2006.

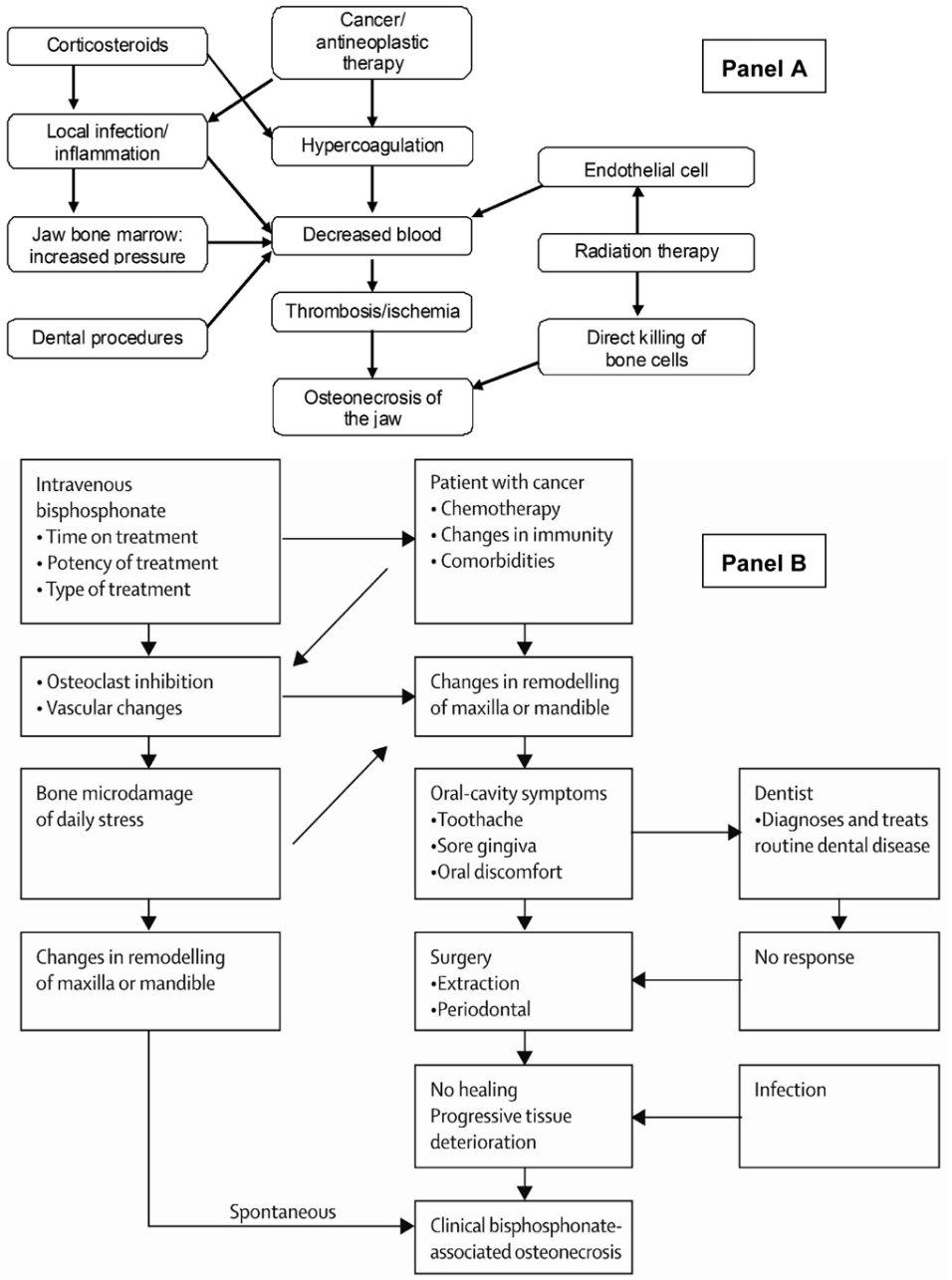

Figure 1.
Models of the development of development of osteonecrosis of the jaw among cancer patients treated with bisphosphonates. Reprinted with permission. Panel A[13]; Panel B[19]

