Review Article

Evolution and Etiopathogenesis of Bisphosphonates Induced Osteonecrosis of the Jaw

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Abstract

Bisphosphonates (BPs) is widely used as the first line of treatment choice for osteoporosis, Paget's disease of bone, bone cancer metastasis and hypercalcemia of malignancy. BPs induced osteonecrosis of the jaw (ONJ) is a relatively rare but severe clinical condition cited in English literature since 2003 while exact pathogenesis of BPs induced ONJ is not known until today, but numerous hypotheses were described in recent literature that promote and interlinked the development of BPs induced ONJ. These hypotheses indicate multifactorial nature of its development and factors responsible for that are; long term administration of intravenous nitrogen containing BPs in cancer patients, biological behavior of jaw, antiangiogenic property of BPs and by soft-tissue toxicity etc., All these factors are compounded by the presence of infection that are responsible for lower the pH of the oral cavity, other drugs like administration of corticosteroid, pathologies that cause hypo-calcification of bone, compromised immune response that alters normal healing such as renal transplantation followed by long term oral BPs therapy or chronic diabetic patients receiving BPs therapy and any dentoalveolar trauma. All literature in this review article is search from PubMed, Med-know and Google search engines.

Keywords: Bisphosphonates, Bisphosphonates induced osteonecrosis of the jaw, Evolution and BPs induced ONJ, Pathogenesis of BPs induced ONJ

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Introduction

Bisphosphonates (BPs) have been first synthesized in Germany dating back to 1865.[1] They are stable analogs of pyrophosphate which are naturally occurring modulators of bone metabolism and have been synthesized and used since the 19th century but their *in-vitro* ability to inhibit the precipitation of calcium phosphate was applied clinically in 1960s.[2] In 2002, Food and Drug Association (FDA) received reports of several patients with cancer, treated with the IV BPs (Zoledronic acid), who developed osteonecrosis of the jaw (ONJ).[3] While in 2003Marx was the first person who reported BPs induced ONJ in the medical literature. The mechanism by which BPs may cause ONJ[3] and actual incidence of ONJ related to the use of BPs is not known until today. The majority of patients who have been diagnosed with BPs induced ONJ have had certain resorptive bone diseases, hypercalcemia, bone metastasis, and under BPs therapy[4,5] Principal action of BPs is to inhibit resorption of bone by inhibiting osteoclast activity and its life span that leads to modulation of the osteoclast–osteoblast interrelation, which results in an increase in the mineral density of bone and a reduction in serum calcium,[6] although other actions such as inhibition of angiogenesis[7] and anti-human endothelial cell proliferation and to modulate endothelial cell adhesion and migration have also been reported.[8] However, according to previous literature, all three above mentioned pharmacological action produced by BPs becomes more aggressive in the presence of other risk factors (drug related, local, demographic/systemic, genetic and preventive)[5,9] that finally leads to a rare but serious clinical condition called BPs induced ONJ.[10]

This article reviewed the literature related to the evolution and etiopathogenesis of BPs induced ONJ.

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Since 2003 enormous literature available on BPs induced ONJ but only those literatures were reviewed in this paper which was appropriate. All literature in this review article is search from PubMed, Med-know and Google search engines.

Evolution of BPs Induced ONJ

BPs is widely used as the first line of treatment choice for osteoporosis, Paget's disease of bone, bone cancer metastasis and hypercalcemia of malignancy. According to previous literature, amino BPs like Zoledronate, Pamidronate, Ibandronate, Alendronate and Risedronate, are developed and preferred to non-amino BPs because of their greater potency, faster efficacy and more persistent inhibitory effects on bone turnover.[4] Recently most commonly used BPs in the field of oncology and hematology are Pamidronate and Zoledronate. At the cellular level, BPs acts by blocking osteoclasts function in several ways such as inhibiting the osteoclasts formation from monocytes, reducing osteoclasts life span and inhibiting the osteoclastic activity on the bone surface. While at the molecular level, BPs is deemed to modulate osteoclast function like interacting with a surface cell receptor or with intracellular enzymes. Considering that they are not metabolized for long, they are internalized in the osteoclasts, which are responsible for osteoclast apoptosis. In addition to the anti-reabsorption effect on the bone, anti-angiogenic effects on animals and/or inhibition of the endothelial cell functions both *in-vivo* and *in-vitro*. Thus, the cells treated with BPs have shown a decreased proliferation capability, an increased level of apoptosis and a reduced capillary vessel formation while other effects are immunomodulating and antineoplastic.[11]

In 2002, FDA received some reports of ONJ in those cancer patients who received intravenous BPs therapy (Zoledronic acid).[3] After 1 year Marx reported a series of 36 patients with ONJ who were treated with Pamidronate or Zoledronic acid. He postulated "a possible implication of BPs in the development of maxillary osteonecrosis".[12] Later on this hypothesis was also supported by many authors, who highlighted a strong correlation between intraoral bone necrosis and BPs treatment especially after avulsion or other dentoalveolar procedures.

