Clinical and Experimental Health Sciences

Comparative Evaluation of Bisphosphonate Effects: Periapical Lesion Frequency, Size, and Radiomorphometric Indices in Osteoporotic Patients

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ABSTRACT

Objective: The aim of the study was to evaluate the effects of bisphosphonate use on periapical lesion frequency, size, and through radiomorphometric indices on jaws.

Methods: This study includes 220 postmenopausal women (110 patients who use bisphosphonate and 110 patients who do not use bisphosphonate) with diagnosis of osteoporosis and 110 women who have a healthy bone structure control group. The complex periapical index (CPI), mental index (MI), panoramic mandibular index (PMI), and mandibular cortical index (MCI) values was evaluated.

Results: The both right and left MI/PMI means in the osteoporotic patients using bisphosphonate were significantly lower than the others ($p < .001$). It was found that while the duration of bisphosphonate use increased, the right MI and right-left PMI means decreased significantly ($p < .05$). The right MI and the right/left PMI means were significantly higher in the group using bisphosphonate via intravenous injection compare to those using it orally. The total number of periapical lesions was significantly less in the group using bisphosphonates than the other two groups ($p = .002$). The number of teeth with the periapical lesions up to 3 mms in diameter was also significantly lower in the group using bisphosphonate than it was in the other two groups ($p = .04$).

Conclusions: It was found that the use of bisphosphonates is associated with a lower mandibular index, which indicates greater severity of osteoporosis. The total number and size of periapical lesions in these patients were significantly less than the other two groups.

Keywords: Osteoporosis, bisphosphonate, mandibular index, periapical lesion, panoramic radiography

1. INTRODUCTION

Osteoporosis has been defined as a progressive metabolic bone disease characterized by increased bone fragility and risk of fracture resulting from low bone mass and defects in the microarchitecture of bone tissue (1). It is highly correlated with aging and mostly affects postmenopausal women (2). In the diagnosis of osteoporosis, dual-energy X–ray absorptiometry (DXA) which measures the bone mineral density of the lumbar spine and proximal femur region is accepted as the gold standard of imaging method (3). Although DXA is a simple non-invasive method, the high cost makes its application impossible for a routine examination (4). In addition to this, panoramic radiography, which is a routinely used imaging technique for patients who consult to a dentist, can be used as a valuable imaging tool for the diagnosis of osteoporosis (5). In the literature, radiomorphometric analyses using panoramic radiographs—such as the mandibular cortical index (MCI) (6), mental index (MI) (7), and panoramic mandibular index (PMI) (8)—have been shown to correlate with bone mineral density (BMD) values in the femur and lumbar spine, making them useful for detecting low BMD (3, 9-13). Furthermore, radiomorphometric analyses such as PMI, MI, and MCI have been successfully used to assess the effects of medication and systemic diseases on jawbones (14,15).

In osteoporosis treatment, bisphosphonates are used to prevent bone loss and increase bone mass. Antiresorptive drugs, such as bisphosphonates, exert their effect by reducing the activity of osteoclasts and increasing their apoptosis (16). Thus, bisphosphonates cause a decrease in bone cycle and provide a net gain in bone mass (17). Considering their effects on the treatment of osteoporosis, bisphosphonates are expected to cause an increase in MCI, MI and PMI values which are used in the diagnosis of osteoporosis. There are

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few studies on the effects of bisphosphonate usage on MCI, MI, and PMI. While no difference was found in some of these studies (5,18), an increase in the indices was observed in others (19,20).

Periapical lesion is an inflammatory disorder which affects the tissues around the apex of the tooth, caused by an infection in the root canal system, and is characterized by the destruction and loss of periapical bone (21). In periapical lesion, pathogens stimulate the innate immune response by releasing chemicals that lead to the production of pro-inflammatory cytokines, which are key to disease progression (22). Based on the evidence, osteoporosis is believed to be unidirectionally associated with periapical lesions (23). It is thought that estrogen deficiency plays a role in the development of periapical lesion in osteoporosis by causing the imbalance of periapical bone metabolism (22,23). Estrogen reduces bone resorption and enhances bone formation by increasing osteoprotegerin (OPG) levels and decreasing receptor activator of nuclear factor kappa-B ligand (RANKL) expression (24). On the other hand, estrogen affects immune cells, and its deficiency results in a chronic low-grade pro-inflammatory state, leading to increased release of inflammatory mediators such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α), which contribute to increased bone resorption (25,26). There are few studies investigating the prevalence of periapical lesions in postmenopausal women with osteoporosis (27-29). Data suggest that osteoporosis contributes to a higher occurrence and larger size of periapical lesions, with estrogen serving as a crucial factor in the relationship between these conditions (23). Studies evaluating the effect of bisphosphonates on periapical lesion size appear to be limited, and more research is needed (29-33).

The aim of study was to evaluate the effects of bisphosphonate use periapical lesions frequency, size and through radiomorphometric indices on jaws in the patients using bisphosphonate due to osteoporosis.

2. METHODS

For this retrospective study complied with the Declaration of Helsinki and, research ethics committee approval was taken from The Ethics Committee of Süleyman Demirel University, Noninvasive Clinic Ethics Committee with the decision of 13/07/2021/245. In the light of the preliminary information obtained from literature, power analysis was performed in determining the sample size; first type error α=0.05; The minimum sample size for each group was found to be 110, with the power of the test being a minimum of 0.80.

