Journal of Dentistry Indonesia

Volume 29 | Number 1 Article 8

4-30-2022

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Tercanlı Alkış, H., Yağmur, B., Parlak, M., & Karayılmaz, H. Mandibular Bone Changes in Children and Adolescents with Type 1 Diabetes Mellitus in Different Metabolic Control States. J Dent Indones. 2022;29(1): 52-60

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Journal of Dentistry Indonesia 2022, Vol. 29, No. 1, 52-60
doi: 10.14693/jdi.v29i1.1331

ORIGINAL ARTICLE

Mandibular Bone Changes in Children and Adolescents with Type 1 Diabetes Mellitus in Different Metabolic Control States

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ABSTRACT

Objective: The aim of this study is to evaluate the cortical and trabecular mandibular bone morphology of children and adolescents with type 1 diabetes mellitus (DM) and control group utilizing fractal dimension analysis (FDA) and different panoramic radiomorphometric indices through digital panoramic radiographic images (DPRIs). **Methods:** The study included 57 patients for the type 1 DM group (25 male and 32 female with a mean age of 11.5±2.4 years) and 57 patients for the control group (28 male and 29 female with a mean age of 10.5±2.1 years). The type 1 DM group was divided into the well-controlled, moderately-controlled, and poorly-controlled subgroups based on HbA1c. Mandibular cortical width (MCW) (according to Lengerton et al.) and panoramic mandibular index (PMI) (according to Benson et al.) were measured, mandibular cortical index (MCI) (according to Klemetti et al) and simple visual estimation (SVE) (according to Lee et al.) were evaluated, and FDA was conducted according to White and Rudolph, resulting in three areas of interest (IAs) being obtained in all of the DPRIs. **Results:** There was no significant difference between type 1 DM group and control according to the mean MCW, mean PMI measurements, MCI and SVE. The mean FD values were not significantly different between type 1 DM group and the control and between type 1 DM subgroups and control. **Conclusion:** This study revealed no cortical and trabecular bone changes in mandibula in children and adolescents with type 1 DM compared to the control group. In addition, metabolic control states of DM did not affect the bone structure.

Key words: cortical bone, fractals, type 1 diabetes mellitus, panoramic radiography, trabecular bone

How to cite this article: Alkış HT, Yağmur B, Parlak M, Karayılmaz H. Mandibular bone changes in children and adolescents with type 1 diabetes mellitus in different metabolic control states. J Dent Indones. 2022;29(1): 52-60

INTRODUCTION

Type 1 DM is caused by an autoimmune reaction in which the body's immune system attacks insulin-producing beta cells in the islets of the pancreas gland. Until recently, bone was not regarded as a target organ for diabetes-related complications. Adults with type 1 DM have up to a six-fold increased risk of bone fractures, which can be seen in children and adolescents with type 1 DM, too.[1] As a result of the decrease in bone formation and destruction mechanism, micro-fracture production is impaired and bone quality may deteriorate in patients with diabetes.[2] In children and adolescents with metabolically poorly controlled type 1 DM, cortical area and trabecular volumetric bone mineral density were found to be decreased,[3,4] while some studies[5,6] found no changes in bone mineral structure.

Panoramic radiographic images can reveal a decrease in bone mineral density (BMD).[7] For this purpose, several different panoramic radiomorphometric indices: mandibular cortical width (MCW), panoramic mandibular index (PMI), mandibular cortical index (MCI), and simple visual estimation (SVE)) have been used in literature.[7-15] Fractal dimension analysis (FDA) is a type of statistical structural analysis used to describe complex shapes and structural features based on fractal mathematics.[16] The FD detected on radiographs has been associated with changes in bone

density and is thought to reflect mineral loss in the bone.[17] While Kursun and Bayrak[18] examined bone mineral content in adult DM patients using FDA, to the best of the author's knowledge, no such study has been conducted in pediatric and adolescent patients with type 1 DM.

The aim of this retrospective study is to evaluate the cortical and trabecular mandibular bone morphology of children and adolescents with type 1 DM and that of a systemically healthy group, utilizing FDA and different panoramic radiomorphometric indices by means of DPRI.

