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Research Article

Serum Markers of Bone Turnover in Medication Related Osteonecrosis of the Jaw Patients

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Abstract

Objective: The aim of this study is to classify MRONJ patients according to the latest staging system as early stage (stage 0) and advanced stage (stage 1, 2, 3) and investigate how these groups affect the serum markers of bone turn-over, inflamation and endocrine function.

Materials and Methods: In this retrospective study; we examined 26 patients with MRONJ who presented between 2017 and 2018 in the our department. We recorded patients' clinical and radiological signs, location of exposed or necrotic bone, existence of infection, pain, degree of osteolysis and results of serum samples. In our study, patients were divided into 2 groups according to the criteria's stated by American Association of Oral and Maxillofacial Surgeons (AAOMS). Patients in Group I were in stage 0 (early stage) and patients in Group II were in stage 1, 2 and 3 (advantage stage). Serum samples were analyzed for thyroid stimulating hormone (TSH), triiodothyronine (T_3), thyroxine (T_4), C-Telopeptide (CTx), 25 Hydroxy vitamin D, bone-specific alkaline phosphatase (BALP), osteocalcin (OCN) and parathyroid hormone(PTH).

Results: There was a significant difference between the groups only levels of serum parathyroid hormone (PTH) showed ($p < 0,05$). Thyroid stimulating hormone (TSH), triiodothyronine (T_3), thyroxine (T_4), bone-specific alkaline phosphatase (BALP) and osteocalcin (OCN) are higher in Group II. The levels of 25 Hydroxy vitamin D and C-Telopeptide (CTx) are higher in Group I.

Conclusion: According to our study results, there was a significant difference between the groups only levels of serum PTH showed ($p < 0,05$). There was no significant difference other endocrine and bone turnover markers. Serum markers of bone turnover have become more available to follow- up early and advanced stages of medication related osteonecrosis of the jaw patients. Hovewer, it is important to remember that individual markers reflect different biochemical and physiological processes and may not, therefore, always show identical changes.

Keywords: *Bisphosphonates; Osteonecrosis of the Jaw; Bone Turnover; Serum Markers; Parathyroid Hormone*

Abbreviations

BPs: Bisphosphonates; HA: Hydroxyapatite; AAOMS: American Association of Oral and Maxillofacial Surgeons; BRONJ: Bisphosphonate Related Osteonecrosis of the Jaw; MRONJ: Medication-Related Osteonecrosis of the Jaw; TSH: Thyroid stimulating hormone; T_3: Triiodothyronine; T_4: Thyroxine; BALP: Bone-specific alkaline phosphatase; OCN: Osteocalcin; PTH: Parathyroid hormone, CTx: C-Telopeptide

Introduction

Bisphosphonates (BPs) are often used in the treatment of osteoporosis, Paget's disease and in the prevention of metastatic bone tumors [1]. It was described in 2003 that osteonecrosis of the jaw bones is caused by Marx [2]. Due to their high affinity to hydroxyapatite (HA) crystals, they tend to bind particularly areas where high remodellation accrues, especially osteoclastic activity. They inhibit osteoclastic activity and cause changes in bone remodeling [3]. In 2007 and 2009 declaration, The "American Association of Oral and Maxillofacial Surgeons (AAOMS)" described "Bisphosphonate Related Osteonecrosis of the Jaw (BRONJ)" as "exposed, necrotic bone in the maxillofacial region that has persisted for more than 8 weeks without history of radiation therapy to the jaws whom had current or previous treatment with a bisphosphonate" [4,5]. In the following years, antiresorptive drugs such as "Denosumab" [6] and anti-angiogenetic drugs such as "Bevacizumab" [7] were reported to be the cause of osteonecrosis as like BP's and it was stated "Medication-Related Osteonecrosis of the Jaw (MRONJ)" [3]. Although the first case of BRONJ is reported in 2003, pathophysiology is not exactly understood, and potential mechanisms are still being discussed [2]. The pathophysiology of MRONJ is explained by modified bone remodeling or suppression of bone resorption, inflammation or infection, inhibition of angiogenesis, soft tissue toxicity, congenital or acquired immunodeficiency, microtrauma and vitamin D insufficiency [8].