2.1. The study group

The participants of this study were postmenopausal 220 women with osteoporosis aged 50-78, who have attended of Suleyman Demirel University, Faculty of Dentistry, Department of Dental and Maxillofacial Radiology with various reasons between 2016-2020. From the medical records of the patients, the following information was obtained; age, systemic diseases, drugs used for osteoporosis, types of these drugs (Alendronic acid, Ibandronic acid, Zoledronic acid, Denosumab) duration of use (0-1 years, 1-3 years, 3-4 years, 4-5 years, 5-6 years) and type of use (orally, intravenously, both orally and intravenously). Two study groups from patients with osteoporosis were created: 110 post-menopausal female patients using bisphosphonate for osteoporosis and 110 post-menopausal female patients not using bisphosphonate for osteoporosis.

2.2. The control group

It consists of 110 post-menopausal female patients.

- The patients who applied to Department of Dental and Maxillofacial Radiology, Suleyman Demirel University, Faculty of Dentistry between 2016-2020 with various dental complaints, whose examination were completed and panoramic radiographs were taken
- Patients aged 50 to 75 years with healthy bone structure (T scores equal to or greater than – 1 SD) were selected from the medical records of those who had DXA measurements performed at the Nuclear Medicine Unit of Süleyman Demirel University, Research and Application Hospital.

DXA measurements of the control patients were taken in the GE Lunar Prodigy device at 76 kilovolt, 3000 milliampere (mA), 43 seconds recording protocol. Digital panoramic radiographs of the all patients who were evaluated retrospectively were taken by Planmeca Promax, (Helsinki, Finland) device with recording parameters of 66-68 kVp, 7-13 mA and 16 sec. All radiographs were obtained by the same type of panoramic device with 1.2 nominal magnification factor. By using Planmeca Romexis 3.8.3 (Helsinki, Finland) program, the analysis on panoramic radiographs were made by single observer with a 3-years of experience on Oral and Maxillofacial Radiology.

Those who were not included in the study are;

- Patients whose medical records could not be accessed.
- Patients where the location of the mental foramen could not be determined.
- Patients with a history of cancer, who received radiotherapy to the head and neck region.
- Patients with a systemic disease or condition that may affect bone metabolism (e.g., Paget disease, hyperparathyroidism, hypoparathyroidism, renal osteodystrophy, etc.).
- Patients using drugs that may affect bone metabolism (e.g., antiepileptics, corticosteroids, cytostatics, estrogen, etc.).
- Patients with any lesion that may cause destruction in the jawbones.
- Patients with a history of trauma or surgical operations.
- Patients with total edentulism.

The analysis made on the panoramic radiograph;

- Radiomorphometric indices MI (7) and PMI (8) were measured bilaterally, while MCI (6) was also evaluated bilaterally.
- The size of the periapical lesions, the relationship between the root and the radiolucent lesion, and the complex periapical index, which evaluates the location of bone destruction, were evaluated.

2.3. Mandibular Inferior Cortical Thickness (MI)

To measure the thickness of mandibula inferior, a line tangent to mandibular cortex and at the level of mental foramen was drawn in the premolar region; A second line passing through foramen mental region was also drawn as perpendicular to this one. At the intersection of these two lines, mandibular cortex thickness was measured (Figure 1).

2.4. Panoramic mandibular index (PMI)

PMI values were calculated by dividing the cortical thickness in the mental foramen by the distance from the lower border of the mental foramen to the lower border of the mandible (Figure 1).

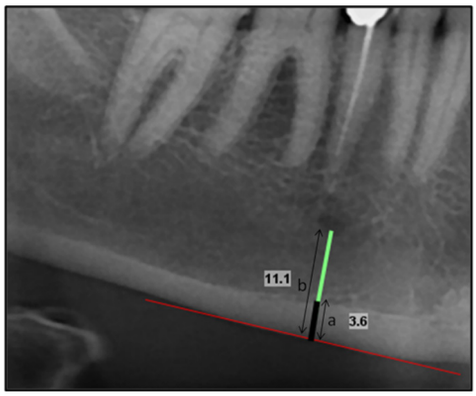

Figure 1. *Mandibular inferior cortical thickness (a), distance from the lower border of the mental foramen to the lower border of the mandible (b), panoramic mandibular index (a/b)*

2.5. Mandibular cortical index (MCI)

MCI, is a qualitative index that evaluates existing porosities in the mandibular cortical bone posterior to the mental foramen on both sides of mandible in three grades as C1, C2 and C3 (Figure 2).

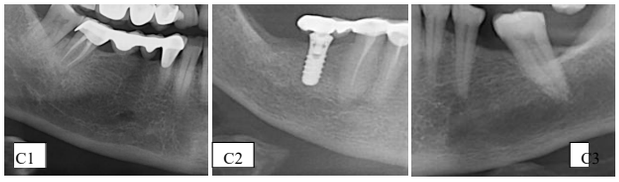

Figure 2. *Mandibuler Cortical Index Stages: C1 The endosteal border of the cortex is even and sharp on both sides of the mandible. C2 The endosteal margin with semilunar defects (lacunar resorption) or endosteal cortical residues on one or both sides. C3 The endosteal margin consists of heavy cortical residues and is clearly porous.*

The complex periapical index (CPI), which was defined by Venskutonis et al. (34) in order to define and classify periapical lesions on panoramic radiography images, was used. In this index, there are 3 parameters; size of the lesion (S), the relationship between lesion and root (R), the location of bone destruction (D) (Figure 3). Lesion size was measured with the largest diameter on panoramic radiography by using Planmeca Romexis 3.8.3 (Helsinki, Finland) program. While S0R0D0 score corresponds to a healthy periapical tissue, all scores except S0R0D0 indicates presence of a periapical lesion. The study group and the control group were evaluated based on the number of missing teeth: no missing teeth, fewer than 10 missing teeth, and more than 10 missing teeth.

