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# ASSESSMENT OF OSSEOUS DENSITY CHANGES IN PATIENTS WITH MEDICATION-RELATED OSTEONECROSIS OF THE JAWS USING CONE-BEAM CT: A CASE CONTROL STUDY

## *İlaç Kullanımına Bağlı Osteonekroz Gelişen Hastaların Kemik Dansitelerinin Konik Işınlı BT ile Değerlendirilmesi: Vaka Kontrol Çalışması*

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## ABSTRACT

**Objective**: In this study, the aim was to analyze density differences in prearranged region of patients with medication-related osteonecrosis of the jaws (MRONJ) and to evaluate potential effected sides in jaws by using cone beam computed tomography (CBCT)

**Material and Methods**: The records of 29 patients diagnosed with MRONJ and under bisphosphonates therapy and examined by CBCT were retrospectively evaluated with age- and gender-matched controls. The gray values (voxel value (VV)) were detected in the maxillary tuberosity (MTs), anterior supporting bone of nasopalatine canal (NPCs), mental foramen regions (MFs), center of symphysis and the bone surrounding the MRONJ area.

**Results**: According to the results, the mostly affected area was the bone under the mental foramen. There were significant differences between MRONJ and controls for right and left MFs (p=0.03, p=0.006 respectively). The mean gray value of right MTs were: 165.04 for controls and 212.4 for patients (p=0.13); left MTs were 208.6 for controls and 268.0 for patients (p=0.32); NPCs were 575.1 for controls and 572.6 for patients (p=0.96); and MSs were 679.2 for controls and 828.2 for patients (p=0.1). The gray value in the inferior peripheral bone of exposed region was the highest.

**Conclusion**: The present study shows that bisphosphonates cause internal morphological changes in jaws. Morphological changes are more frequent in certain parts of the jawbone such as the mental foramen. Gray values obtained by CBCT for quantitative measurements of density differences, can help achieve useful data for prediction of hazardous conditions where MRONJ can occur and how it will progress.

**Keywords**: *Bisphosphonate, bone density, cone beam computed tomography, osteonecrosis*

## ÖZ

**Amaç**: Bu çalışmada, ilaç kullanımına bağlı osteonekroz gelişen hastalarda çenelerin belirli bölgelerindeki kemik yoğunluğunun konik ışınlı bilgisayarlı tomografi (KIBT) ile değerlendilmesi ve potansiyel olarak etkilenen alanların belirlenmesi amaçlanmıştır.

**Gereç ve Yöntemler**: Çalışmada bifosfonat tedavisi gören ve ilaç kullanımına bağlı osteonekroz gelişen 29 hastanın KIBT'leri yaş ve cinsiyet eşleşmeli kontrol grubuyla beraber retrospektif olarak incelendi. Maksiller tuber (MT), nazopalatin kanalın anteriorundaki kemik (NPK), mental foramen bölgesi (MF), simfizisin anterioru ve osteonekrozlu alanın etrafını saran kemiğin gri voksel değerleri ölçüldü.

**Bulgular**: Sonuçlara göre en çok etkilenen alan mental foramenin altındaki kemik olarak bulundu. Sağ ve sol MF değerlendirildiğinde osteonekroz hastaları ve kontrol grubu arasında anlamlı farklılıklar bulundu (p=0.03, p=0.006 sırasıyla). Sağ MT için ortalama gri değerleri kontrol grubunda 165.04, hasta grubunda 212.4 (p=0.13); sol MT için ise kontrol grubunda 208.6 hasta grubunda 68.0 olarak ölçüldü (p=0.32). NPK; kontrol grubunda ortalama 575.1 ve hasta grubunda ortalama 572.6 (p=0.96); ve MS kontrol grubunda 679.2 ve hasta grubunda 828.2 olarak ölçüldü (p=0.1). Etkilenen alanın inferiorundaki kemik yoğunluğunun diğer bölgelerden daha yüksek olduğu belirlendi.

