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Evaluation of Mandibular Morphometry in the Bisphosphonate Users

Evaluación de la Morfometría Mandibular en los Usuarios de Bifosfonatos

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SUMMARY: This study aimed to evaluate the effects of bisphosphonates on the mandibular bone. Bisphosphonates are drugs which are commonly used in the treatment of many diseases related to bone metabolism such as osteoporosis, breast cancer capable of bone metastasis, prostate and lung cancer and bone cancer such as multiple myeloma. Our study group consisted of a total of 100 panoramic radiographs which were obtained from the examinations of 50 individuals using bisphosphonate and 50 individuals in the control group who applied for routine dental examination to the Department of Oral and Maxillofacial Radiology of Akdeniz University Dentistry Faculty between years 2015 and 2016.The calculations of the mandibular cortical thickness (MCT), mandibular cortical index (MCI), panoramic mandibular index (PMI), condylar angle (CA), gonial angle (GA), antegonial angle (AGA), antegonial depth (AGD) and antegonial index (AGI) were made for each patient. It was found that both left and the right MCT and only the left PMI were affected by age. Only the left AGA and both the left and right MCT and AGD were affected by gender. The left and right AGI measurements of the patients using bisphosphonates were statistically lower than those of the individuals in the control group. Our results suggested that bisphosphonates had various effects on the jaw bones. However, further comprehensive studies need to be made to evaluate the long-term effect of bisphosphonates on bone metabolism.

KEY WORDS: Bisphosphonates; Mandible; Panoramic Radiography.

INTRODUCTION

In the present time, bisphosphonates are used in the treatment of many diseases related to bone metabolism. Bisphosphonates are known to inhibit osteoclastic activity which as a result reduces bone resorption. They are generally preferred, to reduce bone resorption for the purpose of bringing many diseases under control. Not only do they affect osteoclastic cells, but also inhibit osteoblastic activity (Luckman *et al*., 1998; Sparidans *et al*., 1998). In addition, Intravenous bisphosphonates which are used against the invasion of tumor cells throughout the extracellular matrix, to inhibit the invasion of the tumor or generally used for treating osteopenia and osteoporosis were primarily used for the treatment of skeletal related conditions such as fractures, bone pain, hypercalcemia resulting in excessive bone resorption and against malignancies such as multiple myeloma, breast, prostate, lung and bone metastatic renal cancers (Torres *et al*., 2015).

Conventional dental radiographs help us to identify pathological fractures, osteosclerotic, osteolytic, reactive periosteal mixed lesions. Osteosclerosis of lamina dura is the first sign of metabolic changes in the bone (O'Ryan *et al*., 2009). Aside from the use of conventional x-ray films, the present circumstances of the development in computing technology allowed digital radiography techniques to be used in dentistry. In contrast to the conventional technique, digital radiography has various advantages such as exposure to less radiation, avoiding the need of dark rooms and bathing procedures, the possibility of making adjustments on the contrast and gray tones, magnification modifications, the possibility of making measurements and the availability to archive and make transfers to a third person on request (Benson *et al*., 1991)

Bisphosphonates reduce remodeling, thus reducing the ability to repair daily micro-trauma. This causes more damage (Li *et al*., 2001). In this context, to our knowledge, there are no studies evaluating the effect of bisphosphonates on mandible except for osteonecrosis. So we aimed to evaluate the effects of bisphosphonate derived drugs on the

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mandible that patients use due to various disorders such as osteoporosis, multiple myeloma, breast, prostate and lung cancer and bone metastatic renal cancer. On the panoramic radiographs, mandibular cortical index (MCI), mandibular cortical thickness (MCT), panoramic mandibular index (PMI), antegonial index (AGI), gonial angle (GA), antegonal angle (AGA), condyle angle (CA) measurements were made, and the obtained data were compared with the healthy individuals in the control group.

MATERIAL AND METHOD

This thesis study was approved by the Ethics Committee of Non-Interventional Clinical Researches of the Institute of Health Sciences of Akdeniz University with the protocol number 470 on 17/08/2016.

The study group of this retrospective research is based on panoramic radiographs obtained for the purpose of routine examination and treatment from a total of 100 individuals from the archives of the Department of Oral and Maxillofacial Radiology of the Faculty of Dentistry of Akdeniz University. Patients that came to the Department of Oral and Maxillofacial Radiology of the Faculty of Dentistry of Akdeniz University for routine examination and were seen to be taking or had taken bisphosphonates for the treatment of various conditions such as osteoporosis, breast cancer, prostate cancer, multiple myeloma and similar metastatic cancers were included in the study group. The anamneses obtained from the patients were considered to be the fundamental factor for the inclusion and exclusion of patients to this study. Therefore, patients with fractures involving jaws or a history of orthognathic surgery and any systemic disease affecting bone metabolism such as Paget's disease, osteogenesis imperfecta, osteomalacia, hypoparathyroidism, hyperparathyroidism and renal osteodystrophy were not included in the study. The control group consists of healthy individuals that don't have any systemic diseases and have similar age with the individuals in the study group.

