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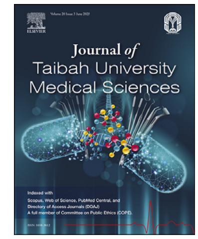

Original Article

Cone beam computed tomography evaluation of maxillary central incisor abnormalities in cleft lip and palate patients

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الملخص

أهداف البحث: هدفت هذه الدراسة إلى فحص الاضطرابات البنيوية في الأسنان، بما في ذلك سمك المينا، وكثافة المينا، وسمك العاج، والعرض الأنسي الوحشي للقواطع المركزية العلوية لدى مرضى الشفة الأرنبية وشق الحنك.

طريقة البحث: تم إجراء مراجعة استعادية للسجلات في كلية الطب ومعهد طب الأسنان في لاهور التابع لمستشفى القوات المسلحة المشترك. شملت الدراسة ٨٤ مريضا غير مصابين بمتلازمات ويعانون من الشفة الأرنبية وشق في الحنك (٤١ حالة شق في الشفة والحنك من جانب واحد، و٤٣ حالة شق في الشفة والحنك من الجانبين)، بالإضافة إلى ٣٩ شخصا كمجموعة ضابطة. تم استخدام صور التصوير المقطعي بالحزمة المخروطية لقياس سمك المينا من الجهة القريبة، وسمك المينا من الجهة البعيدة، وسمك العاج، والعرض الأنسي الوحشي، وذلك بشكل عمودي على المحور الطولي للسن. تم استخدام تحليل التباين الثنائي مع تأثيرات التفاعل لتحديد ما إذا كان الجنس يؤثر على قياسات الأسنان بالإضافة إلى وجود الشق.

النتائج: أظهرت القواطع المركزية أن سمك المينا، وكثافة المينا، والعرض الأنسي الوحشي كانت أقل بشكل ملحوظ لدى مرضى الشفة الأرنبية وشق الحنك مقارنة بالأشخاص غير المصابين. أما العرض الأنسي الوحشي فكان الفرق ذو دلالة إحصائية بين الأشخاص غير المصابين والحالات ذات الشق في الشفة والحنك من الجانبين.

الاستنتاجات: تكون القواطع المركزية العلوية لدى مرضى الشفة الأرنبية وشق الحنك أصغر حجما، مع انخفاض ملحوظ في سمك وكثافة المينا، بينما يظل العاج غير متأثر إلى حد كبير. وتوفر هذه الدراسة دليلًا على أن حالات الشفة الأرنبية وشق الحنك تؤثر على المينا بدرجة أكبر من تأثيرها على العاج. لذلك يوصى بأن يتبع الأطباء نهجا تحفظيا ويستخدموا مواد رابطة مناسبة من الراتنج للحد من تلف المينا أثناء الترميم والعلاج التقويمي.

الكلمات المفتاحية: الشفة الأرنبية وشق الحنك؛ التصوير المقطعي بالحزمة المخروطية؛ الشذوذات السنية؛ القواطع المركزية العلوية؛ التقييم الإشعاعي

Abstract

Objectives: This study aimed to investigate tooth structural abnormalities, including the enamel thickness, enamel density, dentine thickness, and mesiodistal width in maxillary central incisors in patients with cleft lip and palate (CLP).

Methods: A retrospective record review was conducted at CMH-Lahore Medical College and Institute of Dentistry. Eighty-four nonsyndromic CLP patients (41 unilateral CLP (UCLP) and 43 bilateral CLP (BCLP)) and 39 controls were included. Cone beam computed tomography images were used to measure mesial enamel thickness, distal enamel thickness, dentine thickness, and mesiodistal width perpendicular to the long axis of the tooth. Two-way analysis of variance with interaction effects was conducted to determine whether gender influenced the teeth measurements in addition to the cleft.

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Results: In central incisors, enamel thickness, enamel density, and mesiodistal width were significantly smaller in the CLP group compared with the non-cleft group ($p < 0.05$), but no significant difference was found in dentine thickness ($p > 0.05$). Total enamel thickness was 1.94 ± 0.32 mm in the non-cleft group, 1.52 ± 0.25 mm in UCLP, and 1.32 ± 0.34 mm in BCLP. Mesiodistal width measured 8.44 ± 0.54 mm in the non-cleft group, 7.65 ± 0.63 mm in UCLP, and 7.48 ± 0.87 mm in BCLP, with a significant difference between the non-cleft group and BCLP ($p < 0.05$). A similar trend was observed for enamel density. Gender and cleft type exhibited substantial interaction effects for all measures ($p < 0.05$), except for mesiodistal width in the left central incisor, which was not significant ($p > 0.05$).