**Sonuç**: Bifosfonat türevi ilaçlar çene kemiklerinin internal yapısında morfolojik değişikliklere neden olmaktadır. Morfolojik değişimler özellikle mental foramen gibi bölgelerde daha fazladır. Dansite farklılıklarının ölçümünde KIBT ile elde edilen gri değerler ile, osteonekrozun oluşacağı bölge ve gelişeceği doğrultudaki tehlikeli koşulların tahmini için yararlı veriler elde edebilir.

**Anahtar Kelimeler**: *Bifosfonat, kemik dansitesi; konik ışınlı bilgisayarli tomografi, osteonekroz*

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## INTRODUCTION

Bisphosphonates (BP) are inorganic pyrophosphates, which are effective in inhibiting osteoclast-mediated bone resorption (1). They are the first line of management for osteoporosis, metastatic bone cancer, hypercalcemia related to malignancy and Paget's disease (2). Medication-related osteonecrosis of the jaws (MRONJ) is a severe complication of BP medication. The role of imaging and the imaging findings in the diagnosis of MRONJ have previously been described in the literature (3). There are many studies in the dental literature about the utility of computed tomography (CT) for assessing bone morphology and volume using the Hounsfield unit (HU) score. The HU is the parameter defined by CT for quantifying bone quality (4). It is generally defined by means of a linear transformation of the measured x-ray attenuation coefficient of an object with reference to water (HU = 0) (1).

Cone beam computed tomography (CBCT) is a system, which has less radiation than CT and in a single 360° rotation creates multiple views of the patient (5). Recently, several CBCT systems have become available to image the maxillofacial region. This provides new diagnostic options with increased image quality (6). CBCT records might therefore help to describe the radiological range of view of MRONJ. CBCT imaging systems have improved quantification capacity, and the Gray values exceedingly correlate with outcomes of other well-known methods under specific conditions. The Gray values are considered to provide the reliable and objective information on the bone quality (7). The osseous changes in patients under bisphosphonate therapy may be an early indicator of occurring MRONJ. Gray value on CBCT may give beneficial data for prediction of hazardous conditions that are quantitative measurements for determining density differences.

The objective of this study was to predict the most effected potential region in patients with MRONJ by analyzing density differences in jaws using CBCT.

## MATERIALS AND METHODS

*Study Group*

The study group consisted of twenty-nine patients with MRONJ. Inclusion criteria were overt MRONJ patients diagnosed by a maxillofacial surgeon (with 7 years of professional experience) based on generally accepted diagnostic criteria of clinical introduction (8). Patients with MRONJ in Stage 1 and 2 (Stage 1: necrotic bone exposure in asymptomatic patients with no evidence of soft-tissue infection; Stage 2: necrotic bone exposure associated with soft-tissue infection and pain) were included in the study group (9). CBCT images of patients with MRONJ had been archived in Department of Oral and Maxillofacial Radiology, Faculty of Dentistry, Erciyes University. Control group was selected from gender- and age-matched healthy individuals for each MRONJ patient from the same archives. Images of healthy patients without any systemic disease that could affect bone mineral density as osteoporosis and diabetes were used. CBCTs with good quality of clearly observed areas of the same sides of MRONJ patients were included. This was a retrospective study, thus according to local laws and regulations ethical board approval was not required. The department where the study was performed disclaimed the informed consent form. The study was carried out according to the guidelines of the Declaration of Helsinki concerning Ethical Principles for Medical Research Involving Human subjects.

*Imaging Procedures*

All the subjects in the study were imaged by using the New Tom VG (Quantitative Radiology, Verona, Italy) cone-beam computed tomography (CBCT).

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The X-ray parameters (kV, mA) were automatically determined from scout views by the NewTom VG. All images were obtained with the patient in the supine position. Scanning time was 18 seconds, exposure time was 3.6 seconds, and voxel size was 0.3 $mm^3$. For bone density measurements (Gray values), the images were then exported in digital imaging and communications in medicine (DICOM) format for data analysis. The DICOM data sets were imported into a third party viewing software Simplant Pro software, version 13.0 (Materialise HQ, Leuven, Belgium) to determine the Gray values of each scan.

