Original Article / Özgün Araştırma

Evaluation of Trabecular Structure Using Fractal Analysis in Patients Taking Proton Pump Inhibitors

Proton Pompa İnhibitörü Kullanan Hastalarda Trabeküler Yapının Fraktal Analiz ile Değerlendirilmesi

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Abstract

Objective: The aim of this study was to evaluate the changes in the trabecular bone structure in patients using proton pump inhibitors (PPI) by performing measurements with fractal analysis, mandibular cortical width (MCW) and panoramic mandibular index (PMI) on panoramic radiographs.

Materials and Methods: This study consists of 46 patients (20 males and 26 females) using PPI drugs regularly for at least 1 year and systemically healthy 46 persons (20 males, 26 females) as the control group. Fractal analysis was performed in five regions: the mandibular angle (ROI1), posterior mandible (ROI2), interdental area between apical of the second premolar and the first molar (ROI3), maxillary tuber region (ROI4), anterior mandible (ROI5). PMI and MCW as an indicative of osteoporosis, were measured on the panoramic radiographs.

Results: For re-evaluated measurements, interobserver and intraobserver agreements were found to be 0.985 and 0.987, respectively. ROI2-4 (1.732, 1.334, 1.333; respectively) were significantly lower in PPI users, whereas, there was no significant in ROI1 (1.605) and ROI5 (1.694). The values MCW and PMI were not statistically significant in PPI users.

Conclusion: Posterior region of the mandible, maxillary tuberosity and interdental region had lower trabecular microstructures in PPI users. The results of this study show that patients using PPI at least one year should be considered as regarding osteoporotic changes during dental treatment.

Keywords
Osteoporosis, proton pump inhibitors, fractal analysis, radiography, panoramic

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Öz

Amaç: Bu çalışmanın amacı, panoramik radyografilerde fraktal analiz, mandibular kortikal genişlik (MCW) ve panoramik mandibular indeks (PMI) ölçümleri ile proton pompa inhibitörü (PPI) kullanan hastalarda trabeküler kemik yapısındaki değişiklikleri değerlendirmektir.

Gereç ve Yöntemler: Bu çalışma, en az 1 yıldır düzenli olarak PPI ilacı kullanan 46 hasta (20 erkek ve 26 kadın) ve kontrol grubu olarak sistemik olarak sağlıklı 46 hastadan (20 erkek, 26 kadın) oluşmaktadır. Fraktal analiz için 5 bölge değerlendirildi: mandibular açı (ROI1), posterior mandibula (ROI2), ikinci premolar ve birinci molar dişlerin apikali arasındaki interdental alan (ROI3), maksiller tüber bölgesi (ROI4), anterior mandibula (ROI5). Osteoporozun bir göstergesi olarak PMI ve MCW indeksleri panoramik radyografiler üzerinde ölçüldü.

Bulgular: Gözlemciler arası ve gözlemci içi güvenilirlik sırasıyla 0,985 ve 0,987 olarak bulundu. ROI2-4 (sırasıyla; 1,732, 1,334, 1,333), PPI kullanıcılarında kontrol

grubuna göre önemli ölçüde daha düşükken, ROI1 (1,605) ve ROI5'te (1,694) gruplar arasında anlamlı bir farklılık bulunmadı. PPI kullanan hastalarda MCW ve PMI değerleri istatistiksel olarak anlamlı bulunmadı.
Sonuç: PPI kullanan hastalarda posterior mandibula, maksiller tüber ve interdental bölgenin trabeküler mikro yapısında azalma olduğu görülmüştür. Bu çalışmanın sonuçları en az bir yıl düzenli olarak PPI kullanan hastalarda çene kemiklerinde osteoporotik değişiklikler görülebileceğini göstermiştir.

Introduction

Proton pump inhibitors (PPI) are commonly prescribed for peptic ulcer, gastroesophageal reflux disease, Helicobacter pylori infections. PPI irreversibly links the proton pump of the parietal cells in the stomach to hinder acid secretion (1). However, concern for the adverse effects of PPI due to being overprescribed is growing. Recent studies indicated that long-term PPI using increases the risk of osteoporosis and fractures, and causes kidney disease, hypomagnesemia and iron deficiency (2). Lastly, the Food and Drug Administration (FDA) issued a warning in 2010 that spine and hip fractures can be observed in patients who intake PPIs for one year or longer (3). Although the effect of PPI drugs on bone metabolism is not known exactly, hypochlorhydria and hypergastrinemia are reported two main mechanisms. A review of the literature showed that there are several studies indicating that long intake of PPI could negatively affect implant osseointegration and increase the failure rate of implant (4-6).

