Original Research
Prosthesis

Evaluation of trabecular bone changes according to the type of prosthesis in patients using bisphosphonates: a retrospective study

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Abstract: The objective of the study was to retrospectively compare the fractal size values calculated in the trabecular bone according to the type of complete removable denture, removable partial denture, and partial fixed prosthesis between patients using bisphosphonates and healthy patients, retrospectively. Panoramic radiographs of a total of 200 patients, (100 using bisphosphonates,100 control group), were taken from the right and left molar regions before and after treatment with 72 x 72 pixels. The fractal dimension (FD) was computed by using ImageJ Software using the box-counting method on the images obtained. There was an interaction effect between the trabecular bone change-patient group-the type of prosthesis used and the parameters of the area ($p < 0.05$). In patients using complete removable dentures and removable partial dentures in the maxilla and mandibula in the molar region, a greater decrease in FD values was observed in the control group than in the patient group using bisphosphonates. An increase in FD values over time was observed in the patient group using bisphosphonates with partial fixed maxillary and mandibular prostheses compared to the control group. Partial fixed prostheses should be preferred primarily instead of complete removable or removable partial dentures in patients using bisphosphonates to prevent osteonecrosis due to dental trauma.

Keywords: Bisphosphonates; Prostheses and Implants.

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Introduction

Bisphosphonates are pyrophosphate analog drugs that reduce osteoclast activity, bone resorption and turnover, and high binding affinity to hydroxyapatite crystals, and cannot be biodegradable.[1,2] They are used in the treatment of bone metastases of solid tumors, osteoporosis, osteopenia, Paget's disease, osteogenesis imperfecta, multiple myeloma, breast, prostate, and lung cancer. [3,4]

Their principal mechanism of action can be explained by their high affinity for bone minerals and their strong binding to hydroxyapatite, bringing on the selective perception of the target organ and high local concentration in the bone, especially in active bone remodeling sites.[5]

Bisphosphonates act on the bone for a long period and continue to influence bone metabolism even after drug intake is discontinued.[6] Because they are not metabolized for a long time, they are involved in osteoclasts, which are responsible for apoptosis. In addition to its antiresorptive effect on bone, it also has functions such as antiangiogenic effects and inhibition of endothelial cells.[7]

Bisphosphonates are separated into two groups nitrogen-containing aminobiphosphonates (N-BP) and nitrogen-free alkalibiphosphonates (non N-BP).[8] Etidronate, clodronate, and tiludronate are non N-BPs, that are first-generation bisphosphonates. The second-generation bisphosphonates alendronate and pamidronate and the third-generation bisphosphonates are zoledronate, risedronate and ibandronate constitute a group of N-BPs.[9]

There are two forms of use of bisphosphonates, oral and intravenous (IV). While 1% of the dose is absorbed by the gastrointestinal system in oral administration, approximately 50% of the dose reaches the bone in IV administration. Thus, IV use creates a stronger effect than oral use.[5,10]

Despite its great clinical benefits, it has various side effects such as acute phase reactions, bone and muscle pain, skin reactions, hypocalcemia, and gastrointestinal disorders.[10,11] However, one of the major side effects of bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a bisphosphonate.[5] Osteonecrosis of the jaws due to bisphosphonates was first reported by Marx et al.[12] According to the article published by the American Society of Oral and Maxillofacial Surgery (AAOMS) in 2009, the criteria necessary in the diagnosis of BRONJ are not having received radiotherapy for the head and neck region before, ongoing or previously applied bisphosphonate therapy, and having an appearance of bone in the jaws that emerges from the mucosa for more than 8 weeks.[13] However, since not only bisphosphonates but also drugs such as RANK ligand inhibitors (denosumab), bevacizumab, sunitinib showed the same effect in 2014, AAOMS replaced the term osteonecrosis of the jaw because of the bisphosphonates (BRONJ) and suggested the use of medication-related osteonecrosis of the jaw (MRONJ).[14,15,16]

Although there are spontaneous cases of osteonecrosis, in most of the cases (68.8%), it was noted that the patients had a history of dental disease or dental treatment.[5] Marx et al. reported osteonecrosis occurring in their study with 119 patients. It was observed that it occurred after tooth extraction in 45 patients, due to periodontal disease in 34 patients, spontaneously in 30 patients, after periodontal surgery in 5 patients, after implant placement in 4 patients, and after apical resection in 1 patient.[17]

