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MRONJ and VIT D insufficiency

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ABSTRACT

Background: Medication related osteonecrosis of the jaw (MRONJ) is a chronic condition of the oral cavity resulting in mucosal ulceration and exposure of underlying necrotic bone, and the ensuing secondary complications. The aim of this study was to evaluate the relationship between vitamin D deficiency and osteonecrosis of the jaw related to bisphosphonates.

Materials and Methods: This was a case-control study. The samples were 20 patients taking bisphosphonates, that 10 of them were with MRONJ and 10 were non-MRONJ. Clinical examination of patients was performed to diagnose jaw osteonecrosis. Demographic data of the patients were recorded including age, sex, type of drug, duration and cause of drug intake, and measurement of serum vitamin D levels. Data were analyzed using SPSS software.

Results: In the patients without MRONJ, the mean age was 60.60 (±14.975) years, and in the patients with MRONJ, the mean age was 68.30 (69.92) years. As a whole, of the 16 female patients in this study, 10 cases (62.5%) were non- MRONJ and 6 cases (37.5%) were suffered by MRONJ. All of the male patients presented with MRONJ. In control group mean of vitamin D was 63.990 ng/ml (±29.796) and in case group mean of vitamin D was 29.510 ng/ml (±23.723). The serum level of vitamin D (25-OHD) was significantly higher in control group than in the case group (p=0.010).

Conclusion: According to our result, there were statistically significant relationship between age, sex, type of drug, vitamin D level, and MRONJ (p>0.05).

Key words: MRONJ; Vitamin D; Bisphosphonates; Osteonecrosis of the jaws.

Introduction

Vitamin D is not only an essential factor for bone and minerals natural metabolism, but also plays an important role in non-bony metabolism processes [1]. Vitamin D deficiency consequences for other organs except for bone are not fully known but researchers showed that it can cause impaired immunity, increased autoimmunity, myopathy, diabetes mellitus, and an increased risk of colon, breast, and prostate cancers [2].

Vitamin D is produced by skin when exposed to sun or obtained from dietary sources, including supplements. Persons commonly at risk for vitamin D deficiency include those with inadequate sun exposure, limited oral intake, or impaired intestinal absorption. Even people who live in sunny climates are commonly found to be deficient in vitamin D like Middle East, probably because of cultural habits and their clothing [1]. According to the recent systematic review and meta-analysis in our country, the prevalence of vitamin D deficiency among male, female, and pregnant women was estimated to be 45.64%, 61.90%, and 60.45%, respectively and was significantly different in various geographical regions [3]. Vitamin D deficiency is a global public health problem in all age groups, particularly in those who live in Middle East [4].

On the other hand, with the increasing prevalence of osteoporosis and its diagnostic and preventive methods, the use of bisphosphonates has also increased [5]. About 70% of women and 50% of men over the age of 50 tend to have osteoporosis, according to our regional statics. Worldwide, it is estimated that over 200 million people in the world is affected by osteoporosis [6]. Other groups of bisphosphonate users are patient with metastatic cancers (such as breast and prostate cancer and multiple myeloma), hypercalcemia and Paget's [5]. Bisphosphonates are chemical agents for preventing bone loss that alter the morphology and activity of bone marrow cells in different ways [7]. These medication include a central carbon that binds to hydroxyl groups and allows the molecule to bond to calcium [8]. If nitrogen or amine is present in the structure of drug, it is called nitrogen containing bisphosphonate (NBPs), which are 10 to 10,000 times more potent antiresorptive than non-nitrogenous species [9]. Zoledronic acid, a type of NBPs, is the most associated bisphosphonate with the clinical cases of MRONJ [10].

Bisphosphonates affect the differentiation and maturity of osteoclasts and disrupt their function. On the other hand, these drugs cause apoptosis of osteoclasts and reduce bone loss. Ultimately, bone remodeling and fracture risk decrease and structural strength increase [11]. Bisphosphonates cause calcium chelated formulas to bind to the outer surface of the bone hydroxyapatites, prompting the release of factor that prevents precursor cells from fusing to produce osteoclasts [7]. The bisphosphonate has side effects, most notably osteonecrosis of the jaw. MRONJ means necrosis in part of the jaw bone that does not improve over the course of 8 weeks [5]. Risk factors such as infection and trauma are strongly associated with MRONJ, which are obviously likely to be involved in tooth extraction [5,12]. Out of 3918 MRONJ cases reported in a series of studies, dental extraction and periodontal diseases were underlying factors in 61.7% and 5% respectively [5]. Researches showed that oral and dental health is effective in preventing MRONJ, but when the disease occurs, it does not play a significant role in progression anymore [13]. The probability of developing MRONJ in IV type users of bisphosphonates is higher, as well as oral users in combination with steroid drugs [14].