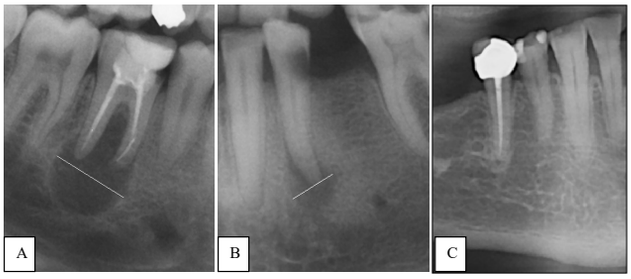

Figure 3. *A. S3R3D2 Cropped panoramic radiographic image of a lesion larger than 5 mm involving both roots and extending into the furcation B. S3R1D1Cropped panoramic radiographic image of a lesion larger than 5 mm involving a single root.C. S0R0D0 Cropped panoramic radiograph image of healthy periapical tissues.*

2.6. Statically Analysis

The data obtained for this study was analyzed through IBM SPSS Statistics V20,0 program (IBM Corp., Armonk, N.Y., USA). The compatibility of the examined features with normal distribution was checked via Kolmogorov–Smirnov Test. Having $p < .05$ in the evaluation was accepted as there was significant difference among groups. One-Way Analysis of Variance (ANOVA) and LSD multiple comparison tests were used to compare the difference of means. Pearson correlation analysis was used to determine the significance and direction of linear correlation among variables. The Chi-square testwas used to examine the relationship among categorically classified variables. One month after the first images were assessed, 30% of them were retaken in order to examine intra-observer reliability. In the evaluation of the intra-observer reliability, kappa analysis was used for categorical variables, and Cronbach alpha coefficient test was used for continuous variables.

3. RESULTS

All of the participants of this study were post-menopausal women. The group using bisphosphonate (65.76 ± 6.87) has a significantly higher mean age than the group not using bisphosphonate (62.01 ± 6.38) and the control group (62.06 ± 4.88). The most commonly used drugs in the group using bisphosphonate were respectively; Alendronic acid

(28.2%), Ibandronic acid (22.7%), Zoledronic acid (11.8%), and the combination of Ibandronic acid and Alendronic acid (10.9%). Additionally, 23 patients used denosumab, an antiresorptive drug, alongside bisphosphonates. In terms of bisphosphonate use, 63.6% of the patients were using it orally, 25.5% intravenously, 10.9% orally and intravenously. When it comes to the duration of bisphosphonate use, 35.5% of the patients had used the drugs between 0-1 year, 35.5% 1-3, 21.8% 3-4 years.

Compared to the control group, the mean MI and PMI values on both the right and left sides were significantly lower in the other two groups ($p < .001$). The group using bisphosphonates had lower right and left MI and PMI means than both the group not using bisphosphonates and the control group ($p < .001$) (Table 1).

Table 1. *Values of MI and PMI in the three examined groups*

MI ve PMI	The osteoporosis group not using bisphosphonates Mean ± SD	The osteoporosis group using bisphosphonates Mean ± SD	Control group Mean ± SD	P value
MI right	$3.14 \pm 0.70_a$	$2.71 \pm 0.70_b$	$3.86 \pm 0.65_c$	**< .001**
MI left	$3.18 \pm 0.73_a$	$2.85 \pm 0.69_b$	$3.83 \pm 0.64_c$	**< .001**
PMI right	$0.30 \pm 0.07_a$	$0.26 \pm 0.07_b$	$0.35 \pm 0.07_c$	**< .001**
PMI left	$0.30 \pm 0.07_a$	$0.27 \pm 0.07_b$	$0.35 \pm 0.07_c$	**< .001**

SD: Standard deviation MI: mental index PMI: panoramic mandibular index One-way Analysis of Variance (ANOVA), a,b,c: Intra-group differences (LSD Post Hoc Test). In each row, the means with the same letter were not found to be different (p > .05).

The most common MCI categories were C1 and C2 in the group not using bisphosphonates, C2 and C3 in the group using bisphosphonates, and C1 in the control group (Table 2). Although the C3 category was most common in the bisphosphonate group, a significant difference was found among all three groups ($p < .001$).

Table 2. *Mandibular cortical index distribution by the groups*

MCI (Klemetti Index)		The osteoporosis group not using bisphosphonates n(%)	The osteoporosis group using bisphosphonates n(%)	Control group n(%)	P value
C1	**Right**	35_a (24.3)	18_b (12.5)	91_c (63.2)	**< .001**
	Left	38_a (27)	22_b (15.6)	81_c (57.4)	**< .001**
C2	**Right**	57_a (44.9)	52_a (40.9)	18_b (14.2)	**< .001**
	Left	54_a (41.5)	48_a (36.9)	28_b (21.5)	**< .001**
C3	**Right**	18_a (30.5)	40_b (67.8)	1_c (1.7)	**< .001**
	Left	18_a (30.5)	40_b (67.8)	1_c (1.7)	**< .001**

One-way Analysis of Variance (ANOVA), a,b,c: Intra-group differences (LSD Post Hoc Test). In each row, the means with the same letter were not found to be different (p > .05).