Conclusions: Maxillary central incisors were smaller in CLP patients, with significantly reduced enamel thickness and density, but dentine was largely unaffected. This study provides evidence that cleft conditions affect enamel more significantly than dentine. Hence, it is suggested that clinicians should adopt a conservative approach and use appropriate resin bonding materials to minimise enamel damage during restoration and orthodontic treatment.

Keywords: Cleft lip and palate; Cone beam computed tomography; Dental anomalies; Radiographic assessment

Introduction

Cleft lip and palate (CLP) is one of the most common birth defects in neonates and is associated with several other orofacial anomalies, including tooth abnormalities.[1] CLP is a result of critical events that affect lip and/or palate development between the 4th and 10th weeks of embryogenesis, which occurs almost concurrently with the odontogenic process. It is hypothesised that factors impeding facial development may also affect odontogenesis.[2–4] Studies have demonstrated a higher prevalence of anomalies related to tooth size, number, structure, shape, and eruption pattern in various CLP phenotypes compared with the general population.[5,6]

Enamel, the epithelial-derived hard tissue covering the tooth crown, is composed of hydroxyapatite crystals. These crystals occupy an extracellular space, the content of which is provided and regulated by enamel-forming cells called ameloblasts. The enamel formation process is genetically controlled but still poorly understood. During enamel formation, sensitive ameloblast cells can be influenced by environmental changes, and their function can also be altered by external factors to affect the development and calcification of the organic matrix.[7,8] Developmental disturbances during ameloblast activity may result in temporary or permanent cell inactivity, leading to different types of enamel deformities: hypoplasia, hypomaturation, and hypocalcification.[7,9,10] The correlation between CLP development and the formation of tooth-related structures, such as enamel, is critical. It is possible that any disorder during the developmental stage could lead to both cleft formation and enamel defects. Genetic factors play vital roles in determining tooth dimensions.[10–12] In addition, certain etiological influences during prenatal and postnatal periods have been linked to structural and dimensional tooth defects.[13–15]

Previous studies measured the thickness of enamel and dentine using standardised intra-oral radiographs, but these images can be distorted and blurred,[16,17] potentially leading to measurement errors. Cone beam computed tomography (CBCT), a modern radiographic method, provides detailed views from any angle, and facilitates more precise linear measurements. CBCT has been used to measure enamel thickness[18] and the mineral density of craniofacial structures.[19–21] CBCT has been applied to cleft patients to assess alveolar bone grafts and teeth development adjacent to the cleft area.[22,23] Previous CBCT analyses of children with clefts detected variations in tooth size, shape, and number,[24] as well as differences in crown height and root length in CLP patients[22] compared with normal children. However, these studies did not obtain information regarding enamel thickness, enamel density, or dentine, which were the focus of the present study. A similar study conducted in 2016 by Chu and colleagues found thin incisor teeth with reduced enamel thickness and enamel density in a mouse model with clefts.[25] However, limited data are available about the internal tooth structure in human CLP patients. Understanding these structural differences is crucial for restorative treatments and optimising dental care plans. Caries can progress through enamel and dentine, potentially damaging the pulp. Recognising these differences can help mitigate caries progression and preserve tooth vitality through appropriate restorative techniques. In addition to enamel thickness, we also assessed the enamel density in children with clefts because lower enamel density may increase the risk of tooth decay. Therefore, in this study, we aimed to obtain novel insights into abnormalities in enamel thickness, enamel density, dentine thickness, and tooth size in the upper central incisors of CLP patients, which may improve dental treatment strategies and oral health care for these patients.

Materials and Methods

Study design

A retrospective record review was conducted in the Orthodontics and Oral Radiology Department at CMH-Lahore Medical College and Institute of Dentistry. The study included 84 nonsyndromic CLP children (41 with unilateral cleft lip and palate (UCLP) and 43 with bilateral cleft lip and palate (BCLP)) compared with 39 control individuals (randomly selected from developing dentition and buccally impacted canine cases). The inclusion criteria for CLP patients were a diagnosis of UCLP or BCLP, age between 10 and 16 years, clear CBCT images, and no history of orthodontic treatment. Patients with caries, restored teeth, or roots with open apices were excluded.

Sample size estimation

This study was part of a larger study where the maximum estimated sample size was 23 per group based on enamel density measurements. The sample size was calculated using a 95 % confidence level, 80 % power, and expected minimum mean difference of 0.1 g/cm^3, with a control group mean density of 2.57 g/cm^3 and standard deviation of 0.12 g/cm^3.[26] The estimated sample sizes for other measures were lower, and the potential for missing teeth or caries had to be considered, so the sample size was increased to 39 for the control group, 41 for UCLP, and 43 for BCLP.