Inappropriate dental prostheses, a thin mucosa, and the pressure of the prosthesis on the tissue may cause MRONJ.[18] As a result of loading the rigid prosthetic bases in a way that does not apply equal pressure to the tissue, traumatic ulcers that kill the mucosal barrier may occur and can lead to bacterial invasion and infection of the bone.[19]

Fractal analysis (FA) is a mathematical method that enables the quantitative description of complex structures and shapes that cannot be expressed with integral dimensions.[20] The parameter used for calculating the complexity of structures dealing with fractal dimension (FD).[21,22] FD can be applied to determine trabecular bone structure due to the similarity of trabecular bone within itself and its branching structure showing fractal features.[21] When this method is applied to trabecular bone images on radiographs, it reflects the microarchitecture of the trabecular bone and can also be considered a noninvasive way of detecting and measuring changes in bone.[23] Fractal size analysis is generally used in dentistry to evaluate trabecular bone structure in conditions such as bone changes, periapical bone, apical healing, and osteoporosis.[22]

The objective of the study was to compare FD values calculated in trabecular bone in the molar region according to the prosthesis type between patients using bisphosphonate and the control group without a systemic disorder. To examine the changes that occur depending on time and to guide clinicians in determining the type of prosthesis that should be preferred primarily in patients using bisphosphonates.

Our null hypothesis is that there will not be a significant difference between the FD values in

the molar region between using bisphosphonates and the control group depending on the type of prosthesis.

Methodology

This study was accepted by the Izmir Katip Çelebi University Non-Interventional Clinical Research Ethics Committee with decision number 542. All authors read the Helsinki Declaration and followed the guidelines in the study.[24] A total of 200 patients, including 100 patients (individuals between the ages of 57-82) using a prosthesis and receiving oral or intravenous bisphosphonate treatment and 100 patients (individuals between the ages of 53-78) using a prosthesis and systemically healthy, were obtained from the archive of Izmir Katip Çelebi University Faculty of Dentistry Department of Prosthetic Dentistry. Radiographs were evaluated retrospectively. In this study, the first panoramic radiograph taken from the patients before the prosthetic treatment and the control panoramic radiograph taken 1 year (± 2 months) after the treatment were evaluated.

Patient selection

Inclusion criteria for the working group were as follows; a) patients wearing complete removable dentures, removable partial dentures, or partial fixed prostheses, b) patients without teeth in at least one of the maxilla and mandibula molar regions, c) patients using bisphosphonates for osteoporosis diseases, d) control radiographs for 1 year (± 2 months) after the prosthesis, e) good and clear image quality of the radiographs. The exclusion criteria were as follows; a) poor image quality of the radiographs, b) any pathology in the area to be analyzed, c) radiotherapy applied to the head and neck region.

The control group included systemically healthy patients who had a completely removable, removable partial or partial fixed prosthesis applied in the Department of Prosthodontics, Izmir Katip Çelebi University and who had control/follow-up radiographs taken by any department in the system.

Fractal analysis operations

All panoramic radiographs were obtained using the same radiation parameters (66 kVp, 10 mA) with Orthopantomograph Op 300 (Instrumentarium, Helsinki, Finland). The necessary procedures for FA were investigated with the box-counting method from White and Rudolph [25] in their 1999 study and using the ImageJ Software (version 1.52a, US National Institutes of Health, Bethesda, USA) program on the same personal computer (Apple Macbook Air).

For patients using maxillary and mandibular prostheses, the region of interest (ROI) was selected for individual regions as right and left (Figure 1).

The required procedures for fractal analysis on selected ROI regions were performed in the following order: a standard 72x72 pixel square ROI was selected from the radiographs of individuals belonging to the patient and control groups according to the type of prosthesis they used. First, the chosen ROI was duplicated (Figure 2a). Then, the duplicated image was blurred using a 35-pixel Gaussian filter (Figure 2b), eliminating the small and medium-scale differences in image brightness. The blurred image using the Gaussian filter was extracted from the original image (Figure 2c). Later, 128 shades of gray were added for each pixel to distinguish areas with different brightness (Figure 2d). With the "Binary" option, the image became a two-color image, black and white (Figure 2e). It was eroded using the "Erode" option to decrease the noise occurring in the image (Figure 2f). Later, the main line of the structure was obtained with the "Dilate" option (Figure 2g). By using the "Invert" option, the white areas were converted to black and the black areas were converted to white (Figure 2h). Finally, with the 'Skeletonize' option, the image was capable of fractal analysis (Figure 2i). The fractal dimension was computed using the "Fractal Box Count" option.

