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Evaluation of mandibular bone quality with respect to enzyme inducement potential of antiepileptic drugs via fractal analysis

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Abstract

Background Epilepsy is a neurological disorder characterized by recurrent seizures and antiepileptic drug (AED) therapy is used in treatment. AED therapy have significant adverse effects as osteopenia, osteoporosis and reduced bone mineral density (BMD).

Purpose The objective of this study is to evaluate the potential effects of AEDs on the trabecular of the mandible by classifying the drugs according to their ability to induce enzymes and comparing them with those of healthy people using fractal analysis.

Materials and methods In this study, dental records of 70 patients (35 AED users and 35 control group) were used. Additionally, the study group was further investigated for the presence of enzyme inducing mechanism. Fractal analysis (FA), panoramic mandibular index (PMI), mandibular cortical width (MCW), and Klemetti index (KI) measurements were performed on panoramic radiographs.

Results No statistically significant difference was observed between the study and control groups in terms of FA results and MCW, PMI and KI. There was not a statistically significant difference between AED subgroups, either.

Conclusion The findings of this study indicate that the microstructural changes and panoramic morphometric indices of the mandible of AED users do not differ from those observed in healthy subjects.

Clinical trial number Not applicable.

Keywords Antiepileptic drug, Enzyme inducing antiepileptic drug, Fractal analysis, Panoramic morphometric indices, Panoramic radiography

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Introduction

Epilepsy is a neurological disorder characterized by recurrent seizures and it is estimated to affect 4 to 10 individuals out of every 1000 people in the general population. Antiepileptic drug (AED) therapy is the most popular form of treatment, with approximately 70% of patients eventually achieving seizure remission [1]. Furthermore, AEDs are prescribed for treating chronic pain, bipolar disorder, migraine and other neurologic/psychiatric disorders in addition to epilepsy [2]. Treatment with AEDs is often long-term and has been demonstrated to have significant adverse effects on bone health, including osteopenia, osteoporosis and reduced bone mineral density (BMD) in both children and adults. The reduced BMD can potentially result in a higher risk of fractures, particularly non-traumatic fractures, by 4–6% [3].

Several AEDs can be administered at appropriate doses, either as monotherapy or in combination therapy, for prolonged periods, sometimes lifelong. Previous studies have found a positive and strong correlation between the cumulative drug load of AEDs and a dose-response relationship regarding the risk of fractures [4]. Although numerous methods hypothesized to explain how AEDs could impact bone tissue, the exact paths by which they contribute to osteoporosis development remain unclear. Enzyme-inducing antiepileptic drugs (EIAEDs) have been reported to reduce bone mineral density, which can result in osteoporosis, by activating the hepatic cytochrome P450 (CYP450) enzyme system and disrupting vitamin K metabolism [2–4]. Based on the available data, older EIAEDs such as carbamazepine, phenobarbital, phenytoin, and primidone have been found to have a more deleterious impact BMD when compared to non-enzyme inducing AEDs (NEIAEDs). However, it is noteworthy that NEIAEDs, including valproic acid, levetiracetam, and lamotrigine, are also associated with decreased BMD. Interestingly, valproate, despite inhibiting the CYP450 enzyme system, still has an impact on BMD and increases the risk of fractures [5].

Fractal analysis (FA) is a mathematical method for analyzing the complex patterns present in images, such as those of bone tissue. Using a quantity known as fractal dimension (FD), this approach assesses the complexity of bone structure. It has been proposed that a higher box count value has a correlation with a more complicated bone structure. The usual method for assessing BMD, which provides information on the quantity of minerals present in the bone, is dual-energy X-ray absorptiometry (DEXA). The lumbar spine and/or the upper section of the femur are the most typically measured sites for BMD [6]. Several studies have found an association between qualitative and/or quantitative evaluations of mandibular bone structure in panoramic radiographs (PR), such as panoramic mandibular index (PMI), mandibular cortical width (MCW), Klemetti index (KI), FA and DEXA results. In this regard, KI grades C2 and C3, as well as low MCW and PMI values, are commonly associated with poor BMD [6–8].

Therefore, the current study's objective was to assess the potential effects of AEDs on the trabecular of the mandible by classifying the medicines according to their ability to induce enzymes and comparing them with those of healthy people. This study hypothesized that statistically significant differences in FD and the radiomorphometric parameters of MCW, PMI, and MCI would be discovered between AED cases and controls, AED subgroups and their controls.

Methods

Study design

The investigators designed and implemented a case-control study. Cases with using AEDs were retrospectively investigated from the records of Department of Oral and Maxillofacial Radiology of the Faculty of Dentistry between 2019 and 2022. The PRs of AED using cases were retrieved from the database and were paired with PRs of healthy sex- and age-matched controls. All images were investigated using FA and radiomorphometric parameters. The study was conducted in accordance with the principles of the Declaration of Helsinki, and its protocol was approved by the Kocaeli University Faculty of Medicine Clinical Research Ethics Committee (GOKAEK-2023/10.09–2023/167).