There was no significant difference between the types of bisphosphonates used and MI, PMI, and MCI ($p > .05$). It was found that, while the duration of the bisphosphonate use increased, the means of right MI and both right/left PMI significantly decreased ($p < .05$) (Table 3). There was no significant difference in mean right MI or right and left PMI between patients receiving denosumab in addition to bisphosphonates and those receiving bisphosphonates alone ($p > .05$). However, the mean left MI was significantly higher in patients receiving bisphosphonates alone ($p = .018$).

Table 3. *Correlation coefficients and significance levels between duration of bisphosphonate use and MI, PMI, and age of the patients*

		Age	MI Right	PMI Right	MI Left	PMI Left
Duration of bisphosphonate use	Pearson Correlation	0.24*	-0.23*	-0.21*	-0.16	-0.19*
	P value	0.01	0.01	0.02	0.09	0.044

** Correlation is significant at the .05 level (2 – tailed) MI: mental index PMI: panoramic mandibular index*

The mean right MI was significantly higher in individuals using bisphosphonates intravenously compared to those using them orally ($p = .05$), while the mean left MI was significantly higher in those using bisphosphonates intravenously compared to both oral and oral + intravenous users ($p = .018$). The mean of right and left PMI was found to be significantly higher in intravenous bisphosphonate users compared to oral users ($p < .05$). There was no significant difference between the type and duration of bisphosphonate use and MCI categories ($p > .05$).

Periapical lesions numbers were close to each other in all three groups. The group not using bisphosphonates had the highest total number of periapical lesions. Significantly fewer periapical lesions were detected in the group using bisphosphonates due to osteoporosis compared to the other two groups ($p = .002$).The number of teeth with periapical lesions of diameter (S1) up to 3 mm was higher in the control group compared to the other two groups. Additionally, the number of the teeth with a lesion diameter (S3) greater than 5 mm was found to be 51.2% in the group not using bisphosphonates. The presence of periapical lesions involving more than one root was significantly higher in the control group than in the other two groups. Fewer such lesions were observed in the bisphosphonate group compared to the other two groups ($p < .05$).

There was no significant difference between the groups regarding the location of endodontically induced bone destruction. Additionally, no significant relationship was found between the type of bisphosphonate, the method of administration, the duration of use, and the size of the lesion, root radiolucent lesions, or the location of bone destruction in the bisphosphonate group ($p > .05$) (Table 4).

A statistically significant inverse correlation was observed between age and right MI, as well as right/left PMI, in both the group not using bisphosphonates ($p < .05$) and the group using bisphosphonates ($p < .05$). However, no such correlation was found between age and right/left MI or PMI in the control group ($p > .05$).

Table 4. *Evaluation of periapical lesions by groups*

		The group with osteoporosis but not using bisphosphonates n(%)	The group with osteoporosis using bisphosphonates n(%)	Control group n(%)	P value
S	S0	14_a (56)	8_a (32)	3_b (12)	.042
	S1	33_a (33.3)	23_a (23.2)	43_b (43.4)	
	S2	18_a (42.9)	12_a (28.6)	12_a (28.6)	
	S3	21_a (51.2)	11_a (26.8)	9_a (22)	
R	R0	14_a (56)	8_a (32)	3_b (12)	.002
	R1	55_a (39.6)	41_a (29.5)	43_a (30.9)	
	R2	12_a (35.3)	2_b (5.9)	20_c (58.8)	
	R3	5_a (55.6)	3_a (33.3)	1_a (11.1)	
D	D0	14_a (56)	8_a (32)	3_b (12)	.290
	D1	59_a (38.8)	41_a (27)	52_a (34.2)	
	D2	11_a (42.3)	4_a (15.4)	11_a (42.3)	
	D3	2_a (50)	1_a (25)	1_a (25)	

S: size of the lesion R: the relationship between lesion and root D: the location of bone destruction

One-way Analysis of Variance (ANOVA), a,b,c: Intra-group differences (LSD Post Hoc Test). In each row, the means with the same letter were not found to be different (p > .05).

There was no significant difference between the group using bisphosphonates for osteoporosis and the group with osteoporosis but not using bisphosphonates in terms of having more than 10 missing teeth. However, significantly fewer people in the control group had more than 10 missing teeth (p = .007). It was found that mandibular cortical thickness decreased significantly as the number of missing teeth increased in all study participants (p < .01). Additionally, the frequency of C2 and C3 categories increased significantly with the number of missing teeth (p < .05).

In this study, Cronbach's alpha coefficient values ranged from 0,88 to 0,99 (good) in the intraobserver agreement assessment of mandibular index measurements. In the evaluation of categorical variables, intraobserver agreement Kappa Test coefficient values were between 0,863 and 1 (excellent).

4. DISCUSSION

In this study, the effects of bisphosphonates on mandibular indices and periapical lesions in patients using bisphosphonates for osteoporosis were evaluated.

Morphological and radiomorphometric analyses evaluated on panoramic radiographs of postmenopausal women have demonstrated high sensitivity and specificity for detecting low BMD (9-13). Similarly, in this study, indices used for detecting bone mineral density were evaluated on panoramic radiographs.