Using the algorithm of the program, the image was separated into 2-64 pixel squares. The total number of frames in the image was calculated for each box series of different pixel sizes. The values calculated on a logarithmic scale are plotted. The most appropriate line is drawn to the points in the

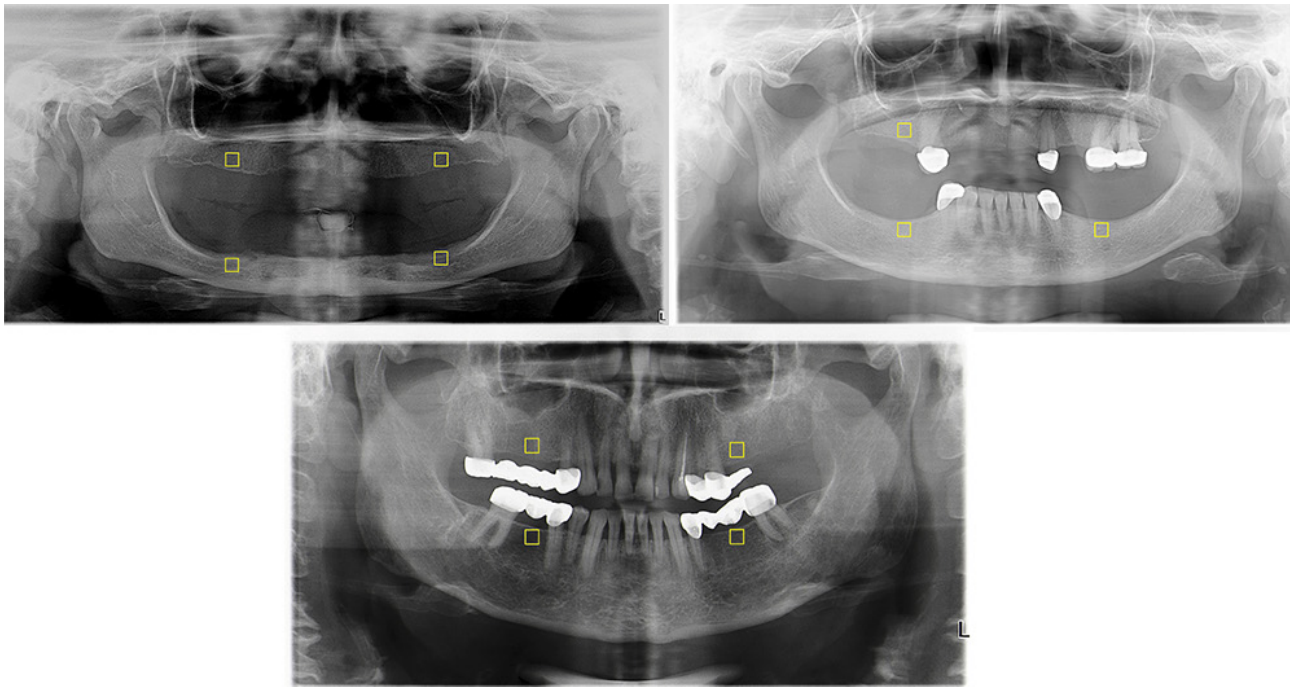

Figure 1. ROI selection of the complete, removable partial denture and partial fixed prosthesis