All of the panoramic radiographs that were evaluated were taken in the Department of Oral and Maxillofacial Radiology of the Faculty of Dentistry of Akdeniz University by the same technician using a Planmeca (OY 00880 Helsinki, Finland) brand digital panoramic device. In order to standardize the panoramic radiographs, the manufacturer's reference points set on the device were fully complied with. In order to avoid the superposition of the cervical vertebra on the anterior of the mandible, patients were appropriately positioned so that their Frankfort horizontal plane was parallel to the floor and sagittal plane was perpendicular. Radiographs were examined on the basis that the boundaries of the mental foramens could be fully observed, the upper and lower boundaries of the cortical bone were clearly visible, no artifacts were seen in the measurement sites and the mandibular margins were clearly visible. Radiographs that did not meet these conditions were excluded from the study.

Radiographic measurements. Panoramic radiographs that were previously taken for routine control and examination purposes were recorded in a TIFF (Tagged Image File Format) format and were assigned numbers from 1 to 100. The measurements of MCI, MCT, PMI, AGI, GA, AGA and CA were made on these radiographs. Measurements were evaluated using a Metasoft Planmeca software program (Planmeca, Helsinki, Finland) on a computer with a 27 inch 1920x1080 resolution LED monitor, Intel Core i7 processor, 3.5 GHz processor speed and 4 GB GDRR5 reserved AMD Radeon HD 7950 graphics card. In order to minimize magnifications related to the panoramic radiographs during the measurements, the automatic magnification calibration of Planmeca was used. Radiographs where the necessary measurements could not be made were excluded from the study. After two weeks, all measurements were repeated by the same observer (B.T.) with the rule of being blind to the first measurements.

Mandibular Cortical Thickness (MCT). According to a method indicated by Ledgerton *et al*. (1999), after determining the mental foramens on the radiograph, two lines were drawn with one of them being tangent to the inferior margin of the mandible and the other one being parallel to the superior margin of the cortical layer of the mandible. This was followed by a tangent line that was drawn to connect the center of the mental foramens and the inferior margin of the mandible. The distance between the two parallel lines that coincide with tangent line that connects the mental foramen and the inferior margin was measured as the width of the cortical layer of mandible (Fig. 1).

Mandibular Cortical Index (MCI). MCI (the appearance of the lower edge of the mandible) was classified according to Klemetti *et al*. (1993). The erosion condition of the mandibular endosteal margin was evaluated as normal (C1), medium (C2) and severe (C3) (Fig. 2).

Condyle Angle (CA). CA measurements were made according to the method indicated by Ledgerton *et al*. The area that was formed between the intersection of a linear tangent line that passed through the condyle neck and a tangent line that was linear to the margin of the ramus was evaluated as the condyle angle (Fig. 1).

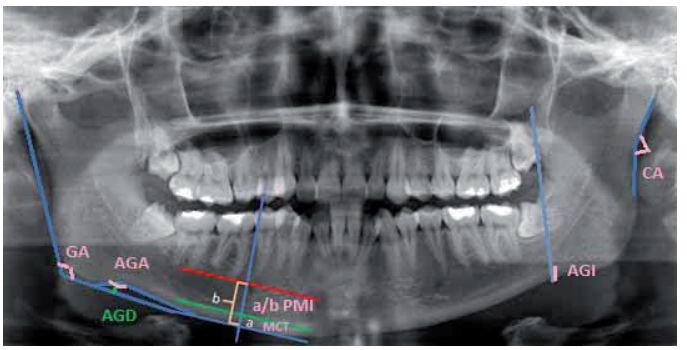

Fig. 1. The presentation of measurements (GA: Gonial Angle; AGA: Antegonial Angle; AGD: Antegonial Depth; MCT: Mandibular Cortical Thickness; PMI: Panoramic Mandibular Index; AGI: Antegonial Index; CA: Condyle Angle).

Gonial Angle (GA). The angle that was formed between the intersection of a tangent line that was drawn on the inferior margin of the mandible and a tangent line drawn on the posterior side of the ramus was measured as the gonial angle. Measurements of the GA were made based on the method indicated by Dutra *et al*. (2004) (Fig. 1).