According to the latest data from the American Surgical Association, the risk factors for MRONJ are categorized to associate with drug, topical, demographic, or systemic, and genetics. Obesity and smoking have recently been identified as a possible risk factor, but the most risk factor for MRONJ is Zoledronic acid using [15]. In treating MRONJ, trying to reduce or eliminate symptoms, slow down or prevent progression of the disease and complete removal of unhealthy bone are the main goals. The gold standard treatment for this disease has not been introduced yet. The proposed treatment methods include antibiotics prescription orally or local, discontinuation of medication if possible, pain control, surgical debridement or bone resection (in case of extensive bone involvement, it is possible that the surgeon performs the partial mandibulectomy or parietal maxillectomy and then uses Fibula grafts and covers it with tissue flaps.) Hyperbaric oxygen, fluorescent-guided bone resection and low-power laser therapy [16].

Other therapeutic concepts that lead to an improvement in the rate of wound healing by using growth factors and tissue differentiation are also being studied, such as autologous transplantation of bone marrow cells into the lesion. Recently, triparathyroid (34-amino acid recombinant with human parathyroid hormone) has also been reported as a treatment for MRONJ. Pentoxifylline and alpha-tocopherol have also been recommended in association with antimicrobial therapy and cause reduced bone loss and disease symptoms. The use of ozone with antibiotic therapy and surgery in exposed bone lesions can reduce the pain, secretion and halitosis in these patients [16]. It is understood from this introduction that knowing the risk factors for MRONJ especially for dentists would be beneficial and in this regard, we have investigated the potential effects of vitamin D deficiency as a public health problem on the incidence of MRONJ.

Materials and Methods

This case-control study was performed in the department of oral and maxillofacial surgery in school of dentistry. Samples and information from patients were collected. The present study was confirmed by the Ethics Committee of the Medical Research University of Tehran (ID IR. TUMS.DENTISTRY.REC.1397.063). A study was conducted on patients with MRONJ who referred to the clinic of oral and maxillofacial surgery of Shariati Hospital in Tehran. Patients in the control group (taking bisphosphonates) were selected from the patients referred for a clinical examination to the clinic of orthopedic of Imam Khomeini Hospital in Tehran. The inclusion criteria for case group is MRONJ and history of oral bisphosphonates, and in control group no MRONJ with history of oral bisphosphonates and written consent was obtained from patients after explaining the conditions of cooperation and their willingness to participate in the project.

In the case group, serum vitamin D levels were measured with other initial tests during admission or onset of treatment. These patients were under clinical examination at the beginning and during the treatment period. The control group generally took the oral form of the drug. The 25OH-VIT D3 test was also requested to check the amount of vitamin D in these patients, and clinical examinations was done for the presence or absence of jaw osteonecrosis. Clinical examination of patients to detection of jaw osteonecrosis, demographic data gathering, time and cause of drug administration, and measurement of serum levels of vitamin D were the main variables for this study. The statistical analysis of data was performed using SPSS (version 20.0). Descriptive statistics were used to describe the data, and independent t-test and regression were used to analyze the data. The value of $P<0.05$ was considered as statistically significant.

Results

In the patients without MRONJ, the mean age (±standard deviation (SD)) was 60.60 (±14.975) years, with a minimum of 25 and a maximum of 81 years. In the patients with MRONJ, the mean age was 68.30 (69.92) years, with a minimum of 59 and a maximum of 78 years. Of the 16 female patients in this study, 10 cases (62.5%) were non-MRONJ and 6 cases (37.5%) were with MRONJ. All of the male patients presented with MRONJ. Of the 11 patients taking the oral form of bisphosphonates, 10 (90.9%) cases were without MRONJ and 1 (9.1%) with MRONJ. Of the 9 patients taking the IV form of bisphosphonates, all (100%) cases had MRONJ. In control group mean of vitamin D was 63.990 ng/ml (±29.796) with a minimum of 35 and a maximum of 115 ng/ml. In case group mean (±SD) of vitamin D was 29.510 ng/ml (±23.723) with a minimum of 7.2 and a maximum of 82 ng/ml. The serum level of vitamin D (25-OHD) was significantly higher (t=-2.2863, p=0.010) in control group (63.990±29.796 ng/ml) than in the case group (29.510±23.723 ng/ml). (Fig-1).