Bisphosphonates inhibit the resorptive activity of osteoclasts when used in therapeutic doses, while they stimulate osteoblasts. The use of high doses of the bisphosphonates results in the formation of intracellular calcium in both osteoblasts and osteoclasts causing cytotoxic effect. As a result, the mechanism of bone regeneration is impaired and necessary remodeling can not take place. Serum parameters associated with bone metabolism as determined by the AAOMS; " thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T_4), C-Telopeptide (CTx), 25 Hydroxy vitamin D, bone-specific alkaline phosphatase (BALP), osteocalcin (OCN) and parathyroid hormone (PTH)" [3]. These values related to bone remodeling and resorptive activity in patients using bisphosphonates and other antiresorptive and antiangiogenic drugs decrease significantly [3].

A number of clinical trials have been conducted with the explanation of the new staging system. However, there are not many studies evaluating the serum markers of patients in the early and advanced stages of MRONJ. The aim of this study is to classify MRONJ patients according to the latest staging system as early stage (stage 0) and advanced stage (stage 1, 2, 3) and investigate how these groups affect the serum markers of bone turn-over, inflamation and endocrine function.

Materials and Methods

In this retrospective study; we examined 26 patients with MRONJ who presented between 2017 and 2018 in the our department. The study was approved by the ethical committee of our university.We recorded patients' clinical and radiological signs, location of exposed or necrotic bone, existence of infection, pain, degree of osteolysis and results of serum samples (Figure 1). Based on these findings, we applied the staging and treatment strategies described by the AAOMS position paper on MRONJ to each patient [3] (Table 1). In our study, patients were divided into 2 groups according to the criteria's stated by AAOMS. Patients in Group I were in stage 0 (early stage) and patients in Group II were in stage 1, 2 and 3 (advantage stage). Serum samples were analyzed for thyroid stimulating hormone (TSH), triiodothyronine (T_3), thyroxine (T_4), C-Telopeptide (CTx), 25 Hydroxy vitamin D, bone-specific alkaline phosphatase (BALP), osteocalcin (OCN) and parathyroid hormone(PTH).

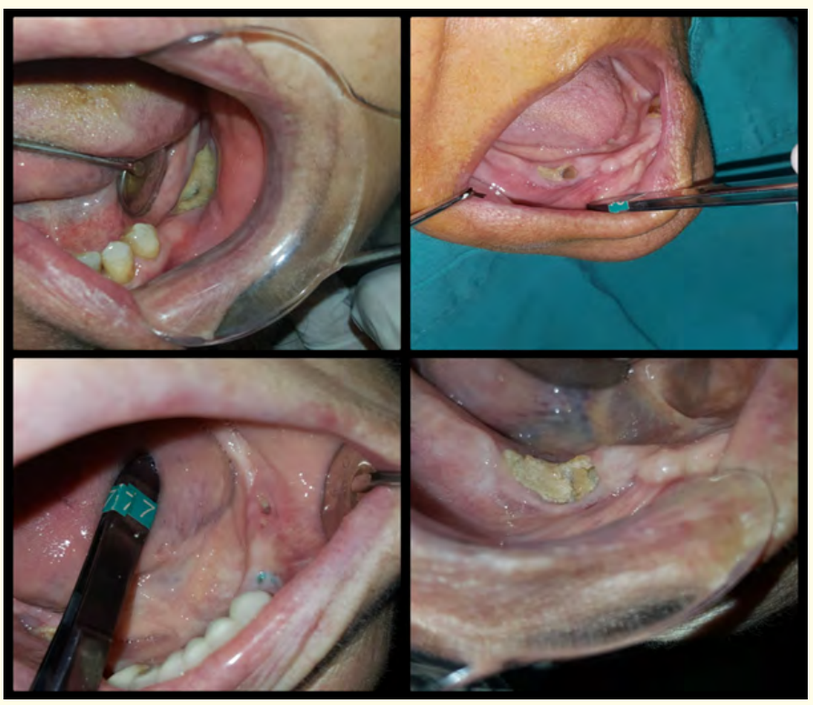

Figure 1: *Clinical findings of some MRONJ patients in this study.*

At risk category: No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates.