Sample size calculation

In order to determine the sample size to be used in our study, the G*Power software (version 3.1.9.7; Heinrich Heine University, Düsseldorf, Germany) was utilized. The calculation was based on the data reported in the study by Ustdal et al., titled "Evaluation of the effect of antiepileptic drugs on mandibular bone quality by fractal analysis" [9]. According to this study, the effect size was determined as $d = 0.7133415$. Since the aim was to evaluate whether there is a statistically significant difference in FD values between the study and control groups, a two-tailed test was selected based on a non-directional hypothesis. With a significance level of $\alpha = 0.05$, a power of 0.80 ($1-\beta$), and an equal allocation ratio between the groups ($N2/N1 = 1$), the required sample size was calculated to be 32 participants per group, totaling 64 participants for the study. However, to minimize potential inaccuracies in the estimation and to increase statistical reliability, the current study was conducted with 35 participants in each group, resulting in a total sample size of 70.

Case selection

The medical anamnesis records of AED using cases provided details about their health conditions, treatments, and prescription drugs. Cases taking AED for at least a year formed the study group which consisted of patients using carbamazepine, oxcarbazepine, valproic acid, sodium valproate, vigabatrin, topiramate, levetiracetam and lamotrigine. Cases with any other systemic diseases and using medications other than antiepileptics were excluded from the study group. The control group was chosen randomly from the age and sex matched cases with PRs taken within the same period and using same device of the study group. PRs with low diagnostic quality, and the presence of any lesion in the body and ramus of the mandible which would prevent the analysis procedures were also excluded.

Subgroup of the study group

The study group was further investigated for the presence of enzyme inducing mechanism. For enzyme inducing mechanism evaluation, the study group was subgrouped into cases using carbamazepine, oxcarbazepine, topiramate as the EIAED group and cases using valproic acid, sodium valproate, vigabatrin, levetiracetam, lamotrigine as the NEIAED group.

Data acquisition

For all PRs, the Planmeca Promax® (Planmeca, Helsinki, Finland), was used in standard mode (65–70 kVp, 5–7 mA, 8.1–10.3 exposure time). All retrieved PRs of both groups were changed to TIFF, resampled to 300 DPI and exported in TIFF format for further analysis procedures. The pixel resolution of the obtained panoramic radiographs was 1182 × 582.

Fractal analysis procedures

For the fractal analysis, three sites of mandibular trabecular bone were selected bilaterally as regions of interest (ROIs). ROI-1 was determined as the geometric center of the area between the mandibular notch and mandibular foramen, ROI-2 was determined as the geometric center of the mandibular angle where the mandibular body and ramus intersect, and ROI-3 was determined as the region mesial to the mental foramen. A specific protocol was applied to ensure standardization and reproducibility in the selection of ROIs. Accordingly:

- ROI-1 was placed directly above the mandibular foramen, centered on a vertical line drawn downward from the deepest point of the mandibular notch.
- ROI-2 was positioned at the geometric center of the mandibular angle; to achieve this, the corner of the ROI square closest to the mandibular canal was aligned with the relevant anatomical point, and the ROI was centered over the angle.
- ROI-3 was placed with its distal edge aligned with the border of the mental foramen, and its inferior edge positioned as low as possible without touching the mandibular sclerotic area.

All reference lines were drawn, and ROI placement was performed using ImageJ 1.4.3.67 public domain software (National Institutes of Health, Bethesda, MD, USA). This method ensured a standardized approach to ROI selection across all panoramic radiographs.

The selected ROIs were 46 × 46 pixels, corresponding to an approximate physical dimension of 11 × 11 mm. The reason for selecting this ROI size is that, in the panoramic images of this study, the largest ROI that could be selected without including anatomical structures and focusing solely on trabecular bone was 46 × 46 pixels (11 × 11 mm). The involvement of any anatomical structure such as mandibular canal, cortical borders, teeth, mental foramen, mandibular foramaen and cortical borders of mandibular and mental foramen in the ROI instead of trabecular bone, which may affect the results of fractal analysis, will have a negative effect on the accuracy of the results. Therefore, after reviewing all panoramic images, the maximum possible ROI size that could be selected from the trabecular mandibular bone without including these structures was determined to be 46 × 46 pixels (11 × 11 mm). In addition, ROI was not selected from the maxilla due to the risk of being affected by dental conditions.

The fractal analysis was performed using the box-counting method suggested by White and Rudolph [10] with the ImageJ 1.4.3.67 public domain software (National Institutes of Health, Bethesda, MD, USA). A series of image processing steps were performed, including the selection and cutout of the ROI, duplication of the cutout region, application of the Gaussian filter (with a sigma (radius) value of 35), subtraction from the original image, addition of the gray value of 128, binarization, erosion, dilation, inversion, and skeletonization. After these steps, the skeletonized image was used to calculate the FD with the "box-counting" algorithmic tool available in ImageJ (Fig. 1).