Fractal analysis is a widely used method in recent years to characterize the trabecular structure of the bone, because it is a non-invasive method, free of charge and allows examining conventional radiographs. It is also a widely used method in medical research for examining microstructure of calcaneus bone, especially in osteoporotic patients.

However, osteoporotic effect of long term PPI intake on maxilla and mandible is still unknown. To answer this question, this study was performed. The aim of this study is to evaluate the altering trabecular structure of maxilla and mandible in PPI users using fractal analysis and mandibular cortical width (MCW) and panoramic mandibular index (PMI) as an indicator for osteoporosis.

Materials and Methods

Study Sample

This retrospective study consisted of 46 patients using PPI (26 female and 20 male, age between 16 and 77 years) and sex, age matched control group who applied to the Department of Oral and Maxillofacial Radiology for various dental complaints. Patients who regularly used PPI at least 1 year included in this study. The number of samples for the fractal dimensions (FD) with a 95% confidence level and an 80% power was determined as minimum n=27 for each group. In study group, 34.7% of patients (n=16) used PPI less than 5 years, 30.4% of patients (n=14) used PPI between 5-10 years, 34.7% of patients (n=16) used PPI at least 10 years. Based on the medical history of patients, active pharmaceutical ingredients were lansoprazole (32.6%), esomeprazole (40%), pantoprazole (30.4%). Exclusion criteria for this study were; patients had bone related diseases or used drugs which affected bone formation, panoramic radiography with distortion, poor image quality, lesion, infection or cyst in selected areas, regions including dentition. Ethics committee approval was obtained from Altınbaş University Clinical Research Ethics Committee (approval number: 28, date: 05.11.2020).

Fractal Analysis

All panoramic images were performed with Newtom 2D Panoramic (Newtom, Verona, Italy) with the same exposure parameters (72 kVp, 7 mA, 13.6 s). FD of samples were calculated using an image processing program, imageJ bundled with 64 bit Java 1.8.0 which was developed by the National Institutes of Health.

In this study, 5 regions of interest (ROI) were identified on the panoramic radiography. Selected ROIs were as follows (Figure 1):

1. ROI1: 35x35 pixels in the mandibular angle
2. ROI2: 30x70 pixels in the posterior mandible
3. ROI3: 18x18 pixels in the area between apical of the second premolar and the first molar
4. ROI4: 18x18 pixels in the maxillary tuber region
5. ROI5: 30x70 pixels in the anterior mandible

FD was performed based on the method used by White and Rudolph (7) (Figure 2).

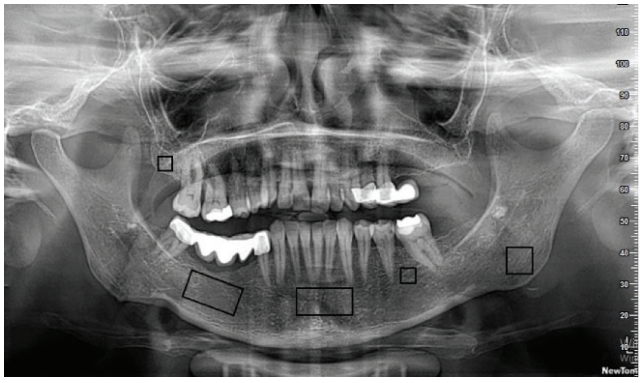

Figure 1. ROIs were selected for fractal analysis on panoramic radiography
ROI: Regions of interest

Initially, selected regions were identified and duplicated (Figure 2A). Then the Gaussian filter (sigma=35 pixels) was used for blurred image and extraction of detail and noise (Figure 2B). The blurred image was removed from the original image and the mean value of 128 was applied to show radiographically components of the bone (Figure 2C). The resulting image was made binary to separate bone marrow from trabeculae (Figure 2D). Median filter was used to remove noise from the image (Figure 2E). Then the binary image inverted to show trabeculae then converted to the skeletonize type (Figure 2F, 2G). This step allows to demonstrate skeletal structure of the bone. Skeletonized image may be superimposed on the original image to show the trabecular structure of the selected region (Figure 2H). Lastly, the image segmented into squares with dimensions of 2, 3, 4, 6, 8, 12, 16, 32, 64. This process is led to measure heterogeneity of the bone as well as. The slope of the logarithmic regression line shows the value of the FD.