Antegonial Angle (AGA). AGA was measured as the angle that was formed between two parallel lines drawn on the inferior cortical margin in the antegonial region (Fig. 1) (Benson *et al*.).

Antegonial Depth (AGD). AGD measurements were evaluated based on the method indicated by Dutra *et al*. (2004). A line was drawn parallel to the lower cortical margin of the mandible. Another line, vertical to the first line was drawn from the deepest point in the antegonial notch concavity and this distance was measured as the antegonial depth (Fig. 1).

Antegonial Index (AGI). AGI measurements were based on the method indicated by Dutra *et al*. (2004) where the cortical thickness was measured in the area formed by a line known as "best fit" drawn between the anterior margin of the ascending ramus in the region in front of gonion and the inferior margin of the mandible (Fig. 1).

Table I. Demographic data for the sample.

		Bisphosphonate Users	Control
Age	Minimum	31	40
	Maximum	79	82
	Mean	59.59±9.52	53.48±7.68
Gender	Female n (%)	32 (64 %)	25 (50 %)
	Male n (%)	18 (36 %)	25 (50 %)
Total		50	50

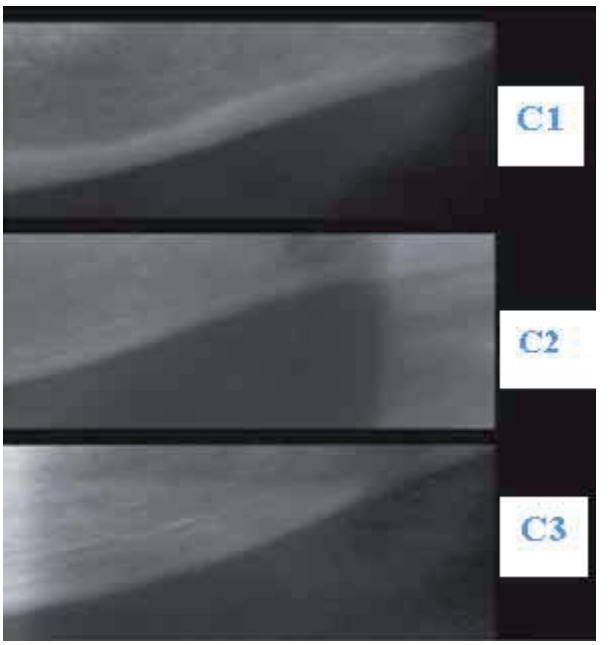

Fig. 2. The presentation of mandibular cortical index (MCI).

Statistical Analysis. Statistical analyses were performed using the SPSS (Statistical Package for Social Sciences, 18.0, SPSS Company, Illinois, USA) package program. Descriptive statistics, Kolmogorov-Smirnov, Wilcoxon, Mann-Whitney U, Spearman's correlation and Chi-square tests were used. In addition, Kappa and reliability analyses were conducted. The results were evaluated at 95 % confidence interval, $p<0.05$ significance level.

RESULTS

Our study group is composed of 50 patients (20 males, 30 females) who are using or had used bisphosphonates and 50 patients (25 males, 25 females) in the control group. The age range of the patients in the control group was between 40 - 82 years (mean 53.38 ± 7.68) while the patients using bisphosphonates were in the age range of 31-79 years (mean 59.59 ± 9.52). Distribution according to sex and the minimum, maximum, mean and standard deviation values for the age for all of the patients are indicated in Table I.

48 % of patients using bisphosphonates were using it due to osteoporosis. 52 % of the patients were cancer patients with bone metastasis (multiple myeloma, breast, prostate and lung cancer) (Table II). The control group was formed by patients that did not have any systemic disease.

Table II. Systemic diseases of patients using bisphosphonates.

Systemic Disease	Number of Patient
Osteoporosis	24 (48 %)
Multiple Myeloma	9 (18 %)
Breast CA	8 (16 %)
Prostate CA	8 (16 %)
Lung CA	1(2 %)

For the reliability of the left and right MCT, PMI, GA, AGA, AGD and AGI values, Cronbach's Alpha values were found to be between 0.810 and 0.942, respectively.

Observer kappa values for right and left MCI were found to be 0.836; 0.822.