In 2004 Ruggiero, *et al*. reported 63 patients with ONJ, out of 63 patients only 56 patients had received intravenous BPs for at least 1 year and rest seven patients were treated with chronic oral BPs.[13] In 2005 Bamias reported overall incidence of development of bisphosphonates-related osteonecrosis of the jaw (BRONJ) was 6.7% in a total of 252 patients while the incidence of ONJ increased with time of exposure to the drugs from 1.5% among patients treated for 4-12 months, to 7.7% for treatment of 37-48 months.[3] Thus a new clinical entity associated with BPs treatment was observed: This condition has been termed avascular necrosis also known as osteonecrosis or osteochemonecrosis of the jaw bone.[4,14] Papapetrou in 2009, reviewed adverse effect of BPs and reported following side effects like upper gastrointestinal tract (GIT) adverse event, renal toxicity, ocular adverse event, acute phase response, hypocalcaemia and secondary hyperparathyroidism, musculoskeletal pain, arterial fibrillation, atypical fractures of the femoral diaphysis, ONJ etc.[3]

The association of ONJ with BPs therapy was discussed in a report of a task force of the American society for bone and mineral research. They reported ONJ as the presence of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider. According to American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper,[5,9] association between IV BPs exposure and BPs induced ONJ may be hypothesized on the basis of following observations: (1) A positive correlation between BPs potency and risk for developing BPs induced ONJ; (2) a negative correlation between BPs potency and duration of BPs exposure prior to developing BPs induced ONJ, and (3) a positive correlation between duration of BPs exposure and developing BPs induced ONJ. Therefore, the current level of evidence does not full support a cause and effective relationship between BPs exposure and necrosis of the jaw. Although causality may never be proven; but emerging experimental and epidemiologic studies have established a firm foundation for a strong association between IV BPs therapy and BPs induced ONJ.

Etiopathogenesis of BPs Induced ONJ

Exact pathogenesis of BPs induced ONJ is not known until today. However, numerous hypotheses in literature that promote and interlinked the development of BPs induced ONJ. Factors which may influence the development of BPs induced ONJ are potency of BPs, biology of jaw bone, antiangiogenic property and soft tissue toxicity of BPs all these factors are compounded by the dentoalveolar procedures, presence of infection, other drugs, pre-existing pathologies, and compromised immune response.

According to the current definition only those patients are considered in BPs induced ONJ category, which received either current or previous treatment with BPs. Structurally BPs have two important entity P-C-P back bone and R_2 side chain that shows a strong affinity for bone mineral and provides potent inhibition of bone turn over both *in-vivo* and *in-vitro* and therapeutic

potency of the BPs respectively. Chemically BPs had two sub-divisions which have a different mechanism of action on osteoclasts based on the presence or absence of a nitrogen side chain on the pyrophosphate group. Nitrogen containing BPs had poorly absorbed by the gastrointestinal tract about 10% and excreted largely unchanged by the kidneys but if given intravenously about 50% of the drugs goes to the bone,[6,15] due to this region nitrogen containing BPs are commonly prepared for IV administration.[5,15,16]

According to Russell non-nitrogen containing BPs that are closely related to pyrophosphate. This non-nitrogen containing BPs (Tiludronate, Clodronate and Etidronate) are taken up by the osteoclasts and antagonized the cellular energy pathways due to intra cellular liberation of methylene that contains toxic analogs of ATP, which probably inhibit ATP-utilizing enzymes and induce osteoclast apoptosis where as Nitrogen containing BPs (Zolendronate, Pamidronate, Alendronate etc.) has a more complex pathway of action where they inhibit the Mevalonate pathway by inhibition of Farnesyl pyrophosphate synthetase leads to prenylation of small guanosine triphosphatase (GTPase) signaling proteins that are essential for osteoclast activity and survival.[4,17,18] Due to alteration of Mevalonate pathway complex biochemical changes occurred that finally lead to intracellular accumulation of isopentenyl diphosphate (IPP). In monocytes, the accumulated IPP results in activation and proliferation of γ and δ T-cells, triggering proinflammatory cytokines release and thus causing acute systemic inflammatory reactions.[19,20]

Another most peculiar feature of BRONJ is the exclusive localization of osteonecrosis to the maxillary and mandibular bones. On the basis of above finding, a basic question arises "why BPs induces osteonecrosis at the mandibular and/or maxillary bones?" The answer of this question related to the pharmacokinetic and pharmacodynamic properties of BPs as discussed above and some peculiarities of the biology of the mandibular and/or maxillary bone as described below.