The mean FD value of each ROI was calculated and used for statistical analysis. First, the FD values of the control and study groups were compared for each ROI. Second, the subgroups of the study group were further investigated. The FD values of each study subgroup (EIAED/NEIAED) ROIs were compared with its respective control group ROI for each case.

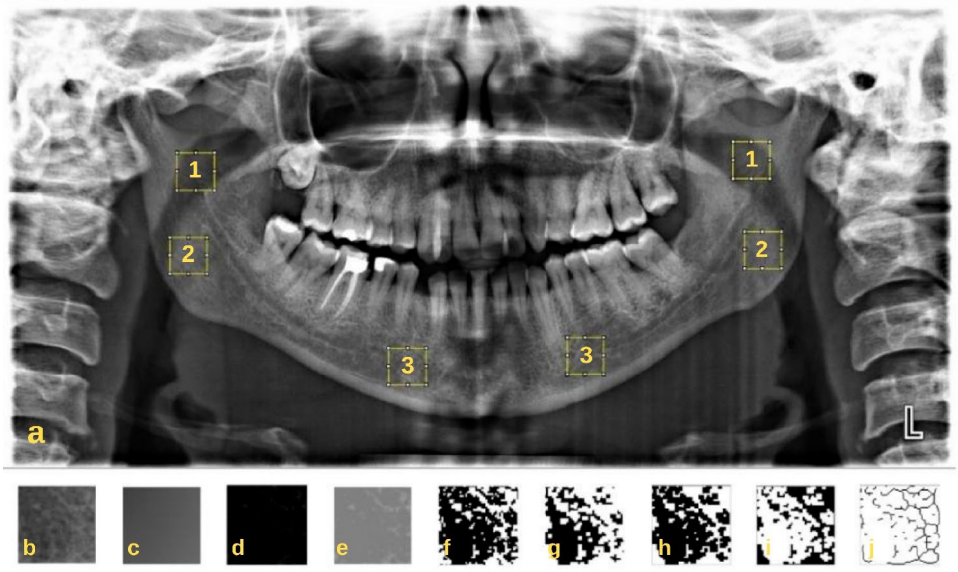

Fig. 1 **a**: Panoramic radiograph with the three selected region of interest areas (ROIs) bilaterally; 1: the geometric center of the area between the mandibular notch and mandibular foramen (ROI 1) 2: the geometric center of the mandibular angle where the mandibular body and ramus intersect (ROI 2) 3: the region mesial to the mental foramen (ROI 3); **b**: cropped and dublicated image; **c**: gaussian blurred image; **d**: substraction image; **e**: an added 128 image; **f**: binarization; **g**: erosion; **h**: dilation; **i**: invertion; **j**: skeletonization

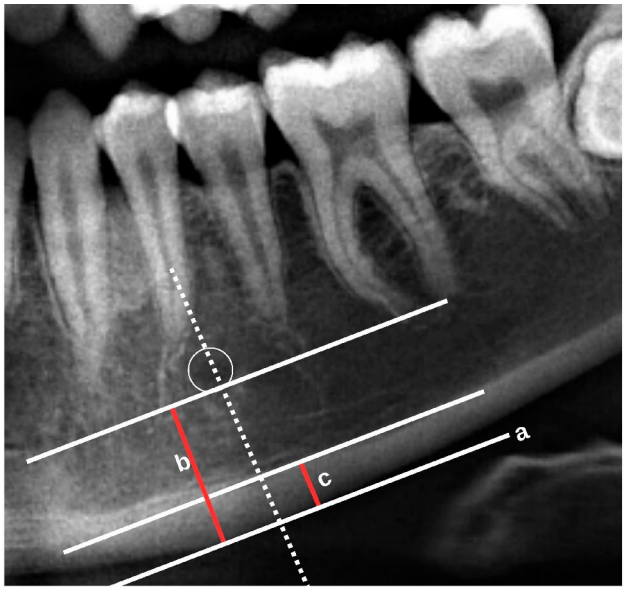

Fig. 2 A line parallel to the inferior border of the mandible (**a**); distance between the inferior border of the mental foramen and "a" line (**b**); mandibular cortical width (**c**); and panoramic mandibular index (**c/b**)

Radiomorphometric analysis procedures

MCW was used to measure the inferior cortex's thickness on both the right and left sides, just below the mental foramen's center. As seen in Fig. 2, this was accomplished by drawing a line that is parallel to the inferior border and cuts through a line traced in the premolar area from the center of the mental foramen. For statistical analysis, the average of the MCW values obtained from each person's right and left sides was used.

PMI is the ratio of mandibular cortex thickness to distance between the mental foremen and inferior mandibular cortex. As seen in Fig. 2, this was accomplished by drawing a line that is parallel to the inferior border and cuts through a line traced in the premolar area from the center of the mental foramen. For statistical analysis, the average of the PMI values obtained from each person's right and left sides was used.