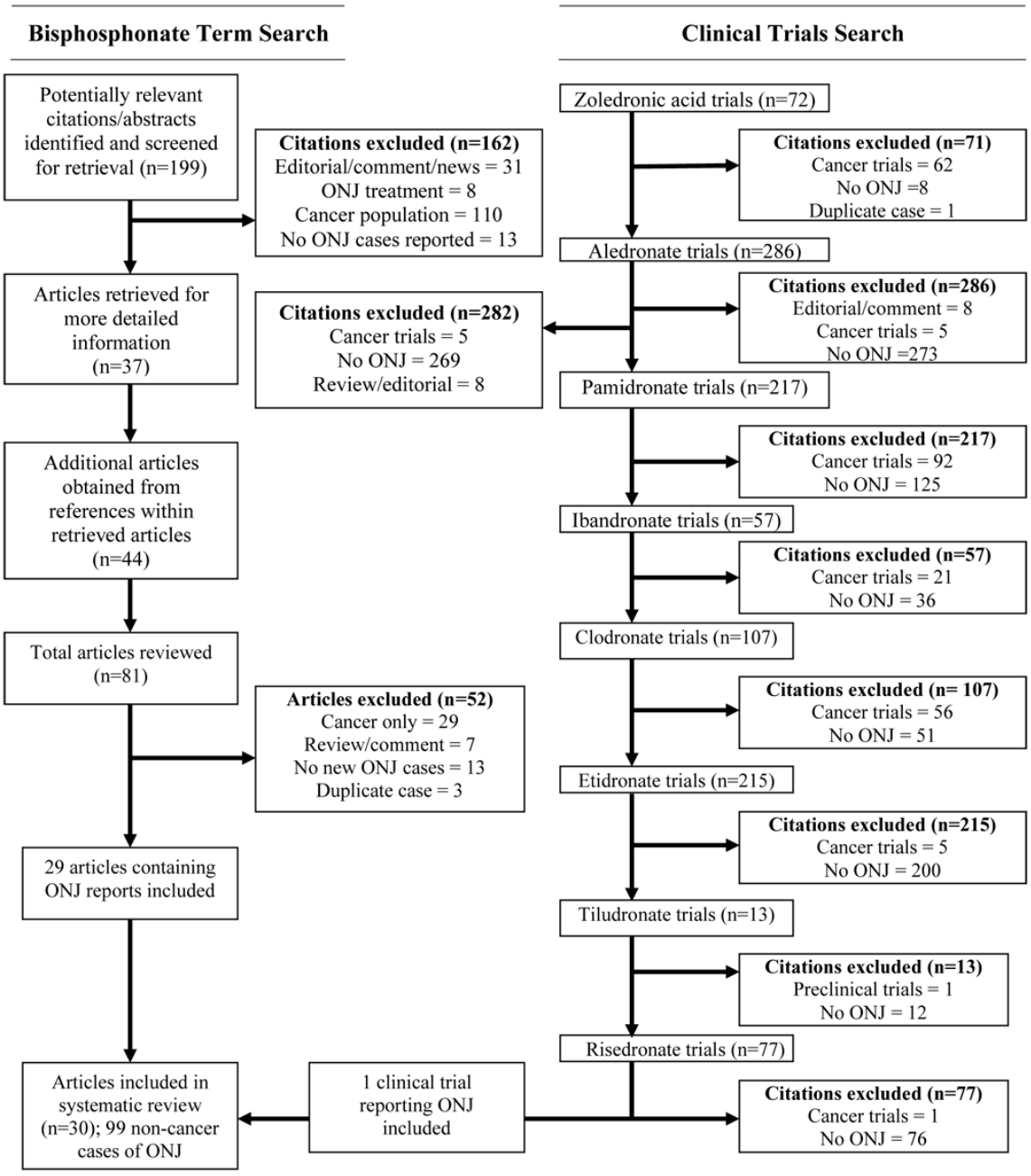

Figure 2.
Results of literature search

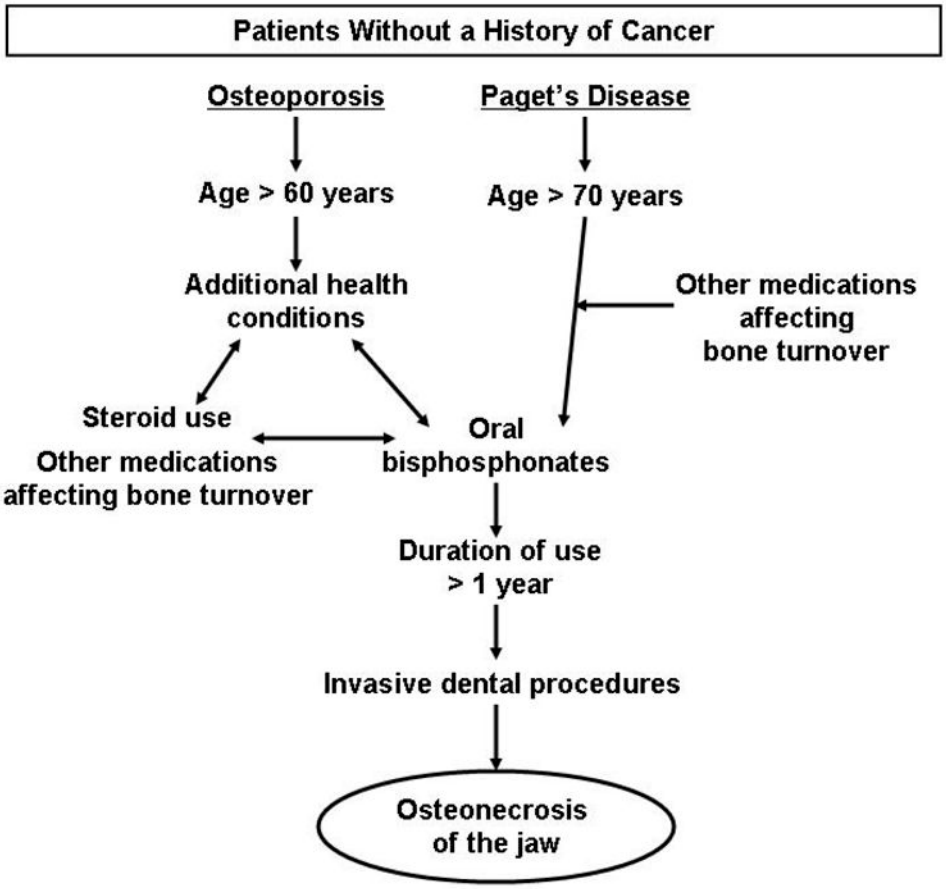

Figure 3.
Proposed model of potential risk factors (> 50% of the study population) associated with osteonecrosis of the jaw among patients with no history of cancer receiving bisphosphonates for osteoporosis or Paget's disease

