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# Demographic characteristics and risk factors in the development of medication-related osteonecrosis of the jaws

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**Abstract**
Retrospective study of 59 patients of medically related osteonecrosis of the jaw admitted to the Maxillofacial Surgery Clinic, St. Marina University Hospital, Varna Medical University for a period of 10 years (2000-2019). Major malignancies were breast and prostate carcinoma at 56% and 20%, respectively. There is an increase in the annual incidence of osteonecrosis and an average incidence of 10.17% of those treated for the entire period. Mean age was 64 ± 14 years and there was female predominance and predominance of localization of MRONJ in the lower jaw. T2DM and hypertension were 36% and 64% of all patients. In 24 patients with MRONJ vitamin D levels were low in 100% of patients.

**Keywords:** Medically related osteonecrosis of the jaw (MRONJ), risk factors, T2DM, hypertension, vitamin D

## 1. Introduction

Medically related osteonecrosis of the jaws is a side effect of long-term treatment with antiresorptive drugs such as bisphosphonates and lately with RANK-L inhibitors such as Denosumab with the diagnosis being made on persistent oral lesions of necrotic mandibular or maxillary bone that can cause pain or be asymptomatic [1-5]. In 2003, first cases of alveolar bone exposure in patients receiving bisphosphonate therapy were published, followed by a number of other publications in the field. Over the past 10 years this has proven to be a growing problem associated with increased frequency of osteonecrosis and new medication groups like antiangiogenenic agents became involoved [6, 7, 8]. Osteonecrosis of the jaws is a rare but potentially serious side effect of treatment with antiresorptive agents in patients with malignant solid tumors and metastatic bone disease or myelomatosis patients on intravenous administration protocols, but also in millions of patients with osteoporosis on oral bisphosphonate protocols [9, 10].

In 2014 The American Association of Oral and Maxillofacial Surgery (AAOMS) recommends the term medication-associated osteonecrosis of the jaws (MRONCH) and assumed that jaw bone osteonecrosis may be present if the following criteria are met: (a) current or prior treatment with anti-resorptive or anti-angiogenic agents; (b) exposure of bone that can be probed through an intraoral or extraoral fistula in the maxillofacial area lasting for more than eight weeks; c) no evidence of previous radiotherapy in the area [2].

The etiology of MRONJ has been extensively studied, but consensus on basic pathophysiology has not yet been reached . The hypotheses on MRONJ etiology include:

a. suppressed angiogenesis and presence of immunosuppression leading to avascular necrosis [5, 6, 11];
b. (b) suppression of bone remodeling due to reduced viability of osteoclasts and osteocytes and osteoblasts [11];
c. fibroblast suppression and the appearance of microfractures [12, 13]; suppression of collagen exchange in bones and soft tissues with decreased viability of oral keratinocytes [14, 15, 16];
d. infection with oral microbial biofilms migrating to exposed jaw bone after dental procedures [29]
e. The role of vitamin D in bone remodeling and osteonecrosis pathogenesis [15, 16].

Bone elasticity and strength, collagen protein and calcium mineral component are of particular importance in the pathophysiology of MRONJ. The bone matrix is a two-phase system in which the mineral phase provides strength and the collagen fibers provide elasticity and energy absorption capacity. Changes in collagen metabolism may affect the bone's mechanical properties and increase fracture risks. Type I collagen is the most common type of collagen and is widespread in almost all connective tissues. It is the major protein in bones and skin and accounts for 95% of bone collagen and about 80% of bone protein [17-19]. Decreased bone collagen production, as shown by the bone resorption markers, is invisible in bone mineral density (BMD) examination using X-ray osteometry [22-24]. On the other hand, the prognostic ability of the BMD for fracture risk assessment does not exceed 50% multiple clinical trials,

since only the mineral phase, rather than the overall bone structure, is evaluated. In experimental studies decreased viability of oral keratinocytes was also found, which could be the likely explanation for bone exposure in the clinical presentation of MRONJ [13-15]. Prolonged administration of bisphosphonates may result in bone microfractures visualized by a scanning electron microscope, due to the elevated chewing pressure in both lower and upper jaw seen in both animal models and clinical trials. The presence of microfractures is associated with reduced bone remodeling through suppressed osteoclast function as well as a first asymptomatic phase of the disease which, after an initiating factor such as tooth extraction and bacteria microfilm insertion may progress to its second and manifest phase of pain, bone sequestration and inflammation [20, 21].