METHODS

This study was approved by the Clinical Research Ethics Committee of the Faculty of Medicine at the Akdeniz University Scientific Research and Publication Ethics Board University (Ethics approval number: 70904504/552).

This retrospective study was conducted in the Department of Pedodontics, Faculty of Dentistry, Akdeniz University and Department of Pediatric Endocrinology, Faculty of Medicine, Akdeniz University. The records of patients who presented to the Department of Pedodontics between 2012 and 2019 were assessed, and 69 type 1 DM patients were identified. DPRIs of the 69 patients were retrospectively obtained from the Department of Oral and Maxillofacial Radiology and the following inclusion and exclusion criteria were applied: Inclusion criteria were: (1) Must be aged between seven and sixteen years, (2) must have had no systemic disease other than type 1 DM and must not have used any medication other than insulin, (3) must have been followed up at the Department of Pediatric Endocrinology, (4) must have had DPRI taken close to the period when the HbA1c test was taken (maximum three months), (5) must have all teeth or teeth germs present (except third molar), and (6) must have DPRI with radiologically periodontally healthy tissues. Exclusion criteria were: (1) having other systemic diseases than type 1 DM, (2) the image having poor quality and horizontal and vertical distortions, (3) suspected temporomandibular joint pathology, (4) having DPRI which has a sclerotic area in the mandibula, (5) having DPRI where the mental foramen could not be clearly visualized, and (6) having DPRI where the region of interests for FDA could not be clearly visualized or that had anatomical superposition to these areas.

When these criteria were taken into consideration, radiographic images of two patients with missing teeth, and ten patients whose mental foramen could not clearly be visualized, were excluded from the study; therefore, 57 patients were included in the study for the type 1 DM group. HbA1c values of the 57 patients were obtained from the Department of Pediatric Endocrinology, Faculty of Medicine and the mean HbA1c from the most recent year of follow-up was categorized into <7.5%, 7.5–9%, and >9% for each participant, indicating well-controlled, moderately-controlled, and poorly-controlled type 1 DM, respectively[5]. For the control group, except for the second, third, and fourth criteria of the aforementioned inclusion criteria were applied, and a number of patients equal to that of the type 1 DM group who did not have any systemic disease were included (n = 57). The anamnesis and HbA1c data of the patients were obtained using the Metasoft Dentasist program (version 3.0.448 (Eskişehir, Turkey)) and MIA-MED (version 1.0.13767), respectively.

All DPRIs were obtained by one x-ray technician using a Planmeca ProMax device (Planmeca Oy, Helsinki, Finland) in accordance with the manufacturer's instructions. DPRIs were evaluated using the same LED monitor and by the same investigator (an expert in dental radiology with seven years of experience) at a distance of approximately 40–50cm from the LED monitor. The evaluation was conducted in a low-light environment, with tonal adjustments made to the images to maximize the view. Only five panoramic images were reviewed each day in order to prevent investigator fatigue. Measurements were automatically calibrated with the Planmeca Romexis 4.0 software, which was specially developed for the Planmeca ProMax device (Planmeca Oy: 00880, Helsinki, Finland), in accordance with the manufacturer's instructions.

Radiomorphometric indices

MCW was assessed according to the technique used by Ledgerton et al.[9]: The mental foramen was identified on the DPRI, and two lines were drawn tangent to the lower border of the mandible and parallel to the upper border of the mandibular cortical layer. A vertical line was drawn connecting the center of the mental foramen and the lower border of the mandible. The distance between the two parallel lines was measured as MCW (Figure 1). MCW was measured separately on the right and left mandibular sides, and the mean values were calculated.

