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The Effects of Celiac Disease on Mandibular Bone Complexity: Evaluation Using the Fractal Analysis Method

Çölyak Hastalığının Mandibular Kemik Kompleksi Üzerindeki Etkileri: Fraktal Analiz Yöntemi Kullanılarak Değerlendirme

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ABSTRACT

Objective: This study aimed to evaluate mandibular bone quality in celiac patients using radiomorphometric parameters, including trabecular bone fractal analysis and cortical bone assessments.
Methods: Panoramic radiographs of 37 celiac patients and an age- and sex-matched control group were retrospectively examined. Fractal dimension values in nine mandibular regions, mandibular cortical width (MCW), and mandibular cortical index (MCI) were assessed. Statistical significance was set at $P<.05$.
Results: Significantly lower fractal dimension values were observed in the condyle, angle, and molar regions of celiac patients, indicating a reduction in trabecular bone complexity. No significant differences were found in MCW (P:.699) or MCI distribution (P:.421), but the control group exhibited more frequent intact cortical borders (C1). High reliability was found in the measurements.
Conclusion: Celiac disease is associated with the deterioration of trabecular bone quality in the mandible, although no significant differences were detected in cortical changes. The reduction in trabecular bone complexity suggests a simplification of the bone structure. Radiomorphometric evaluations may contribute to the early detection of bone changes in celiac patients, thereby aiding in management strategies.
Keywords: Celiac disease, panoramic radiography, fractal, jaw, mandible

ÖZ
Amaç: Bu çalışma, çölyak hastalarında mandibular kemik kalitesini değerlendirmek için trabeküler kemik fraktal analizi ve kortikal kemik parametrelerini içeren radyomorfometrik parametreleri kullanmayı amaçlamıştır.
Yöntemler: 37 çölyak hastası ve yaş-cinsiyet uyumlu kontrol grubunun panoramik radyografileri retrospektif olarak incelenmiştir. Mandibulanın dokuz bölgesindeki fraktal boyut değerleri, mandibular kortikal genişlik (MCW) ve mandibular kortikal indeks (MCI) değerlendirilmiştir. İstatistiksel analizlerde anlamlılık P:<.05 olarak kabul edilmiştir.
Bulgular: Çölyak hastalarında kondil, açı ve molar bölgelerde anlamlı derecede düşük fraktal boyut değerleri gözlenmiştir, bu da trabeküler kemik karmaşıklığının azaldığını göstermektedir. MCW'de (P:699) veya MCI dağılımında (P:.421) anlamlı fark bulunmamıştır, ancak kontrol grubunda daha sık sağlam kortikal kenarlar (C1) gözlemlenmiştir. Ölçümlerde araştırmacılar arası güvenilirlik yüksek bulunmuştur.
Sonuç: Çölyak hastalığı, mandibulada trabeküler kemik kalitesinin bozulmasıyla ilişkilidir, ancak kortikal değişikliklerde anlamlı bir fark tespit edilmemiştir. Trabeküler kemik karmaşıklığındaki azalma, kemik yapısının daha basitleşmiş bir hale geldiğini gösterir. Radyomorfometrik değerlendirmeler, çölyak hastalarında kemik değişikliklerini erken tespit ederek yönetim süreçlerine katkı sağlayabilir.
Anahtar Kelimeler: Çölyak hastalığı, panoramik radyografi, çene, fraktal, mandibula

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INTRODUCTION

Celiac disease is an immune-mediated condition caused by a lifelong intolerance to gluten, primarily affecting the gastrointestinal system. This condition is defined by persistent inflammation in the mucosal and submucosal layers of the small intestine, along with a range of systemic manifestations. It can onset at any age, including childhood, adolescence, and is also quite prevalent in adults.[1-3]

Historically, celiac disease was typically diagnosed due to symptoms like steatorrhea and other signs of malabsorption. Frequently observed conditions included anemia, weight loss, deficiencies in vitamins and trace elements, and skin issues such as dermatitis herpetiformis, psoriasis, urticaria, vitiligo, oral lichen planus.[4]

Currently, the sole successful therapy for celiac disease involves strict adherence to a lifelong gluten-free diet. However, approximately 30% of patients experience limited response to treatment, largely due to challenges in adhering to dietary restrictions.[3,5,6]