Descriptive Statistics for Patients Using Bisphosphonates. The minimum (min), maximum (max), mean and standard deviation values for the right and left MCT, PMI, CA, GA, AGA, AGD and AGI for the patients using bisphosphonates are given in Table III. The distribution of the categories of the left and right MCI values for the patients using bisphosphonates is given in Table IV. For the patients using bisphosphonates, the most dominant category for the left and right MCI values was category C1 (for right a total of 26, 52 % - for left a total of 26, 54 %). The MCI categories were found as 52 % C1, 42 % C2 and 6 % C3 for the right and 54.2 % C1, 37.5 % C2 and 8.3 % C3 for the left, respectively. For the right MCI values, while the most dominant category was C1 for females, it was C2 for males (Table IV). For males, the C3 category was not observed on the right, but was observed to be 2.1 % on the left (Table IV). The result of the measurements indicated that MCI, PMI, right CA, GA, AGA, AGD and AGI values didn't show any statistically significant differences according to sex (p?0.05). Only the left CA and both left and the right MCT values showed statistically significant differences according to sex ($p < 0.05$) (Table III). While the right CA values were higher in females, both left and the right MCT values were higher in males (Table III).

There was no significant difference between the right and left measurements of both males and females in patients using bisphosphonates ($p > 0.05$) (Table III).

Descriptive Statistics for Patients in the Control Group. For the control group, the minimum (min), maximum (max), mean and standard deviation values for the right and left MCT, PMI, CA, GA, AGA, AGD and AGI are given in Table V.

When the right and left MCI categories of the individuals in the control group were evaluated, it was found that C1 category was the most dominant. (For right a total of 31.62 % - for left a total of 32.64 %, Table VI). C2 category was higher in males. C3 category for females in both left and the right side was not observed (Table VI).

Table III. Descriptive statistics and p-values to the sex of MCT, PMI, CA, GA, AGA, AGD, AGI measurements of patients using bisphosphonate.

	MALE				FEMALE				To gender	Right-Left Male	Right-Left Female
	Min	Max	Mean	SD	Min	Max	Mean	SD	p value	p value	p value
MCT (right)	3.1	6.8	4.33	1.06	1.4	5.4	3.55	0.96	0.024*	0.085	0 .274
MCT (left)	3	5.8	4.27	0.98	1.6	5.2	3.45	0.88	0.009**		
PMI (right)	0.22	0.5	0.32	0.08	0.13	0.49	0.31	0.08	0.792	0.417	0 .483
PMI (leftt)	0.2	0.43	0.31	0.07	0.19	0.5	0.3	0.07	0.784		
CA (right)	158.04	171.71	165.06	3.94	148.2	169.71	161.6	4.66	0.014*	0.145	0 .911
CA (left)	148.99	175.3	164.11	6.26	151.23	170.48	161.44	4.71	0.14		
GA (right)	108.96	140.3	123.52	8.85	100.44	135.08	120.88	8.37	0.455	0.085	0 .161
GA (left)	110.16	140.08	121.96	7.53	100.07	139.02	121.49	8.01	0.984		
AGA (right)	147.99	176.12	163.68	7.99	148.08	173.13	162.78	6.94	0.531	0.510	0 .888
AGA (left)	150.43	175.3	164.04	7.95	137.5	173.92	162.6	8.2	0.505		
AGI (right)	0.6	4.3	1.61	0.94	0.4	3.3	1.53	0.75	0.919	0.773	0 .820
AGI (left)	0.6	4	1.5	0.93	0.6	3	1.53	0.64	0.517		
AGD (right)	1.2	3.2	2.03	0.47	1	3.4	1.96	0.56	0.627	0.095	0 .967
AGD (left)	1.5	3	2.1	0.46	1.2	4.2	2.05	0.67	0.549		

Min: Minimum. Max: Maximum. SD: Standart Deviation. * $p < 0.05$

Table IV. Distribution of right and left MCI categorizations by sex in patients using bisphosphonates.

		MCI (right)			Total	MCI (left)			Total	Right-Left
		C1	C2	C3		C1	C2	C3		p value
Female	n	18	11	3	32	18	11	3	32	0.351
		36 %	22 %	6 %	64 %	37.50 %	20.80 %	6.30 %	64.60 %	
Male	n	8	10	0	18	8	8	2	18	0.248
		16 %	20%	0 %	36 %	16.70 %	16.70 %	2.10 %	35.40 %	
Total	n	26	21	3	50	26	18	4	48	
		52 %	42 %	6 %	100 %	54.20 %	37.50 %	8.30 %	100 %	
To sex p-value			0.000*				0.000*			

**p<0.01

The right AGA and both left and the right AGD values for the patients in the control group showed statistically significant differences according to sex (p<0.05) (Table V). The right AGA values were seen to be higher in females. Both left and the right AGD values were seen to be higher in males (Table V).