Mandibular and maxillary bones have two important components like alveolar bone and periodontium. These two structures of the jaw bone are characterized by particularly high bone turnover. That's why bones maintain a high remodeling status throughout life in response to continuous mechanical stress or as a result of tooth movements or loss. In case of human, the bone remodeling rate of cortical bone of the jaw (alveolar process) was 10-20 times faster than that of iliac bone.[21] Naturally bone remodeling is a physiologically coordinated process involving bone formation by osteoblasts and bone resorption by osteoclasts. Imbalance between these two entities may lead to skeletal abnormalities characterized by increases or decreases in bone density. In contrast to other skeleton, Jaw bones especially alveolar process and periodontium have relatively high vascularity, bone turnover and remodeling because of continuous mechanical stress. In response to continuous mechanical force, osteocytes and osteoblasts of the alveolar process activate bone remodeling by stimulating local over expression of various cytokines, which induces maturation of many new osteoclasts from medullary monocytes precursor and recruit them to the bone surface. While Periodontium contain human gingival fibroblast and human periodontal ligament cell that have a role in osteoclastogenesis through the expression of receptor activator of nuclear factor kappa β ligand (RANKL) on their cell surface. Due to increased mechanical stress, increases expression of RANKL on human periodontal ligament cell. On the other hand, formation of osteoclasts required interaction between TNF family molecule RANKL and its receptor RANK. At the same time, human gingival fibroblast and human periodontal ligament cell secrete osteoprotegerin that easily bound to RANKL and inhibits osteoclastogenesis. With the advancement of the age, jaw bone remodeling will increase along with periodontal disease and elevated systemic bone turn over are the most important reasons for the development of the BPs induced ONJ.[4,10,22]

In 2006Ardine *et al*.[23] reported that patients with BPs induced ONJ had persistently higher parathyroid hormone (PTH) levels compare to normal and they suggested that higher PTH level may involve in the pathogenesis of ONJ. While in 2009 Papapetrou[3] reported in some cases of BPs induced secondary hyperthyroidism there may be a relatively smaller reduction of bone turnover caused by the BPs because of the antagonistic effect of the high PTH. In those conditions, bone turnover is higher than expected that may lead to accumulation of higher concentration of the drugs in the bone microenvironment. This causes localized, relatively increased BPs induced production of interleukin-6 as well as other proinflammatory cytokines and an inflammatory reaction localized to bones.

In previous literature, many authors suggested that BPs causes local impairment of the response to localized bone injury due to decrease in cellularity and blood flow in bone. In BPs induced ONJ large number of osteoclasts has been detected close to actively resorbing bone and this accumulation is likely to mimic the healing process while alterations in the intraosseous blood flow have been hypothesized as pathological cause of BPs induced ONJ. The effect of these alterations has been named as "drug induced avascular necrosis of the jaw." Hellstein and Marek

in 2005 reported intact vascular channels, even in areas with acute inflammatory infiltrates and bacterial over growth in his own histologic finding of several cases of ONJ and reported non-vital bone fragments with reduced evidence of osteoclastic action but no any vascular alteration. However, in 2006 Woo, *et al*. reported the blood flow in the mandibular and maxillary bone could be altered by BPs via inhibition of intraosseous angiogenesis on the basis of histological finding. Therefore, antiangiogenic properties of BPs may explain the apparent ischemic changes in ONJ that was also demonstrated in an animal models but only in pathologic tissues (neoplastic or Paget's disease tissue).[4,14] Therefore, administration of more potent BPs in cancer patients, have antiangiogenic property that participate on development of BPs induced ONJ. On the basis of this evidence Vincenzi, *et al*. evaluated the role of vascular endothelial growth factor (VEGF) as a predictive marker of BPs induced ONJ and found decreased VEGF circulating levels at day 7 and 21 after the 1st administration of N-BPs thus author conclude that the anti-angiogenic properties of N-BPs are directly linked to BPs induced ONJ pathogenesis and serum VEGF levels could represent an effective early predictive marker.[7]

