ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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The Investigation of Osteoporotic Changes in Patients with Primary Hyperparathyroidism with Radiomorphometric Indices Determined on Panoramic Radiography

Primer Hiperparatiroidili Hastalardaki Osteoporotik Değişikliklerin Panoramik Radyografide Belirlenen Radyomorfometrik İndeksler ile İncelenmesi

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ABSTRACT Objective: The aim of this study was to compare osteoporotic changes of jaw bones between normal population and patients with primary hyperparathyroidism (pHPT) by using panoramic radiomorphometric analyses. **Material and Methods:** Panoramic radiographs of 48 healthy individuals and 48 patients with pHPT were evaluated. The values of the panoramic mandibular index (PMI), mental index (MI) mandibular cortical width (MCW), amount of alveolar bone resorption (AABR) were measured. Mandibular cortical index (MCI) was recorded on panoramic radiographs according to C1, C2 and C3 classes with increased trabecular structure of the cortical bone. In panoramic radiographs, carotid artery calcification was examined. **Results:** There was no statistically significant difference between the patient group and the control group for PMI, MI, MCW and AABR values from radiomorphometric measurements. While there was a significant difference between categories C1 and C3 of MCI values between patient and control group; there was no significant difference for category C2 values. Unilateral carotid artery calcification was observed on panoramic radiography of 5 individuals in the patient group. **Conclusion:** Osteoporotic changes were not observed in patients with pHPT as compared with control group by using radiomorphometric analysis, while mandibular cortical destruction was observed in pHPT patient group.

Keywords: Primary hyperparathyroidism; cortical bone; radiomorphometry; panoramic radiography

ÖZET Amaç: Bu çalışma, primer hiperparatiroidili (pHPT) hastalardaki çene kemiğine ait osteoporotik değişikliklerin, panoramik radyografi kullanılarak belirlenen radyomorfometrik indeksler ile değerlendirilmesini amaçlamıştır. **Gereç ve Yöntemler:** pHPT tanısı alan 48 birey ile kontrol grubunu oluşturan sağlıklı 48 bireyin panoramik radyografileri üzerinde; panoramik mandibular indeks (PMI), mental indeks (MI), mandibular kortikal kalınlık (MKK), alveoler kemik rezorpsiyon miktarı (AKRM) ölçüldü. Mandibular kortikal indeks (MKI) panoramik radyografiler üzerinde, kortikal kemiğin artmış trabeküler yapısının C1, C2 ve C3 sınıflarından uyumlu görünüm sergilediği sınıfa göre kaydedildi. Panoramik radyografide, karotid arter kalsifikasyonu varlığı araştırıldı. **Bulgular:** Radyomorfometrik ölçümlerden PMI, MI, MKK ve AKRM değerleri için hasta grubu ile kontrol grubu arasında istatistiksel olarak anlamlı fark bulunmadı. Hasta grubu ile kontrol grubu arasında MKI sınıflandırmalarından C1 ve C3 sınıf değerleri arasında anlamlı bir fark var iken; C2 sınıf değerleri arasında anlamlı bir fark bulunmamıştır. Hasta grubundaki, 5 bireyin panoramik radyografisinde unilateral karotid arter kalsifikasyonu izlendi. **Sonuç:** Radyomorfometrik analizler ile pHPT hastalarında kontrol grubuna kıyasla anlamlı osteoporotik değişiklikler izlenmemiş olmakla birlikte pHPT'li hastalarda, mandibular kortikal destrüksiyon tespit edilmiştir.