Panoramic Mandibular Index

A ratio of MCW to distance between inferior border of mandible and mental foramen was calculated for PMI measurement based on the method of Benson et al. (8) (Figure 3A).

Mandibular Cortical Width

Two parallel lines were drawn across the inferior and superior border of the mandibular cortex at the level of mental foramen. Then a perpendicular line between two parallel lines was measured (Figure 3B).

Statistical Analysis

IBM SPSS 25.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. Normality of the sample data was assessed using Shapiro-Wilk test. We used a student t-test as a parametric test for radiomorphometric indexes, and Mann-Whitnet U test as a non-parametric test for fractal analysis. FD calculations for 20% of all samples were applied twice by two oral and maxillofacial radiologists who had 4 years experience for both observers at 2 weeks intervals. Interobserver and intraobserver agreement were evaluated by intraclass correlation coefficient (ICC). The level of statistical significance is set as $p<0.05$.

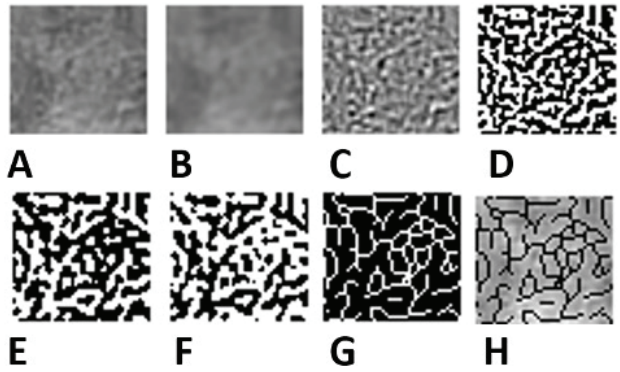

Figure 2. Fractal analysis procedures. Image was selected and duplicated (A). Gaussian filter was applied on the selected image (B). The blurred image was subtracted from the original image (C). The image made binary (D). Median filter was used to remove noise from original image (E). Invertion (F). Skleletonization (G). Demonstration of trabeculation on original image (H)

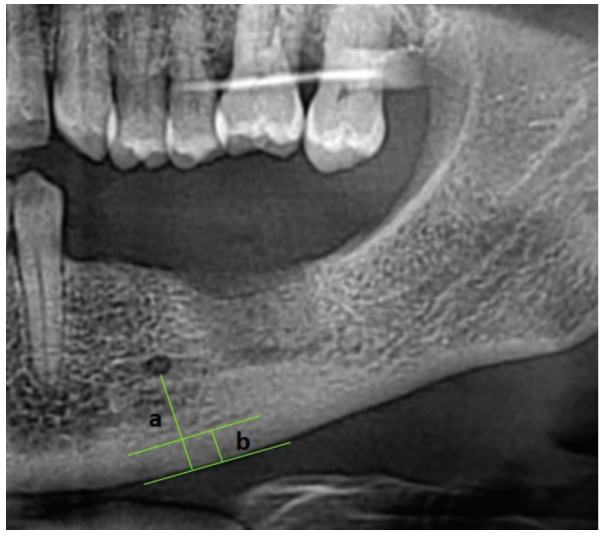

Figure 3. Measurements of PMI and MCW on panoramic radiography
PMI: Panoramic mandibular index, MCW: Mandibular cortical width

Results

For re-evaluated measurements, interobserver and intraobserver agreement was found to be 0.974 and 0.970, respectively which shows excellent reliability (Table 1). Descriptive analysis and results based on student t-test were shown in Table 2. FD values of posterior area of mandibula were higher than anterior for both groups. Posterior mandibula (ROI2), interdental bone (ROI3) and tuber maxilla (ROI4) were significantly lower in PPI users whereas, there was not significant in mandibular angle (ROI1) and anterior mandibula (ROI5). Whereas, tuber maxilla (ROI4) has the highest difference (p=0.01), difference of the interdental bone (ROI3) was the lowest rate (p=0.041) among selected interested regions. The values of MCW and PMI as a radio morphometric index were not statistically significant in PPI users.