*Measurements*

The average Gray values were measured within a rectangle area of 4 $mm^2$. Any sagittal, coronal and axial views used to determine center of the region and primarily the sagittal views for posterior and coronal views for anterior region were used for sampling. Measurements were repeated three times for each region and mean values were used for statistical analysis. Acquisition of 3D data was performed by one radiologist with 4 years of experience in head-and-neck imaging.

The measurements were performed as follows on CBCT scans obtained from MRONJ patients and healthy controls. The Gray values were detected in maxillary tuberosity (MT) (Figure 1a), anterior to the nasopalatine canal (NPC) (Figure 1b), center of mandibular symphysis (MS) (Figure 1c), below to mental foramen (MF) (Figure 1d, e) and surrounding bone of MRONJ area (Figure 2a-d).

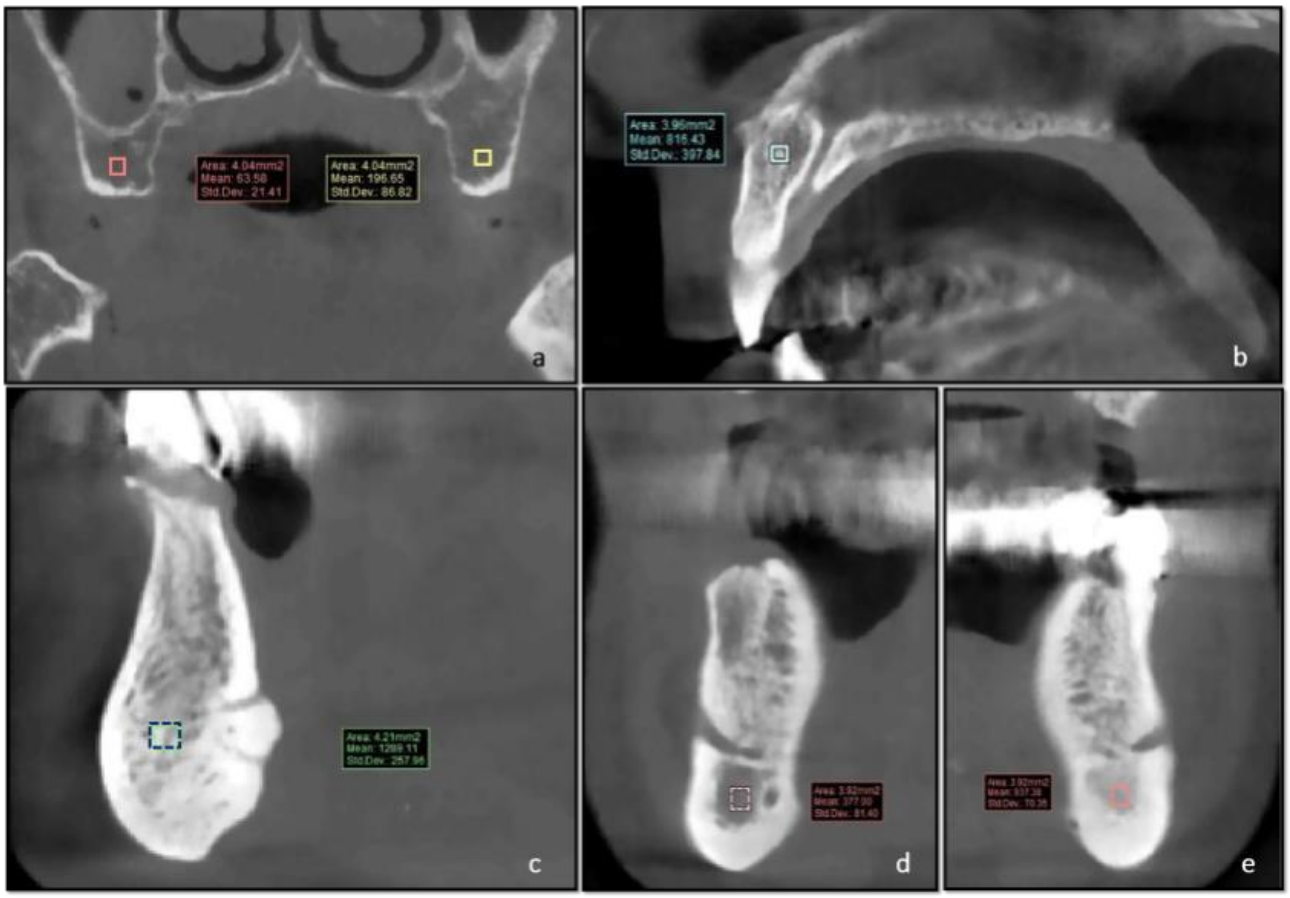


**Figure 1**: Measurements of Gray values, in 4 $mm^2$ squares. a; center of posterior maxilla tuber region, b; anterior region of the nasopalatine canal, c; center of mandibular symphysis, d, e; below the mental foramen.

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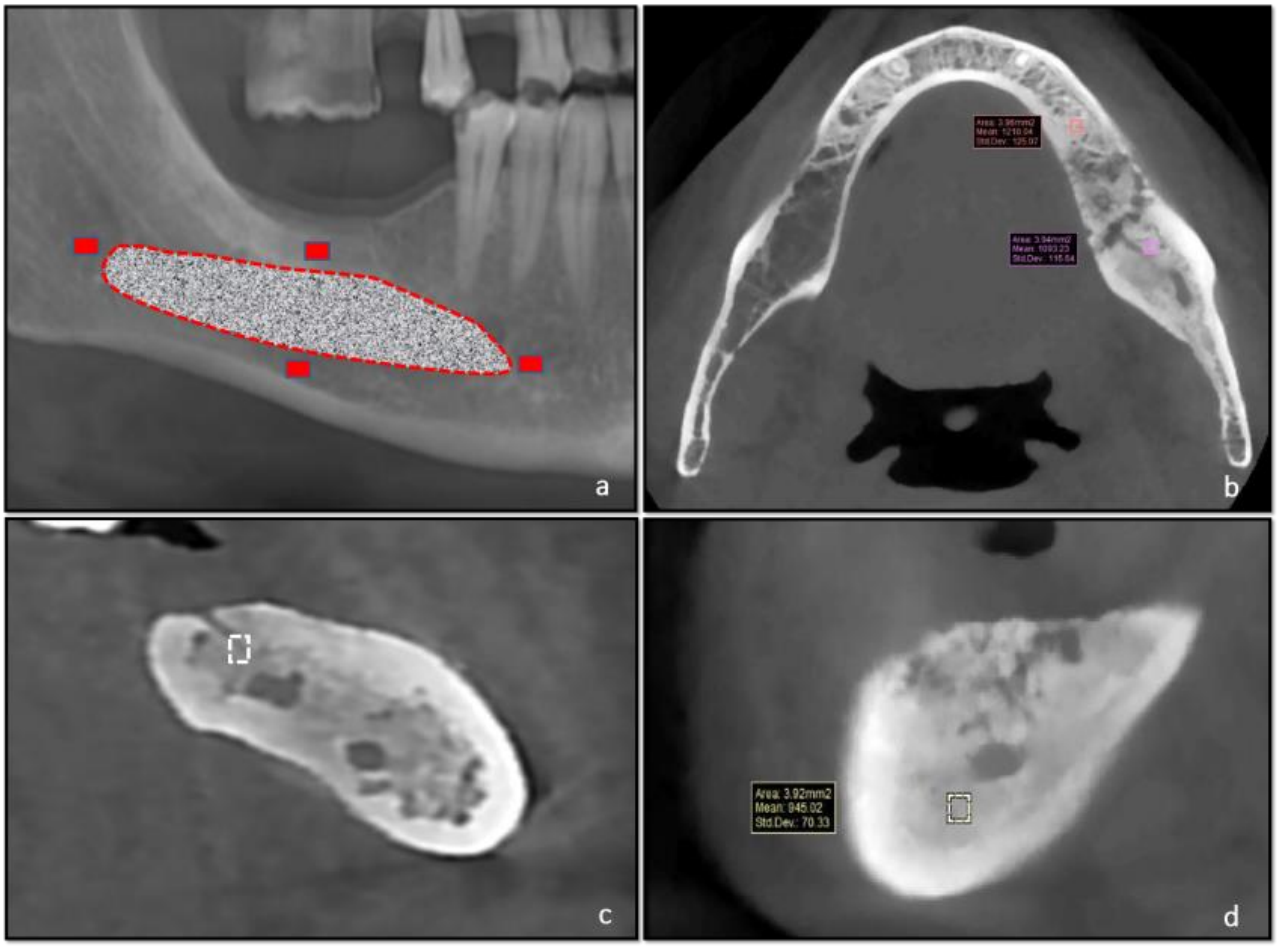