There weren't any statistically significant differences between the left and the right MCT, MCI, CA, GA, AGA, AGD and AGI values for the patients in the control group (p> 0.05) (Table VI). However, in both males and females, the left AGA value was statistically significantly greater than the right AGA value (p <0.05) (Table V).

Table V. Descriptive statistics and p-values to the sex of MCT, PMI, CA, GA, AGA, AGD, AGI measurements of the control group.

	MALE				FEMALE				To	Right-Left	Right-Left
	Min	Max	Mean	SD	Min	Max	Mean	SD	p value	p value	p value
MCT (right)	2.8	5.7	4.19	0.69	2.8	5.5	3.93	0.68	0.186	0.070	0.173
MCT (left)	3	5.3	4.04	0.62	2.6	5.6	3.8	0.77	0.207		
PMI (right)	0.21	0.41	0.32	0.05	0.24	0.48	0.34	0.06	0.125	0.253	0.447
PMI (leftt)	0.25	0.39	0.31	0.04	0.23	0.52	0.34	0.07	0.209		
CA (right)	153.77	168.76	162.34	3.77	143.8	169.05	161.06	5.71	0.614	0.294	0.657
CA (left)	152.14	171.57	163.09	4.21	145.5	174.03	160.98	5.84	0.09		
GA (right)	106.88	135.68	121.52	7.69	113.75	137.08	125.14	5.87	0.088	0.158	0.677
GA (left)	110.47	137	123.39	8.13	115.84	136.7	124.35	5.12	0.58		
AGA (right)	133.88	171.64	160.55	8.77	150.02	179	165.94	7.14	0.021*	0.01**	0.037*
AGA (left)	142.67	177.7	163.98	8.23	154.97	180.15	168	6.03	0.093		
AGI (right)	0.6	5.3	2.28	1.18	0.2	3.3	1.58	0.83	0.042*	0.699	0.251
AGI (left)	0.4	4.4	2.05	1.04	0.3	3	1.34	0.74	0.013*		
AGD (right)	1.6	3.7	2.37	0.56	1.2	4.5	2.35	0.85	0.472	0.219	0.118
AGD (left)	1.3	3.6	2.4	0.61	1.6	4.2	2.42	0.61	0.838		

Min: Minimum. Max: Maximum. SD: Standart Deviation. * p< 0.05

Table VI. Distribution of right and left MCI categorizations by sex in the control group.

		MCI (right)			Total	MCI (left)			Total	Right-Left
		C1	C2	C3		C1	C2	C3		p value
Female	n	19	6	0	25	20	5	0	25	0.317
		38 %	12 %	0 %	50 %	40.00 %	10.00 %	0.00 %	50.00 %	
Male	n	12	12	1	25	12	12	1	25	0.128
		24 %	24 %	2 %	50 %	24.00 %	24.00 %	2.00 %	50.00 %	
Total	n	31	18	1	50	32	17	1	50	
		62 %	36 %	2 %	100 %	64.00 %	34.00 %	2.00 %	100 %	
To gender p-value			8%				5%			

Evaluation of the Differences between the Groups. There were statistically significant differences between the left and right AGI values between the groups (p <0.05) (Table VII). For all of the other measurements, there weren't any statistically significant differences between the groups (p> 0.05) (Table VII).

Table VII. p-values of all measurements according to the groups.

	p value		p value
MCT (right)	0.156	GA (right)	0.379
MCT (left)	0.258	GA (left)	0.092
MCI (right)	0.088	AGA (right)	0.975
MCI (left)	0.101	AGA (left)	0.092
PMI (right)	0.116	AGI (right)	0.008*
PMI (left)	0.147	AGI (left)	0.001*
CA (right)	0.314	AGD (right)	0.055
CA (left)	0.775	AGD (left)	0.406
*p<0.01			

The mean values of the AGI were seen to be higher in patients using bisphosphonates ($p < 0.05$) (Tables III and V).

For the patients using bisphosphonates, the relationship between the age and other variables was evaluated with Spearman's correlation test; there was a statistically weak and negative correlation between age and the right AGA, left AGA and the right CA ($p < 0.05$ rho values -0.286, -0.327 and -0.323, respectively). In addition, it was seen that there was a weak yet a statistically significantly positive relationship between age and left MCI values ($p < 0.05$ rho value 0.397).

DISCUSSION

In this study, morphological changes in the mandible that may occur due to the use of bisphosphonate-derived drugs, which have become increasingly widespread due to various diseases, have been evaluated by panoramic radiography. There are not enough studies in literature on the subject of bisphosphonate drugs having altering effects on the mandible.