Table 1

List of publications identified

Publication	Cases Reported	Concomitant medications provided	Dental work information provided
Black et al.[10]	Osteoporosis = 1	NO	YES
Brooks et al.[48]	Osteoporosis=1 Osteopenia=1	YES	YES
Carter et al.[23]	Paget's Disease = 3	YES	YES
Cheng et al.[32]	Osteoporosis = 3 Paget's Disease = 2	YES	YES
Clarke et al.[45]	Osteoporosis = 1	YES	YES
Danneman et al.[44]	Osteoporosis = 3	NO	YES
Dimitrakopoulos et al.[56]	Fibrous Dysplasia = 1	NO	YES
Farrugia et al.[46]	Osteoporosis = 4 Paget's disease = 1	NO	YES
Friedrich and Blake[57]	Diabetes = 1	YES	YES
Heras-Rincón et al.[49]	Osteoporosis = 2	NO	YES
Hoefert and Eufinger[31]	Osteoporosis = 1	YES	YES
Kademani et al.[12]	Osteoporosis = 1	YES	NO
Khamaisi et al.[15]	Osteoporosis = 1 Rheumatoid arthritis = 1	NO	NO
Levin et al.[54]	Osteoporosis = 1	YES	YES
Malden and Pai[50]	Osteoporosis = 1 Rheumatoid arthritis = 1	YES	YES
Marunick et al.[40]	Osteoporosis = 1	YES	YES
Marx et al.[39]	Osteoporosis = 4[c]	NO	NO
Mavrokokki et al.[6]	Osteoporosis = 24[a] Paget's disease = 4[b]	NO	NO
Merigo et al.[43]	Osteoporosis = 3	NO	YES
Migliorati et al.[25]	Osteopenia = 1	YES	YES
Milillo et al.[55]	Osteoporosis = 9	NO	YES
Najm et al.[30]	Osteoporosis = 3	NO	YES
Nase and Suzuki[52]	Osteoporosis = 1	Partial	YES
Oltolina et al.[42]	Microfractures = 1	YES	YES
Phal et al.[51]	Osteoporosis = 4	NO	YES
Pozzi et al.[53]	Osteoporosis = 1	NO	NO
Purcell and Boyd[38]	Osteoporosis = 1	NO	YES
Ruggiero et al.[37]	Osteoporosis = 7	NO	NO
Shlomi et al.[29]	Osteoporosis = 3	YES	YES
Wang et al.[47]	Osteoporosis = 1	YES	YES
Yeo et al.[41]	Osteoporosis = 1	YES	YES

[a] 3 additional cases were previously reported in Cheng et al.[32], and are removed from this analysis to avoid duplication

[b] 2 additional cases were previously reported in Cheng et al. [32], and are removed from this analysis to avoid duplication

[c] Three osteoporosis cases were previously reported by Marx et al.[24]