CBCT imaging parameter

The Planmeca ProMax® 3D Classic system from Finland was used to obtain CBCT scans of teeth, specifically the central incisors in the maxilla. The CBCT scans were performed by the same radiologist with the following settings and resolution: voxel size (200 μm), 15-bit grayscale image, tube voltage (90 kV), tube current (7 mA), and scan time (12 s), and Hounsfield units (HU) were calibrated with a quality assurance phantom. After scanning, DICOM files (in dcm format) were transferred to the Planmeca Romexis Viewer (version 4.4.0). In the sagittal view, the tooth crown portion and root portion were adjusted to an upright position, ensuring that grid lines passed vertically from anterior to posterior through the mid-portion of the tooth (Figure 1). To differentiate between enamel and dentine, the contrast was set to zero. The average slice thickness was set at 0.2 mm and enamel and dentine were identified based on gray shade, and verified based on the HU of enamel and dentine, where the HU was higher for enamel than dentine.

Previous studies have demonstrated the effectiveness of CBCT imaging in assessing bone, enamel, and dentine density using various phantoms.[27,28] In particular, each voxel in a CBCT image provides a more accurate representation of the gray value than HU. Therefore, different phantom materials (such as acryl, aluminium, and oxygen) were scanned inside the ProMax system for calibration purposes. The coefficient of variation for the CBCT instrument was 8 %.[29] By using a calibrated curve specific to the same CBCT scanner, the gray values obtained from scanned phantoms were converted into corresponding density values.

Tooth crown measurements

Tooth crown width was measured using a method similar to that described by Alvesalo and colleagues.[30,31] The mesiodistal width, mesial enamel thickness, and distal enamel thickness were measured perpendicular to the long axis of the tooth crown. The following reference points were used to measure permanent maxillary central incisors: maximum mesiodistal width of the tooth crown (M−D), mesial enamel layer (M−M1), distal enamel layer (D−D1), and the distance between the mesial and distal dentino−enamel junctions, representing dentine thickness (M1−D1). In addition, the software provided the maximum enamel density at the point where the enamel thickness was measured (Figures 2 and 3).

Statistical analysis

The data were analysed using IBM SPSS version 20.0 (IBM Corp., USA). Descriptive statistics (mean and standard deviation) were calculated for central incisors based on groups and gender. To evaluate differences among various measurements in the central incisors of CLP and control groups, two-way analysis of variance (ANOVA) with interaction effects was conducted to determine whether gender affected enamel thickness, enamel density, dentine thickness, and mesiodistal width in conjunction with cleft type.

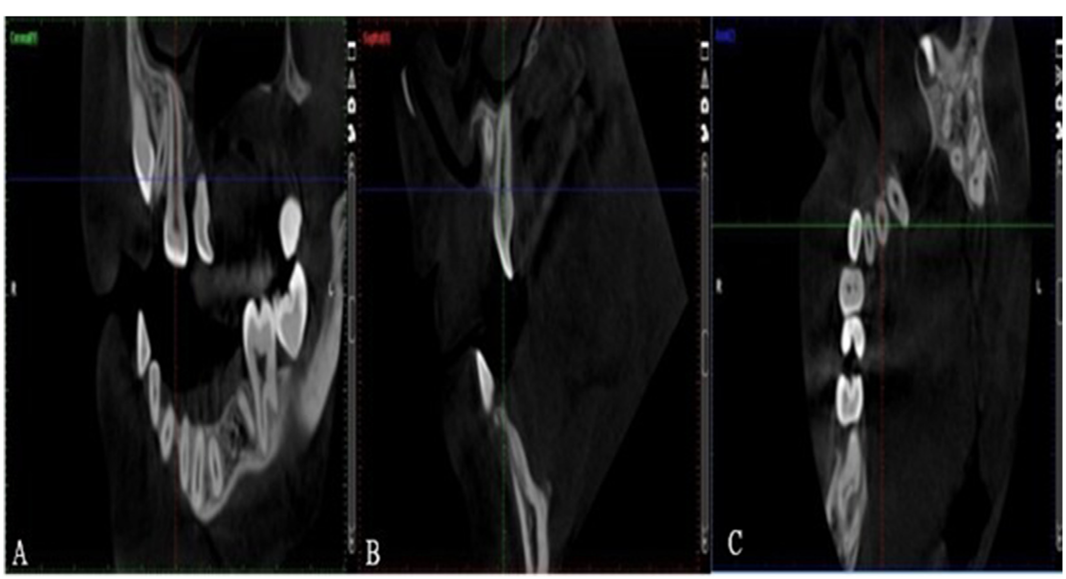

Figure 1: CBCT views of the permanent maxillary central incisor: (A) coronal, (B) sagittal, and (C) axial views, showing horizontal and vertical grid lines passing through the middle of the tooth.