The occurrence of low bone mineral density, encompassing osteopenia and osteoporosis as measured by dual-energy x-ray absorptiometry (DXA), varies among celiac patients. Prevalence rates range from 38 to 72% at diagnosis and 9 to 47% in patients adhering to a gluten-free diet.[7] Numerous studies have indicated that initiating a gluten-free diet for celiac disease leads to enhanced bone mineralization over time.[8,9]

Fractal analysis (FA) is a quantitative imaging technique used to characterize the structure, form, and pattern of bone architecture.[10] Fractal analysis is a quantitative method used to assess the structure, form, and arrangement of bone. The result of FA, known as the fractal dimension (FD), is calculated using a box-counting algorithm that evaluates the boundary between trabecular bone and bone marrow. Fractal dimension values that are higher indicate a more detailed and complex bone structure. Fractal analysis has been extensively utilized in the evaluation and quantification of bone mineral density, changes in bone, healing at the root apex, periapical bone conditions, and the impact of systemic diseases and medications on jawbone health.[11-14] Dental panoramic radiographs (DPRs) are highly regarded in the field of dentistry due to their advantages, including low radiation exposure, cost-efficiency, and wide accessibility. These radiographs are particularly effective for detecting abnormalities in the mandibular bones. Existing research demonstrates that DPRs, in conjunction with fractal analysis and radiomorphometric techniques, have been used successfully to assess the influence of medications and systemic diseases on the mandible.[15,16]

Celiac disease, as a systemic condition that can affect bone health, may also influence the structure of the jawbone. However, studies investigating the relationship between radiomorphometric parameters applied to the jaws and celiac disease are limited. There is a need for further research in the literature to better understand the relationship between celiac disease and changes in jawbone structure. This study aims to examine the relationship between radiomorphometric parameters and celiac disease in greater depth, addressing the gap in the existing literature.

METHODS

This research comprised a retrospective cross-sectional analysis of panoramic radiographs obtained from individuals diagnosed with celiac disease, alongside age and gender-matched controls, ensuring that both groups had similar dental alignment and tooth counts, within the Oral and Maxillofacial Radiology Department, spanning from 2019 to 2020. Each group included 7 males and 30 females. Approval for the study was granted by the Ethics Committee under Date:September 18, 2023 approval number 2023/09–14. All participants provided verbal consent for the use of their radiographs during their clinical examinations for our study.

Participants included in the study had no systemic conditions impacting bone development or metabolism other than celiac disease, and their radiographic images met the defined quality criteria. Exclusions comprised individuals using medications or affected by systemic illnesses influencing bone development or metabolism, images displaying artifacts or oral/maxillofacial syndromes, and those with uncertain celiac disease status.

Panoramic radiographs were captured using an ORTHOPHOS XG device from Sirona, USA, employing exposure parameters of 60 kV, 3 mA, and an exposure time of 14.1 seconds. Subsequently, the images were converted to DICOM (Digital Imaging and Communications in Medicine) format and analyzed using ImageJ software from the U.S. National Institutes of Health in Bethesda, MD, USA. All panoramic radiographs (OPTGs) were taken by the same technician, following standardized imaging techniques. Two oral and maxillofacial radiologists, one with ten years and the other with six years of experience, conducted the analyses. Inter-examiner reliability was assessed by a separate oral and maxillofacial radiologist. The radiologists who performed the measurements conducted the data analysis on a 23-inch computer in the darkroom where the panoramic data was reported, in order to eliminate the loss of grayscale sensitivity due to prolonged radiological examination and to standardize the data analysis. The analysis was performed for a maximum of three hours per day. A high FD reflects a more intricate bone structure with fewer voids, whereas a low FD value indicates a bone with a more porous composition.[17] As per Kato et al.'s methodology we established nine regions of interests for fractal analysis. Using ImageJ software, we manually outlined squares measuring 50 × 50 pixels in the condyle, angle, molar, premolar, and anterior regions bilaterally.[18] Additionally, we demarcated regions of interests in the cortical bone on both sides, tracing from the mental foramen to the posterior aspect of the third molar, employing the Polygon tool (Figure 1).

Figure 1. Regions of interests for fractal analysis were chosen, including manually delineated squares measuring 50 × 50 pixels in the condyle, angle, molar, premolar, and anterior regions. Additionally, bilateral regions of interests of the cortex were manually outlined.