In the literature, there are a limited number of studies evaluating the changes that may occur in the cortical and trabecular structure of the jaw bones due to bisphosphonate use (5,19,35-39). Barngkgei et al. (5) reported that the use of bisphosphonates in patients with osteoporosis had no effect on the MI value. In another study, it was reported that bisphosphonate used for osteoporosis caused a significant increase in mandibular cortical thickness, but did not cause any change in trabecular bone (37). In some studies, a significant increase in mandibular cortical thickness was found in patients using bisphosphonates compared to control patients (19,39). Yajima et al. (36) found no significant difference in terms of MI in postmenopausal female patients who received bisphosphonate treatment and alternative treatments (Selective Estrogen Receptor Modulator (SERM) and parathormone). Kubo et al. (40) found, in their study, MI was significantly less in the non-bisphosphonate-related osteonecrosis of the jaw (BRONJ) group using bisphosphonate compared to the BRONJ group and the control group. The result of this study was similar to Kubo et al.'s study. In the osteoporotic group using bisphosphonates, the mean MI was significantly lower compared to both the control group and the osteoporotic group not using bisphosphonates (p = .000). Unlike the present study, in the majority of the studies that found an increase in mandibular cortical thickness, the patients were under bisphosphonate therapy for multiple myeloma and cancers capable of bone metastasis. Such situations require the use of high doses of bisphosphonates. The patients in this study mostly used low-dose bisphosphonates orally due to osteoporosis, and the duration of bisphosphonate use was between 0-3 years in 79% of the patients.

Torres et al. (19) found no significant difference in the mean MI between patients using Zolendronate and patients using other bisphosphonates. Similarly, in this study there was no significant difference in terms of MI and type of drugs since the patients used 4 types of antiresorptive drugs and their combination. Yajima et al. (36) reported that mandibular cortical thickness increased with increasing duration of bisphosphonate use. Barngkgei et al. (5) found that bisphosphonate therapy used over a period of 4.3-5 years had no effect on mandibular thickness. Diniz-Freitas et al. (20) found statistically inverse correlation between MI and the duration of use of oral bisphosphonates. In this study, similar to the study of Diniz-Frietas et al. (20), it was determined that MI values decreased significantly with increasing duration of bisphosphonate use (p = .015). In a study by Musulluoğlu et al. (38) investigating the effect of oral and intravenous bisphosphonate use on jaw bone density in patients with osteoporosis, it was found that the MI values of dentate individuals using intravenous bisphosphonates were higher than those of dentate individuals using oral bisphosphonates, although the difference was not significant.In this study, mean MI, PMI was significantly higher in individuals on intravenous bisphosphonates compared with those on oral bisphosphonates.

Tanrıkol et al. (39) reported that the mean of PMI values in patients using bisphosphonates and the control group were not statistically significant. In this study, it was determined that PMI value in the group using bisphosphonate was significantly lower than the other two groups (p = .000).

The difference between the two studies may be due to the smaller sample size in Tanrıkol et al.

In a study of osteoporosis patients treated with denosumab, lower T-scores were associated with significantly lower MI values (41). Furthermore, a significant increase in PMI over one year was observed in patients with osteoporosis or osteopenia. In this study, the mean right MI and PMI were similar between patients receiving both Denosumab and bisphosphonates and those receiving bisphosphonates alone, but the left MI was significantly higher in the latter group. The difference between the two studies can be attributed to variations in their methodologies.

Tanrıkol et al. (39) detected that the most dominant category for right and left MCI values in patients using bisphosphonates was C1. Yamada et al. (35) observed significantly more C2 and C3 categories of MCI in patients using bisphosphonate due to osteoporosis. In their study, Grgić et al. (18) reported that the C3 category of MCI was higher in osteoporosis groups with and without bisphosphonate use, but this difference was not significant. In this study, the most common MCI category in the group using bisphosphonates due to osteoporosis was C2 and C3. In the group using bisphosphonates due to osteoporosis, the C3 category was detected in significantly more people than the other groups (p = .000). The studies reported C1 category was predominant in the patients using bisphosphonates, unlike this study, were evaluated in cases with bisphosphonate-induced osteonecrosis or patients using bisphosphonates due to malignancy (39,40,42). The results of our study were similar to the work of Yamada et al. (35) and Grgić et al. (18).

There are studies in literature evaluating the frequency of periapical lesions in patients using bisphosphonates due to osteoporosis. In a study conducted by Lopez et al. (27), in postmenopausal women, they reported that at least one periapical lesion was detected in 25% of patients with both osteopenic and osteoporotic bone structure, while this rate was only 7.4% in the healthy group. In another study by Katz and Rotstein (28), the prevalence of periapical lesions was found to be significantly higher in patients with osteoporosis compared to the general patient population of the hospital. In addition, it was reported that the prevalence of periapical lesion was lower in the osteoporosis group using bisphosphonates than in the osteoporosis group not using bisphosphonates. In the study by Cadoni et al., patients with osteoporosis were found to have a lower rate of periapical lesions compared to the control group, with no significant difference in the number of teeth affected. In addition, the prevalence of periapical lesions was found to be lowest in patients using bisphosphonates (29). Despite there was no significant difference in the number of individuals with periapical lesions among the groups in this study, when the total number of periapical lesions in each group was examined, significantly fewer lesions were detected in the group using bisphosphonates for osteoporosis compared to the other two groups (p = .002). The result of this study is in agreement with the studies of Cadoni et al. and Kats and Rotstein. The reason for this situation may be that the treatment of the teeth that could be the focus of infection was completed before starting to use bisphosphonates. In addition to this, the inhibitory effect of bisphosphonate on bone resorption may also have been effective in bone structure.