Discussion

In recent years, researchers indicated some adverse effects of PPI including Vitamin B12 deficiency, hypomagnesaemia, increased risk of bone fracture, thrombocytopenia (2). Lastly, FDA warned that long-term using of PPI may increase the risk of bone fracture (3).

Table 1. Inter-rater and intra-rater reliability

	ICC	%95 confidence limits		p
Intra-observer	0.974	0.942	0.988	0.000*
Interobserver	0.970	0.934	0.987	0.000*

*Statistically significant in the study group *p<0.05, ICC: Intraclass correlation coefficient

Association between PPIs and increased fracture risk is still unknown. There are a lot of conflicting results between previous studies. Increasing of the histamine level, hyperparathroidism, hypochlorhydria, an adverse impact of PPI on bone turnover have been recently discussed by the researchers (5,9-11). Our results promote previous findings and reveal that long-term effects of PPIs may be deleterious on bone formation. In accordance with the FDA warnings, a majority of clinicians are still overprescribing this medicine. Strict controls on the administration of PPI should be applied by clinicians.

The recent literature linked some drugs may interact with PPIs (12,13). A cohort study with a large population indicated coadministration PPIs with bisphosphonates could be a high risk of hip fractures happening. Researchers denoted a growing concern about oral bisphosphonates and PPIs, which were commonly used by elderly patients. Authors remarked this result needed further studies to explain interaction between two drugs (12). Another study assessed the efficacy of risedronate and PPIs on vertebral structures. This randomized clinical trial revealed that using risedronate with PPIs was not relevant to vertebral fractures (13). Since patients had bone formation disorders and used drugs that affect bone formation were excluded in our study, the relationship between bisphosphonates and fracture risk was not evaluated. On the other hand, in our study, patients were often taking PPIs to impair the effect of non-steroidal anti-inflammatory drugs (NSAI) on gastrointestinal systems. PPI coadministration with NSAI could cause osteoporotic changes on bone.

Table 2. Descriptive analysis of sample data

	PPI users						Control group						p
	N	Mean	SD	Min	Max	Range	N	Mean	SD	Min	Max	Range	
ROI1	46	1.605	0.004	1.597	1.610	0.013	46	1.609	0.018	1.598	1.690	0.092	[1]0.394
ROI2	46	1.732	0.059	1.567	1.833	0.266	46	1.76	0.061	1.641	1.868	0.227	[1]0.019*
ROI3	46	1.337	0.021	1.29	1.365	0.075	46	1.346	0.023	1.318	1.4	0.082	[1]0.041*
ROI4	46	1.333	0.022	1.267	1.365	0.098	46	1.346	0.025	1.309	1.409	0.100	[1]0.010*
ROI5	46	1.694	0.020	1.61	1.753	0.143	46	1.704	0.038	1.642	1.834	0.192	[1]0.379
MCW	46	3.182	0.653	1.6	4.5	2.9	46	3.268	0.565	2	4.1	2.1	[2]0.582
PMI	46	0.230	0.078	0.12	0.532	0.413	46	0.3	0.066	0.171	0.456	0.284	[2]0.792

Min: Minimum, Max: Maximum, SD: Standard deviation, *Statistically significant in the study group *p<0.05, [1]Mann-Whitney U test, [2]Student's t-test, PPI: Proton pump inhibitors