Like in all radiographical methods, due to magnification and distortion, the reliability of panoramic imagery is controversial in dimensional and angular measurements (Akcam *et al*., 2003; Cakur *et al*., 2010). In rotational panoramic radiography, it is stated that there is no significantly statistical difference between the left and the right side due to repeatability (Lucchesi *et al*., 1988). In panoramic radiography, linear measurements which don't pass the midline and cover the left and the right side are very close to actual measurements (Larheim & Svanaes, 1986). It is stated that it is possible to do longitudinal studies with the obtained panoramic radiographs after filming with the same device (Catic *et al*., 1998).

In literature, to evaluate the morphological structure changes of the mandible, panoramic radiography (Kjellberg *et al*., 1994; Dutra *et al*., 2004; Jung, 2005) and lateral cephalometry (Ceylan *et al*., 1998; Ohm & Silness, 1999; Ogawa *et al*., 2012) were used. In lateral cephalometric radiography, since the right and left anatomical structures overlap, an average value is obtained. Whereas, in panaromic imagery since it is possible to assess the right and left anatomic structures independently, it gives a more precise result (Mattila *et al*., 1977; Ogawa *et al*.; Upadhyay *et al*., 2012). In the recent years, there are studies using computed tomography (CT) to evaluate mandible morphology (Casey & Emrich, 1988; Benson *et al*.; Sato *et al*., 2005). Although CT gives exact and more detailed results, it is not routinely used because of its radiation dose and cost when compared to panoramic radiography.

In our research panaromic radiography was used due to it being used routinely, it's capability to enable independent right and left measurements and its cost and radiation dose.

In this research, healthy individuals without any systemic disease and patient using bisphosphonates had their left and right GA, AGA, CA, MCT, PMI, AGI, AGD measurements calculated on panoramic radiographs. Keeping in mind the effects of bisphosphonates on bone metabolism, it's possible effects on the mandible bone were also evaluated.

Torres *et al*. found that the average MCT value was the highest among individuals who use biphosphonates and have bisphosphonate related jaw osteonecrosis (BRONJ). Also patients that didn't have BRONJ and were using bisphosphonates had a higher average MCT value than the healthy individuals.

In our study, in terms of MCT, there was no significant difference between the patients using bisphosphonates and the patients in the control group. However, the right and left average MCT value was higher in males who used bisphosphonate than the males in the control group. For females, the MCT value was observed to be higher than the females in the control group. This could be due to the MCT showing differences according to sex.

Ozcan *et al*. (2016) studied the morphological differences of the mandible in 32 healthy individuals and 32 individuals with BRONJ on their panoramic radiographs and CBCT images. In their study, they evaluated CA, GA, AGA, AGD and condyle and ramus height using panoramic radiography and used CBCT to evaluate MCI and bone quality index. They stated that individuals with BRONJ had significant differences between the right and left MCI values

and specifically the side with BRONJ had a statistically significant difference in MKI value compared to the patients in the control group. Neither of the sides had any differences in regards to sex.

In Tozoglu & Cakur's study (Tozoglu & Cakur, 2014) evaluating mandibular changes in patients with our without teeth using CBCT, the right side didn't show any differences in MCI values for patients with and without teeth, while the left side showed differences. They stated that neither of the sides showed any differences in MCI values in regards to sex.

Grgic *et al*. (2017) used panoramic radiography to evaluate the effect of bisphosphonate treatment on bone mineral density and oral health in post-menopausal females. 3 groups including patients with osteoporosis not using medicine, patients with osteoporosis using bisphosphonate and healthy patients were studied. In all three groups there was no difference between the MCI values. In our study, in terms of MCI value, groups and sexes did not show a significant difference.

Dutra *et al*. (2007) studied the panoramic radiographs of 10 dry mandibles' GK, AGI and MCI measurements. They concluded that all of their measurement methods were not enough to diagnose osteopenia or osteoporosis alone. In the same study they suggested that MCT measurements of the mental region was more viable, AGI and GT's measurements provided less information on identifying osteoporosis risk groups.

Benson *et al*. studied panoramic radiographs of 353 patients between ages 30 and 79. After measuring the distance from the lower margin of the mental foramens to the lower margin of the mandible, their results showed that age was an important criterion. In our study, neither of the groups had any significant correlation between the right PMI value and age, however found a weak but statistically significant correlation between the left PMI value and age in only healthy individuals. The data we obtained was not consistent with the data from Dagistan & Bilge (2010), Ledgerton *et al*., Gulsahi *et al*. (2008), Hastar *et al*. (2011), and Knezovic´ Zlataric´ *et al*. (2002). This inconsistency might be explained due to difference in studied sample groups and uneven dispersion of individuals in the age groups.