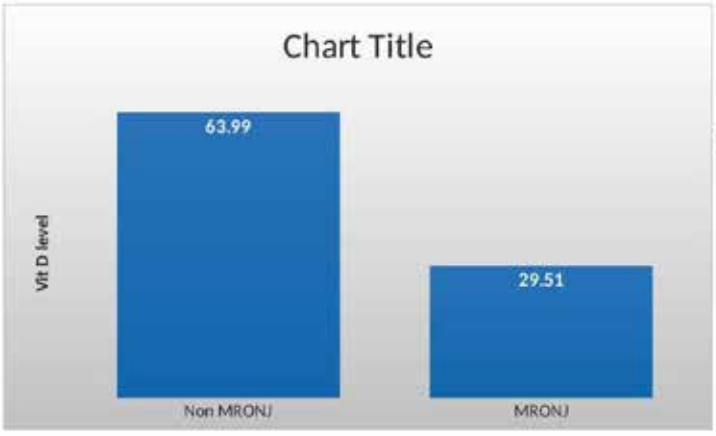

Fig1- Vit D level in both MRONJ and Non MRONJ patients.

Fig 1. Vit D level in both MRONJ and Non MRONJ patients.
MRONJ: medication related osteonecrosis of the jaws.
Non MRONJ: non medication related osteonecrosis of the jaws.

Discussion

Today, vitamin D deficiency has become a global health problem, and the prevalence of deficiency in the Middle East is more than any other region [4]. Since this vitamin plays a significant role in the function of various organs of the body, its effect on various diseases is significant [2]. In some cases, the use of bisphosphonates in the treatment of osteoporosis and cancers with primary bone lesions or skeletal metastases, can lead to the bisphosphonate related osteonecrosis of the jaw as a side effect of these medications [5]. Risk factors such as infection and trauma are strongly associated with bisphosphonate related osteonecrosis of the jaw, which are obviously likely to be related to each other in tooth extraction. Other local factors are infective teeth, dental abscess, endodontic treatment and tori. This lesion is the result of interaction between bone metabolism, local trauma, an increase in the need for bone repair in the area, infection, and hypovascularity [5,12].

Research shows that oral health is effective in preventing MRONJ, but does not play a role during disease [13]. Dental treatments, especially invasive treatments, are a risk factor for the onset of MRONJ, so dentists should be aware of the systemic conditions of patients and the special treatment considerations for these patients. On the other hand, dental treatments before taking bisphosphonates, may reduce the risk of developing MRONJ over the course of consumption [12]. As the results of this study also show, the likelihood of MRONJ occurring is higher in older patients, and in these age groups, vitamin D deficiency was more reported also. Therefore, older age groups are more prone to MRONJ and require more care. The probability of developing MRONJ is higher in injecting users of bisphosphonates as well as oral administrated patients with taking steroid medications [14]. In this study also, most cases of MRONJ were patients who were injecting bisphosphonates, and in one case of oral bisphosphonate, the patient reported a history of long term oral corticosteroid use.

Therefore, in patients taking the injectable form of bisphosphonates, we are more likely to have MRONJ, and it is better to do dental treatments before or after drug administration, since dental treatments, especially invasive treatments, are an important factor for starting osteonecrosis of Jaw. Also, in patients taking oral medication, it would be better to ask for the history of taking steroid medications. The prevalence of vitamin D deficiency in women is higher than in men [1]. The results of this study indicate that both vitamin D deficiency and MRONJ are more common in women. The higher prevalence of vitamin D deficiency in women specially in our country is probably due to the type of female clothing [1]. However high BMI and low physical activity should be considered too. The effect of female hormones should be investigated.

In patients who use bisphosphonates, consumption can be discontinued for an interim period, which is called “drug holiday”. Most cases of MRONJ are seen in patients with a history of 3 years or more injectable bisphosphonates who have had a drug holiday of one year or less [17]. The results of this study also shows that patients who used bisphosphonates long-term, are more prone to MRONJ.

Conclusion

As we know vitamin D deficiency is an important factor for many diseases associated with bone metabolism. Based on Our result MRONJ is not an exception, so it is recommended that patients who are taking bisphosphonates, especially IV type, be monitored for serum vitamin D levels before taking bisphosphonates or during the course of treatment. Since dental treatments are the risk factor for starting MRONJ, dentists should be aware of the systemic condition of patients. It also suggested to know the therapeutic considerations in patients who take bisphosphonates. In women, older age groups and IV drug users who are more likely to develop MRONJ, careful consideration is needed. The levels of vitamin D in our patients with MRONJ are lower than those without MRONJ. Based on our sample size, designing larger studies would be worth.