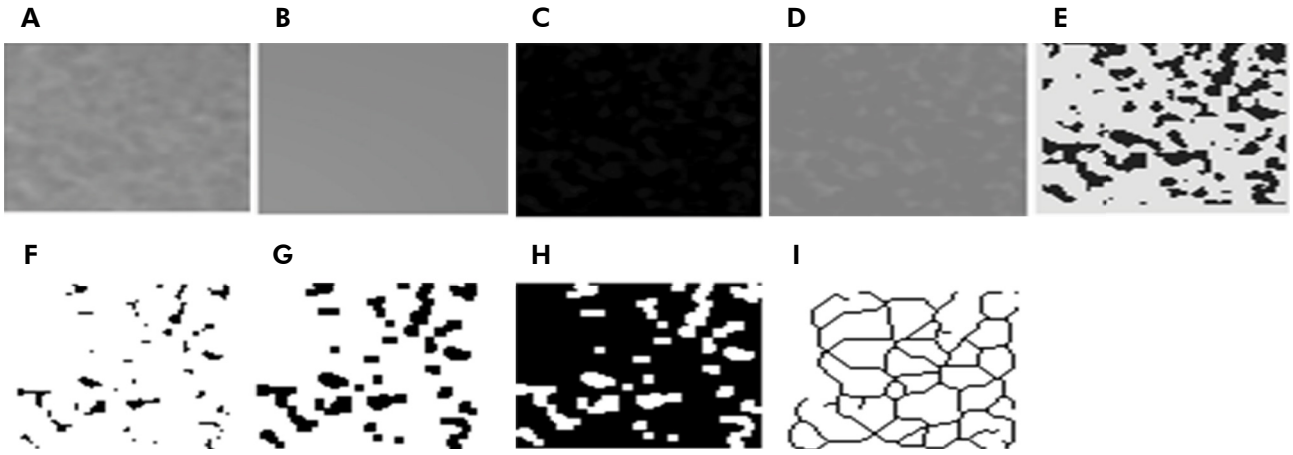

Figure 2. Fractal Analysis Steps a) Duplicated ROI b) Blurred image with 35 pixel Gaussian filter c) Substraction the blurred image from the original image d) Added 128 grayscale images e) Converting the image to a two-color image with the binary process f) Erode g) Dilate h) Invert i) Skletonize

graph. As a result, the slope of the drawn line gives the FD value of the trabecular structure.

Statistical analysis

Statistical analysis of the data obtained as a result of the calculated FD values was investigated by using the IBM SPSS Statistics Ver. 22 (2013, SPSS Inc., Chicago, USA) software. Parametric test assumptions such as normal distribution and homogeneous group variances of the data obtained were evaluated with the Kolmogorov-Smirnov test. Mixed design repeated measure variance analysis was used for

the comparison of the groups showing a normal distribution. Multiple comparisons were made with the corrected Bonferroni test. For the dependency between variables in groups with categorical data between the patient and control groups, chi-square (x^2) and continuity correction was used. The results are given as the mean, ± standard deviation, and a $p < 0.05$ was assumed to be statistically significant.

At the end of the GPower 3.1.9.2 program analysis, when deciding the sample size, it was agreed to include a total of 200 patients in the study for 81,0599 % statistical power (alpha:0.05, beta:0.20).[26]

Results

As a result of the statistical analysis, when the time-dependent measurements were examined, there was an interaction effect between the trabecular bone change - group and the type of prosthesis used ($p < 0.05$).

It was noted that there was a statistically significantly greater decrease in FD values in the control group than in the patient group using bisphosphonates in the molar region for complete removable and removable partial dentures in the maxilla and the mandible.

A significant increase in FD values over time was observed in the patient group using bisphosphonates with partial fixed maxillary and mandibular prostheses compared to the control group ($p < 0.05$) (Table 1).

As a result of the chi-square test evaluated between the patients using bisphosphonates and the control group, there was no significant difference obtained between the groups according to age, gender, and the type of prosthesis used. The mean ages for the patient and control groups were 68.52 and 67.37, respectively (Table 2).

There was no statistically significant change in the time between patients using oral bisphosphonates and patients using IV bisphosphonates (Table 3) ($p = 0.099$). It was statistically significant in patients using bisphosphonates for less than 3 years and 3 years or more (Table 4) ($p = 0.036$). The interaction effect between the type of prosthesis used and the drug type was statistically significant (Table 5) ($p = 0.036$).

Table 1. The repeated measure analysis of variance according to the prosthesis type and the molar region.