Following the protocol outlined by White and Rudolph fractal analysis steps in ImageJ software were executed. Following Gaussian filtering with a sigma of 35 to mitigate broad-scale brightness fluctuations, the duplicated image underwent subtraction of the blurred version from the original.[17] This step facilitated the differentiation between trabecular bone and bone marrow spaces, which was succeeded by the addition of 128 Gy values. After binarization transformed the image into a two-colored (black and white) format, noise reduction was achieved through erosion, while dilatation sharpened external structure lines. Following inversion, trabecular bone areas appeared black, and bone marrow spaces white. Subsequently, skeletonization was conducted. Fractal analysis involved counting 2–64 pixel-sized boxes on the skeletonized image using the Fractal box count plugin in ImageJ software (Figure 2). Fractal dimension averages within the regions of interests, including the condyle, angle, molar, and premolar regions bilaterally, were documented. Two oral and maxillofacial radiologists assessed inter- and intra-examiner reliability by independently analyzing 20% of the total sample.

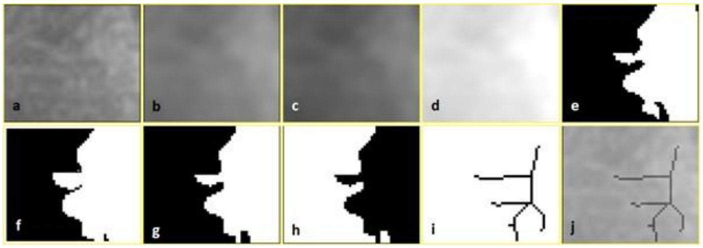

Figure 2. Steps involved in fractal analysis include: (a) Duplicating the image after cropping, (b) Applying a Gaussian filter (sigma, 35) to blur the image, (c) Subtracting the blurred image from the original, (d) Adding 128 Gy values to the resulting image, (e) Binarizing the image, (f) Performing erosion to eliminate noise, (g) Dilating to sharpen external lines, (h) Inverting the image, (i) Skeletonizing the image, and (j) Overlapping the skeletonized image with the cropped one.

Bilateral assessments of the cortical bone encircling the mental foramen were executed. This entailed sketching two parallel lines, extending from the upper to the lower borders of the cortex. Following this, a third line was added perpendicular to the aforementioned parallel lines, intersecting at the center of the mental foramen. The distance between the two parallel lines along this third line indicated the mandibular cortical width.[19] The averages of these measurements from both sides were documented (Figure 3). Two oral and maxillofacial radiologists evaluated inter- and intra-examiner reliability by independently analyzing 20% of the total sample.

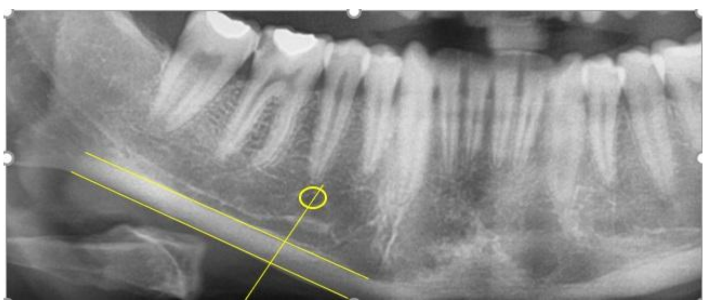

Figure 3. Two lines were sketched parallelly, spanning from the upper to the lower borders of the cortex. Then, a third line was drawn perpendicular to these, intersecting at the center of the mandibular foramen. The distance between the two parallel lines along this third line was measured as the mandibular cortical width.

Utilizing Klemetti et al.[20]'s classification system, the mandibular cortical index was established, categorizing erosion patterns of the mandibular cortical bone into three groups: C1 (intact cortical margin on both upper and lower sides), C2 (moderate erosive defects on at least one side), and C3 (multiple defects and porosity along the cortical margin).[20] Evaluation was performed independently on each side, with the highest observed category recorded (Figure 4). Inter- and intra-examiner reliability were assessed by two oral and maxillofacial radiologists, who independently analyzed 20% of the total sample using Cohen's kappa coefficient.