Conflict of Interest

There is no conflict of interest to declare.

References

[1] Moradzadeh K, Larijani B, Keshtkar A, Hossein Nezhad A, Rajabian R, Nabipoor I, et al. Normal values of Vitamin D and prevalence of Vitamin D deficiency among Iranian population. SJKU. 2006; 10 (4): 22-42.

[2] Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: when to test and how to treat. Mayo Clin Proc. 2010; 85 (8): 752-7; quiz 7-8. https://doi.org/10.4065/mcp.2010.0138

[3] Tabrizi R, Moosazadeh M, Akbari M, Dabbagh-

manesh MH, Mohamadkhani M, Asemi Z, et al. High Prevalence of Vitamin D Deficiency among Iranian Population: A Systematic Review and Meta-Analysis. Iran J Med Sci. 2018; 43 (2): 125-39.

[4] Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol. 2014; 144 Pt A: 138-45. https://doi.org/10.1016/j.jsbmb.2013.11.003

[5] George EL, Lin Y-L, Saunders MM. Bisphosphonate-related osteonecrosis of the jaw: a mechanobiology perspective. Bone reports. 2018; 8: 104-9. https://doi.org/10.1016/j.bonr.2018.03.003.

[6] Reginster J-Y, Burlet N. Osteoporosis: a still increasing prevalence. Bone. 2006; 38 (2): 4-9. https://doi.org/10.1016/j.bone.2005.11.024

[7] Zara S, De Colli M, Di Giacomo V, Zizzari VL, Di Nisio C, Di Tore U, et al. Zoledronic acid at subtoxic dose extends osteoblastic stage span of primary human osteoblasts. Clin Oral Investig. 2015; 19 (3): 601-11. https://doi.org/10.1007/s00784-014-1280-8

[8] Russell RGG. Bisphosphonates: the first 40 years. Bone. 2011; 49 (1): 2-19. https://doi.org/10.1016/j.bone. 2011.04.022

[9] Drake MT, Clarke BL, Khosla S, editors. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clinic Proceedings; 2008: Elsevier. https://doi.org/10.4065/83.9.1032.

[10] Zafar S, Coates DE, Cullinan MP, Drummond BK, Milne T, Seymour GJ. Effects of zoledronic acid and geranylgeraniol on the cellular behaviour and gene expression of primary human alveolar osteoblasts. Clin Oral Investig. 2016; 20 (8): 2023-35. https://doi.org/10.1007/s00784-015-1706-y.

[11] Vohra F, Al-Rifaiy MQ, Almas K, Javed F. Efficacy of systemic bisphosphonate delivery on osseointegration of implants under osteoporotic conditions: lessons from animal studies. Arch Oral Biol. 2014; 59 (9): 912-20. https://doi.org/10.1016/j.archoralbio. 2014.05.016.

[12] Miloro M, Ghali G, Larsen P, Peterson LJ, Waite P. Peterson's principles of oral and maxillofacial surgery. 3 ed.: PMPH-USA; 2019. p.

[13] Krimmel M, Ripperger J, Hairass M, Hoefert S, Kluba S, Reinert S. Does dental and oral health influence the development and course of bisphosphonate-related osteonecrosis of the jaws (BRONJ)? J Oral Maxillofac Surg. 2014; 18 (2): 213-8. https://doi.org/10.1007/s10006-013-0408-3

[14] Taylor T, Bryant C, Popat S. A study of 225 patients on bisphosphonates presenting to the bisphosphonate clinic at King's College Hospital. Br Dent J. 2013; 214 (7): E18. https://doi.org/10.1038/sj.bdj. 2013.327.

[15] Nisi M, La Ferla F, Karapetsa D, Gennai S, Miccoli M, Baggiani A, et al. Risk factors influencing BRONJ staging in patients receiving intravenous bisphosphonates: a multivariate analysis. Int J Oral Maxillofac Surg. 2015; 44 (5): 586-91. https://doi.org/10.1016/j.ijom.2015.01.014.

[16] Fliefel R, Troltzsch M, Kuhnisch J, Ehrenfeld M, Otto S. Treatment strategies and outcomes of bisphosphonate-related osteonecrosis of the jaw (BRONJ) with characterization of patients: a systematic review. Int J Oral Maxillofac Surg. 2015; 44 (5): 568-85. https://doi.org/10.1016/j.ijom.2015.01.026.

[17] Jung SY, Suh HS, Park JW, Kwon JW. Drug holiday patterns and bisphosphonate-related osteonecrosis of the jaw. Oral Dis. 2018. https://doi.org/10.1111/odi.12966.

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