Jaw bones do not appear to accumulate BPs at a significant higher concentration than the reminder of the skeleton despite its higher turnover. Reid in 2009 also reported, BPs causes soft tissue toxicity that might be responsible for the development of BPs induced ONJ. According to his publication exposure to micromolar concentrations of these compounds in solution produces toxic effects in many cells including monocytes, macrophages, periodontal ligament fibroblasts, endothelial cells, variety of tumor cells, osteoblasts and epithelial cells. But not clear that what concentration of BPs on bone surfaces are toxic to adjacent cells. While in 2008 Coxon, *et al*. explain mechanism for BPs toxicity on non-osteoclast cells. According to him, absence of bone surface, BPs in solution is taken up by cells, resulting in toxicity mediated through its inhibition of the Mevalonate pathway while in the presence of bone surface BPs shows more affinity to hydroxyapatite crystals and was not available for non-bone cells. Thus, it proved that BPs causes direct toxic effect on the soft tissues of the oral cavities *in-vitro*, an effect which was increased in low pH environment that most commonly found in cases of presence of local infection. The uptake of BPs by the skeleton is so efficient than concentrations in human plasma are immeasurable within a short period of BPs administration and there is no evidence that BPs released from bone during its metabolism, even in the presence of increased resorption associated with low pH, reaches concentrations sufficient to be toxic.[15-24]

Normally oral microbial flora contains more than 750 species and most of them are organized in complex multispecies biofilms.[25] Biofilm formation encouraged lysogenic interactions between viruses and microbial hosts and may contribute to pathogenicity.[26] In 2012 Ji *et al*. suggested that oral infection and inflammation plays a crucial role in the development of BPs induced ONJ.[25] While Sedghizadeh *et al*. reported BPs induced ONJ was most commonly seen in those patients who received invasive dental procedures because oral microbes gain access to the exposed jaw bone and play an important role in the etiopathogenesis of this condition. Recent investigations also show that BPs inhibits oral wound healing and helps in bacterial colonization as well as BPs accumulation on bony surfaces.[26,27] Due to complex multi species biofilms microbial cultures have not been helpful in directing therapy because specific pathogens have not been identified. Recently Ji *et al*. using 16S r-RNA molecular technique reflects that the use of systemic antibiotics failed to restrict the bacterial colonization without effective healing of the lesion after the onset of BPs induced ONJ.[25] Gupta *et al*. in 2011 reported high affinity of nitrogen containing BPs for hydroxyapatite bone mineral while the administration of N-BPs along with graft material led to enhanced linear bone formation at the surgical site. They also reported that, this bone targeting properties of BPs can be harnessed along with regenerative materials to enhanced potential osseous regeneration.[28]

According to Khamaisi *et al*. incidence of BPs induced ONJ was higher in diabetes patients. Normally diabetes is associated with microvascular ischemia of the bone, endothelial cell dysfunction and decreased bone turn over and remodeling as well as induced apoptosis of osteoblasts and osteocytes. *In-vivo* and *in-vitro* data uniformly support the concept that new bone formation, as well as bone micro architectural integrity, is altered in the diabetic state, leading to an increased risk of fragility fracture and inadequate bone regeneration after injury, as well as delayed wound healing. In diabetic patients, glutathione is reduced at the cellular level that may be responsible for increasing oxidative stress. Regarding this author suggested that oxidative stress alone may be sufficient to promote the development of the osteonecrosis while the administration of BPs may further exacerbate these states.[29,30] While Park *et al*. in 2012 reported, BPs induced ONJ also developed in those compromised patients who undergo renal transplantation followed by administration of long term oral BPs therapy. He also reported extraction was the main provoking factor for the development of BPs induced ONJ. Therefore, adequate dental care is required before and after renal transplantation to reduce the risk of BPs induced ONJ.[31]