Descriptive statistics were employed to examine the distribution of each variable within the groups. The mandibular cortical index distributions between the celiac disease and control groups were compared using the McNemar–Bowker test. Additionally, Student's t-test was employed to assess the differences in mean mandibular cortical width and fractal dimension values between the celiac disease and control groups, as well as the mean mandibular cortical width across various celiac disease and mandibular cortical index subgroups. Statistical analyses were performed using SPSS software (IBM SPSS Statistics 20.0; IBM Corp., Armonk, NY, USA) with a confidence interval of 95%. Significance was established at *P*<.05 for all analyses.

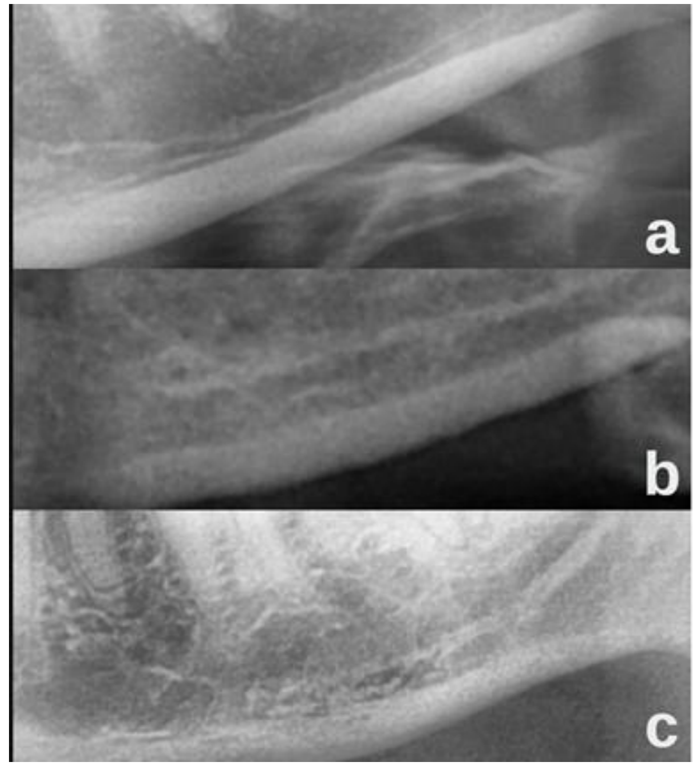

Figure 4. The radiographic representation of mandibular cortical index which is a radiographic method used to evaluate the quality and integrity of the mandibular cortex, is depicted as follows: **a:** C1 (intact cortical margin on both upper and lower sides), **b:** C2 (moderate erosive defects on at least one side), and **c:** C3 (multiple defects and porosity along the cortical margin), (Klemetti et al., 1994).

RESULTS

The average age of individuals diagnosed with celiac disease and controls was 31.46 ± 14.19 years (range: 9–72 years). In Table 1, a comparison of fractal dimension values across various regions between the two groups is presented. Lower fractal dimension values were observed in the condyle, angle, molar, premolar, and anterior regions of celiac patients compared to individuals in the control group.These differences were statistically significant (Table 1).

Additionally, Table 1 presents a comparison of mandibular cortical width between the two groups. Although the mean mandibular cortical width was higher in the control group, this variation was not statistically significant (*P*= .699).

Furthermore, Table 2 illustrates a comparison of mandibular cortical index distributions between celiac patients and controls. It reveals similar distributions of mandibular cortical index categories between the two groups, with no statistically significant differences observed. Specifically, the proportions of C1, C2, and C3 classifications were 24.3%, 56.8%, and 18.9%, respectively, in the celiac group, and 37.8%, 48.7%, and 13.5%, respectively, in the control group (*P*=.421).

Table 1. Comparison of fractal dimensions of anatomic regions between the patients of Celiac Disease and control groups.

Region	Groups	N	Mean	Std. deviation	Std. error mean	P*
Anterior	**CD**	37	1.0956	.28106	.04827	**.015**
	Control	37	1.1757	.08503	.04827	
Premolar	**CD**	37	1.1138	.25182	.04316	**.023**
	Control	37	1.1753	.07431	.04316	
Molar	**CD**	37	1.1264	.17600	.03114	**.025**
	Control	37	1.2024	.07006	.03114	
Angulus	**CD**	37	1.0877	.25865	.04532	**.012**
	Control	37	1.2039	.09532	.04532	
Condyle	**CD**	37	1.0315	.27185	.05177	**.003**
	Control	37	1.1574	.15890	.05177	
MCW index	**CD**	37	38.7297	12.10980	2.92768	.699
	Control	37	44.1892	13.05722	2.92768	

N, number of patients; MCW:mandibular cortical width,CD: Celiac Disease, p Student's t test.*

Table 2. Distributions and comparison of the mandibular cortical index between the patients of Celiac Disease and control groups.