Prosthesistype	T0	T1	p-value
	x̄±ss	x̄±ss	
Study group			
Maxillary complete removable denture	1.385 ± 0.03001	1.331 ± 0.03155	
Maxillary removable partial denture	1.379 ± 0.03086	1.331 ± 0.02887	
Maxillary fixed prosthesis	1.382 ± 0.04976	1.399 ± 0.04889	
Control			
Maxillary complete removable denture	1.372 ± 0.02929	1.284 ± 0.02838	
Maxillary removable Partial denture	1.380 ± 0.04741	1.311 ± 0.04714	
Maxillary fixed prosthesis	1.372 ± 0.04183	1.371 ± 0.04218	
Study group			0.03*
Mandibular complete removable denture	1.380 ± 0.03482	1.320 ± 0.03678	
Mandibular removable partial denture	1.379 ± 0.03198	1.334 ± 0.03071	
Mandibular fixed prosthesis	1.379 ± 0.03825	1.396 ± 0.03923	
Control group			
Mandibular complete removable denture	1.366 ± 0.03072	1.278 ± 0.02824	
Mandibular removable partial denture	1.366 ± 0.03387	1.292 ± 0.03452	
Mandibular fixed prosthesis	1.378 ± 0.04091	1.377 ± 0.04097	

Table 2. Characteristics of patients using bisphosphonates and control group.

Variable	Biphosphonate users (100 patients)	Control group (100 patients)	p-value
Age (average value ± standart deviation	68.52 ± 5.38	67.37 ± 6.23	p > 0.05
Gender			
Woman	85	73	p > 0.05
			Continuity Correction (Yates)
Man	15	27	
Prosthesis type			
Maxillary complete removable denture	21 (21.1%)	22 (12.1%)	
Maxillary Removable Partial Denture	31 (18.1%)	32 (17.6%)	x^2=19.38 p > 0.05
Maxillary fixed prosthesis	35 (20.5%)	40 (22%)	
Mandibular complete removable denture	19 (11.1%)	21 (11.5%)	
Mandibular removable partial denture	36 (21.1%)	38 (20.9%)	
Mandibular fixed prosthesis	29 (17%)	29 (15.9%)	
Usage of drug			
Oral	69		
IV	31		
Type of biphosphonate used			
Alendronat	38		
İbandronat	31		
The duration of drug use			
Lower than 3 years	30		
More than 3 years			

Table 3. The repeated measure analysis of variance according to the type of drug use.

Prosthesis type	Usage type	T0	T1	p-value
		x̄±ss	x̄±ss	
Maxillary removable denture complete	Oral	1.377 ± 0.03543	1.335± 0.03557	0.099*
	IV	1.385 ± 0.03836	1.345 ± 0.04111	
Maxillary removable partial denture	Oral	1.383 ± 0.03738	1.345± 0.0407	
	IV	1.378± 0.03152	1.334 ± 0.02937	
Maxillary fixed prosthesis	Oral	1.375 ± 0.04515	1.372± 0.04843	
	IV	1.383 ± 0.0377	1.379 ± 0.04183	
Mandibular complete removable denture	Oral	1.383 ± 0.03766	1.355± 0.04637	
	IV	1.367 ± 0.04325	1.343 ± 0.04134	
Mandibular removable partial denture	Oral	1.373 ± 0.0412	1.349 ± 0.0459	
	IV	1.374 ± 0.03314	1.351 ± 0.03303	
Mandibular fixed prosthesis	Oral	1.372 ± 0.0383	1.368± 0.04355	
	IV	1.376 ± 0.03885	1.374 ± 0.04072	

Table 5. The repeated measure analysis of variance according to the type of drug used).

Prosthesis type	Type of drug	T0	T1	p-value
		x̄±ss	x̄±ss	
Maxillary complete removable denture	Alendronat	1.381 ± 0.03161	1.336 ± 0.04047	
	Ibandronat	1.375 ± 0.03848	1.344 ± 0.03203	
Maxillary removable partial denture	Alendronat	1.402 ± 0.03214	1.362 ± 0.03686	
	Ibandronat	1.365 ± 0.03335	1.328 ± 0.0373	
Maxillary fixed prosthesis	Alendronat	1.373 ± 0.0434	1.372 ± 0.04819	
	Ibandronat	1.379 ± 0.04839	1.373 ± 0.04972	0.036*
Mandibular complete removable denture	Alendronat	1.389 ± 0.04138	1.359 ± 0.04918	
	Ibandronat	1.374 ± 0.03018	1.350 ± 0.04226	
Mandibular removable partial denture	Alendronat	1.387 ± 0.03515	1.365 ± 0.04005	
	Ibandronat	1.365 ± 0.04258	1.340 ± 0.04701	
Mandibular fixed prosthesis	Alendronat	1.370 ± 0.03666	1.366 ± 0.04359	
	Ibandronat	1.375 ± 0.04275	1.372 ± 0.04443	

Table 4. The repeated measure analysis of variance according to the duration of drug use.