Although there are studies evaluating the effect of bisphosphonate use on periapical lesion size in animals (26,30-32), there is limited evidence on this topic human study in the literature (29). In animal studies, it was found that the periapical lesions were significantly larger in the ovariectomized group compared to the control groups (26,30-32). The bone resorption observed in periapical lesions is largely carried out by osteoclasts. Bisphosphonates were thought to provide direct lesion expansion control by inhibiting the activity of these cells. Animal studies have shown that when periapical lesions are treated with bisphosphonates, resorption is greatly reduced; however, bisphosphonates were observed to increase the risk of BRONJ in the presence of pre-existing periapical lesions (30-32). In this study, periapical lesions were evaluated using CPI. The number of teeth with periapical lesions up to 3 mm in the control group was higher than the other two groups. In addition, the number of the teeth with a lesion diameter (S3) greater than 5 mm was found to be 51.2% in the group not using bisphosphonates. This is in line with the results of animal studies (26,30-32). There was no significant difference in lesion sizes in the group using bisphosphonates with osteoporosis compared to the other two groups. Since this retrospective study lacks clinical information, it was not possible to distinguish whether the existing periapical lesions in the patients were healing lesions or not.

Dereci et al. (43) found that as the duration of bisphosphonate use increased, the number of non-healed and partially healed teeth increased after the treatment of periapical lesions. Hisao et al. (44) reported that periapical lesions healed less, in a non-significant way, in the group using bisphosphonates orally compared to the control group. In this study, no significant relationship was found between the type of bisphosphonate, the type of use, the duration of use and the size of the lesion in the osteoporotic group using bisphosphonates.

The main strength of this study is that it included only patients using bisphosphonates for postmenopausal osteoporosis and patients with osteoporosis who were not using bisphosphonates, with the control group consisting of individuals who underwent DXA measurements.

This study has several limitations. Due to its retrospective design, the patients' eating habits, smoking habits, and age at menopause are not known. It is important to note that many variables—such as low body weight, family history of osteoporotic fractures, and lifestyle—may influence bone structure and increase susceptibility to osteoporosis. Patients used four different types of bisphosphonates and their combinations; additionally, 23 patients used denosumab. Bisphosphonates were mostly administered orally, and the

duration of use was short. Future studies should include homogeneous populations undergoing long-term use of the same bisphosphonate type and route of administration. Moreover, prospective studies are considered more reliable for measuring individual changes in mandibular indices and periapical lesion size. The most significant limitation of this study is the lack of DXA values in patients with osteoporosis. Previous studies (3, 9-13) have shown a correlation between lower DXA scores, which indicate lower bone mineral density, and lower mandibular indices. In this study, the mandibular index values of the group using bisphosphonates for osteoporosis were significantly lower than those of the other two groups. This finding could be better explained with access to their DXA scores. Planning future studies with these limitations in mind will provide us with more valuable information in this area.

5. CONCLUSION

According to the results of our study, it was found that osteoporosis patients using bisphosphonates have a lower mandibular index. The absence of an increase in mandibular indices might be attributed to the lower dosage of bisphosphonates typically administered for osteoporosis treatment. In addition, the fact that bisphosphonates were primarily used orally and the duration of use was short may have affected the results of our study. Both the total number and size of periapical lesions were significantly smaller in the bisphosphonate group compared to the other two groups. Bisphosphonates used in the treatment of osteoporosis may have favorable effects on the healing of periapical lesions.

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REFERENCES

[1] Cosman F, de Beur SJ, Le Boff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R; National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int. 2014;25(10):2359-2381. DOI: 10.1007/s00198.014.2794-2.

[2] Munhoz L, Morita L, Nagai AY, Moreira J, Arita ES. Mandibular cortical index in the screening of postmenopausal at low mineral density risk: A systematic review. Dentomaxillofac Radiol. 2021;50(4):20200514. DOI: 10.1259/dmfr.20200514.

[3] Kato CN, Barra SG, Pereira MJ, Gomes LT, Amaral TM, Abreu LG, Brasileiro CB, Mesquita RA. Mandibular radiomorphometric parameters of women with cemento-osseous dysplasia. Dentomaxillofac Radiol. 2020;49(4):20190359. DOI: 10.1259/dmfr.20190359.

[4] Barra SG, Gomes IP, Amaral TMP, Brasileiro CB, Abreu LG, Mesquita RA. New mandibular indices in cone beam computed tomography to identify low bone mineral density in postmenopausal women. Oral Surg Oral Med Oral Pathol Oral Radiol. 2021;131(3):347-355. DOI: 10.1016/j.oooo.2020.07.016.

[5] Barngkgei I, Halboub E, Almashraqi A. Effect of bisphosphonate treatment on the jaw bone: An exploratory study using periapical and panoramic radiographic evaluation. Oral Radiol. 2019;35(2):159-170. DOI: 10.1007/s11282.018.0358-4.

[6] Klemetti E, Kolmakow S. Morphology of the mandibular cortex on panoramic radiographs as an indicator of bone quality. Dentomaxillofac Radiol. 1997;26(1):22-25. DOI: 10.1038/sj.dmfr.4600203.

[7] Ledgerton D, Horner K, Devlin H, Worthington H. Radiomorphometric indices of the mandible in a British female population. Dentomaxillofac Radiol. 1999;28(3):173-181. DOI: 10.1038/sj/dmfr/4600435.

[8] Benson BW, Prihoda TJ, Glass BJ. Variations in adult cortical bone mass as measured by a panoramic mandibular index. Oral Surg Oral Med Oral Pathol. 1991;71(3):349-356. DOI: 10.1016/0030-4220(91)90314-3.