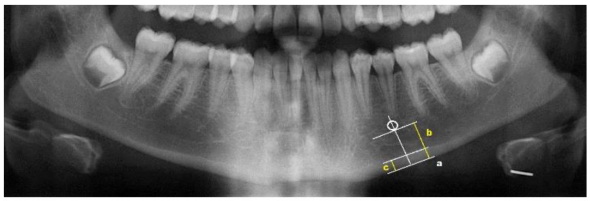


Figure 1. A line parallel to the inferior border of the mandible (a); distance between the inferior border of the mental foramen and "a" line (b); mandibular cortical width (c); and panoramic mandibular index (c/b)

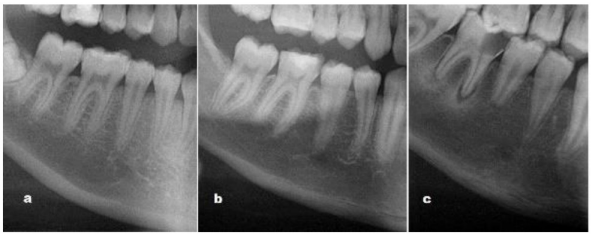


Figure 2. C1: endosteal margins of the cortex are sharp and equal on both sides (a); C2: endosteal margins show defects in the form of semiulnar (lacunar resorption), and / or endosteal cortical residues on one or both sides (b); C3: the cortical layer contains heavy endosteal cortical residues and is clearly porous (c)

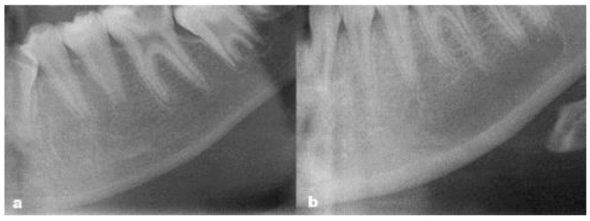


Figure 3. Classification of simple visual estimation: thin (a); not thin (b)

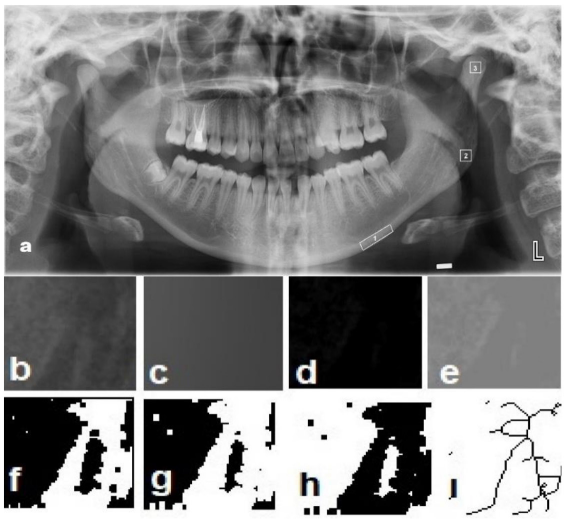


Figure 4. Interest areas; 1: on the cortical bone, 2: on the angulus mandible, 3: on the condyle (a); cropped and duplicated image (b); a gaussian blurred image (c); a subtraction image (d); an added 128 image (e); binarization (f); erosion (g); dilation (h); and skeletonization (i)

PMI was assessed using the technique described by Benson et al.[10]: The ratio of the thickness of the mandibular cortex to the distance from the inferior edge of the mental foramen to the lower border of the mandible was calculated. The PMI was measured separately for the right and left mandibular sides, and the mean values were calculated (Figure 1).

MCI was evaluated according to the technique used by Klemetti et al.[7]: This approach is based on the morphologic changes in the cortical bone at the mandibular base. C1: The endosteal margins of the cortex are sharp and equal on both sides, C2: The endosteal margins show defects in the form of semilunar (lacunar resorption) and/or endosteal cortical residues on one or both sides, and C3: The cortical layer contains heavy endosteal cortical residues and is clearly porous (Figure 2).

SVE was evaluated according to the technique used by Lee et al.,[14] and the cortex was classified into two categories based on a simple visual estimation of the mandibular inferior cortex widths: thin and not thin (Figure 3).