Table 2

Cases identified

Case	Year reported	Age	Gender	Other conditions	Dental, procedure	Other medications	Bisphosphonate used	Dose	Duration
OSTEOPOROSIS									
1	2004[37]	77	F	NS	NS	NS	Oral Alendronate	NS	NS
2	2004[37]	82	F	NS	NS	NS	Oral Alendronate	NS	NS
3	2004[37]	80	F	NS	NS	NS	Oral Risedronate	NS	NS
4	2004[37]	72	M	NS	NS	NS	Oral Alendronate + IV Zoledronate	NS	NS
5	2004[37]	59	F	NS	NS	NS	Oral Alendronate	NS	NS
6	2004[37]	60	F	NS	NS	NS	Oral Alendronate	NS	NS
7	2004[37]	68	F	NS	NS	NS	Oral Alendronate	NS	NS
8	2005[38]	67	F	NS	NS	Prednisonolone, leflunomide[f], celecoxib	Oral Alendronate	NS	NS
9	2007[39]	70	F	Controlled hypertension	None	NS[c]	Oral Alendronate	70 mg/wk	5 years
10	2007[39]	58	F	Osteopenia	Six dental implants (occluding against a fixed prothesis)	NS, steroid for 5 days during infection	Oral Alendronate	70 mg/wk	5 years
11	2007[39]	58	F	None	Dental implant	NS[c]	Oral Alendronate	10 mg/day, followed by 70 mg/week	1 year followed by 3 years
12	2007[39]	60	F	NS	Root canal, extraction	Atenolol, hydro-chlorothiazide	Oral alendronate	10 mg/day followed by 70 mg/week	3 years followed by 7 years
13	2005[25]	61	F	NS	Oral surgery[a]	Losartan, amlodipine, furosemide, esomeprazole, aspirin, potassium	Oral Alendronate	NS	3 years
14	2005[40]	59	F	Rheumatoid arthritis	Tooth extraction	Prednisone, methotrexate [a]	Oral Alendronate	70 mg/wk [a]	~ 3 years [a]
15	2005[41]	58	F	Lupus erythematosus	Tooth extraction	Prednisolone, glucosamine sulfate	Oral Alendronate	weekly	NS
16[b]	2005[32]	72	M	NS	Tooth extraction	None	Oral Alendronate	40 mg/wk	3 years
17[b]	2005[32]	60[g]	M	NS	Tooth extraction	None	Oral Alendronate	40 mg/wk	1 year
18[b]	2005[32]	58	F	NS	Deep bony impacted wisdom tooth removal	Bactrim, neurontin, amitriptyline	Oral Alendronate	40 mg/wk	Started alendronate after tooth removal
19	2005[42]	64	M	Cardiac graft, micro-fractures of the spinal column	Tooth extraction	Cyclosporine, high-dose steroids	IV Pamidronate	90 mg/4 wk [a]	18 months [a]
20	2005[30]	45	M	NS	None	Cortisone	IV Pamidronate + IV Zoledronate	P: 30mg/ 3mo + Z: 4mg/mo	79 months
21	2005[30]	83	F	NS	Removal of dental implant		Oral Alendronate	70 mg/wk	44 months
22	2005[30]	84	F	NS	Tooth extraction	Cortisone	Oral Alendronate	70 mg/wk	25 months
23	2005[29]	73	F	Rheumatoid arthritis[a]	Tooth extraction[a]	Prednisone[a]	Oral Alendronate	NS	5 years
24	2005[29]	48	F	Diabetes[a]	Tooth extraction[a]	Oral hypoglycemic agent[a]	Oral Alendronate	NS	2 years
25	2005[29]	72	F	Diabetes[a]	Tooth extraction[a]	Insulin, daily[a]	Oral Alendronate	NS	5 years
26	2005[31]	65	F	Hypertonic disease[a]	Oral surgery[a]	Premarin, aspirin, enalapril, fluvastatin [a]	Oral Alendronate	70 mg/wk	2 years
27	2006[12]	64	F	NS	Tooth extraction	Antibiotics	IV Pamidronate	NS	NS
28	2006[43]	70	F	NS	Tooth extraction	NS[c]	Oral Alendronate	70 mg/wk	3 years
29	2006[43]	61	F	NS	Tooth extraction	NS[c]	Oral alendronate	70 mg/wk	2.5 years
30	2006[43]	78	F	NS	Tooth extraction	NS[c]	Oral Alendronate	70 mg/wk	~5 years
31	2007[44]	NS	F	NS	Tooth extraction	NS	Oral Alendronate	NS	>5 years

