

Prevalence of Osteonecrosis of the Jaw Secondary to Antiresorptive Therapy in Patients Who have Undergone Dental Surgical Procedures: A Retrospective Study

Review Article

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Introduction

Osteonecrosis is defined as “necrosis of bone due to obstruction of its blood supply” [1]. Although osteonecrosis of the jaw (ONJ) can occur spontaneously or idiopathic, etiologic agents most often serve as modifiers for a specific case of ONJ. ONJ can result from radiation therapy to the head and neck, chronic corticosteroid use, herpes zoster virus infection in immunocompromised patients, anti-angiogenesis medications, uncontrolled infections or major trauma, and antiresorptive medications [2, 3].

ONJ secondary to antiresorptive medications has been previously known as Bisphosphonate-related osteonecrosis of jaw (BRONJ), Bisphosphonate - induced osteonecrosis of the jaw (BIONJ), Bisphosphonate - associated osteonecrosis of the jaw (BONJ), and Bisphosphonate - associated Osteonecrosis (BON) [4]. However, due to the introduction of non-bisphosphonate antiresorptive agents such as Denosumab and Cathepsin K inhibitors, the American Dental Association has proposed the term Antiresorptive agent-induced osteonecrosis of the jaw (ARONJ) to better encompass all medications that have been shown to increase a patient's risk for developing ONJ [5, 6].

Antiresorptive medications are widely used in the prevention and treatment of metabolic bone disorders such as osteoporosis, cancer metastasis, multiple myeloma, and Paget's disease [7, 8]. The number of patients taking antiresorptive medications is projected to rise as well as the associated risks including ARONJ.

According to the American Association of Oral and Maxillofacial Surgeons (AAOMS), ARONJ is defined as exposed bone in the maxillofacial region persisting for more than eight weeks in

a patient who is taking, or has taken an antiresorptive agent and has not had radiation therapy to the head and neck. The clinical presentation of ARONJ varies from case to case, although common signs and symptoms include pain, soft tissue swelling and infection, loosening of teeth, halitosis, drainage, and exposed bone [9, 10]. ARONJ can occur spontaneously although more often precipitated by tooth extraction [11]. Other potential risk factors and comorbidities reported in the literature include diabetes mellitus [12], clinically and radiographically apparent periodontitis [13], denture wearing [9, 14], and smoking [15]. Corticosteroid use has not been consistently found to be a risk factor for ARONJ [11, 16-18].

Reported estimates of ONJ from oral antiresorptives range from 0.00038% to 4% [8, 19-22]. The highest prevalence of ARONJ in a large study population using oral bisphosphonates was approximately 0.10% [22]. The occurrence of ARONJ has been shown to be higher in cancer patients than osteopenic or osteoporotic patients. According to a systematic review the overall weighted prevalence of ARONJ in cancer patients was 6.1%, ranging from 0.7% in studies with undocumented follow-up to 13.3% in studies with well documented follow-up [23]. Finally for non-bisphosphonate antiresorptive agents, the prevalence of ARONJ has been reported to as 0.061% in patients with low bone density and 2% in patients with bone metastasis [24, 25].

Although the reported estimates of ARONJ risk are low, clinicians are unable to determine a patient's risk for developing ARONJ prior to dental surgery procedures. The purpose of this study was to determine the prevalence of antiresorptive agent-induced osteonecrosis of the jaw (ARONJ) in patients who have taken antiresorptive medications and undergone a surgical proce-

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cedure at NSU CDM and determine potential risk factors.

Materials and Methods

An Institutional Review Board (IRB) exemption was obtained prior to commencing the research project. The electronic health records of all Nova Southeastern University, College of Dental Medicine patients were queried for a history of antiresorptive use. Table 1 lists the oral and parental formulations searched for on the database. Only patients with a prior history of antiresorptive use who had also undergone a dental surgery procedure were included in the study. A dental surgery procedure consisted of any procedure that involved direct bone manipulation. Patient charts were reviewed for the 1.) age and gender of patient, 2.) details of medication including name, reason for use, dose, frequency, route of administration, and length of time taking it, 3.) presence of potential risk factors such as Diabetes Mellitus, periodontitis, smoking, denture wearing, and corticosteroid use, 4.) type of surgical procedure performed on patient, 5.) whether or not the patient developed ARONJ following surgical procedure, and 6.)

length of documented follow-up. The development of ARONJ was assessed using the AAOMS Staging Criteria as shown in Table 2. Patients were placed in one of the five categories in the ARONJ classification based on the clinical signs and symptoms reported on their health records at follow-ups- At Risk, Stage 0, Stage 1, Stage 2, or Stage 3.