KI was applied to the cortical region under the mandibular foramen. From the mental foramen to the third molar area, erosions in the mandibular cortical bone were studied. In simple terms, a mandibular cortex with a uniform and distinct endosteal edge on a panoramic dental radiograph was classed as '1', the presence of lacunar resorption or endosteal cortical residues was defined as '2', and obvious porosity was classified as '3' (Fig. 3). After determining the quantitative characteristics, KI was examined 30 days later using Adobe Photoshop 7.0 (Adobe Systems) with a 66% zooming in. The images were 300 dpi, 8 bits, and 26 × 14 cm in size. The greater of the two grades determined each person's KI after evaluating the right and left mandibular cortical bones.

Intraclass correlation

One oral radiologist who was blind to the participants clinical information carried out the fractal analysis and examined the panoramic morphometric indices. The examiner had more than 20 years of experience in oral and maxillofacial radiology. For statistical analysis, the mean values of FD (for each ROI), MCW, PMI, and KI were determined. One month later, the 20% of PRs that

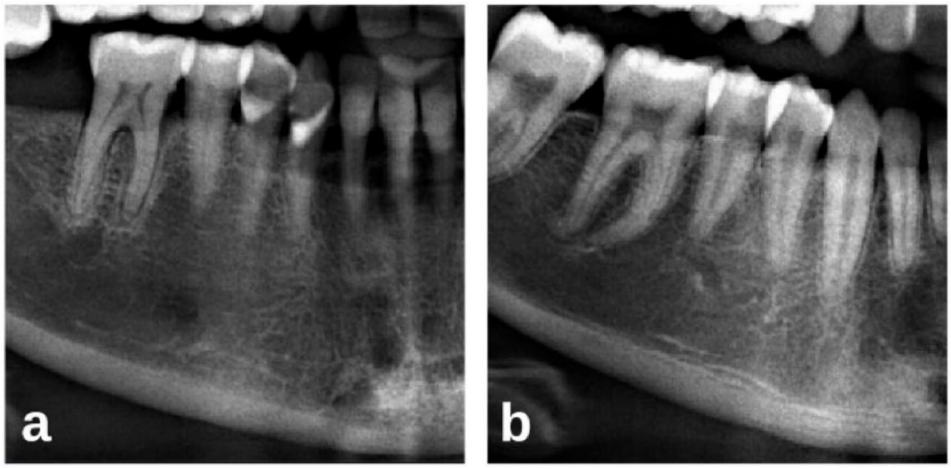

Fig. 3 Classification of mandibular cortical index. C1: endosteal margins of the cortex are sharp and equal on both sides (**a**); C2: endosteal margins show defects in the form of semiulnar (lacunar resorption), and / or endosteal cortical residues on one or both sides (**b**); C3: the cortical layer contains heavy endosteal cortical residues and is clearly porous

were randomly chosen were reevaluated to determine the intra-observer reliability. Measurements were obtained to determine intra-examiner agreement using intraclass correlation coefficients (ICC). There was nearly perfect agreement throughout all intraclass correlation coefficients (ICCs), which were all greater than 0.81 (p 0.001) [11].

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 21.0 for Windows (SPSS Inc, Chicago, IL, USA) served as the tool for the statistical analysis. The statistical distribution of the data was examined using the Kolmogorov-Smirnov test. For FD parameters, ROI-L2, ROI-L3, ROI-R1, ROI-R2, ROI-R3 measurements all had normal distributions, whereas FD was shown to have a non-normal distribution in the ROI-L1 ($p < 0.05$). For radiomorphometric parameters, MCW and PMI had also normal distributions. For the normally distributed data, independent samples T-test were used whereas the Mann-Whitney U test was utilized for the non-normally distributed data. To compare the control and study groups for radiomorphometric KI measurements, Fisher's exact test and Pearson's Chi-square test were also used. Additionally, for the normality analysis of the subgroups, Shapiro-Wilk was used since the sample size was less than 50. Independent samples T-test was used for normally distributed data and Mann-Whitney U test was used for non-normally distributed data to compare for FA, MCW and PMI values of the drug subgroups. The KI distribution was investigated according to drug subgroups using the chi-squared test. The analyses were conducted using a 95% confidence level, and a statistically significant value of $p < 0.05$ was used.