Anahtar Kelimeler: Primer hiperparatiroidi; kortikal kemik; radyomorfometri; panoramik radyografi

Parathyroid hormone (PTH) is an essential hormone that regulates the homeostasis of free serum calcium and plays a key role in bone remodeling. Primary hyperparathyroidism (pHPT) is an endocrine disorder that often develops due to parathyroid adenoma, resulting in excessive secretion of parathyroid

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hormone. Excessive release of PTH leads to hypercalcemia. Calcium salts are stored in the skeleton; however, unorganized calcium salts accumulate in soft tissues such as ligaments and arteries due to the development of hypercalcemia, causing heterotopic calcification. The resulting hypercalcemia picture impairs the mechanism of bone remodeling, and accordingly arthralgia, bone pain, pathological fractures, and brown tumors occur. Cortical bone is affected by impaired remodeling mechanism more than trabecular bone.[1] The decrease in density results in increased radiolucency on radiographs. Thinning in the inferior border of the mandible, sinus floor, and the cortical border of the mandibular canal, and depending on the severity of the disease, loss of lamina dura, internal and external root resorption may occur.[2]

Radiomorphometry is a bone density assessment technique based on the ratio of cortical bone thickness to total bone thickness.[3] They are suitable reference points for analysis because of the visibility of the cortical bone and the distance of the mental foramina from the masticatory muscle attachments.[4]

Techniques such as single-photon absorptiometry, dual photon absorptiometry, dual X-ray absorptiometry, quantitative computed tomography, and quantitative ultrasonography are used for bone mineral density measurement. Dental radiographs can be used to measure radiomorphometric bone mineral density due to their advantages over various bone density measurement techniques such as easy accessibility and less exposure to radiation.[5] Studies have indicated that the current osteoporotic status for cortical bone can be determined using radiomorphometric index measurements on panoramic radiographs.[4-7]

Gumussoy et al. investigating the mandibular bone changes in pHPT reported no significant difference between the patient and control group, while they argued that the evaluation to be made with a larger patient population would strengthen the results.[8] Henriques et al. reported that the changes observed in the mandibular bone were significant in patients with severe secondary HPT, but they argued that these changes were not specific to secondary HPT.[9] Rai et al. stated that the mandibular cortical thickness showed a significant difference between the patient and control groups in pHPT; however, only mandibular cortical thickness was examined among the panoramic radiomorphometric analyses in this study, and the study was limited to a narrow patient population.[10] The aim of our study was to investigate the presence of pHPT-specific mandibular bone changes in a larger patient population compared to the literature.

This study aimed to compare the osteoporotic changes in the jawbone of patients with pHPT with normal healthy individuals using panoramic radiomorphometric indices.

MATERIAL AND METHODS

The compliance of our study with scientific ethical rules was approved by the Clinical Research Ethics Committee of Atatürk University, Faculty of Medicine (ethics committee approval number: 30/2019 date: 26.09.2019). Consent forms were signed by the patients.

STUDY POPULATION

The patient group consisted of 48 individuals aged 18 years and over with a confirmed diagnosis of pHPT by Atatürk University, Faculty of Medicine, Department of Internal Sciences, Internal Diseases Council between 2019-2020. The control group consisted of healthy individuals without a systemic disease affecting bone metabolism. For both groups, individuals under the age of 18 years who had other systemic diseases affecting bone metabolism and who were on medications that may affect bone metabolism were excluded from the study. The patient and control group referred to Atatürk University, Faculty of Dentistry, Department of Oral and Maxillofacial Radiology for their dental treatment requirements underwent clinical and radiological examinations.

IMAGING PROCEDURES

All of the panoramic radiographs were performed by the same person in Atatürk University, Faculty of Dentistry, Department of Oral and Maxillofacial Radiology using the same device (ProMax®, Planmeca Oy, Helsinki, Finland), with the average scan parameters of 62 kVp, 4mA, 16.2 seconds, following the reference points indicated by the device, with the Frankfort horizontal plane parallel to the ground, and the sagittal plane perpendicular to the ground, considering the cervical vertebra superposition of the patients positioned in the ski position. Radiomorphometric measurements were obtained on digital panoramic radiographs using the Turcasoft Medical Viewer (V20.0.44125, Samsun, TR).