Stage 0: No clinical evidence of necrotic bone, but non-specific clinical findings and symptoms.

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 infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage.

Stage 3: Exposed and necrotic bone in patients with pain, infection and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e. inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral antral/oral nasal communication, or osteolysis extending to the inferior border of the mandible of sinus flor.

Table 1: *Staging and Treatment Strategies (Ruggiere., et al. 2014).*

Statistical evaluations will be performed with SPSS 21.0 (Statistical Package Social Science) package program. Comparisons of categorical variables were made with Chi-square or Fisher's exact Chi-square tests. Student's t-test will be used to compare the quantitative variables between groups. All data were evaluated at a significance level of $p < 0.05$.

Results

Patient Characteristics

26 patients (8 males and 18 females) who met the inclusion criteria for this study were included. The demographic data of the patients are shown in table 2. 11 of these patients were Group I (stage 0) (3 male, 8 female) and 15 were Group II (stage 1-2-3) (5 males, 10 females). In both groups, more MRONJ was found among the females. The mean age of the patients was 60.49 ± 12.61 (44 - 72) in group I and 64.82 ± 10.47 (42 - 79) in group II. MRONJ was found in the mandible in 16 of the patients (7 patients in group I and 9 patients in group II). Drugs were mainly used due to osteoporosis and oncological purposes. Considering local etiologic factors that cause MRONJ the most common factor in both groups was the dental extraction (Group I: 8 cases, Group II: 9 cases). When drugs that cause MRONJ were investigated, Alendronate in Group I and zoledronic acid in Group II were the most common drugs. The mean duration of medication use in Group I was 26 months (1 - 5 years) and 40 months (2 - 9 years) in Group II.

	Group I (stage 0) (11 cases)	**Group II (stage 1-2-3) (15 cases)**	
Age (Mean age ± standard deviation)	60.49 ± 12.61	64.82 ± 10.47	t = -0.272, p >0.05
Gender			
Males	3 (27.2%)	5 (33.3%)	p > 0.05
Females	8 (72.8%)	10 (66.7%)	(Fisher's Exact Test)
Disease	Lung cancer: 0 case (0%)	2 cases (13.3%)	
	Renal cancer: 2 cases (18.1%)	0 cases (0%)	
	Breast cancer: 2 cases (18.1%)	4 cases (26.6%)	
	Multiple myeloma: 1 case (9.1%)	2 cases (13.3%)	
	Nasopharynx cancer: 0 case (0%)	1 case (6.6%)	
	Osteoporosis: 4 cases (36.5%)	3 cases (20.3%)	
	Over cancer: 1case (9.1%)	2 cases (13.3%)	
	Prostate cancer: 1 case (9.1%)	1 case (6.6%)	
	Drug Ibandronate : 3 cases (27.2%)	Ibandronate: 3 cases (20.3%)	
	Alendronate: 7 cases (63.7%)	Alendronate: 3 cases (20.3%)	X^2 =37.70, p < 0.01
	Residronate : 1 case (9.1%)	Zolendronic acid: 7 cases (46.1%)	
		Denosumab:2 cases (13.3%)	
Duration of drug therapy	26 months (1-5 years)	40 months (2-9 years)	
Location of the MRONJ			
Mandible	7 cases (63.7%)	9 cases (60.1%)	X^2 = 3.79, p > 0.05
Upper Jaw	4 cases (36.3%)	5 cases (33.3.%)	
Both upper jaw and mandible	0 case (0%)	1 cases (6.6%)	
Local etiologic factors (osteonecrosis)			
Dental extractions	8 cases (72.8%)	9 cases (60.2%)	X^2 = 1.64; p > 0.05
Prosthesis	2 cases (18.1%)	4 cases (26.6%)	
Spontaneous	1 case (9.1%)	1 case (6.6%)	
Implant treatment	0 case (3.6%)	1 case (6.6%)	