**Figure 2**: Measurement of Gray values in bone surrounding the MRONJ area, in 4 $mm^2$ squares. a. Illustration of measurements on cropped panoramic view and measurements on the; b. anterior and posterior side of MRONJ area, c. superior of MRONJ area and d. inferior of MRONJ area.

*Statistical analysis*

All the measurements were repeated once more again 1 week later and intra-observer reliability showed a high correlation. The intra-observer correlation coefficient was 0.95 for measurements. Statistical analyses were conducted using SPSS software (SPSS 16.0 for Windows; SPSS Inc., Chicago, IL, USA). The measurements were evaluated using the independent t-test to compare the means of the all values between MRONJ and healthy sites as well as values of control patients. Values of $P<0.05$ were considered to indicate statistical significance.

## RESULTS

All comparisons were performed reciprocally between both sides of patients with MRONJ and age-gender matched healthy individuals, expect non-measurable sites due to osteonecrosis. Thirteen females, 16 males with mean age 70.3 years; age range 49–84 years with MRONJ were included in study group. Gender- and age-matched healthy individuals for each MRONJ patient from the same archives (13 females, 16 males, mean age 70.2 years; age range 51-82 years) were used for control group.

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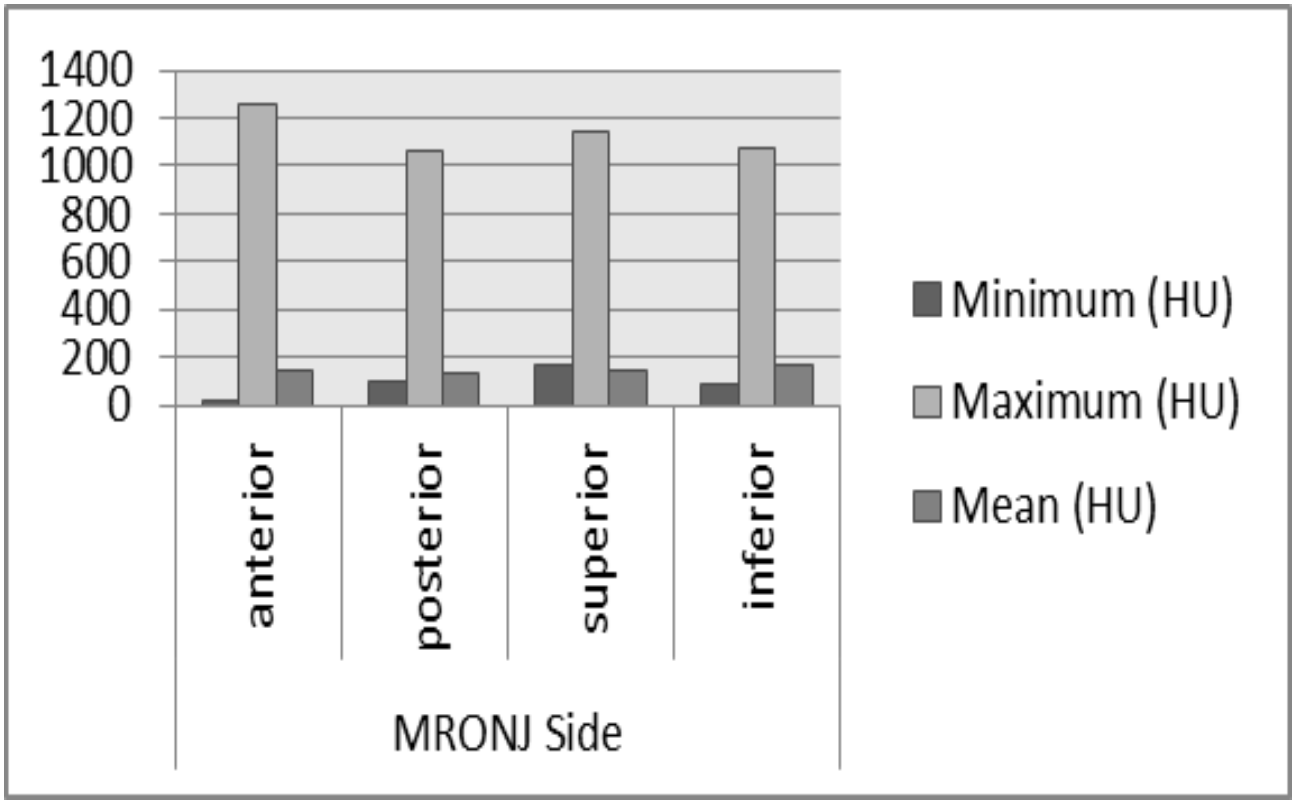
There were significant differences between MRONJ and controls for right and left MFs (p=0.000, p=0.006 respectively). The mean gray value of right MTs were: HU=165.04 for controls and HU=212.4 for patients (p=0.13); left MTs were HU=208.6 for controls and 268.0 for patients (p=0.32); NPCs were HU=575.14 for controls and HU=572.61 for patients (p=0.96); and MSs were HU=679.2 for controls and HU=828.19 for patients (p=0.11) (Table 1). The gray value in the inferior peripheral bone of exposed region was the highest (Table 2). When we compared right and left side, no significant differences were found for all measurements of MRONJ patients and patients in control group.