RADIOMORPHOMETRIC MEASUREMENTS

On the panoramic radiographic images of the patient and control groups, the following measurements were done:

Panoramic Mandibular Index (PMI): It was recorded by taking the ratio of the thickness of the mandibular cortical bone to the distance between the mental foramen and the inferior mandibular cortical bone (Figure 1).[11]

Mental Index (MI): It was recorded by measuring the distance between the mental foramen and the inferior mandibular cortical bone (Figure 2).[12]

Mandibular Cortical Width (MCW): It was recorded by measuring the mandibular cortical thickness at the intersection of the line drawn tangent to the inferior mandibular cortical bone and the line

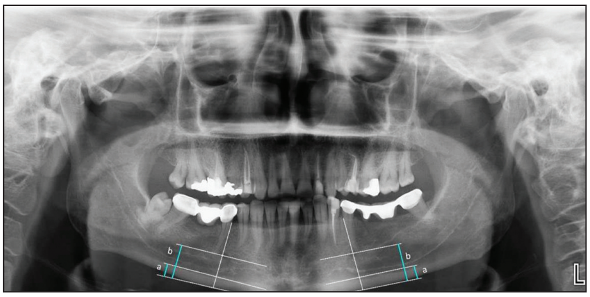

FIGURE 1: Panoramic mandibular index; cortex thickness/distance from the inferior margin of the mental foramen to the inferior border of the mandible (a/b).

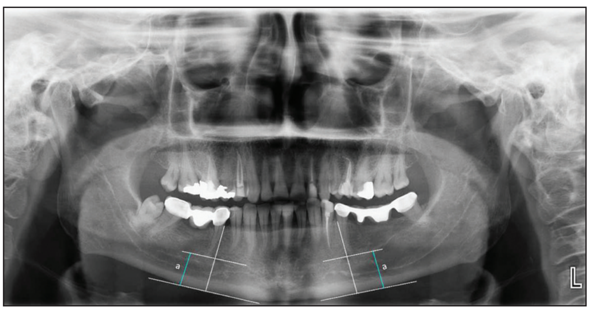

FIGURE 2: Mental index; cortical width at the mental foramen region (a).

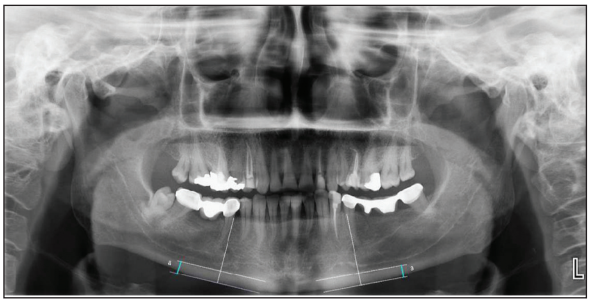

FIGURE 3: Mandibular cortical width; mandibular cortical thickness at the mental foramen border (a).

passing through the middle of the mental foramen (Figure 3).[13]

Mandibular Cortical Index (MCI): The trabecular pattern of the cortical bone at the inferior border of the mandible is classified by Klemetti et al. into three groups:[3]

C1: Even and continuous cortical bone on both sides

C2: Semilunar defects in the cortical bone

C3: Severe erosion and increased porosity are visualized in the cortical bone (Figure 4).

Amount of Alveolar Bone Resorption (AABR): The ratio of the distance of the line passing through the center of the mental foramen to the inferior border of the mandible to the distance from the inferior border of the mandible to the alveolar crest was calculated from the right and left regions and their averages were recorded. The AABR was calculated according to Wical's technique using the following formula: (2.9 x b) -a. According to Wical, the b/a ratio is 1/2.9 (Figure 5).[14]

***Carotid Artery Calcification*:** It was evaluated on panoramic radiographs as unilateral, increased radiopacity at the C3-C4 intervertebral level below the angle of the mandible (Figure 6).[15]

STATISTICAL ANALYSIS

A single investigator (the second author of article, a research assistant who has been studying for a doctorate in oral and maxillofacial radiology for three years) evaluated all of the parameters. After 20 days, the image analysis was repeated twice on 40 randomly selected radiographs by the same investigator