Case	Year reported	Age	Gender	Other conditions	Dental, procedure	Other medications	Bisphosphonate used	Dose	Duration
32	2007[44]	NS	F	NS	Tooth extraction	NS	Oral Alendronate	NS	>5 years
33	2007[44]	NS	F	NS	Tooth extraction	NS	Oral Alendronate	NS	>5 years
34	2007[15]	71	F	Impaired fasting glucose	Dental Surgery [a]	NS	Oral Alendronate	70 mg/wk	>6 months [a]
35	2007[45]	75	F	Hypertension; hyperlipidemia; history of fibromuscular dysplasia, cerebral aneurysm[a]	Recent dental work	Hydrochlorothiazide + losartan, simvastatin, nifedipine, omeprazole [a]	Oral Alendronate	NS	1 year
36	2006[46]	83	F	NS[d]	Tooth extraction	NS[d]	Oral Alendronate	NS	NS
37	2006[46]	77	F	NS[d]	Tooth extraction	NS[d]	Oral Alendronate	NS	NS
38	2006[46]	63	F	NS[d]	Tooth extraction	NS[d]	Oral Alendronate	NS	NS
39	2006[46]	78	F	NS[d]	Tooth extractions	NS[d]	Oral Alendronate	NS	NS
40	2007[10]	NS	F	NS	Oral surgery	NS	IV Zoledronic acid	5 mg/year	NS
41	2007[47]	65	F	Arthritis, periodontitis, endentulism with functional deficit	Tooth extraction, dental implant	Calcium; teriparatide (at discontinuation of aledronate following dental implant); postsurgical azithromycin, hydrocodone, acetaminophen, ibuprofen, cephalexin	Oral Aledronate	Daily	10 years
42	2007[48]	70	F	Advanced periodontitis; chronic obstructive pulmonary disease	Extraction	Prednisone; sertaline; clonidine; hydrochlorothiazide; fexofenadine; ipratropium and albuterol inhaler; tiotropium inhaler; fluticasone and salmeterol inhaler; potassium; supplemental oxygen	Oral risedronate	35 mg/week	~2 years
43	2007[48]	62	F	Advanced periodontis	Dental implant	NS	Oral risedronate	35 mg/week	1 year
44	2007[49]	75	F	NS	Tooth extraction [a]	NS	Oral alendronate	NS	NS
45	2007[49]	73	F	NS	Tooth extraction [a]	NS	Oral alendronate	NS	NS
46	2007[50]	64	F	Periodontal disease with regular tooth extractions	Tooth extraction	NS	Risedronate	NS	NS
47	2007[51]	82	F	NS	Tooth extraction	NS	Oral alendronate	NS	NS
48	2007[51]	70	F	NS	Tooth extraction	NS	Oral alendronate	NS	NS
49	2007[51]	85	F	NS	Tooth extraction	NS	Oral alendronate	NS	NS
50	2007[51]	74	F	NS	None	NS	Oral alendronate	NS	NS
51	2006[52]	78	F	Renal insufficiency, diverticulosis, clinical depression, poor oral self-care, gingivitis, xerostomia	Tooth extraction	Tolterodine, sertraline, atorvastatin, aspirin, calcium salt, cholecalciferol, ginko bilboa	Oral alendronate	10 mg/day	5 years
52	2005[53]	NS	F	Myelodysplasia [a]	Patient edentulous, with prosthesis [a]	Steroid	NS	NS	NS
53	2007[54]	66	F	Hypertension, hypercholester olemia [a]	No (removable partial denture)	Statin, calcium channel blocker [a]	Oral alendronate	10 mg/day followed by 70 mg/week	6 years followed by 2 years
54–62[e]	2007[55]	NS	NS	NS	Tooth extraction (all pts)	NS	Oral alendronate OR Oral aledronate + clodronate	NS	NS
63–85[e]	2007[6]	NS	NS	NS	NS	NS	Oral alendronate (n=19) Risedronate (n=2) Alendronate + Risedronate (n=2)	NS	NS
PAGET'S DISEASE									
P1	2005[23]	73	M	NS	Tooth extraction	Amlodipine, tramadol, perindopril	Oral Alendronate	40 mg/day	5 years
P2	2005[23]	78	F	NS	None	None	IV Pamidronate	90 mg/mo	18 months