Table 2: *Characteristics of MRONJ patients.*

Laboratory Results

Mean serum levels of markers of bone turnover, inflammation and endocrine function are shown in table 3. There was a significant difference between the groups only levels of serum parathyroid hormone (PTH) showed ($p < 0,05$). There was no significant difference between other endocrine markers and bone turnover markers ($p > 0,05$). Thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), bone-specific alkaline phosphatase (BALP) and osteocalcin (OCN) are higher in Group II. The levels of 25 Hydroxy vitamin D and C-Telopeptide (CTx), are higher in Group I.

Biochemical Markers	Group I (stage 0)	Group II (Stage 1-2-3)	Reference	P value*
Bone-specific alkaline phosphatase (BALP)	12 ± 6	16 ± 8	6.5 - 22 µg/L	0.28
Osteocalcin (OCN)	12 ± 4	14 ± 10	11 - 50 ng/mL	0.19
Parathyroid hormone (PTH)	36 ± 9	48 ± 11	11 - 67 µg/L	0,012
C-telopeptide (CTx)	231 ± 106	224 ± 113	50 - 580 pg/mL	0.54
Triiodothyronine (T_3)	122 ± 26	126 ± 28	60 - 180 ng/dL	0.32
Thyroxine (T_4)	9 ± 2	10 ± 2	5 - 11 µg/dL	0.80
Thyroid-stimulating hormone (TSH)	1.8 ± 1	2 ± 2	0.4 - 3.0 µIU/mL	0.29
25-hydroxyvitamin D	37 ± 8	32 ± 11	30 - 75 µg/L	0.24

Table 3: *Serum biochemical markers.*

**P-values were calculated from Student's t-tests.*

Discussion

The pathophysiology of this disease has not been exactly understood, despite the time since the first BRONJ case in the literature. Studies to date, pathogenesis of MRONJ was attempted to explain with theories such as over-suppression of bone resorption or increased inhibition of bone resorption, inhibition of angiogenesis, micro fracture due to persistent micro trauma and combination of bacterial invasion through periodontium, innate or acquired immunosuppression, D vitamins inadequacy, toxicity and inflammation caused by BP's in soft tissues or infection [9,10].

According to the AAOMS staging system, updated in 2014, clinical and radiological findings and serum bone markers have great importance for the diagnosis of MRONJ patients. BP's and other antiresorptive drugs increase apoptosis by inhibiting osteoclast differentiation and function, thus lead reduced bone resorption and remodeling [11]. Although osteoclast differentiation and function play an important role in the reconstruction of all bones of the skeletal system, osteonecrosis only occurs in the jaw bones can be explained by the high rate of resorption and formation in the jaw bones [12]. There are a few studies focused on the serum bone markers of MRONJ patients in the literature for prevention of this serious complications. There is no consensus on which serum levels of markers of bone turnover, inflammation and endocrine function should be used for diagnosis, staging and treatment of MRONJ cases. So this study was managed to investigated the associations of these markers as risk predictors of MRONJ.

Serum CTx level is an indication of osteoclastic activity used to measure bone remodeling and resorption. According to study of Marx., *et al.* when the serum CTx value is higher than 149 pg/ml, there is no risk for osteonecrosis. When the value is between 126 - 149 pg/ml, the minimum risk for osteonecrosis is intermediate between 100 - 125 pg/ml and less than 100 pg/ml they reported that the risk of osteonecrosis was high but these values should not be seen as definitive findings [13]. Hutcheson., *et al.* investigated the CTx values of oral BP treatment in patients with osteoporosis. They reported that the CTx value of < 150 pg/mL after tooth extraction was 3-fold higher than the MRONJ risk. Also in their study, four patients with CTx values of > 150 pg/mL developed MRONJ after tooth extraction [14]. Similarly, Lazarovici., *et al.* a CTx value of < 150 pg/mL was significantly associated with BRONJ development when investigating both osteoporosis