Groups	MCI classification, n (%)			N (%)	P*
	C1	C2	C3		
Celiac Disease	9	21	7	37 (100)	.421
Controls	14	18	5	37 (100)	
Total	23	39	12	74 (100)	

MCI, mandibular cortical index; N–n, number p McNemar–Bowker Test.*

Inter-examiner reliability assessments yielded consistent results: good reliability for fractal dimension (intraclass correlation coefficient (ICC) = 0.721), excellent reliability for mandibular cortical width (ICC = 0.905), and good reliability for mandibular cortical index using Cohen's kappa coefficient (κ = 0.644).

DISCUSSION

Fractal analysis serves as a mathematical method for assessing the intricacy of shapes or structures. Its strength lies in analyzing irregular and fragmented shapes that defy conventional geometric methods. Fractal analysis produces a dimensionless parameter called the fractal dimension, where a higher fractal dimension indicates greater complexity or irregularity within the structure.[21] Fractal analysis has found application in oral medicine, particularly in examining the trabecular bone pattern within the mandible.[22] Trabecular bone, forming the majority of the mandible's interior, has a spongy structure. Fractal analysis is a useful tool for examining changes in the mandible related to various diseases. By quantifying the complex patterns of trabecular bone, it provides insights into the pathophysiology of conditions like osteoporosis, osteoarthritis, and oral cancer.

Osteoporosis is defined by systemic skeletal degeneration, characterized by decreased bone mass and microarchitectural modifications. Fractal analysis has emerged as a valuable method for identifying changes in the trabecular bone pattern of the mandible in individuals with osteoporosis.[23] White et al.[24] conducted a study revealing significantly lower fractal dimension values in the mandibular trabecular bone of osteoporotic patients compared to healthy counterparts, indicating a loss of trabecular bone complexity. Smoking, age, alcohol dependence, physical inactivity, low dietary calcium, and systemic diseases such as hyperparathyroidism and rheumatoid arthritis are among the other risk factors for osteoporosis, leading to a decrease in fractal dimension.[17] Fractal dimension increase can be observed in conditions such as bisphosphonate use, osteogenesis imperfecta, squamous cell carcinoma, and Paget's disease.[25] Similar to previous studies, the present study found statistically lower fractal dimension values in various mandibular regions among celiac patients, consistent with the findings[17] who reported a decrease in trabecular bone complexity in osteoporotic individuals.

Rheumatoid arthritis, a degenerative joint condition, may affect the temporomandibular joint, resulting in changes to the structure of the mandibular bone. Türkmenoglu et al.[26] utilized fractal analysis to investigate trabecular bone patterns in the mandibular condyle among rheumatoid arthritis patients. Their study revealed lower fractal dimension values in rheumatoid arthritis individuals compared to healthy counterparts. Furthermore, Demirbaş et al.[27] revealed diminished FD values in the mandibles of thirty patients with sickle cell anemia compared to healthy subjects. Similarly, Serindere et al.[28] observed decreased fractal dimension values in the mandibles of 30 thalassemia and 30 sickle cell anemia patients compared to healthy individuals. Similar to the studies[26-28] the present study also observed altered fractal dimension values in the mandibular bone, with lower FD, MCW and MCI values among celiac patients compared to healthy controls, which aligns with findings in other conditions affecting bone structure, such as osteoarthritis and sickle cell anemia. This current study, significant differences in the fractal structure of the mandible were observed in celiac patients without selecting specific regions. Systemic diseases appear to affect bone structure throughout the entire body, without being region-specific.