Fractal dimension analysis

The FDA for each image was conducted according to White and Rudolph's[19] technique using the box-counting method. The images were analyzed via ImageJ version 1.3 software (National Institutes of Health, Bethesda, MD), which can be downloaded from the following link: http://rsb.info.nih.gov/ij/download.html. Three areas of interest (IA) from the left side of the mandible were determined for the FDA IA 1: A rectangle in the basal cortical bone, distal to the mental foramen, extending to the distal root of the first permanent molar [11]; IA 2: A 64x64 pixel square in the geometric center of the angle of mandible; and IA 3: A-64x64 pixel square in the geometric center of the condyle. The steps of FDA are given in Figure 4.

After 4 weeks, MCW, PMI measurements, MCI, SVE and FDA were repeated for 50 randomly selected patients and inter-observer variability was assessed.

Statistical analysis

The obtained data were statistically analyzed using an SPSS software package (version 23.0, SPSS Chicago, USA). After the homogeneity of variance and normal distribution had been verified using Levene's test, quantitative variables were compared between the groups using the student's t-test, Kruskal–Wallis test, or Mann-Whitney U test. Qualitative variables were analyzed using the Kruskal–Wallis, Mann-Whitney U, chi-square, and exact Fisher tests. Intra-observer reliability was assessed via the interclass correlation coefficient (ICC)[20] and the kappa coefficients.[21] Statistical significance was assumed at $p < 0.05$.

RESULTS

While 16 well-controlled, 17 moderately-controlled, and 24 poorly controlled type 1 DM patients were included in the study, the control group consisted of 57 participants in total. The type 1 DM group comprised

Table 1. The minimum, maximum, mean, standard deviation and p values of MCW and PMI measurements in all groups

Parameter	Group	min (mm)	max (mm)	mean (mm)	SD	p
	Type 1 DM	2.25	8.5	4.9	1.07	.138
	control	2.60	8.10	4.6	1.11	
	Well-controlled	3.35	7.35	4.94	1.27	.301
	control	2.60	8.10	4.6	1.11	
MCW	Moderately -controlled	3.85	6.35	4.9	0.57	.139
	control	2.60	8.10	4.6	1.11	
	Poorly-controlled	2.65	8.50	4.88	1.22	.311
	control	2.60	8.10	4.6	1.11	
	Type 1 DM	0.2	0.56	0.33	0.08	.378
	control	0.21	0.53	0.32	0.07	
	Well-controlled	0.23	0.49	0.33	0.07	.504
	control	0.21	0.53	0.32	0.07	
PMI	Moderately -controlled	0.26	0.52	0.34	0.08	.461
	control	0.21	0.53	0.32	0.07	
	Poorly-controlled	0.2	0.56	0.33	0.09	.570
	control	0.21	0.53	0.32	0.07	

MCW, mandibular cortical width; PMI, panoramic mandibular index; DM: diabetes mellitus; min: minimum; max: maximum; mm: milimeter; SD: standard deviation

25 male and 32 female patients with a mean age of 11.5 ± 2.4 years. The control group comprised 28 male and 29 female patients with a mean age of 10.5 ± 2.1 years.

The ICC values indicated good reliability for each measurement, including IA 1 (ICC = 0.828), IA 2 (ICC = 0.833), IA 3 (ICC = 0.82), MCW (ICC = 0.898), and PMI (ICC = 0.929), and the kappa coefficients were 0.908 and 0.919 for MCI and SVE, respectively.

There was no significant difference between the mean MCW and PMI measurements of the type 1 DM group and control groups. Table 1 displays the minimum, maximum, mean, standard deviation, and p values of the MCW and PMI measurements for all groups (the well-controlled, moderately-controlled, poorly controlled type 1 DM, and control groups).

According to MCI classification, while forty-one C1, 12 C2, and four C3 patients were discovered in the type 1 DM group, forty-five C1, nine C2, and three C3 patients were detected in the control group. According to SVE classification, there were 25 ‘’thin” and 32 “not thin” patients in the type 1 DM group, and 21 ‘’thin” and 36 “not thin” patients in the control group. There were no significant differences found between the type 1 DM and control groups according to MCI and SVE (p = .39 and p = .447, respectively).