## Materials and methods

Retrospective study of patients with MRONJ admitted to the Department of Oral and Maxillofacial Surgery and Special Image Diagnostics, Faculty of Dental Medicine,, St. Marina University Hospital, Varna University, Bulgaria for the period 2000-2019. A total of 59 patients with MRONJ were evaluated according to AAOMS criteria[2], with assessment of age, gender, X-ray, risk factors such as diabetes mellitus and arterial hypertension[24], as well as the status and location of osteonecrosis as well as major malignant underlying tumors. In 13 patients with bisphosphonate treatment and with MRONJ vitamin D concentrations were evaluated.

## Laboratory Methods

Vitamin D is a fat-soluble vitamin with two major biological forms: D3 (cholecalciferol) and D2 (ergo-calciferol). Vitamin D deficiency is widespread especially in the elderly and is a risk factor for vascular, neoplastic and neurodegenerative diseases. The status of vitamin D has been investigated in patients with MRONJ and studies have been conducted to increase vitamin D levels in such patients.

*Vitamin D* - determined by ECLIA - an immunological, electrochemical, high-value method. An automated analyst Elecsys 2010, Roche Diagnostics, Switzerland, was used to determine the total volume 25 (OH) . Vitamin D is the major regulator of blood calcium levels. Increases gastrointestinal absorption and renal tubular reabsorption of calcium, stimulates calcium release from bones. Its levels depend on parathyroid hormone and calcitonin. Normal values above 30 ng / ml (50 nmol / L) (Serious deficiency <12 ng / ml (25 nmol / L), Deficiency 12-30 ng / ml).

## Statistical methods

Statistical data grouping - the variables are sorted according to their type in variation, interval, category statistic rows. Statistical estimation method - point estimates - for mean of continuous variables and percentage.

Graphic methods - Microsoft Office Professional Plus Exel is used to visualize and describe demographic data and patient risk characteristics.

## Results

Table 1 shows demographic data of 59 patients enrolled in the study with an average age of 64 ± 14 years, with female prevalence of 67%. Most of the patients were in -stage III MRONJ-56%, the remaining 44% were in stage II according MRONJ to the 2014 American Association of Oral and Maxillofacial Surgery (AAOMS) recommendations. 36% of patients had diabetes mellitus and 46% had high blood pressure. The frequency of MRONJ during the entire period of 560 patients treated with bisphosphonate / denosumab was 10.17%.

**Table 1:** Demographic data for patients with MRONJ included in the study

| Patients Total | Age years | Gender females | Stage III | Type2 DM % | Hypertension % | FrequencyMRONJ |
|---|---|---|---|---|---|---|
| 59 | 64± 14 | 67% | 56% | 36% | 64% | 10,17% |

MRONJ's annual frequency is growing significantly especially between 2014-2018. (Fig 1).

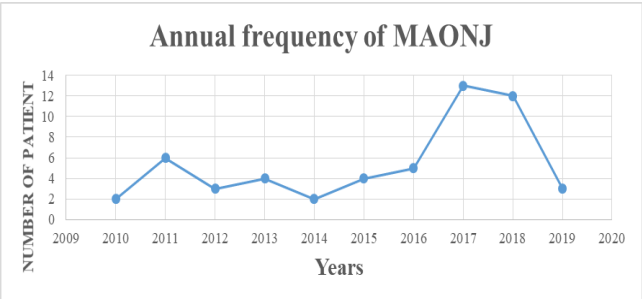


**Fig 1:** Annual frequency of medically related osteonecrosis of the jaw in the period 20010-2019

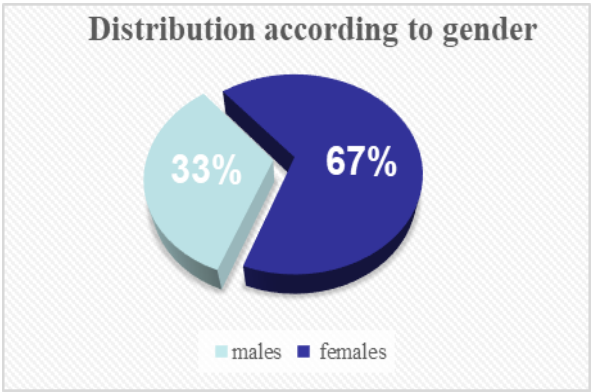


**Fig 2:** Distribution by sex of patients with MRONJ

The female sex predominates with two-thirds of the women being affected in Fig.2.