The overall weighted prevalence of ARONJ was determined for the study population. Assessed if there were associations between ARONJ and 1.) the medication name, dose, frequency, route of administration, length of time taking the antiresorptive agent, 2.) potential risk factors such as Diabetes Mellitus, periodontitis, smoking, denture wearing, corticosteroid use, and 3.) the invasiveness of the surgical procedure. Associations were found to be statistical significance with ($p < 0.05$) using the Fisher's Exact Test and the Logistic Regression Model.

Results

For the preliminary results a total of 255 patients fit the inclu-

Table 1. Antiresorptive Agents.

Oral Formulations	Parenteral Formulations
Actonel (Risedronate)	Aredia (Pamidronate)
Atelvia (Risedronate)	Bonefos (Clodronate)
Bonefos (Clodronate)	Boniva IV (Ibandronate)
Bonviva (Ibandronate)	Prolia (Denosunab)
Boniva (Ibandronate)	XGEVA (Denosunab)
Didronel (Etidronate)	Reclast (Zoledronic acid)
Generic Etidronate	Aclasta (Zoledronic acid)
Fosamax (Alendronate)	Zometa (Zoledronic acid)
Fosamax Plus (Alendronate cholecalciferol)	
Generic Alendronate	
Skelid (Tiludronate)	

Table 2. AAOMS Staging Criteria [10].

Category	Criteria
At Risk	Clinically normal, asymptomatic patients who have received antiresorptive therapy
Stage 0	No clinical evidence of exposed bone, but presence of non-specific symptoms or clinical and/or radiographic abnormalities
Stage 1	Exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection
Stage 2	Exposed and necrotic bone associated with pain and/or signs of infection in the region of bone exposure with or without purulent drainage
Stage 3	Exposed and necrotic bone in patients with pain, infection, and at least one of the following: exposure and necrosis extending beyond the local alveolar tissues; radiographic evidence of osteolysis extending to the inferior mandibular border or the maxillary sinus floor; pathologic fracture; oro-antral, oro-nasal or oro-cutaneous communication

sion criteria and were included in the study. The mean age of the study population was 70.31 ± 10.9 years with the majority being female in gender 228: 27. Of all the participants - 59% had taken Fosamax, 20% had taken Actonel, 13% had taken Boniva, and 9% comprised of patients having taken another type of antiresorptive agent. A large majority of the population (186 patients) was on antiresorptive medications to prevent and treat low bone density compared to only 10 patients that were taking the medications for either multiple myeloma or cancer metastasis. Figure 1 divides the patients depending on the documented time for taking the antiresorptive agent, with 46 patients taking AR agents for less than 1 year, 39 patients for 1 to 2 years, 33 patients for 2 to 3 years, 19 patients for 3 to 4 years, and 71 patients for over 4 years.

When examining the development of ARONJ within this population, 230 patients were categorized in the At Risk category, 19 patients in the Stage 0 category, and 6 patients in the Stage 1-3 category as shown in Figure 2. Therefore, 90.20% of patients showed no clinical signs and symptoms of ARONJ but are at an increased risk for developing ARONJ, 7.45% of patients had no clinical evidence of exposed bone but presented with non-specific symptoms or clinical and/or radiographic abnormalities, and 2.35% of patients had ARONJ ranging from Stage 1 to 3 with varying degrees of exposed and necrotic bone, pain, and purulent

drainage.