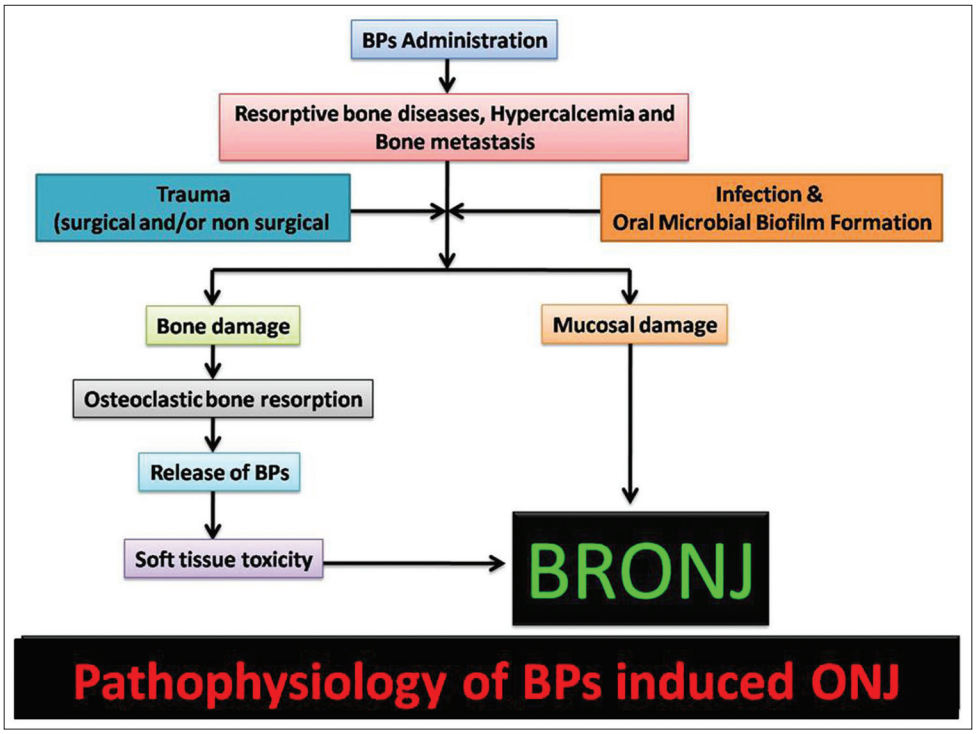

Figure 1: Etiopathogenesis of bisphosphonates-related osteonecrosis of the jaw

Conclusion

BPs associated ONJ is a relatively rare but severe clinical condition while exact pathogenesis of BRONJ is not known until today, but numerous hypotheses were described in previous literature that promote and interlinked the development of BPs induced ONJ. During reviewing the Pathophysiology of BRONJ, we found it is multifactorial such as long term administration of intravenous N-BPs in cancer patients, biological behavior of the mandibular or maxillary bone, antiangiogenic property of BPs and by soft tissue toxicity etc. All these factors are compounded by the presence of infection that are responsible for lower the pH of the oral cavity, other drugs like administration of corticosteroid, pathologies that cause hypo-calcification of bone, compromised immune response that alters normal healing such as chronic diabetic mellitus or severe renal dysfunction and trauma to jaw bones [Figure 1].

References

1. Fleisch H. Development of bisphosphonates. Breast Cancer Res 2002;4:30-4.
2. Russell RG. Bisphosphonates: From bench to bed side. Ann NY Acad Sci 2006;1068:367-401.
3. Papapetrou PD. Bisphosphonate – associated adverse events. Hormones (Athens) 2009;8:96-110.
4. Bertoldo F, Santini D, LoCascio V. Bisphosphonates and osteomyelitis of the jaw: A pathogenic puzzle. Nat Clin Pract Oncol 2007;4:711-21.
5. 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 jaw-2009 Update. Approved by the Board of Trustees January 2009. Accessed Month Date, Year, at, http://www.aaoms.org/docs/position_paper/bronj_updatepdfAAOMSPositionPaperonBisphosphonates-RelatedOsteonecrosisoftheJaw-2009Update [Last accessed date 22 Nov. 2012].
6. Suzuki BJ, Klemes AB. Osteoporosis and Osteonecrosis of the Jaw. American Dental Hygienists Association. Special Supplementary Issue-MAR 2008. ADHA. Supplement to Access–March 2008.
7. Vincenzi B, Napolitano A, Zoccoli A, Iuliani M, Pantano F, Papapietro N, *et al*. Serum VEGF levels as predictive marker of bisphosphonate-related osteonecrosis of the jaw. J Hematol Oncol 2012;5:56.
8. Compston JE, Bilezikian JP. Bisphosphonate therapy for osteoporosis: The long and short of it. J Bone Miner Res 2012; 27:240-2.
9. NSW Health Guide line. Prevention of osteonecrosis of the jaw (ONJ) on patients with Bisphosphonates therapy. GL 2010_010 July 2010. Accessed Month Date, Year, at, http://www.health.nsw.gov.au/policies/gl/2010/pdf/GL2010_010.pdf [Last accessed date 16 Sep. 2012].
10. Lam DK, Sándor GK, Holmes HI, Evans AW, Clokie CM. A review of bisphosphonate-associated osteonecrosis of the jaws and its management. J Can Dent Assoc 2007;73:417-22.
11. Andriani A, Petrucci MT, Caravita T, Montanaro M, Villivà N, Levi A, *et al*. Evolution of bisphosphonate-related osteonecrosis of the jaw in patients with multiple myeloma and Waldenstrom's macro globulinemia: A retrospective multicentric study. Blood Cancer J 2012;2:e62.
12. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: A growing epidemic.