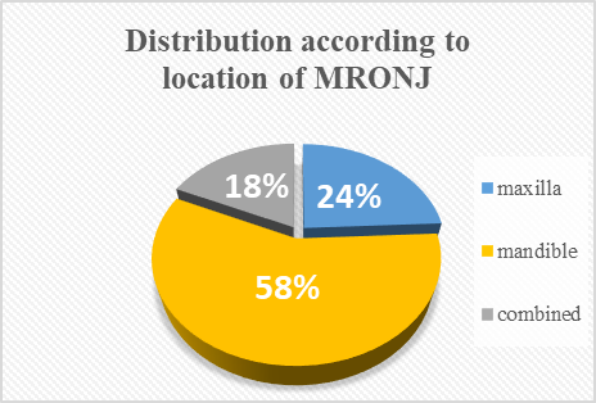


**Fig 3:** Percentage distribution according to the location of MRONJ

The distribution of cases according to the localization of the disease indicates predominance of osteonecrosis of the lower jaw in 58%, localization in the upper jaw - in 18% and mixed localization in 18%. (Fig. 3)

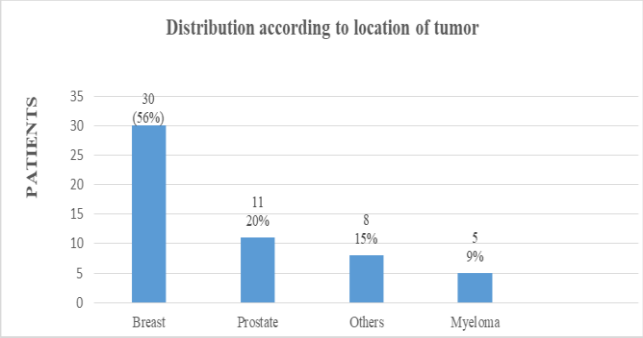


**Fig 4:** Distribution of patients according tumor location

Women with breast cancer 56%, prostate cancer in men - 20%, other tumors including brain, kidney, urinary bladder and liver - 15% and multiple myeloma - 9% are the most frequently affected. (Fig 4).

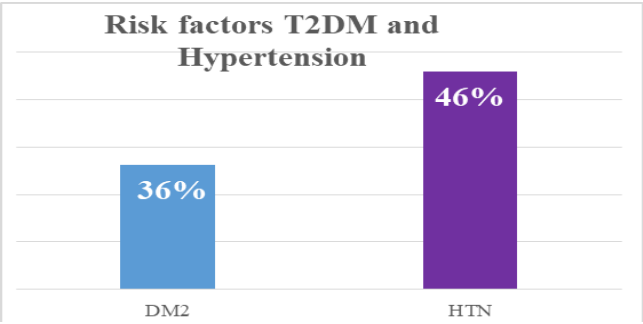


**Fig 5**: Distribution of patients according to risk factors for type 2 diabetes mellitus and arterial hypertension.

There are also other risk factors such as type 2 diabetes mellitus in 36% and arterial hypertension in 46% of patients (Fig 5).

**Vitamin D in patients with MRONJ**

Table 2 shows the values of vitamin D and Table 3 is the distribution of concentrations of vitamin D. Vitamin D values are severely deficient in 64% of MRONJ+ individuals.

**Table 2:** Values of vitamin D in patients with MRONJ

| Patients | Number | Age | Vitamin D ng/ml Serious deficit < 12 Deficit 12 - 30 Normal > 30 |
|---|---|---|---|
| MRONJ+ | 14 | 64±11 | 20,2±11,5 |

**Table 3:** Values of vitamin D in patients with MRONJ

| Biomarker | Values | MRONJ+% |
|---|---|---|
| Vit D | <12 ng/ml | 64 (9) |
| | >12<30 ng/ml | 29 (4) |
| | >30 ng/ml | 7 (1) |