Of the patients who developed ARONJ Stage 1 to 3, 16.7% (1 out of the 6 patients) had a history of taking Actonel, 16.7% (1 out of the 6 patients) had a history of taking Fosamax, 16.7% (1 out of the 6 patients) had a history of taking Boniva, 16.7% (1 out of the 6 patients) had a history of taking both Aredia and Zometa, and 33.3% (2 out of the 6 patients) had a history of taking Zometa. Furthermore, 50% of the patients that developed ARONJ had taken IV formulations of antiresorptive agents for cancer treatment as seen in Figure 3.

The prevalence of developing ARONJ after a surgical procedure for patients with low bone density and cancer is outlined in Figure 4. Of the patients taking antiresorptive agents for low bone density, the estimated risk for developing ARONJ was 1.2 to 1.6% and of the patients taking antiresorptive agents for cancer treatment, the estimated risk for developing was 30%.

Patients that were classified as Stage 0 did not have exposed bone that persisted for over eight weeks yet presented with signs and symptoms that were considered abnormal. There were a total of 19 patients that fell into this category and the signs included bony spicules or sequestrum alone, bony spicules or sequestrum

Figure 1. Length of Time Patients on Antiresorptive Agents Prior to Surgery.

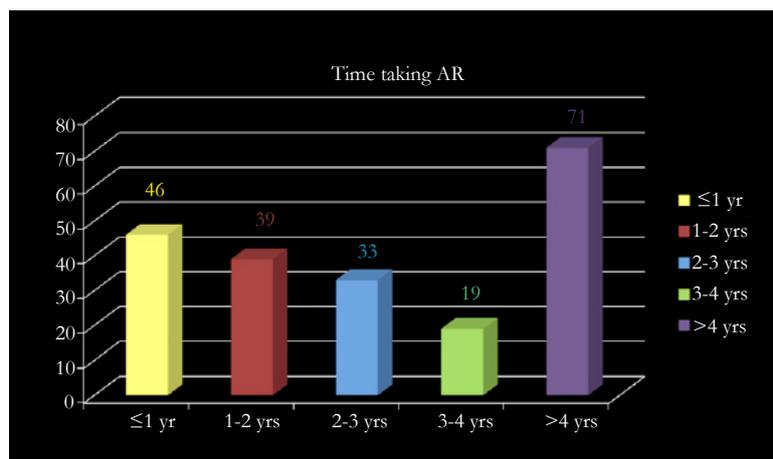


Figure 2. Prevalence of ARONJ in Study Population.

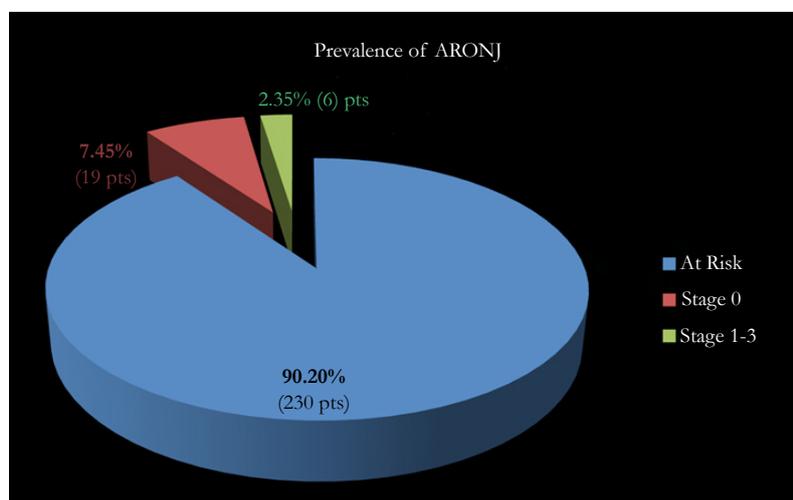


Figure 3. Medications Taken by Patients with Stage 1 to 3 ARONJ.