J Oral Maxillofac Surg 2003;61:1115-7.
13. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: A review of 63 cases. J Oral Maxillofac Surg 2004;62:527-34.
14. Woo SB, Hellstein JW, Kalmar JR. Narrative corrected review: Bisphosphonates and osteonecrosis of the jaws. Ann Intern Med 2006;144:753-61.
15. McLeod NM, Brennan PA, Ruggiero SL. Bisphosphonate osteonecrosis of the jaw: A historical and contemporary review. Surgeon 2012;10:36-42.
16. Popovic KS, Kocar M. Imaging findings in bisphosphonate-induced osteonecrosis of the jaws. Radiol Oncol 2010;44:215-9.
17. Russell RG. Bisphosphonates: Mode of action and pharmacology. Pediatrics 2007; 119(Suppl 2): S150-62.
18. Hewitt C, Farah CS. Bisphosphonate-related osteonecrosis of the jaws: A comprehensive review. J Oral Pathol Med 2007; 36:319-28.
19. Roelofs AJ, Thompson K, Gordon S, Rogers MJ. Molecular mechanisms of action of bisphosphonates: Current status. Clin Cancer Res 2006;12:6222s-30.
20. Tanvetyanon T, Stiff PJ. Management of the adverse effects associated with intravenous bisphosphonates. Ann Oncol 2006;17:897-907.
21. Kim YG, Lee YD, Kwon YD, Suh JH, Jeen SM. Study on bisphosphonates-related osteonecrosis of the jaw (BRONJ): Case report and literature review. J Korean Assoc Oral Maxillofac Surg 2010;36:291-302.
22. Borgioli A, Viviani C, Duvina M, Brancato L, Spinelli G, Brandi ML, *et al*. Biphosphonates-related osteonecrosis of the jaw: Clinical and physio-pathological considerations. The Clin Risk Manag 2009; 5:217-27.
23. Ardine M, Generali D, Donadio M, Bonardi S, Scoletta M, Vandone AM, *et al*. Could the long-term persistence of low serum calcium levels and high serum parathyroid hormone levels during bisphosphonate treatment predispose metastatic breast cancer patients to undergo osteonecrosis of the jaw ? Ann Oncol 2006;17:1336-7.
24. Reid IR. Osteonecrosis of the jaw: Who gets it, and why? Bone 2009;44:4-10.
25. Ji X, Pushalkar S, Li Y, Glickman R, Fleisher K, Saxena D. Antibiotic effects on bacterial profile in osteonecrosis of the jaw. Oral Dis 2012;18:85-95.
26. Sedghizadeh PP, Yooseph S, Fadrosh DW, Zeigler-Allen L, Thiagarajan M, Salek H, *et al*. Metagenomic investigation of microbes and viruses in patients with jaw osteonecrosis associated with bisphosphonate therapy. Oral Surg Oral Med Oral Pathol Oral Radiol 2012;114:764-70.
27. Pazianas M. Osteonecrosis of the jaw and the role of macrophages. J Nat Cancer Inst 2011;103:232-40.
28. Gupta J, Gill AS, Sikri P. Evaluation of the relative efficacy of an alloplast used alone and in conjunction with an osteoclast inhibitor in the treatment of human periodontal infra bony defects: A clinical and radiological study. Indian J Dent Res 2011;22:225-31.
29. Khamaisi M, Regev E, Yarom N, Avni B, Leitersdorf E, Raz I, *et al*. Possible association between diabetes and bisphosphonate-related jaw osteonecrosis. J Clin Endocrinol Metab 2007;92:1172-5.
30. Ewing GW, Parvez SH. The multi-systemic nature of diabetes mellitus: Genotype or phenotype? N Am J Med Sci 2010;2:444-56.
31. Park W, Lee SH, Park KR, Rho SH, Chung WY, Kim HJ. Characteristics of bisphosphonate-related osteonecrosis of the jaw after kidney transplantation. J Craniofac Surg 2012;23:e510-4.

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