**Discussion**

In 2007 the risk of MRONJ in cancer patients treated with high doses of intravenously administered BP was established in the range of 1% to 10%. Until recently, it was claimed that MRONJ is only related to intravenous use of bisphosphonates. The relative MRONJ risk from oral bisphosphonates in the past was estimated at 0.05 to one case per 100,000 person-years of exposure to oral BF. However, retrospective articles published since 2009 concluded that the actual risk of MRONJ of oral bisphosphonates is 4% and even 8% [1, 2, 3, 9, 10]. The proportion of patients with MRONJ on oral BP increases as the frequency approaches that of patients receiving parenteral BP [3, 9, 10]. The increased incidence of MRONJ is based on a retrospective analysis of data collected from different clinical centers in Europe. A large review to evaluate risk factors for MRONJ identified age over 63 years, female gender, duration of treatment with BF over 12 months, diabetes mellitus, hypertension, hypercholesterolemia, treatment with corticosteroids, chemotherapy and tooth extraction [1]. In this study risk factors like age, female gender, diabetes and hypertension were also found. The number of patients with MRONJ has increased in Japan [26]. This 2018 large-scale survey of included 4 797 cases and established women's predominance and twice as frequent occurrence of the lower jaw compared to maxilla. Most patients were in Stage II (61.4%), followed by Stage I (20.7%) and Stage III (16.8%). The most common primary disease were malignant neoplasm (46.5%), followed by osteoporosis (including prevention - 45.3%).

The role of vitamin D in patients with MRONJ is not well-established and it is generally suggested that low vitamin D levels may predispose to the development of MRONJ. In a 2-year retrospective study vitamin D values were compared in patients without exposed bone to stage II patients and a significant difference was found 29.5 vs. 20.49 ng / ml with recommendation for adequate substitution of vitamin D in patients treated with antiresorptive drugs [17]. In another study MRONJ + and MRONJ - patients treated with bisphosphonates were compared with respect to vitamin D levels, parathyroid hormone, bone alkaline phosphatase, C terminal collagen telopeptide I. There was vitamin D deficiency defined as 25-OH-D <50 nmol / l in 62% of MRONJ + and 59% MRONJ- patient and the study suggested that vitamin D deficiency is present but is not likely to be a risk factor in MRONJ etiology [27]. Serious deficit of vitamin D in this study was found in 67% of

patients and in 93% of patients vitamin D was found low, but vitamin D deficiency is frequent in this age group and scientific evidence says that chronic conditions like diabetes, hypertension, rheumatoid arthritis, cardiovascular disease and most common cancers are frequently affected. [28].

## Conclusion

1. The incidence of MRONJ has risen in the last 10 years and reaches 10,17 % of those treated with bisphosphonates / denosumab.
2. Females predominate in a 2: 1 ratio in 67% of cases. The average age is 64 ± 14. The most common solid tumors are breast cancer in women and prostate cancer in men. Lesion prevalence is most commonly in the lower jaw in 58% of patients.
3. Low vitamin D was found in 93% of patients, but vitamin D deficiency is frequent in this age group and in the presence of many accompanying disease states.