Table 1 Descriptive values of FD, MCW and PMI in the control and study groups

	Kolmogorov-Smirnov		*N*	Mean ± SD	*p*
ROI-L1	0,004	Case	35	1.20 ± 0.159	0,086*
		Control	35	1.26 ± 0.154	
ROI-L2	0,200	Case	35	1.21 ± 0.160	0,276
		Control	35	1.25 ± 0.148	
ROI-L3	0,200	Case	35	1.35 ± 0.122	0,208
		Control	35	1.31 ± 0.103	
ROI-R1	0,056	Case	35	1.19 ± 0.167	0,156
		Control	35	1.25 ± 0.175	
ROI-R2	0,200	Case	35	1.21 ± 0.164	0,104
		Control	35	1.27 ± 0.124	
ROI-R3	0,200	Case	35	1.34 ± 0.110	0,282
		Control	35	1.31 ± 0.120	
MCW	0,200	Case	35	4.52 ± 0.625	0,099
		Control	35	4.81 ± 0.788	
PMI	0,200	Case	35	0.329 ±	0,713
		Control	35	0.067 0.334	
				± 0.055	

*Mann-Whitney U test results

Results

The mean age of AED users and controls was 30.23 ± 11.95 years (range 12–55 years.) There is not a statistically significant difference between the study and control groups in terms of ROI-L1, ROI-L2, ROI-L3, ROI-R1, ROI-R2, ROI-R3, MCW and PMI measurements ($p > 0.05$) (Table 1) (Fig. 4). There were no significant differences for the mean FA, MCW and PMI values between the enzyme inducing (Table 2), non-enzyme inducing subgroups (Table 3) and compared with their respective control groups ($p > 0.05$). There was statistically not significant difference between the study and control group and AED subgroup in terms of KI distribution ($p > 0.05$) (Table 4) (Fig. 5).

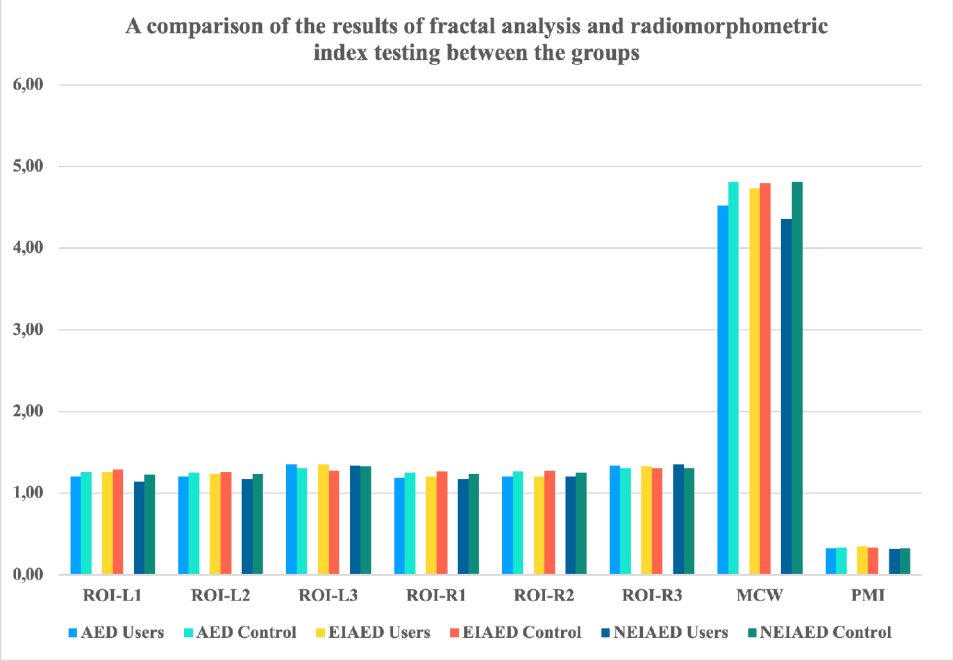

Fig. 4 A comparison of the results of fractal analysis and radiomorphometric index testing between the groups

Table 2 Descriptive values of FD, MCW and PMI in the enzyme inducing subgroup and the respective control group

	Shapiro-Wilk		*N*	Mean ± SD	*p*
ROI-L1	0,193	Subgroup	15	1,26 ± 0,129	0,577
		Control	15	1,29 ± 0,142	
ROI-L2	0,126	Subgroup	15	1,24 ± 0,135	0,719
		Control	15	1,26 ± 0,140	
ROI-L3	0,660	Subgroup	15	1,36 ± 0,106	0,079
		Control	15	1,28 ± 0,112	
ROI-R1	0,396	Subgroup	15	1,20 ± 0,179	0,299
		Control	15	1,27 ± 0,180	
ROI-R2	0,295	Subgroup	15	1,20 ± 0,162	0,169
		Control	15	1,28 ± 0,129	
ROI-R3	0,420	Subgroup	15	1,33 ± 0,131	0,790
		Control	15	1,31 ± 0,139	
MCW	0,893	Subgroup	15	4,74 ± 0,536	0,789
		Control	15	4,80 ± 0,737	
PMI	0,817	Subgroup	15	0,347 ± 0,070	0,709
		Control	15	0,338 ± 0,067	

Table 3 Descriptive values of FD, MCW and PMI in the non-enzyme inducing subgroup and the respective control group