In the type 1 DM group, while the mean MCW values correlated with the SVE ($p < .001$), the mean PMI values did not (p = .14). In comparison, the mean MCW and PMI values did not correlate with the MCI (p = .05 and p = .842, respectively). The mean MCW values were 4.27 ± 0.7 mm and 5.39 ± 1.03 mm in the “thin” and “not thin” groups, respectively, and the mean PMI values were 0.31 ± 0.09 mm and 0.35 ± 0.06 mm in the “thin” and “not thin” groups, respectively.

In the control group, the mean MCW and PMI values correlated with the SVE ($p < .001$ and p = .013, respectively), while the mean MCW and PMI values did not correlate with the MCI (p = .35 and p = .882, respectively). The mean MCW values were 3.81 ± 0.89 mm and 5.06 ± 0.97 mm in the “thin” and “not thin” groups, respectively, and the mean PMI values were 0.29 ± 0.06 mm and 0.34 ± 0.07 mm in the “thin” and “not thin” groups, respectively.

The mean FD values of the type 1 DM and control groups were found to be almost identical without a statistically significant difference. When IAs were taken into consideration, the mean FD values did not differ significantly between regions in the type 1 DM and control groups. In addition, the mean FD values, IA 1 FD values, IA 2 FD values, and IA 3 FD values were not significantly different across regions in the well-controlled, moderately-controlled, poorly controlled, and control groups. Table 2 displays the minimum, maximum, mean, standard deviation, and p values of FD in all groups.

Table 2. The minimum, maximum, mean, standard deviation and p values of FD in all groups

Parameter	Group	min	max	mean	SD	p
	Type 1 DM	1.04	1.44	1.25	0.07	.29
	Control	1.11	1.45	1.26	0.07	
	Well-controlled	1.04	1.35	1.24	0.09	.26
	Control	1.11	1.45	1.26	0.07	
FD	Moderately-controlled	1.14	1.44	1.27	0.08	.701
	Control	1.11	1.45	1.26	0.07	
	Poorly-controlled	1.14	1.34	1.24	0.05	.143
	Control	1.11	1.45	1.26	0.07	
	Type 1 DM	0.99	1.25	1.06	0.06	.224
	Control	0.99	1.24	1.07	0.06	
	Well-controlled	1	1.16	1.05	0.05	.212
	Control	0.99	1.24	1.07	0.06	
IA 1 FD	Moderately-controlled	0.99	1.25	1.08	0.08	.715
	Control	0.99	1.24	1.07	0.06	
	Poorly-controlled	0.99	1.16	1.05	0.04	.089
	Control	0.99	1.24	1.07	0.06	
	Type 1 DM	0.73	1.58	1.33	0.17	.22
	Control	1.05	1.89	1.36	0.13	
	Well-controlled	0.73	1.58	1.29	0.2	.086
	Control	1.05	1.89	1.36	0.13	
IA 2 FD	Moderately-controlled	0.99	1.52	1.34	0.17	.564
	Control	1.05	1.89	1.36	0.13	
	Poorly-controlled	1.07	1.58	1.35	0.1	.58
	Control	1.05	1.89	1.36	0.13	
	Type 1 DM	1	1.82	1.34	0.14	.795
	Control	1.07	1.89	1.34	0.13	
	Well-controlled	1	1.82	1.35	0.2	.965
	Control	1.07	1.89	1.34	0.13	
IA 3 FD	Moderately-controlled	1.21	1.61	1.35	0.1	.747
	Control	1.07	1.89	1.34	0.13	
	Poorly-controlled	1.11	1.46	1.32	0.1	.408
	Control	1.07	1.89	1.34	0.13	

FD: fractal dimension; IA 1: basal cortical bone region; IA 2: angulus mandible region; IA 3: condyle region; DM: diabetes mellitırus; min: minimum; max: maximum; SD: standard deviation