**Table 1**. The mean Gray values of the regions and p values of MRONJ patients and control patients.

| Region | Side | MRONJ (HU) | Control (HU) | p |
|---|---|---|---|---|
| Tuber | right | 212.4 | 165.04 | 0.13 |
| | left | 268 | 208.6 | 0.32 |
| Anterior of NPC | | 572.61 | 575.14 | 0.96 |
| Inferior of MF | right | 708.54 | 458.93 | 0.001* |
| | left | 669.32 | 396.22 | 0.006* |
| Symphisis | | 828.19 | 679.2 | 0.11 |
| p<0.05 Correlation is significant* | | | | |

*Correlation is significant at level p<0.05.

**Table 2**. The minimum, maximum and mean Gray values of peripheral bone of MRONJ area.



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## DISCUSSION

MRONJ is a serious drug reaction that causes bone destruction in the maxillofacial region. Two pharmacological agents can cause osteonecrosis: antiangiogenic and antiresorptive drugs including BP (2). Our study group consisted of BP medicated patients. Numerous reports have been published about MRONJ occurring after maxillofacial surgery in patients under long-term drug therapy (9-11). No clear demonstration of a relationship between MRONJ and BP treatment has been shown so far (11). In the present study, we aimed to investigate the radiological presentation of MRONJ and the associated gray values and to assess the reliability of the gray voxel values for evaluating osseous differences in patients under BP therapy. Quantitative and accurate pre-operative assessment of bone density is crucial to help provide clinicians an indicator of planning therapy to bone. Numerous studies described cluster failures that might be related with poorer bone quality (12-14).