	Shapiro-Wilk		*N*	Mean ± SD	*p*
ROI-L1	0,114	Subgroup	20	1,14 ± 0,162	0,103
		Control	20	1,23 ± 0,161	
ROI-L2	0,058	Subgroup	20	1,18 ± 0,177	0,286
		Control	20	1,24 ± 0,157	
ROI-L3	0,007	Subgroup	20	1,34 ± 0,136	0,617*
		Control	20	1,33 ± 0,092	
ROI-R1	0,041	Subgroup	20	1,18 ± 0,161	0,250*
		Control	20	1,24 ± 0,174	
ROI-R2	0,155	Subgroup	20	1,21 ± 0,170	0,357
		Control	20	1,25 ± 0,123	
ROI-R3	0,563	Subgroup	20	1,35 ± 0,094	0,102
		Control	20	1,31 ± 0,107	
MCW	0,410	Subgroup	20	4,36 ± 0,651	0,067
		Control	20	4,81 ± 0,843	
PMI	0,304	Subgroup	20	0,315 ± 0,062	0,347
		Control	20	0,332 ± 0,046	

*Mann-Whitney U test results

Table 4 Distribution of KI categories by control-study groups and AED subgroups

	KI	Study *n* (%)		Control *n* (%)		*p*
Control and study groups	C1	9 (25,71)		13 (37,14)		0,303*
	C2	26 (74,28)		22 (62,85)		
	C3	0 (0)		0 (0)		
		Enzyme inducing group n (%)	Enzyme inducing control group n (%)	Non-enzyme inducing group n (%)	Non-enzyme inducing control group n (%)	
Enzyme inducing and non-enzyme inducing subgroups	C1	5 (33,3)	6 (40)	4 (20)	7 (35)	0,600*
	C2	10 (66,6)	9 (60)	16 (80)	13 (65)	
	C3	0 (0)	0 (0)	0 (0)	0 (0)	

*Significant difference between groups is indicated by $p < 0.05$*Chi-square

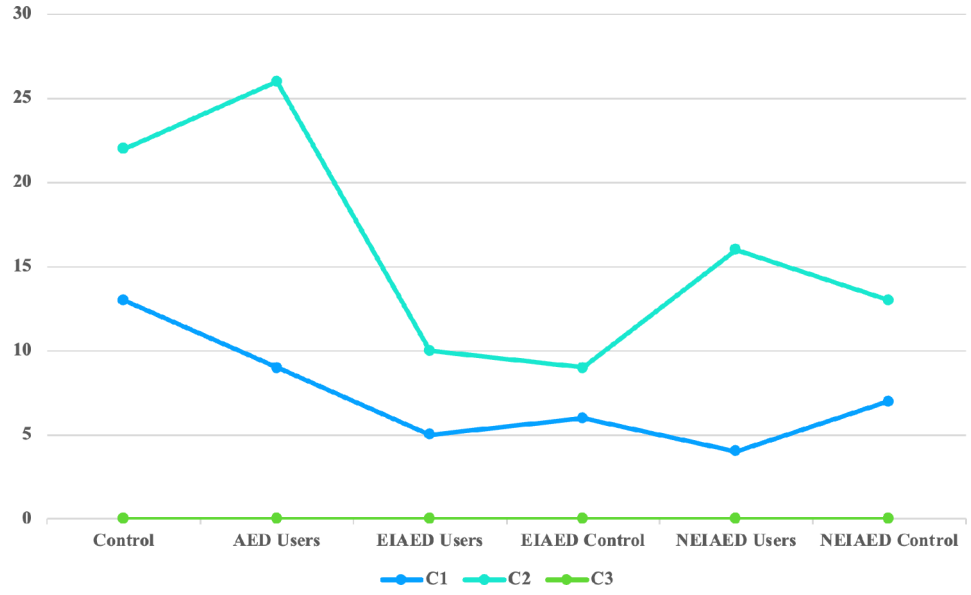

Fig. 5 Assessment of differences between groups according to the klemetti index

Discussion

Significant use of FA via textural analysis as a non-invasive tool for quantitative data acquisition of structural changes in the bone trabeculae has been a topic of interest in dentomaxillofacial radiology. Alveolar bone is a fractal tissue and FA is reported to be an appropriate non-invasive approach for analysis of mineral content and architecture for osteoporotic patients [12]. Dental radiographs may give a long-term window for screening low BMD patients with minimum exposure [13]. Recent studies in dentomaxillofacial radiology have employed fractal analysis to assess the impact of systemic diseases and medications on jaw bone quality, yielding valuable findings in this area [14–18]. However, the literature on the effects of AEDs on jawbone using FA remains very limited, and there is no study specifically examining the impact of EIAEDs on jawbone through their enzyme induction mechanisms. In the present study, we employed the FA method to evaluate bone architecture on panoramic radiographs in patients using AEDs, aiming to investigate how the bone architecture differs between individuals using enzyme-inducing versus non–enzyme-inducing AEDs, as well as in comparison to healthy individuals, and whether significant differences exist among these groups.