Regarding the HbA1c values in the type 1 DM group, the mean MCW values were found to be 4.94 ± 1.27 mm, 4.9 ± 0.57 mm, and 4.88 ± 1.22 mm; the mean PMI values were 0.33 ± 0.07 mm, 0.34 ± 0.08 mm, and 0.33 ± 0.09 mm; the mean FD values were 1.24 ± 0.09, 1.27 ± 0.08, and 1.24 ± 0.05; the mean IA 1 FD values were 1.05 ± 0.05, 1.08 ± 0.08, and 1.05 ± 0.04; the mean IA 2 FD values were 1.29 ± 0.2, 1.34 ± 0.17, and 1.35 ± 0.1; and the mean IA 3 FD values were 1.35 ± 0.2, 1.35 ± 0.1, and 1.32 ± 0.1 in the well-controlled, moderately-controlled, and poorly controlled groups of type 1 DM, respectively. Table 3 shows the p values for all parameters regarding the HbA1c values in type 1 DM.

When IAs were taken into consideration, no significant difference was seen between IAs and both MCI and SVE values in the type 1 DM and control groups.

Table 3. p values The in all parameters considering the HbA1C in type 1 Diabetes Mellitus group

Parameter	Type 1 DM	Well controlled	Medium controlled	Poorly controlled
MCW	Well-controlled	----	.92	.893
	Moderately-controlled	.92	----	.947
	Poorly-controlled	.893	.947	----
PMI	Well-controlled	----	.952	.928
	Moderately-controlled	.952	----	.884
	Poorly-controlled	.928	.884	----
FD	Well-controlled	----	.305	.983
	Moderately-controlled	.305	----	.149
	Poorly-controlled	.983	.149	----
IA 1 FD	Well-controlled	----	.259	.863
	Moderately-controlled	.259	----	.180
	Poorly-controlled	.863	.180	----
IA 2 FD	Well-controlled	----	.43	.33
	Moderately-controlled	.43	----	.93
	Poorly-controlled	.33	.93	----
IA 3 FD	Well-controlled	----	.87	.62
	Moderately-controlled	.87	----	.25
	Poorly-controlled	.62	.25	----

DM: diabetes mellitus; MCW: mandibular cortical width; PMI: panoramic mandibular index; FD: fractal dimension; IA 1: basal cortical bone region; IA 2: angulus mandible region; IA 3: condyle region

DISCUSSION

Diabetes mellitus can have an effect on bone structure. It is critical to monitor the disease by keeping track of the blood glucose levels of diagnosed individuals at regular intervals. Limeira et al [22] found lower values for some radiomorphometric parameters in poorly controlled type 1 DM than in non-diabetic patients. Nemtoi et al.[23] discovered a significant correlation between bone quality and glycosylated hemoglobin values, as well as an inverse correlation between cortical and trabecular bone density values and HbA1c. Deveraja et al.[4] examined the impact of type 1 DM on skeletal microstructure and found detrimental changes in bone microarchitecture, which may be a result of poorly controlled diabetes. In the current study, no statistically significant differences in mean MCW and PMI values were observed between the subgroups of type 1 DM and the control group in the mean MCW and PMI values. This discrepancy can be explained by the fact that it is not known how long and in which subgroups of type 1 DM the patients that were included in the presented study. It may take some time before poorly controlled type 1 DM causes changes to bone structure. Perhaps the patients included in the current study had been in the well-controlled group for a long period of time and were assigned to the poorly controlled group by chance at the time the DPRIs were taken.

Numerous methods have been developed to obtain quantitative data from radiograph evaluations. One of these is digital subtract radiography, which has been reported to reveal as small as 5% mineral loss with high accuracy.[24] FDA is a viable alternative to this method as it is unaffected by projection geometry,[25] and has been used more frequently in recent years. FD detected on radiographs reflects the changes in trabecular bone density and mineral loss in the bone.[16,17,26] The effects of many systemic diseases on the jaw have been investigated using FD in the literature.[11,13,17,18,26] However, only two studies so far have applied FDA to DM patients.[18,27]

Childhood and adolescence are critical periods for bone mass gain, since about 90 % of BMD is acquired before the age of 18, and a low BMD may increase the risk of fractures in adulthood.[28] FDA has been applied to radiographic images of adult patients in virtually all studies.[13,17,18] While Apolinário et al.[11] applied FDA to radiographic images of children with osteogenesis imperfecta, Demirbaş et al.[26] applied FDA to radiographic images of sickle cell anemia patients aged 11–40 years. To the best of the author's knowledge, the present study is the first to apply FDA to DPRIs of children and adolescents with type 1 DM and a control group.