Cancer frequently induces changes in bone structure, necessitating the application of fractal analysis to identify such alterations, particularly in patients with oral cancer. A recent study by Ravichandran et al. [29] utilized fractal analysis to assess the mandibular bone pattern in individuals diagnosed with oral squamous cell carcinoma. Their findings revealed a reduced fractal dimension in cancer patients compared to healthy subjects, indicating a decline in the complexity of the mandibular bone pattern. Similarly, Tepe et al. [30] observed a statistically significant decrease in FD, MCW and MCI values in the mandibles of patients with nasopharyngeal carcinoma. Dağıstan and Bilge[31] argued that the mandibular FD, MCW, and MCI values of osteoporotic women were lower compared to the control group. Bulut et al. [32] concentrated solely on fractal dimension analysis of condyles in patients, revealing a significant difference between the control and celiac patiens. In contrast, Neves et al.[33] focused exclusively on FD, MCW and MCI analysis in the premolar region's bone, reporting no difference between the two groups. Additionally, in partial agreement with the study by Neves et al. [33], by analyzing nine regions of interest in the mandible for FD assesment was lower in the celiac patient group compared to the control group, while no significant differences were observed in MCW and MCI values. This current study, although significant differences were observed in the mandibular trabecular bone structure of celiac patients, no significant difference was found in mandibular cortical width and index values compared to the control group. Furthermore, MCI is a parameter that requires further discussion in the literature, and similarly, no significant difference in MCI values was observed in this study. These results suggest that changes in the trabecular bone structure are more pronounced in celiac patients, while the deterioration of cortical structure may be less evident. Fractal dimension is crucial in dentistry for evaluating bone structure, particularly in jawbones and dental implant procedures. An increase in fractal dimension suggests a denser, more complex bone structure, which may lead to more successful implant placement. Conversely, a decrease in fractal dimension indicates a more porous bone, which can increase the risk of fractures and complications, especially in conditions like osteoporosis or periodontal disease. Monitoring fractal dimension helps in assessing bone health, planning surgeries, and ensuring the success of dental treatments, making it an essential tool for clinicians in both diagnosis and surgical planning.

Nestares et al.[34] explored bone quality in children with celiac concerning the Mediterranean diet and physical activity. Their results revealed lower bone mineral index, bone mineral content, lean mass, and bone Z-scores in children with celiac disease. However, children following the Mediterranean diet and engaging in physical activity showed significant improvements in bone quality and lean mass.This current study found no significant difference in mandibular cortical index between celiac and control groups. However, the higher prevalence of the healthiest cortical group (C1) in the control group suggests a potential fragility of the cortical structure in celiac patients.

Limitations: One of the key limitations of this study is the relatively small sample size, which may limit the generalizability of the findings. A larger sample size would allow for a more robust analysis and improve the applicability of the results to broader populations.

CONCLUSION

This study reveals structural differences in mandibular trabecular and cortical bone between individuals with celiac disease and healthy controls. The lower fractal dimension values in celiac patients highlight potential changes in bone quality and microarchitecture, reflecting systemic skeletal involvement. While no significant differences were found in cortical width or index, the control group showed a higher prevalence of the healthiest cortical classification (C1), suggesting cortical fragility in celiac patients. These findings emphasize the value of incorporating oral and skeletal assessments in managing celiac disease, with dental imaging serving as a useful tool for evaluating systemic bone health.

Ethics Committee Approval: Approval for this study was obtained from Van Yüzüncü Yıl University Non-Interventional Clinical Research Ethics Committee (Date:18.09.2023 No: 2023/09-14)

Informed Consent: In this study, panoramic radiographs used during routine radiologic examination of patients admitted to our clinic were used. Therefore, no consent form was obtained.

Peer-review: Externally peer-reviewed

Author Contributions: Concept – S.K,A.K; Design - S.K,A.K; Supervision - A.K; Resources - A.K; Materials – S.K; Data Collection and/or Processing – S.K; Analysis and/or Interpretation - S.K,A.K; Literature Search - S.K,A.K; Writing Manuscript - S.K,A.K; Critical Review -A.K.

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Hasta Onamı: Bu çalışmada kliniğimize başvuran hastaların rutin radyolojik muayenesi esnasında kullanılan panoramik radyografiler kullanılmıştır. Bu nedenle onam formu alınmamıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Konsept – S.K,A.K; Tasarım - S.K,A.K; Denetim – A.K; Kaynaklar – A.K; Malzemeler – S.K; Veri Toplama ve/veya İşleme – S.K; Analiz ve/veya Yorum - S.K,A.K; Literatür Taraması - S.K,A.K; Yazma - S.K,A.K; Eleştirel İnceleme – A.K.

Teşekkürler: İstatistiksel analizlerdeki paha biçilmez yardımları için Naci Murat'a minnettarız.

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