In a study that investigated BMD in panoramic radiographs of patients using antiepileptic drugs and healthy individuals through fractal analysis, Ustdal et al. found a significant relationship in all ROI's between the study group and control group ($p < 0.005$), contrary to the current study [9]. Although it is assumed that FA values are not affected by changes in film exposure, alignment, FA can affect by the size, shape, and position of the ROI [19]. Pekince et al. noted in their study that even angular variations in ROI placement within the same anatomical region can affect fractal dimension values, highlighting the lack of standardization in ROI selection as a significant limitation in the literature [20]. In our study, we attempted to select ROIs from regions equivalent to those used by Ustdal et al. [9]. However, while they used 60×60 pixel ROIs, we were limited to 46×46 pixels (approximately 11×11 mm). This limitation was due to the fact that, in our panoramic radiographs, 46×46 pixels was the largest possible ROI size that could be selected while including only trabecular bone and avoiding any cortical structures or other anatomical landmarks. Furthermore, evaluating ROI size in physical units (mm), rather than pixels alone, allows for more accurate comparisons. Since panoramic radiographs can vary in pixel resolution depending on the device, pixel-based comparisons may be misleading. Unfortunately, Ustdal et al. did not report the physical dimensions of their ROIs [9], which prevents a direct comparison. Such inconsistencies in standardization may explain the differences observed between the two studies.

One of the major side effects of AEDs is their adverse impact on bone metabolism. Several mechanisms have been proposed to explain this effect, including modulation of cytochrome P450 (CYP450) enzyme activity, inhibition of osteocalcin production or function, increased catabolism of vitamin D, and enhanced urinary calcium excretion [3]. Long-term use of AEDs may exacerbate these negative effects, and studies have shown that individuals using AEDs for extended periods tend to have lower vitamin D levels compared to those using them for shorter durations [21]. However, there is insufficient

evidence supporting a consistent and significant association between any serum biochemical marker and BMD measurements [4]. Although findings on vitamin D deficiency, elevated parathyroid hormone levels, and altered serum calcium levels in AED users vary across studies, supplementation with these substances has been shown to help prevent BMD loss associated with AED use [4, 22]. Accordingly, clinicians recommend that individuals on AED therapy maintain adequate intake of vitamin D and calcium, engage in weight-bearing exercises, follow a balanced diet, and reduce external risk factors such as alcohol consumption and smoking to mitigate BMD loss [23]. In the present study, we evaluated differences in jawbone BMD between individuals using AEDs and healthy controls using both fractal analysis and panoramic morphometric indices, and found no significant difference. This outcome may be due to the variability of the aforementioned factors among individuals. Future research that incorporates detailed data on serum vitamin D and PTH levels, urinary calcium excretion, supplement use, and physical activity in AED users could yield more robust scientific conclusions. Both our study and that of Ustdal et al. share a retrospective design, which limited the inclusion of biochemical and clinical parameters in both studies. This similarity suggests that individual differences among AED users may have influenced the findings in each case, and the results should be interpreted accordingly.

Regarding the osteoporotic effect of AEDs on bone mechanism, parathyroid hormone stimulation was reported to be responsible for the resorption potential of these drugs [3]. A number of studies in the literature employ FA to investigate the impact of parathyroid hormone-related alterations on BMD in the jaw bones. Accordingly, in a study using cone-beam computed tomography (CBCT), images of individuals with secondary hyperparathyroidism caused due to chronic renal failure, these patients' jaw bones had more obvious osteoporotic bone abnormalities [24]. Cantürk et al. identified significant disparities in calcium, vitamin D, parathormone, and phosphorus levels between individuals diagnosed with primary hyperparathyroidism and the control group. They also reported that FD values were significantly lower in those with primary hyperparathyroidism compared to healthy individuals, as determined by fractal analysis of panoramic radiographs [25]. The findings indicate that variations in parathormone levels may result in discrepancies in jawbone BMD, which can be identified by fractal analysis. From this viewpoint, the observation that AED may not consistently alter parathormone levels, coupled with the absence of parathormone level assessment in our study, could account for the lack of a significant difference between AED users and healthy individuals.

The type and duration of AED therapy are known to influence BMD. Studies have indicated that AED use in the form of polytherapy, as well as prolonged use over time, may lead to greater BMD loss compared to short-term or monotherapy regimens [26–29]. Patients who have recently started AED treatment, particularly within the first year, appear to show minimal or no measurable reduction in BMD [30–33]. These findings underscore the importance of long-term AED exposure as a risk factor for skeletal changes. In the present study, although only patients with a history of AED use for at least one year were included, detailed information regarding the exact duration of therapy and whether the patients were on monotherapy or polytherapy could not be retrieved from the available records. This limitation may have affected the results and should be considered when interpreting the findings. Likewise, the study by Ustdal et al. also did not report whether the patients were using multiple AEDs or the duration of their treatment, which may partly explain the differences observed between the two studies.