Prosthesis type	Years	T0	T1	p-value
		x̄±ss	x̄±ss	
Maxillary complete removable denture	< 3	1.380 ± 0.04155	1.332 ± 0.03551	
	≥ 3	1.376 ± 0.02883	1.338 ± 0.03619	
Maxillary removable partial denture	< 3	1.387 ± 0.03483	1.351 ± 0.04291	
	≥ 3	1.379 ± 0.03991	1.339 ± 0.03822	
Maxillary fixed prosthesis	< 3	1.372 ± 0.04679	1.366 ± 0.05045	
	≥ 3	1.379 ± 0.04377	1.379 ± 0.04593	
Mandibular complete removable denture	< 3	1.379 ± 0.0441	1.350 ± 0.05823	0.036*
	≥ 3	1.386 ± 0.03037	1.360 ± 0.0304	
Mandibular removable partial denture	< 3	1.370 ± 0.04112	1.342 ± 0.04361	
	≥ 3	1.375 ± 0.04199	1.354± 0.04807	
Mandibular fixed prosthesis	< 3	1.364 ± 0.03838	1.359 ± 0.04337	
	≥ 3	1.376 ± 0.03805	1.374 ± 0.04327	

Discussion

According to the data obtained, the null hypothesis of the study was rejected because it was seen that the interaction effect between the trabecular bone - group and prosthesis type. It was statistically significant between patients using bisphosphonates and the control group in the molar region when time-dependent measurements were examined.

Following tooth loss, the alveolar bone joins an accelerated resorption period for an average of 10

weeks, tracked by slower but progressive resorption.[27] Alveolar bone loss in the edentulous jaw is a lifelong action for the person using a prosthesis.[28] Studies have shown that the pressure exerted on the bone because of the use of removable prostheses causes residual ridge resorption.[29] It has been noted that tooth-supported and implant-supported prostheses slow the resorption process.[30]

As a general approach, higher FD values demonstrate a complex bone structure with denser and less porous trabeculae.[21] Torres et al[31] reported that higher FD values were observed in the study group than in the control group between patients with bisphosphonate-associated osteonecrosis of the jaw and healthy individuals, and an important difference was obtained only in the trabecular bone located in the upper part of the mandibular canal.

In the study reported by Demiralp et al[32] comparing the trabecular bone pattern of cancer patients with healthy individuals, FD values were found to be higher in the study group than in the control group, but there was not any statistically significant difference. When the FD values of the ROI selected according to gender in the study group were compared, the distal region of the second premolar located in the upper part of the mandibular canal was considered to be statistically significantly lower in female patients than in men on both the right and left sides.

Although bisphosphonates have many advantages, osteonecrosis of the jaw is a major complication for patients. MRONJ generally occurs in the alveolar bone. Therefore, ROIs closer to the alveolar bone seems to be the most favorable site for detecting bone changes affiliated with bisphosphonates.[31]

Marx et al.[33] explained an osteoporotic bone disorder that occurred as a result of bisphosphonate treatment and caused avascular osteonecrosis. In addition, MRONJ causes significant changes to occur that lead to positive bone turnover.[34] Therefore, it is thought that a rise in bone mineral density (BMD) is associated with general osteosclerosis of the jaws as a result of bisphosphonate therapy. In addition to their antiresorptive effects, N-BPs increase the proliferation of osteoprogenitor cells, osteoblasts, collagen type II, and osteocalcin, thus leading to an increase in bone matrix formation and bone turnover.[35]

Takaishi et al.[36] observed that in a case receiving bisphosphonate therapy and two extractions at the same time, BRONJ only occurred in the area where there was high alveolar bone density. As a result, they suggested that the determination of increased alveolar bone density as a result of high bone turnover resulting from the microdamage accumulation and hard, fragile and inactive bone development in the jawbone after bisphosphonate therapy is useful to determine the bone quality and possibly one of the factors that cause BRONJ.