[9] Devlin H, Karayianni K, Mitsea A, Jacobs R, Lindh C, van der Stelt P, Marjanovic E, Adams J, Pavitt S, Horner K. Diagnosing osteoporosis by using dental panoramic radiographs: The OSTEODENT project. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;104(6):821-828. DOI: 10.1016/j.tripleo.2006.12.027.

[10] Passos JS, GomesFilho IS, Sarmento VA, Sampaio DS, Gonçalves FP, Coelho JM, Cruz SS, Trindade SC, Cerqueira EM. Women with low bone mineral density and dental panoramic radiography. Menopause 2012;19(6):704-709. DOI: 10.1097/gme.0b013e318240f938.

[11] Gaur B, Chaudhary A, Wanjari PV, Sunil M, Basavaraj P. Evaluation of panoramic radiographs as a screening tool of osteoporosis in post menopausal women: A Cross Sectional Study. J Clin Diagn Res. 2013;7(9):2051-2055. DOI: 10.7860/JCDR/2013/5853.3403.

[12] Kim OS, Shin MH, Song IH, Lim IG, Yoon SJ, Kim OJ, Lee YH, Kim YJ, Chung HJ. Digital panoramic radiographs are useful for diagnosis of osteoporosis in Korean postmenopausal women. Gerodontology 2016;33(2):185-192. DOI: 10.1111/ger.12134.

[13] Carmo JZB, Medeiros SF. Mandibular inferior cortex erosion on dental panoramic radiograph as a sign of low bone mineral density in postmenopausal women. Rev Bras Ginecol Obstet. 2017;39(12):663-669. DOI: 10.1055/s-0037.160.6622.

[14] Temur KT, Magat G, Ozcan S. A retrospective comparative fractal and radiomorphometric analysis of the effect of 3 generations of anti-epileptic drugs on the mandible. Oral Surg Oral Med Oral Pathol Oral Radiol. 2023;136(2):255-262. DOI: 10.1016/j.oooo.2023.04.014.

[15] Temur KT, Magat G, Yılmaz M, Ozcan S. Evaluation of the effect of sickle cell disease on the mandibular bone of children and adolescents by image texture and radiomorphometric

analysis. Oral Radiol. 2023;39(4):792-801. DOI: 10.1007/s11282.023.00704-8.

[16] Kanis JA, Cooper C, Rizzoli R, Reginster JY; Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and the Committees of Scientific Advisors and National Societies of the International Osteoporosis Foundation (IOF). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2019;30(1):3-44. DOI: 10.1007/s00198.018.4704-5.

[17] Demircan S. Nitrojen içeriği, bifosfonata bağlı çene kemiği osteonekrozunun nedeni mi? Fareler üzerinde deneysel çalışma. Türkiye Klinikleri Journal of Dental Sciences 2020;26(2):153-158. (Turkish)

[18] Grgić O, Kovačev-Zavišić B, Veljović T, Novaković-Paro J, Maravić T, Bajkin B. The influence of bone mineral density and bisphosphonate therapy on the determinants of oral health and changes on dental panoramic radiographs in postmenopausal women. Clin Oral Investig. 2017;21(1):151-157. DOI: 10.1007/s00784.016.1767-6.

[19] Torres SR, Chen CS, Leroux BG, Lee PP, Hollender LG, Lloid M, Drew SP, Schubert MM. Mandibular inferior cortical bone thickness on panoramic radiographs in patients using bisphosphonates. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;119(5):584-592. DOI: 10.1016/j.oooo.2015.02.005.

[20] Diniz-Freitas M, Fernández-Montenegro P, Fernández-Feijoo J, Limeres-Posse J, González-Mosquera A, Vázquez-García E, Diz-Dios P. Mandibular cortical indices on cone-beam computed tomography images in osteoporotic women on treatment with oral bisphosphonates. Gerodontology 2016;33(2):155-160. DOI: 10.1111/ger.12121.

[21] Nair PN. Pathogenesis of apical periodontitis and the causes of endodontic failures. Crit Rev Oral Biol Med. 2004;15(6):348-381. DOI: 10.1177/154.411.130401500604.

[22] Stanev E, Vasileva RI. Influence of osteoporosis on the course of apical periodontitis. Eur J Dent. 2024 May 17. Epub ahead of print. DOI: 10.1055/s-0044.178.5533.

[23] Ye L, Cao L, Song W, Yang C, Tang Q, Yuan Z. Interaction between apical periodontitis and systemic disease (Review). Int J Mol Med. 2023;52(1):60. DOI: 10.3892/ijmm.2023.5263.

[24] Gomes-Filho JE, Wayama MT, Dornelles RC, Ervolino E, Yamanari GH, Lodi CS, Sivieri-Araújo G, Dezan-Júnior E, Cintra LT. Raloxifene modulates regulators of osteoclastogenesis and angiogenesis in an oestrogen deficiency periapical lesion model. Int Endod J. 2015;48(11):1059-1068. DOI: 10.1111/iej.12403.

[25] Fischer V, Haffner-Luntzer M. Interaction between bone and immune cells: Implications for postmenopausal osteoporosis. Semin Cell Dev Biol. 2022;123:14-21. DOI: 10.1016/j.semcdb.2021.05.014.

[26] Brasil SC, Santos RM, Fernandes A, Alves FR, Pires FR, Siqueira JF Jr, Armada L. Influence of oestrogen deficiency on the development of apical periodontitis. Int Endod J. 2017;50(2):161-166. DOI: 10.1111/iej.12612.