Various radiographic findings in MRONJ have been described using panoramic radiography, intraoral radiographs, magnetic resonance imaging (MRI), positron emission tomography (PET) and CT. Panoramic radiography offers an excellent general assessment of the whole jaw, but mineral loss cannot be detected until it is as high as 50%. In panoramic radiography, we assess bone destruction but we are not able to differentiate internal structure of normal bone and osteolytic lesions (15). HU unit derived from CT is used to assess bone quality. HU should be better understood as “relative” density rather than “true” density. The relative density represents the total X-ray attenuation of different body tissues by CT numbers (12).

Some studies suggested that gray values obtained by CBCT can be used to assess bone density (16). Swennen and Schutyser indicated that, the image value of a voxel of a tissue depends on the situation in the image volume on CBCT. In different parts of the scanned volume, the X-ray attenuation of CBCT systems currently produces different gray values for similar osseous and soft tissue structures (17). However, a strong linear correlation occurs, which may permit descending real HU units from CBCT by linear regression models. Similar to the HU values of CT, that of CBCT could also be predictive for the subjective bone quality assessment using gray voxel values. Therefore, the density of bone by using CBCT was evaluated in the present study (14).

For detecting the MRONJ, bone density and bone quality should be assessed before necrotic bone becomes visible. Bone mineral density (BMD) and bone micro architecture serve as the most important tool for determining the mechanical properties of bone and it can only be estimated by using histomorphometric procedures (18). MRONJ at Stage 0 is defined as a great risk for developing more severe stages (19,20). Thus, it is critical to diagnose the early silent (asymptomatic) stage of MRONJ. Radiological bone changes specifying possibility of MRONJ might help dentists with preventive approach and treatment planning for patients under BP therapy (2,21,22).

In the literature, the radiological findings of MRONJ lesions in CBCT were described as increase in sclerotic expressions, failure of post-surgical remodeling, erosion on the cortical bone and subperiosteally bone deposition which are the most common and most characteristic features of MRONJ (1, 23). Guggenberger et al. proved the benefits of CBCT in diagnosing MRONJ by qualitative and quantitative image parameters (24). Torres et al. used CBCT for evaluation of fractal dimension and mandibular cortical bone to diagnose early features of MRONJ (25). They found significant differences in both study parameters between patients with BP medication and controls. Phal et al. have also reported the sclerotic change

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encroached on the mandibular canal in 3 subjects of 15 patients with MRONJ (26).

Though many theories have been proposed by many authors, the pathogenesis of MRONJ is unclear (27, 28). In this study, most cases of MRONJ occurred in the alveolar region of the posterior mandible where the cortical bone is thickest. According to our results, in the mandible both mental foramen and symphysis regions are areas that are affected more than maxilla concerning bone density change. This is thought to be due to the high BP concentration in the region as a result of high bone turnover and high drug concentration (29,30). This condition inhibits osteoclastic activity, by means of reducing bone remodeling and influencing the bone accumulated micro-damage and potentially triggering the initiation of osteonecrosis. In patients under BP therapy, we can assess bone density and compare it with healthy jaws and predict possibility of necrosis before MRONJ occurs. Especially in mental foramen region and posterior mandible, increased density shows that vascularization of bone decreases in that side and this indicates necrosis of bone. To avoid necrosis, drug dose and type may be changed and dentists should avoid to implement traumatic therapy to these affected sides.

This pilot study may prove to be successful to guide future studies for detection of the region to analyze bone change related to bisphosphonates. Although the parameters of this retrospective study were not affected by clinical information, the primary limitation of this study was the absence of data about the type of bisphosphonates and dose and duration of treatment. Moreover, the study was limited to the cases of MRONJ that were archived at the Oral and Maxillofacial Radiology Clinic. The results of this study have shown that the density measurements of jaws, especially in mandible, using CBCT might be a simple and useful method for the diagnosis of high risk regions even without developing MRONJ.

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