Taniguchi et al.[37] compared the status of mandibular cancellous and cortical bone with computed tomography (CT) between patients using and not using bisphosphonates, and CT values of trabecular bone in patients treated with bisphosphonates and BRONJ were found to be increased.

In this study, there was a greater decrease observed in FD values in the control group than in the patient group when using complete removable and removable partial dentures in the maxilla and mandibula for the molar region. At the same time, an increase in FD values over time was obtained in the patient group with partial fixed maxillary and mandibular prostheses compared to the control group.

Bisphosphonates are pharmacological agents taken orally or intravenously. It is considered that intravenously administered bisphosphonates are generally stronger than those administered orally, the estimated incidence of MRONJ is higher in patients receiving intravenous bisphosphonates while on oral therapy, and there are more risk factors for inducing MRONJ.[38]

Considering the patients using bisphosphonates according to the way they used the drug, it was observed that there was no statistically significant change in the time between patients using oral bisphosphonates and patients using IV bisphosphonates. It is thought that the reason for this situation was that the number of patients participating in using the drug intravenously was less than that using the drug orally.

Patients are at minimal risk when oral bisphosphonate therapy is administered regularly and for less than 3 years. In cases where the duration of use exceeds 3 years, the long duration of use increases the risk.[4,39]

When the patients using oral bisphosphonates were evaluated according to the duration of drug use, an interaction effect between the type of prosthesis used and period of the time of drug use was observed. It was statistically significant in patients using bisphosphonates for less than 3 years and 3 years or more. Overall, less reduction has been observed in patients using oral bisphosphonates for over 3 years than in patients using bisphosphonates for less than 3 years.

According to a study conducted by Marx et al., the average time from the first use of bisphosphonate to the initial diagnosis of the exposed bone area by the patient, dentist or medical expert is 14.3 months for those who use only pamidronate and 12.1 months for those who stop using pamidronate and start using zoledronate and using only zoledronate. It was observed that the presence of exposed bone after oral alendronate use occurred after 9.4 months and, on average, after 3 years.[33]

Oral bisphosphonates, including clodronate, ibandronate, risedronate, tiludronate, and alendronate, are generally prescribed to patients with osteoporosis.[40] In most cases, the commonly used bisphosphonate is alendronate. It has been observed in clinical studies that these agents increase bone mineral density and decrease the risk of vertebral fracture.[41]

Miller et al.[42] investigated whether ibandronate treatment administered once a month increased lumbar spine and total hip BMD or to the same degree alendronate. As a result of the study, the increase in BMD in both the lumbar spine and total hip after 12 months in postmenopausal osteoporosis patients was proven to be similar to alendronate and orally administered ibandronate. Similar improvements in BMD were observed after 12 months with both treatments and appeared to have similar profiles in terms of tolerability.

Considering the patients using oral bisphosphonates according to the type of drug they used, the interaction effect between the type of prosthesis used and the drug type was noted to be statistically significant. An overall greater reduction was observed in patients using alendronate compared to patients using ibandronate. Considering the importance of the duration of oral bisphosphonate use, it can be considered that resulted from only the drug type evaluation.

The limitations of our study are that the intraoral findings of the patients could not be evaluated because it was a retrospective study with a heterogeneous sample population in the medication group, the value of FD in clinical applications and the differences between panoramic images and CBCT images. There are factors such as an insufficient number of patients to evaluate subgroups such as duration-dependent drug type.

Conclusion

Consequently, the FD value according to the type of restoration and bisphosphonates was increased. According to our results, the primary outcome of this study is that fixed partial prostheses should be preferred over completely removable or removable partial dentures in patients taking bisphosphonates for the prevention of osteonecrosis due to dental trauma. However, more clinical studies are needed on this subject.

Acknowledgments

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (The Non-Interventional Clinical Research Ethics Committee of Izmir Katip Çelebi University approved this study with decision no: 2019/290) and with the Helsinki Declaration of 1964 and later versions.

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