In literature, PMI measurements are usually done on female patients (Kribbs, 1990; Knezovic´ Zlataric´ *et al*.; Metzler *et al*., 2012; Tozog˘lu & Cakur). For this reason studies that indicate sex difference are scarce (Klemetti *et al*.; Gulsahi *et al*.). In other studies, females' mean PMI values are between 0.31 and 0.38 (Yüzügüllü *et al*., 2009; Metzler *et al*.). In our study, individuals who use bisphosphonate have a mean PMI value of 0.31, in females 0.31, in males 0.32 and in the control group the mean PMI value is 0.33, in females 0.35 and in males 0.32. The data we obtained was consistent with the range indicated in literature and females in the control group had a higher mean PMI value than males. But these differences between the groups were not statistically significant ($p>0.05$).

Tozoglu & Cakur evaluated mandibular changes in patients with and without teeth using CBCT. In their study, there were no significant differences between CA value of the right and left sides in both groups. However, they found that there is a significant difference in the right side of the patients without teeth in regards to sex. In our study, while the left CA was not affected by age and sex, the right CA was affected. There was a negative correlation between age and the right CA value and as age increased the right CA value decreased.

Ozcan *et al*. made evaluations in their study by comparing mandibular changes between patients with BRONJ and healthy patients and found no difference between the groups in terms of the CA values. In our study, we compared the CA value of individuals taking bisphosphonates and healthy individuals and found no significant difference.

Consistent with the results of Raustia & Salonen (1997), Ceylan *et al*. and Dutra *et al*. (2004), our study showed that right and left GA measurements in the individuals that used bisphosphonates and the control group showed no difference between age groups. Ohm & Silness found out that age makes a difference when comparing GA using lateral cephalometric radiography. However, they pointed out that age had a weaker correlation than dental status and sex. One must take into consideration the differences in measurement methods. Upadhyay *et al*. measured GA on lateral cephalometric radiographs and found that as age increases GA value decreases. Nonetheless, they pointed out that this relationship is weak and not reliable and other parameters should be considered.

Although there are a number of studies suggesting that GA does not vary according to sex (Benson *et al*.; Kjellberg *et al*.; Ceylan *et al*.; Horner & Devlin, 1998), there are also studies suggesting otherwise (Mattila *et al*.; Raustia & Salonen; Huumonen *et al*., 2010; Joo *et al*., 2013). In this study, GA was found to be 3°-5° lower in healthy males compared to females but, males using bisphosphonates had higher GA value than females. The difference between the two was not statistically significant. Findings of our study were consistent with the findings of Raustia & Salonen, Ohm & Silness, Dutra *et al*. (2004) and Tozoglu & Cakur.

Dutra *et al*. (2004) and Ghosh *et al*. (2010) stated that AGA and AGD did not differ according to age and that females had wider AGA and lower AGD values compared to males. Osato *et al*. (2012) also reported that females with a wide GA had a wider AGA compared to males. They also indicated that females with a narrower GA had higher AGD values than males.

In this study, for the patients using bisphosphonate, a statistically significant but a weak and negative correlation was found between age and the right and left AGA measurements. However, for the control group, no significant correlation between AGA and age was found. Among the groups, AGA values did not show any significant differences. Males using bisphosphonate had higher AGA values than females. However, males in the control group had lower AGA values than females. The reason our findings differed from these studies might be due to, Dutra *et al*. (2004) neglecting the factor of sex in patients over 40 years of age and Ghost *et al*. patient sample differed from our sample in terms of age.

Due to the remodeling of the antegonial region, while resorption is seen along the lowest margin of the mandible, deposition is seen on the anterior side of the antegonial region (Dutra *et al*., 2004). Ali *et al*. (2005) states that the problems in condylar growth are conducted via the masseter and medial pterygoid muscles unto the lower part of the mandible and thus forming the antegonial notch. The differences between sexes could be explained in connection to the factors affecting bone metabolism. Bruxism should also be considered as an affecting factor. Bruxism is more prevalent in females than males.

The reduction in gonial thickness (GT), which is considered to be one of the effects of the metabolic bone diseases on the mandible, has been investigated in various studies (Bras *et al*., 1982; Knezovic Zlataric *et al*.; Bollen *et al*., 2004).