Case	Year reported	Age	Gender	Other conditions	Dental, procedure	Other medications	Bisphosphonate used	Dose	Duration
P3	2005[23]	84	F	NS	Tooth extraction	Diltiazem, simvastatin, ferrous sulfate, aspirin, bendrofluazine	IV Pamidronate	60 mg/mo	6 months
P4[b]	2005[32]	69	M	NS	Tooth extraction	Metformin, atenolol, simvastatin, morphine, calcitonin, amitriptyline	Oral Alendronate	40 mg/wk	6 months
P5	2005[32]	82	F	NS	Tooth extraction	Thyroxine, NSAIDs	IV Pamidronate + Oral Alendronate	P: 90 mg (1 dose) + A: 20mg/day	P: 5 years A: 1 year
P6	2006[46]	79	M	NS[d]	None	NS[d]	Oral alendronate	NS	NS
P7–10[e]	2007[6]	NS	NS	NS	NS	NS	Oral alendronate (n=2) Pamidronate (n=2)	NS	NS
OTHER									
OT1	2006[56]	59	F	Maxillary fibrous dysplasia [a]	None	None [a]	IV zoledronic acid	NS	6 months
OT2	2007[15]	73	F	Rheumatoid arthritis, impaired fasting glucose	Dental surgery [a]	NS	Oral alendronate	70 mg/wk	>6 months [a]
OT3	2007[57]	75	F	Diabetes, sarcoidosis	Tooth extraction	Prednisone, insulin	IV zoledronic acid	NS	3 years
OT4	2007[50]	56	F	Rheumatoid arthritis	Tooth extraction	Leflunomide, prednisone, diclofenac, iron, omeprazole	Oral alendronate	NS	NS

NS = not stated

[a] Personal communication with author

[b] Incorrect dose/drug prescribing error noted in TGA report associated with this case[58]

[c] Patient was not taking corticosteroids

[d] Although details of medications/illnesses were not provided, publication states there were none that could have contributed to the ONJ

[e] Summary data only, no individual case details provided

[f] Contraindicated in patients over age 65 due to increased risk of infection

[g] Per author, the original publication incorrectly noted this patient's age as 39. The correct age of this patient was 60.

Table 3

Summary of potential contributing factors among patients with ONJ while taking bisphosphonates

Potential Contributing Factor	Osteoporosis	Paget's disease	Other	TOTAL
Age, mean (SD)	68.7 (9.4)	77.5 (5.6)	65.7 (9.6)	**69.4 (9.4)**
Dental procedures	92.5%	67%	75%	**88.9%**
Medications affecting bone turnover, in addition to bisphosphonate use	69.6%	80%	67%	**71%**
Duration of bisphosphonate use				
< 6 months	3.3%	0%	0%	2.6%
6 months - <1 year	3.3%	40%	66.7%	13.2%
1- <5 years	53.3%	20%	33.3%	47.4%
≥ 5 years	40%	40%	0%	36.8%
Underlying medical conditions	**90.0%**	**50%**	**100%**	**80.6%**
Rheumatoid arthritis/lupus	21.1%	0%	50%	19.4%
Diabetes/impaired glucose*	15.8%	10%	50%	19.4%
Periodontal disease/other oral	26.3%	0%	25%	19.4%
Hypertension/hyperlipidemia/hypercholesterolemia*	21.1%	75%	0%	22.6%
Other cardiac	10.5%	0%	0%	6.5%

* explicitly stated or implied by medication use

Table 4

Summary of concomitant use of medications that impact bone turnover

Osteoporosis	Medications
Case 8	Steroids; immunosuppressant
Case 10	Steroids
Case 12	Diuretic; beta-blocker
Case 13	Calcium channel blocker; diuretic; angiotensin receptor blocker; proton pump inhibitor
Case 14	Steroids; methotrexate
Case 15	Steroids
Case 19	Steroids; immunosuppressant
Case 20	Steroids
Case 22	Steroids
Case 23	Steroids
Case 26	ACE inhibitor; statin; hormone replacement therapy
Case 35	Calcium channel blocker; diuretic; angiotensin receptor blocker; proton pump inhibitor; HMG CoA reductase inhibitor
Case 41	Thyroid hormone
Case 42	Diuretic; steroids
Case 51	Statin, calcium salt, cholecalciferol (Vit D)
Case 52	Steroids
Case 53	Statin, calcium channel blocker
Paget's Disease	
Case P1	Calcium channel blocker; ACE inhibitor
Case P3	Calcium channel blocker; statin; diuretic
Case P4	Statin; beta blocker; calcitonin
Case P5	Thyroid hormone
Other	
Case OT3	Steroids
Case OT4	Proton pump inhibitor; steroids