Panoramic radiomorphometric indices have been shown in studies to be a preliminary diagnostic tool for identifying osteoporotic changes, and there is an important correlation between panoramic radiographs and BMD values [34]. There is a significant amount of variation in the reported results for the several linear and qualitative panoramic morphometric indices that have been offered as diagnostic tools for diminished BMD. However, three most reported indices MCW, PMI, KI could be useful tools to screen for reduced BMD [8]. These indices have the benefit that, like fractal analysis, dental professionals may utilize them as simple, affordable methods, to find early indications of osteopenia/osteoporosis. Ustdal et al. in their study, they also compared the effects of antiepileptic drugs on bone based on morphometric indices and showed that the patients using the drug had a significant decrease in MCW and PMI values compared to the control group. In addition, because of the comparison of KI values, they stated that the patients using antiepileptic drugs were in the C2 category significantly more than the control group [9]. On the other hand, in present study, in alignment with the findings we observed in FA values, no significant difference was identified in MCW, PMI and KI values compared to the control group of patients using antiepileptic medicines, and among the subgroups.

A numerous studied investigated enzyme inducing capability of AEDs for initiating osteoporosis regarding their effect on bone metabolism. Additionally, there are differing views in the literature about the claim that AEDs that induce enzymes harm bones more severely than those that don't [4]. There is no study in the literature that has evaluated the effect of enzyme-inducing AEDs

on bone by means of FA and panoramic radiographs. For this reason, our study is a pilot study. In current study, no significant difference was found between FA values when subgroups were evaluated. This may be due to the fact that the effect of AEDs and especially EIAEDs on bone quality and BMD reduction in the jaw bones is more limited compared to other bone regions.

A reduction in BMD in the jawbones and the presence of osteoporotic conditions can significantly impact oral health, particularly in relation to the outcomes and prognosis of periodontitis, orthodontic treatments, dental implant procedures, and tooth extractions [35–38]. It is acknowledged that a decrease in BMD in the jaws may contribute to accelerated bone resorption caused by periodontitis, suggesting a potential link between jaw osteoporosis and periodontal disease [36]. In addition to periodontal status, osteoporotic changes in the jaws may lead to increased peri-implant bone loss, reduced initial implant stability, and lower survival rates. Therefore, assessing jawbone quality prior to implant therapy is of critical importance [35]. Similarly, decreased bone quality in the jaws can also affect orthodontic treatment. The presence of osteoporosis may alter the biological mechanisms of tooth movement, potentially prolonging treatment duration and increasing the risk of relapse after treatment completion [39, 40]. In light of this information, if AED use leads to osteoporotic changes in the jaws, it could adversely affect both periodontal tissue health and the success of dental implant treatments. Moreover, considering the large pediatric population using AEDs, reduced jaw BMD in these individuals could pose additional challenges for orthodontic treatment planning. However, in our study, no significant differences in jawbone BMD were observed between individuals using AEDs—whether enzyme-inducing or non–enzyme-inducing—and healthy controls. Nevertheless, the existence of a fractal analysis study indicating that AEDs may result in a reduction of BMD in the jawbone, while our investigation found no such correlation, gives rise to two divergent and conflicting perspectives in the literature. In this regard, recognizing the limitations of both our research and that of Üstdal et al., in addition to different factors that may contribute to result variability, it is evident that more extensive and thorough prospective investigations are required in this subject. Regarding the retrospective nature of our study, we were not able to verify the DEXA results and serological data of patients. Therefore, quantitative evaluation and correlation of the control and study groups with above mentioned data were not performed. This was a limitation of this study and may have prevented acquisition of statistically significant results.

In conclusion, the fractal analysis methodology demonstrated that the AED and enzyme induction processes of the AED did not have an impact on the density of the jaw bones. Considering the integration attemps of artificial intelligence (AI) in dentomaxillofacial radiology, the FA and AI enhanced softwares may correlate biochemical data in evalution of panoramic radiographs as a routine procedure which may help in preliminary diagnoses in future studies. Further studies with larger populations and inclusion of biochemical data, such as vitamin D and parathormone levels, should be performed to establish the clinical validity of the FA method in AED users.

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Author contributions
A.K: Design, Concept, Definition of content, Literature search, Data acquisition, Manuscript preparation, Statistical Analysis. U.S: Literature search, Manuscript preparation, Manuscript editing, Manuscript review. S.B: Design, Literature search, Manuscript preparation. Manuscript editing, Manuscript review. A.U: Literature search, Data acquisition, Manuscript preparation E.A.S: Design, Data analysis, Manuscript editing, Manuscript review. All authors reviewed the manuscript.

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Data availability
The data obtained in this study may be requested from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the principles of the Declaration of Helsinki, and its protocol was approved by the Kocaeli University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (GOKAEK-2023/10.09–2023/167). With the approval of the Non-Interventional Ethics Committee of Kocaeli University, consent for patient participation in this study was waived.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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