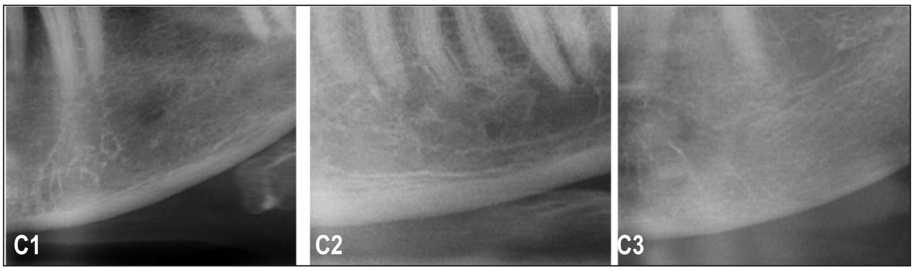

FIGURE 4: Mandibular cortical index: examination of the trabecular pattern in the mandibular cortical area. It has three classes;
C1- Endosteal cortical margin is even and sharp on both sides, normal cortex;
C2- Endosteal margin has semi-lunar defects or endosteal cortical residues on one or both sides;
C3- Cortical layer forms heavy endosteal cortical residues, clearly porous, severely eroded cortex.

to evaluate the intra-observer reliability. The intraviewer reliability was 0.930 (Cohen's kappa coefficient). Besides that, in cases where the observer was in doubt about the measurement, the patient was consulted with the first author of the article (with sixteen years of experience in dentomaxillofacial radiology). The decision was taken by consensus in suspicious cases.

The results obtained for the statistical analysis of the measurements were evaluated using the SPSS software package (IBM, SPSS 22.0, Chicago, IL). The Student's t-test was used for MI, MCW, PMI values since they were homogeneously distributed. Whereas, the non-parametric Mann-Whitney U test was used for AABR since it did not show a homogeneous distribution. A Chi-square test was performed for MCI values. A p-value of <0.05 was considered statistically significant for the evaluation.

RESULTS

A total of 96 patients, 48 (7 male, 41 female) patients diagnosed with pHPT and 48 (13 male, 35 female) healthy individuals without any systemic disease, were evaluated. The mean age of the patient group with pHPT was 53.46±11.48 years, while the mean age of the healthy control group was 53.52±12.16 years.

After the radiomorphometric examinations, no significant difference was found between the patient and control groups for MCW, MI, and PMI values (Table 1). In terms of MCI values, there was a significant difference between the patient and control groups for C1 and C3 values (p<0.05), while there was no significant difference between the patient and control groups for C2 value (p>0.05) (Table 2). In the AABR analysis, there was no significant difference (p=0.115) between the patient and control groups (Table 3). Five patients with pHPT had carotid artery calcification, while this calcification was not observed in the healthy control group.

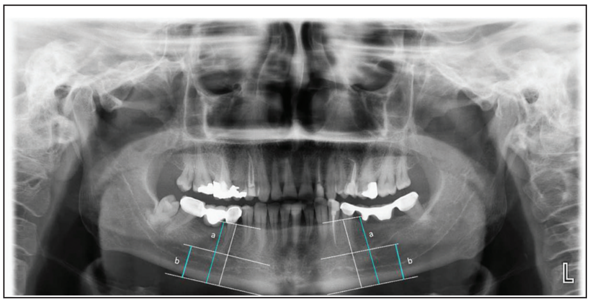

FIGURE 5: Amount of alveolar bone resorption: distance of the line passing through the midpoint of the mental foramen to the border of the inferior mandible is the distance from the border of the inferior mandible to the top of the alveolar crest. [(2.9 x b) –a].

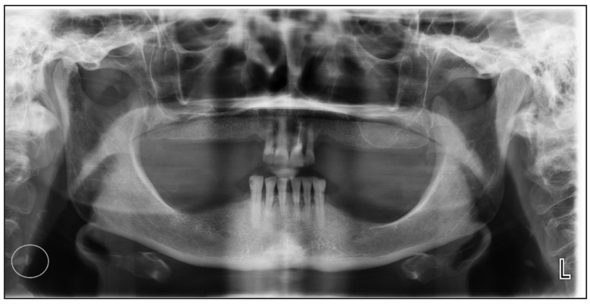

FIGURE 6: Carotid artery calcification: C3-C4 intervertebral space as nodular, point radiopacity.