Bras *et al*. states that it is not possible to observe GT before adolescence and that it stays relatively stable between ages 15-60. They observed a decrease in cortical thickness in postmenopausal females after 60 years of age and therefore indicated that the use of GT measurements could be used as a parameter to assess metabolic bone loss in this region.

In their study evaluating mandibular bone density, body mass index, and radiomorphometric measurements on 136 panoramic radiographs, Knezovic Zlataric *et al*., found a correlation between bone mineral density and body mass index in all measurements including AGI (Knezovic Zlataric *et al*.).

In our study, there was a statistically significant difference in the AGI measurements between individuals in the control groups and individuals who received bisphosphonate treatment. In literature, since there are insufficient studies about the AGI values of patients using bisphosphonate, exact comparisons could not be made. However, as described by Knezovic´ Zlataric´ *et al*., the relationship between AGI and bone mineral density should be considered. In our group of patients who use bisphosphonate, the bone mineral density decreased and this difference may be due to this.

In our study, the right and left AGD measurements did not show a statistically significant difference with age. This result is consistent with Dutra *et al*. (2004) and Ghosh *et al*. For the mean AGD values, it was observed that male patients using bisphosphonates had a higher AGD, whereas the left AGD were higher in females ($p<0.05$). In the control group, AGD values were lower in females ($p <0.05$). The mean AGD value bilaterally in the control group was higher than those using bisphosphonate ($p <0.05$).

Limitation. This study had some limitations. First, in the study time interval, there were only 100 subjects, who met the criteria for group. Second, the study had a retrospective design. Hence, it was not possible to obtain the patient's entire history such as learning the type of bisphosphonate used, the duration of use, the method of administration (oral or i.v.) and by carrying out the patient's long-term follow-up.

CONCLUSION

According to the results of this study, AGI values were statistically different between the patients in the control group compared to the patients who were or are using bisphosphonates. This result may indicate that evaluation and the measurements of AGI can be used as a parameter to evaluate metabolic bone loss. Patients that started or starting bisphosphonate treatment must be informed about its possible risks on the jaw bone, the dental treatment and the importance of the follow-up of this treatment. Before the initiation of a bisphosphonate treatment, consultation between the patient's physician and the dentist must be made and a steady team work should be ensured to consider possible risks. In future studies, further clarified information can be accessed about the possible short and long term effects of bisphosphonates on bone metabolism by providing a wider range of sample groups and learning the type of bisphosphonate used, the duration of use, the method of administration (oral or i.v.) and by carrying out the patient's long-term follow-up.

BUSRA, T. & GULDANE, M. Evaluación de la morfometría mandibular en los usuarios de bifosfonatos. *Int. J. Morphol., 37(2)*:654-663, 2019.

RESUMEN: Este estudio tuvo como objetivo evaluar los efectos de los bifosfonatos en el hueso mandibular. Los bifosfonatos son medicamentos que se usan comúnmente en el tratamiento de muchas enfermedades relacionadas con el metabolismo óseo, como la osteoporosis, el cáncer de mama, metástasis óseas, cáncer de próstata y pulmón y el cáncer de hueso como el mieloma múltiple. Nuestro grupo de estudio consistió en un total de 100 radiografías panorámicas que se obtuvieron de los exámenes de 50 individuos que utilizaron bisfosfonato y 50 individuos en el grupo de control que solicitaron un examen dental de rutina al Departamento de Radiología Oral y Maxilofacial de la Facultad de Odontología de la Universidad de Akdeniz, entre los años 2015 y 2016. En cada paciente se realizaron los cálculos del grosor cortical mandibular (GCM), índice cortical mandibular (ICM), índice mandibular panorámico (IMP), ángulo condilar (AC), ángulo gonial (AG), ángulo antegonial (AAG), profundidad antegonial (PAG) y el índice antegonial (IAG). Se encontró que tanto el GCM izquierdo como el derecho y solo el IMP izquierdo estaban afectados por la edad. Solo el AAG izquierdo y el GCM izquierdo y derecho y el AGD fueron afectados de acuerdo al sexo. Las mediciones de IAG izquierdo y derecho de los pacientes que utilizan bifosfonatos fueron estadísticamente más bajas que las de los individuos en el grupo de control. Nuestros resultados sugirieron que los bifosfonatos tienen varios efectos en los huesos de la mandíbula. Sin embargo, es necesario realizar estudios más exhaustivos para evaluar el efecto a largo plazo de los bifosfonatos en el metabolismo óseo.

PALABRAS CLAVE: Bifosfonatos; Mandíbula; Radiografía panorámica.

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