[27] López-López J, Castellanos-Cosano L, Estrugo-Devesa A, Gómez-Vaquero C, Velasco-Ortega E, Segura-Egea JJ. Radiolucent periapical lesions and bone mineral density in post-menopausal women. Gerodontology 2015;32(3):195-201. DOI: 10.1111/ger.12076.

[28] Katz J, Rotstein I. Prevalence of Periapical lesions in patients with osteoporosis. J Endod. 2021;47(2):234-238. DOI: 10.1016/j.joen.2020.10.019.

[29] Cadoni E, Ideo F, Marongiu G, Mezzena S, Frigau L, Mela Q, Capone A, Duncan HF, Cotti E. Periapical status in patients affected by osteoporosis: A retrospective clinical study. Clin Exp Dent Res. 2022;8(5):1068-1075. DOI: 10.1002/cre2.604.

[30] Kang B, Cheong S, Chaichanasakul T, Bezouglaia O, Atti E, Dry SM, Pirih FQ, Aghaloo TL, Tetradis S. Periapical disease and bisphosphonates induce osteonecrosis of the jaws in mice. J Bone Miner Res. 2013;28(7):1631-1640. DOI: 10.1002/jbmr.1894.

[31] Rao NJ, Wang JY, Yu RQ, Leung YY, Zheng LW. Role of periapical diseases in medication-related osteonecrosis of the jaws. Biomed Res Int. 2017;2017:1560175. DOI: 10.1155/2017/1560175.

[32] Silva RAB, Sousa-Pereira AP, Lucisano MP, Romualdo PC, Paula-Silva FWG, Consolaro A, Silva LAB, Nelson-Filho P. Alendronate inhibits osteocyte apoptosis and inflammation via IL-6, inhibiting bone resorption in periapical lesions of ovariectomized rats. Int Endod J. 2020;53(1):84-96. DOI: 10.1111/iej.13206.

[33] Song M, Alshaikh A, Kim T, Kim S, Dang M, Mehrazarin S, Shin KH, Kang M, Park NH, Kim RH. Preexisting periapical inflammatory condition exacerbates tooth extraction induced bisphosphonate-related osteonecrosis of the jaw lesions in mice. J Endod. 2016;42(11):1641-1646. DOI: 10.1016/j.joen.2016.07.020.

[34] Venskutonis T, Plotino G, Tocci L, Gambarini G, Maminskas J, Juodzbalys G. Periapical and endodontic status scale based on periapical bone lesions and endodontic treatment quality evaluation using cone-beam computed tomography. J Endod. 2015;41(2):190-196. DOI: 10.1016/j.joen.2014.10.017.

[35] Yamada S, Uchida K, Iwamoto Y, Sugino N, Yoshinari N, Kagami H, Taguchi A. Panoramic radiography measurements, osteoporosis diagnoses and fractures in Japanese men and women. Oral Dis. 2015;21(3):335-341. DOI: 10.1111/odi.12282.

[36] Yajima N, Munakata M, Fuchigami K, Sanda M, Kasugai S. Influence of bisphosphonates on implant failure rates and characteristics of postmenopausal woman mandibular jaw bone. J Oral Implantol. 2017;43(5):345-349. DOI: 10.1563/aaid-joi-D-17-00015.

[37] Barngkgei I, Khattab R. Detecting the effect of bisphosphonates during osteoporosis treatment on jaw bones using multidetector computed tomography: The OSTEOSYR project. J Investig Clin Dent. 2018;9(3):e12332. DOI: 10.1111/jicd.12332.

[38] Musulluoğlu F, Alan H, Yılmaz S. Investigation of the effect of oral and internal bisphosphonate use on bone density in the jaws in patients with osteoporosis in panoramic radiography. Oral Surg Oral Med Oral Pathol Oral Radiol. 2023;136(3):284-293. DOI: 10.1016/j.oooo.2023.02.009.

[39] Busra T, Guldane M. Evaluation of mandibular morphometry in the bisphosphonate users. Int. j. Morphol. 2019;37(2):654-663.

[40] Kubo R, Ariji Y, Taniguchi T, Nozawa M, Katsumata A, Ariji E. Panoramic radiographic features that predict the development of bisphosphonate-related osteonecrosis of the jaw. Oral Radiol. 2018;34(2):151-160. DOI: 10.1007/s11282.017.0293-9.

[41] Rupel K, Dal Broi C, Ottaviani G, Bellassai L, Bogdan Preda TM, Di Lenarda R, Biasotto M. Changes in mandibular radiomorphometric indices in osteoporosis patients treated with denosumab: A retrospective case-control study. BMC Oral Health 2024;24(1):89. DOI: 10.1186/s12903.024.03870-1.

[42] Özcan G, Şekerci AE, Gönen ZB. Are there any differences in mandibular morphology of patients with bisphosphonate-related osteonecrosis of jaws?: A case-control study. Dentomaxillofac Radiol. 2016;45(6):20160047l. DOI: 10.1259/dmfr.20160047.

[43] Dereci Ö, Orhan EO, Irmak Ö, Ay S. The effect of the duration of intravenous zolendronate medication on the success of non-surgical endodontic therapy: A retrospective study. BMC Oral Health 2016;(16):1-9. DOI: 10.1186/s12903.016.0163-6.

[44] Hsiao A, Glickman G, He J. A retrospective clinical and radiographic study on healing of periradicular lesions in patients taking oral bisphosphonates. J Endod. 2009;35(11):1525-1528. DOI: 10.1016/j.joen.2009.07.020.

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