## References


1. Khosla S, Burr D, Cauley J, *et al*. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2007; 22(10):1479-1491.
2. Ruggiero SL, Thomas B. Dodson John Fantasia, Reginald Goodday, Tara Aghaloo Mehrotra.. Maxillofacial Surgeons Position Paper on Medication-Related Osteonecrosis of the Jaw Update J Oral Maxillofac Surg. 2014; 72:1938-1956.
3. Rizzoli R, Burlet N, Cahall D, *et al*. Osteonecrosis of the jaw and bisphosphonate treatment for osteoporosis. Bone. 2008; 42(5):841-847.
4. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg. 2003; 61(9):1115-1117.
5. Migliorati CA. Bisphosphanates and oral cavity avascular bone necrosis. J Clin Oncol. 2003; 21(22):4253-4254.
6. Carter GD, Goss AN. Bisphosphonates and avascular necrosis of the jaws. Aust Dent J. 2003; 48(4):268.
7. Estilo CL, Van Poznak CH, Williams T, *et al*. Osteonecrosis of the maxilla and mandible in patients with advanced cancer treated with bisphosphonate therapy. Oncologist. 2008; 13(8):911-920.
8. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/ osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. J Oral Maxillofac Surg. 2005; 63(11):1567-1575.
9. Sedghizadeh PP, Stanley K, Caligiuri M, *et al*. Oral bisphosphonate use and the prevalence of osteonecrosis of the jaw: an institutional inquiry. J Am Dent Assoc. 2009; 140(1):61-66.
10. Otto S, Abu-Id MH, Fedele S, *et al*. Osteoporosis and bisphosphonates-related osteonecrosis of the jaw: not just a sporadic coincidence—a multi-centre study. J Craniomaxillofac Surg. 2011; 39(4):272-277.
11. Santini D, Vincenzi B, Avvisati G, *et al*. Pamidronate induces modifications of circulating angiogenetic factors in cancer patients. Clin Cancer Res. 2002; 8(5):1080-1084.
12. Hoefert S, Schmitz I, Tannapfel A, Eufinger H. Importance of microcracks in etiology of bisphosphonate-related osteonecrosis of the jaw: a possible pathogenetic model of symptomatic and non-symptomatic osteonecrosis of the jaw based on scanning electron microscopy findings. Clin Oral Investig. 2010; 14(3):271-284.
13. Mashiba T, Mori S, Burr DB, *et al*. The effects of suppressed bone remodeling by bisphosphonates on microdamage accumulation and degree of mineralization in the cortical bone of dog rib. J Bone Miner Metab. 2005; 23(suppl):36-42.
14. Walter C, Klein MO, Pabst A, *et al*. Influence of bisphosphonates on endothelial cells, fibroblasts, and osteogenic cells. Clin Oral Investig. 2010; 14(1):35-41.
15. Landesberg R, Cozin M, Cremers S, *et al*. Inhibition of oral mucosal cell wound healing by bisphosphonates. J Oral Maxillofac Surg. 2008; 66(5):839-847.
16. Koch F, Yekta SS, Merkel C, *et al*. The impact of bisphosphonates on the osteoblast proliferation and Collagen gene expression in vitro. Head Face Med, 2010, 12.
17. Heim N, Warwas F, Wilms C, Reich R, Markus V. Vitamin D (25-OHD) deficiency may increase the prevalence of medication-related osteonecrosis of the jaw J Oral Maxillofac Surg. 2017; 46(2):151-156.
18. Simon MJ, Niehoff P, Kimmig B, *et al*. Expression profile and synthesis of different collagen types I, II, III, and V of human gingival fibroblasts, osteoblasts, and SaOS-2 cells after bisphosphonate treatment. Clin Oral Investig. 2010; 14(1):51-58.
19. Niyibizi C, Eyre DR. Structural characteristics of cross-linking sites in type V collagen of bone. Chain specificities and heterotypic links to type I collagen. Eur J Biochem. 1994; 224(3):943-950.
20. Bjarnason NH, Sarkar S, Duong T, *et al*. Six and twelve month changes in bone turnover are related to reduction in vertebral fracture risk during 3 years of raloxifene treatment in postmenopausal osteoporosis. Osteoporos Int. 2001; 12(11):922-930.
21. Bone HG, Hosking D, Devogelaer JP, *et al*. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med. 2004; 350(12):1189-1199.
22. Garnero P, Sornay-Rendu E, Chapuy MC, Delmas PD. Increased bone turnover in late postmenopausal women is a major determinant of osteoporosis. J Bone Miner Res. 1996; 11(3):337-349.
23. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ. 1996; 312(7041):1254-1259.
24. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018; 71:e127-e248.
25. Schuit SC, Van Der Klift M, Weel AE, *et al*. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. Bone. 2004; 38(4):195-202.
26. Shibahara T, Morikawa T, Yago K, Kishimoto Imai Y, Kurita K. National Survey on Bisphosphonate-Related

Osteonecrosis of the Jaws in Japan. Osteoporos Int. 2018; 29(10):2315-2321.
27. Bedogni A, Bettini G, Bedogni G, Basso D, Gatti D, Valisena S, *et al*. Is vitamin D deficiency a risk factor for osteonecrosis of the jaw in patients with cancer? A matched case-control study. J Craniomaxillofac Surg. 2019, pii: S1010-5182(18)31039-4.
28. Holick MF. The vitamin D epidemic and its health consequences. J Nutr. 2005; 135:2739-2748.
29. Russmueller G, Weiss K, Stadler V. The association of medication-related osteonecrosis of the jaw with Actinomyces spp. Infection Scientific Reports volume 6, Article number, 2016, 31604.