TABLE 1: Measurement averages of patient and healthy group for MCW, MI and PMI.

	n	MCW (±SD)	MI (±SD)	PMI (±SD)
Patient	48	6.6 mm (±1.9)	26.3 mm (±4.3)	0.25 (±0.07)
Control	48	8.5 mm (±2.3)	28.9 mm (±4.9)	0.29 (±0.06)
Levene's	F	0.404	0.254	0.08
Test for equality variances	**Sig***	**0.526**	**0.616**	**0.929**

*Significance values; SD: Standard deviation; MCW: Mandibular cortical width; MI: Mental index panoramic; PMI: Mandibular index.

DISCUSSION

The aim of our study was to investigate the osteoporotic changes in the jawbone of patients with pHPT using panoramic radiomorphometric indices. The impairment of the bone remodeling mechanism due to the development of hypercalcemia as a result of HPT leads to a decrease in bone density of the jawbones. Previous studies have reported that MI and PMI are the best panoramic radiographic parameters demonstrating decreased bone density since the mandibular cortical thickness is proportional to the decrease in bone density.[16,17] Benson et al. considered 0.3 and above as the limit for PMI value.[11] Devlin and Horner considered the normal limit for MI value as 3 mm, while Klemetti et al. considered it as 4 mm, stating that it would not be a sufficient classification alone.[3,18] In our study, it was observed that the MI and PMI values were within the normal limits for both groups.

Other radiomorphometric indices utilized in the evaluation stage of osteoporotic changes in the jawbone of patients with pHPT in our study were MCW and MCI. In HPT, the disease has been reported to cause subperiosteal bone resorption.[19] In studies conducted on this subject, cortical destruction has been reported to be visualized on panoramic radiographs of 49.6% of patients with HPT.[4] While Drozdzowska et al. and Klemetti et al. argued that this technique was not significant between normal and osteoporotic groups in studies conducted to determine bone density using MCI, there are also studies revealing a significant difference between the two groups.[3,4,20-22] In their study, Henriques et al. argued that MCI could be used in patients with chronic renal failure to demonstrate increased mandibular cortical erosion and the progression of the disease.[9] Although there was no significant difference between the patient and control groups for C2 in our study, in the patient group with pHPT, C3 was more common than the control group and C1 was less common than the control group. Although studies have stated that mandibular cortical erosion is a pathognomonic finding for PHT, our study showed that mandibular cortical erosion was increased but could not be evaluated as a pathognomonic finding.[2]

TABLE 2: Distribution of MCI according to C1, C2 and C3 categories of the patient and healthy groups.

	C1 n/%	C2 n/%	C3 n/%
Patient	8/16.7	27/56.2	13/27.1
Control	20/41.7	27/56.2	1/2.1
Total	28/29.2	54/56.2	14/14.6
Sig*	**0.021**	**0.256**	**0.043**

*Significance values; MCI: Mandibular cortical index.

TABLO 3: Values of measurement of alveolar bone resorption amount of patient and healthy group.

	Mean±(SD)	Maximum	Minimum	Sig*
Patient	20.214 mm ± (12.38)	46.24 mm	5.09 mm	**0.115**
Control	12.53 mm ± (5.55)	38.26 mm	4.24 mm	

*Significance values; SD: Standard deviation.

Although MCI has the advantage of being an easy-to-use technique, it has been reported to have disadvantages such as variability of evaluation depending on the experience of the oral radiologist, as well as instability of observers in cases of transition between classes.[23] Because of such disadvantages, in their study, Ledgerton et al. suggested the modification of MCI by dividing C2 into early and late C2 changes since the C2 classification includes a large group.[13]

Calcifications may occur in soft tissues of patients with pHPT due to hypercalcemia. Carotid artery calcifications can be visualized on panoramic radiographs as nodular, punctiform, vertical radiopacities at the C3-C4 intervertebral junction below the angle of the mandible.[15,24] The fact that 10.4% of the patients in our study had radiopacity, which was thought to be unilateral carotid artery calcification, once again revealed that HPT should also be included in the differential diagnosis of soft tissue calcifications.