Regarding the study conducted by Kursun and Bayrak[18], the mean MCW and PMI values were 2.06 ± 0.57 mm and 0.28 ± 0.07 mm, respectively, in type 1 DM patients and were 2.62 ± 0.76 mm and 0.33 ± 0.06 mm, respectively, in the control group. In the present study, the mean MCW values were 4.9 ± 1.07 mm and 4.6 ± 1.11 mm while the mean PMI values were 0.33 ± 0.08 mm and 0.32 ± 0.07 mm in the type 1 DM and control group, respectively. This higher value is thought to be attributable to the fact that age is a significant factor in evaluating MCW[18,29,30] and that PMI is a variable dependent on MCW. As a result, Kursun and Bayrak[18] found that the mean MCW and PMI values were significantly lower in type 1 DM patients compared to the control group. However, the current study discovered no difference between these values between the two groups.

Similarly to the current investigation, Kursun and Bayrak[18] observed no relationship between diabetes and control groups regarding mean FD measurements. While it is known that BMD diminishes with age,[31,32] the similarity of the results obtained in both studies can be interpreted as the bone trabecular structure of type 1 DM patients being unaffected by age.

Kursun and Bayrak[18] did not discover the conditions for group C3 according to MCI classifications in either the DM or control groups, and, similarly to the current study, they did not find any correlation between the type 1 DM and control groups according to MCI.

Kursun and Bayrak[18] included individuals with well-controlled type 1 DM in their study. The authors in the present study divided the type 1 DM group into three subgroups based on HbA1c. In this study, no significant differences were found in mean FD values between the well-controlled and poorly controlled groups, the well-controlled and moderately-controlled groups, and the moderately-controlled and poorly-controlled groups ($p = .983$, $p = .305$ and $p = .149$, respectively). In addition, there were no significant relationships between the subgroups of the type 1 DM and control groups' mean FD values in the current study ($p = .26$, $p = .701$ and $p = .143$, respectively). From these results, it can be concluded that bone trabecular structure density is not affected by whether diabetes is controlled or not. However, as previously stated, it is unknown how long these patients had been in the well-controlled, moderately-controlled, or poorly controlled groups in current study.

Apolina rio et al.[11] discovered a correlation between MCW measurements in the SVE and MCI ($p < .05$ and $p = .001$, respectively). In the current study, while there was a correlation between the MCW and SVE in both the type 1 DM and control groups ($p < .001$ in both groups), no correlation was found between the MCI and MCW measurements in both groups ($p = .05$ in the type 1 DM group and $p = .35$ in the control group). While MCW values ranged between 2.5–2.8 mm in the "thin" group, the MCW values ranged between 3.5–3.7 mm in the "not thin" group in the study by Apolina rio et al.[11] In the current study, the mean MCW values were 4.27 ± 0.7 mm and 5.39 ± 1.03 mm in the "thin" and "not thin" groups, respectively. The fact that the mean MCW in the present study is higher than that in the mentioned study can be explained by the fact that osteogenesis imperfecta has a greater effect on bone structure than type 1 DM does.

The absence of dual-energy x-ray absorptiometry performed on the analyzed individuals is considered a limitation for the current study. However, the current study is the first to evaluate radiomorphometric indices and FD in children and adolescents with type 1 DM based on HbA1c levels. Therefore, further studies that use bone metabolism biomarkers and dual-energy x-ray absorptiometry in conjunction with DPRI are needed.

CONCLUSION

This study concluded that children and adolescents with type 1 DM had no cortical and trabecular bone changes in the mandibula when compared to the healthy control group. Type 1 DM and its metabolic control states do not affect bone structure in children and adolescents.

CONFLICT OF INTERESTS

The authors declares that they have no conflict of interest**.**

FUNDING

There are no financial or other relations that could lead to a conflict of interest

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(Received December 24, 2021; Accepted April 12, 2022)