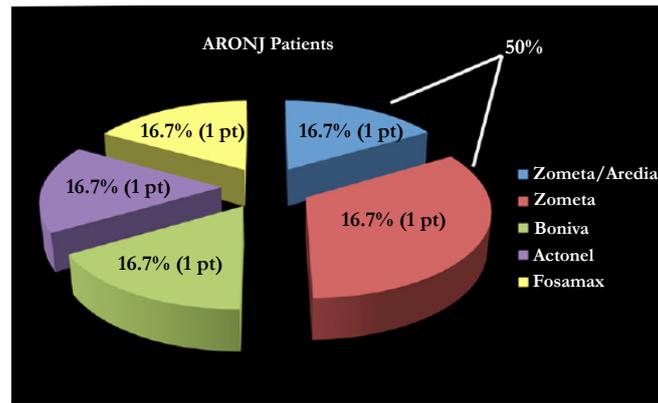


Figure 4. The Prevalence of ARONJ in Patients being Treated for Low Bone Density Versus Cancer.

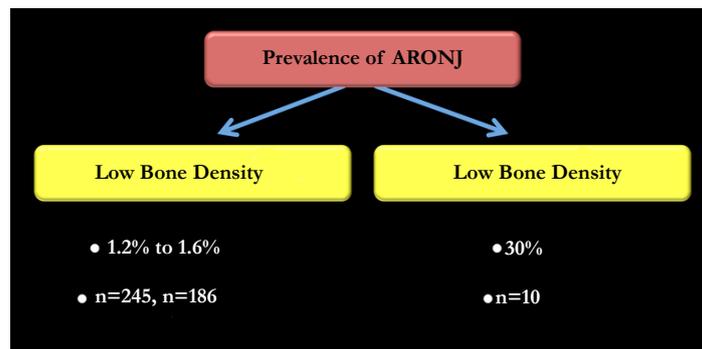
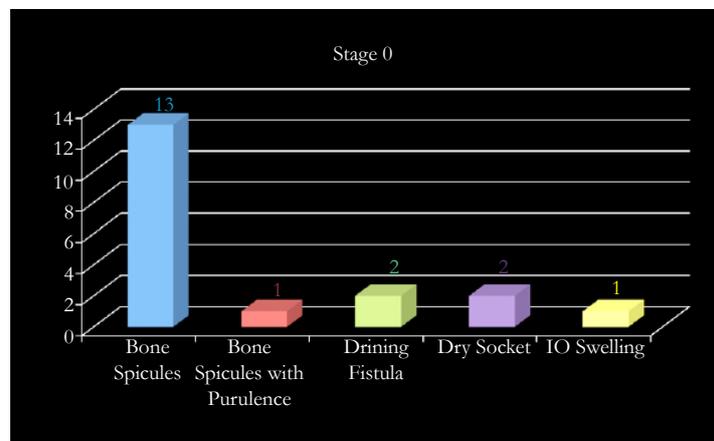


Figure 5. Unspecific Signs and Symptoms of Patients with Stage 0.



with purulence, draining fistula, dry socket, and intraoral swelling. About 74% (14 out of 19) of the Stage 0 cases had the presence of bony spicules or sequestrum with or without purulence as noted in Figure 5. These symptoms may or may not be related to their use of antiresorptive agents.

Of all the variables that were studied for an association with ARONJ including 1.) the medication name, dose, frequency, route of administration, length of time taking the antiresorptive agent, 2.) potential risk factors such as Diabetes Mellitus, periodontitis, smoking, denture wearing, corticosteroid use, and 3.) the invasiveness of the surgical procedure, the only variable that was found to have a statistical significant association with developing ARONJ was type of medication. The small sample size as well as missing pertinent information in incomplete records limited possible relevant associations.

The mean follow-up for the patients studied was 17.03 months with a range of 0 to 65 months.

Conclusion

Limitations of this study include its retrospective design, a relatively small sample size, incomplete medical history and records, and some patients included in the study had short term follow-ups. With the limitations of the study, it is the first study that examines the prevalence of ARONJ after all types of surgical procedures and not solely limited to extractions. More research is needed because most of the latest guidelines proposed by the ADA are primarily based on expert opinion rather than evidence based literature. The number of patients taking these medications and the length of time patients will be on antiresorptive agents is

expected to rise leading to an increased occurrence of ARONJ. Therefore, as dental professionals it is imperative that we become knowledgeable of these medications and risks associated to better serve and educate our patients.

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