Number of studies evaluating dental procedures affected by PPI-related bone formation disorder are limited to date. In recent years, the retrospective cohort study assessed the impact of PPI intake on dental implant osseointegration in 1,918 implants and the failure rate of osseointegration was found 4.30 times more likely among PPI users than nonusers (7). Similarly, another large cohort study investigated whether the negative effect of PPI on osseointegration and rate of implant failure was found 6.8% and 3.2% in PPI users and nonusers, respectively (6). However, these retrospective studies had some potential confounding factors such as duration of treatment, regular user and type of PPI. Regular PPI intake is crucial due to the fact that based on detailed anamnesis obtained from patients in this study, most of the patients only used PPI for 2 or 3 weeks when they had a gastrointestinal system related symptoms. In our study, patients used PPI regularly at least one year were included. Recently, Al Subaie et al. (4) observed the postoperative effect of PPI on osseointegration in rats tibia by using Micro-computed tomography. Results of this study indicated the serious effects of administration of omeprazole after implant surgery on bone healing. Younger rats were preferred for this study due to having a better bone healing process. However, outcomes of the study indicated that the effect of administration of PPI could be likely more harmful in elderly patients. Our concern is that long-term preoperative use of PPI may have more deleterious effects on bone healing than only postoperative use for 2 weeks.

To our knowledge, this is the first study to evaluate trabecular structure on panoramic radiographs using fractal analysis in PPI users. In the present study, we selected the ROIs as large as possible based on suggestions of the study by White and Rudolph (7). Alterations in anterior maxilla and posterior mandible were found statistically significant in a previous study evaluating morphological structure of maxilla and mandible among osteoporosis and control groups (8). Another study reported that the supracortical area above the angulus mandible and anterior to the mental foramen were significantly lower among patients using the aromatase inhibitors (14). In our study, FD values of posterior mandible (ROI2) and tuber maxilla (ROI4) were found significantly lower among PPI users than control group, whereas the difference in anterior region of mandible (ROI5) was not statistically significant. Alterations in the tuber maxilla is the highest difference among selected ROIs, and corpus mandible is the second region. A possible explanation of this result may be that because osteoporotic changes associated with cancellous bone and maxilla had more trabecular structure and less cortical bone than mandible (15). Bones with the high ratio of trabecular bone to cortical bone are eightfold more sensitive to blood circulation due to high turnover of trabecular bone (16). Additionally, explanation of being not different in the mandibular anterior region may be this reason. In the present study, the maxillary tuber region had the highest difference among selected ROIs. This result revealed that osseointegration of implant in the maxillary tuberosity could be difficult in the long term of PPI use due to low bone quality. We could not select maxillary anterior region because the image quality of maxilla anterior bone is low due to artefacts (16).

Our results revealed that values of MCW and PMI were not statistically significant. The possible explanation of this result could be that osteoporotic alterations developed more rapidly in trabecular bone than cortical bone and parameters of MCW and PMI depend on cortical bone of mandible (17).

In our study, changes in bone microstructure was assessed by using fractal analysis. Fractal analysis is non-invasive, free of charge and high reproducibility technique. There are numerous applications of fractal analysis in dentistry (17-20). Principle of fractal analysis depends on the box counting method and calculates the number of FDs. FD values inversely correlate with the bone mass. However, standardization of parameters on radiographs is a crucial factor for reliable outcomes. A recent study indicated that parameters of radiography such as exposure time can change the voxel size which result in different outcomes (21). Another study showed that differences in image resolution between panoramic radiography and cone beam computed tomography result in different FD values. Authors offered that using panoramic radiography in fractal analysis studies due to high image resolution of panoramic radiography (22).

As a limitation of the present study, patients have used drug for different durations so their effects may be different from each other in clinical practice.

Further studies are needed to evaluate the relationship between duration of use and osteoporosis risk. One other limitation is that the radiologic bone structure of the patient before using the drug is not known exactly. Therefore comparative radiological studies before and after PPI use are needed to obtain more meaningful clinical results.

Conclusion

Current study aims to evaluate the trabecular structure of mandible and maxilla in patients intake PPI at least one year. Posterior region of mandible, maxillary tuberosity and interdental region had lower trabecular microstructure in PPI users. PMI and MCI as an indicator of osteoporosis were not statistically significant. Patients using PPI at least one year should be considered as regard osteporotic changes while dental treatment.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Altınbaş University Clinical Research Ethics Committee (approval number: 28, date: 05.11.2020).

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: Ş.Ö., Design: Ö.O., Z.Z.Y., Data Collection or Processing: Ş.Ö., Analysis or Interpretation: Ş.Ö., Ö.O., Literature Search: Ş.Ö., Z.Z.Y., Writing: Ş.Ö., Ö.O., Z.Z.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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