and cancer patients [15]. On the contrary, Bagan., *et al.* didn't find any relationship between serum CTx and the risk of developing BRONJ in patients receiving both oral and intravenous bisphosphonates [16]. Also Kunchur., *et al.* found no relationship between Ctx values and the development of MRONJ in a study of patients who were planned for tooth extraction. However, patients with a CTX value of < 150 mg suggested as a "risk zone" [17]. In this present study, no statistically significant relationship was found between CTx values and early and advanced stages of MRONJ patients. However, higher CTx values were found in the early stages of MRONJ.

As a serum marker of the bone resorption, bone-specific alkaline phosphatase (BALP) is a highly represents ostoeblastic cellular activity. Lazarovici., *et al.* analyzed the predictive value of serum levels of CTx, bone specific alkaline phosphatase (BALP), and parathyroid hormone (PTH) for the development of BRONJ. A CTx value of < 150 pg/mL was significantly associated with BRONJ development when investigating both osteoporosis and cancer patients. The BALP levels were significantly lower in patients taking oral BPs who developed BRONJ. However, PTH values were similar in patients who did and did not develop BRONJ [15]. Serum BALP values can useful, but their true value awaits supplemental laboratory examinations. In their study, PTH doesn't seem to have any predictive indicator for the development of BRONJ [15]. On the contrary, in our present study, the only levels of PTH that we found statistically significant difference between the groups. Parathyroid hormone stimulates bone formation, prevents or reverses bone loss, increases bone mass, bone strength and provides protection against fractures. PTH stimulates osteoclasts by activating osteoblastic cytokines (such as IL-6). As a result, it allows for bone formation and recovery with bone resorption. Aim of the using teriparatide, which obtained from PTH, was to increases bone build-up and bone density, at the same time to reduce bone fractures. Teriparatide is used to reduce bone pain in osteoporosis patients and to reduce symptoms in MRONJ patients. Kim., *et al.* analyzed serum markers of bone turnover in a study of BRONJ and non-BRONJ patients. According to the results of the their study, only PTH values were significantly higher in the BRONJ group [18]. In this present study we found that PTH levels were significantly higher in the advanced stages of MRONJ, in accordance with study of Kim., *et al.*

According to the studies in the literature, there was no significant relationship between endocrine markers such as thyroid stimulating hormone (TSH), triiodothyronine (T_3), thyroxine (T_4) and MRONJ development. Thumbigere-Math., *et al.* associated in their study that the value of endocrine markers in BRONJ patients who discontinue long-term intravenous BP therapy are similar to those in non-BRONJ controls receiving intravenous BP therapy [19]. In this present study, there was no statistically significant relationship was found between levels of endocrine markers and early and advanced stages of MRONJ patients.

Conclusion

According to our study results, there was a significant difference between the groups only levels of serum PTH showed ($p < 0,05$). There was no significant difference other endocrine and bone turnover markers. Bone tissue is such a dynamic and complex tissue that formation and resorption events are cycling consecutively each other where numerous elements and factors are involved. To monitor this active turnover of bone tissue effectively, measurements of some protein products and enzymes formed and released during this turnover so called biochemical markers can be performed. Serum markers of bone turnover have become more available to follow- up early and advanced stages of medication related osteonecrosis of the jaw patients. However, it is important to remember that individual markers reflect different biochemical and physiological processes and may not, therefore, always show identical changes. The limitation of our study was that the number of patients was insufficient to assess the definite risk of clinical osteonecrosis after surgery in the results of serum markers of the early stages of medication related osteonecrosis of the jaw. Future studies should aim to measure serum markers of bone turnover in larger groups of patients in the early diagnosis of medication related osteonecrosis of the jaw.

Conflict of Interest

The authors have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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