Another evaluation criteria included in our study within the scope of osteoporotic changes developing due to HPT is the AABR. In their study on dentate individuals, Wical and Swoop argued that the ratio of the distance between the cortical border of the mandible and the mental foramen to the total bone height was 1/2.90±0.23 on panoramic radiographs and that it could be used as 1/3 in practice.[25] When the AABR values measured according to Wical's technique were analyzed in our study, no statistically significant difference was found between the patient and control group values.[18] But studies on this subject have shown that factors such as osteoporosis, tooth extraction, duration of edentulous, age, and excessive occlusal forces will increase alveolar bone resorption.[26-28] The fact that the patient and control groups included in our study were not dentate can be considered a limitation in the standardization stage of the patient group.

Common panoramic radiographic changes in HPT have been reported as increased radiolucency, cortical destruction, and loss of lamina dura.[4] Although the loss of lamina dura is thought to be pathognomonic for HPT, it has been reported that the incidence of loss of lamina dura loss is low.[7,14,29] The examination of the loss of lamina dura will require periapical radiographs from several regions in addition to a panoramic radiograph. In this case, an additional imaging technique was not included in the study protocol not to increase the radiation dose exposed by the patient. For this reason, failure to evaluate the loss of lamina dura can be considered another limitation of our study.

Given studies conducted to evaluate osteoporotic changes in the jawbones using radiomorphometric indices, most of them consisted of patients with osteoporosis; however, there are also studies conducted on patients with chronic renal failure.[4,30-34] Studies have shown that osteoporotic changes can be visualized on panoramic radiographs and can be used for bone mineral density measurement. Loss of lamina dura, brown tumors, increased radiolucency in trabecular bone have been reported as common radiographic findings on panoramic radiographs in HPT.[4] There are studies carrying out radiomorphometric analyses in secondary HPT (sHPT), which have reported osteoporotic changes.[9] In the literature, the visualization of radiolucency-radiopacity together on radiographs, displaced teeth, and thinning of the cortical bone have been frequently reported in sHPT, while radiolucency is frequently visualized on radiographs and thinning of the cortical bone has been reported less frequently in pHPT than in sHPT.[4] A study comparing several radiomorphometric measurements on panoramic radiographs in pHPT with those of a patient group with controlled thyroid disease found no significant differences between the two groups.[2] Another study on pHPT reported that the patient group with pHPT had irregular lamina dura and thinner mandibular cortical thickness compared to the control group on the examination of panoramic radiographs.

We are of the opinion that our study will contribute to the literature with its aspects of investigating MI and PMI, which have not been studied in a large patient population with pHPT in the literature and are considered indicators of decreased bone density, and examining class distributions in MCI analyses and carotid artery calcification.[16,17]

CONCLUSION

The reason for not observing osteoporotic changes in patients with pHPT may be not including the trabecular bone changes in the analysis, except for radiomorphometric analysis techniques. Besides radiomorphometric analysis techniques, the evaluation of the trabecular bone and comparison with other techniques measuring bone mineral density will be a clearer method to determine the detectability of osteoporotic changes on panoramic radiographs. In pHPT, cortical changes can be observed in the cortical bone due to subperiosteal resorption. Soft tissue calcifications, which may develop due to hypercalcemia, may appear within the imaging area of a panoramic radiograph. Carotid artery calcifications can be easily noted on routine panoramic examinations.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

***Idea/Concept:** Özkan Miloğlu, Furkan Cantürk; **Design:** Furkan Cantürk, Gülsüm Akkaya; **Control/Supervision:** Özkan Miloğlu, Arzu Bilen; **Data Collection and/or Processing:** Furkan Cantürk, Arzu Bilen; **Analysis and/or Interpretation:** Gülsüm Akkaya, Furkan Cantürk; **Literature Review:** Gülsüm Akkaya; **Writing the Article:** Gülsüm Akkaya, Özkan Miloğlu; **Critical Review:** Arzu Bilen; **References and Fundings:** Özkan Miloğlu; **Materials:** Gülsüm Akkaya, Furkan Cantürk.*

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