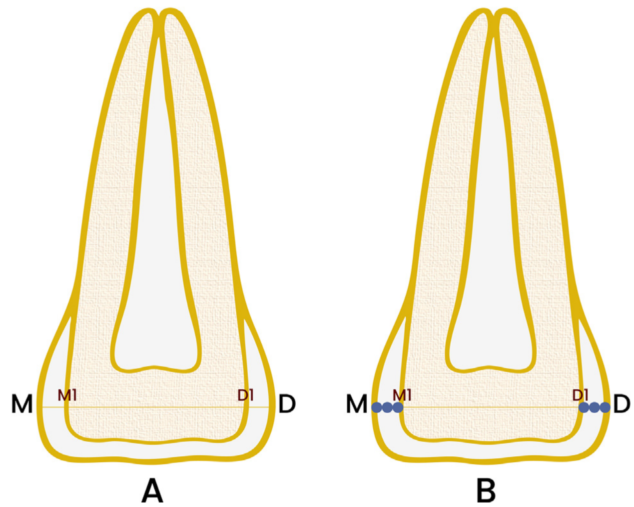

Figure 2: Schematic illustration of the method used for measuring a tooth in a coronal CBCT image: (A) The line M–D represents the maximum mesiodistal dimension of the tooth crown; M–M1indicates the mesial enamel layer; D–D1 indicates the distal enamel layer; and M1–D1 shows the distance between the mesial and distal dentino–enamel junctions or thickness of dentine. (B) The blue spot represents the maximum enamel density between the dentino–enamel junction and the outer enamel surface at any point on the measured enamel thickness; M–M1 denotes the mesial enamel density; and D–D1 denotes the distal enamel density.

Multiple comparisons were performed based on Tukey's post hoc honestly significant difference (HSD) test, focusing on significant cleft types.

If the interaction between cleft type and gender was significant according to the main ANOVA, six groups were

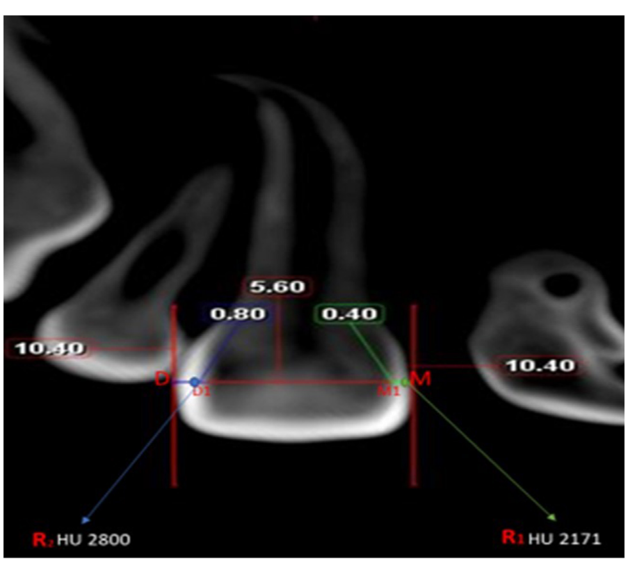

Figure 3: Coronal view of the maxillary central incisor in the UCLP group. The figure shows the maximum mesiodistal, mesial enamel layer, distal enamel layer, and dentine thickness. R1 enamel density (mesial) is HU 2171 and R2 enamel density (distal) is HU 2800.

formed based on the interaction: (1) male control, (2) male UCLP, (3) male BCLP, (4) female control, (5) female UCLP, and (6) female BCLP. One-way ANOVA with Tukey's HSD test was conducted to assess differences among these groups. In the post-hoc analysis, each group was assigned a unique letter label (a–f). When comparing subsequent groups, if the difference in means between the current and previous group was not statistically significant, the letter assigned to the previous group was prefixed to the new letter for the current group. However, if there was a statistically significant difference, the prefix was not used. A p-value ≤ 0.05 was considered to indicate a statistically significant difference.

To evaluate intra-examiner and inter-examiner reliability, 20 % of the CBCT scans were randomly selected and re-measured after a minimum interval of one month. Intra-examiner and inter-examiner reliability values for enamel thickness, enamel density, dentine thickness, and mesiodistal width were determined using intra-class correlation coefficients (ICCs).

Results

This study was part of a comprehensive investigation examining various aspects and metrics for different teeth among CLP individuals compared with a healthy control group of children aged 10–16 years. In particular, this part of the study focused on comparing measures indicative of abnormalities in central incisors between the CLP cases and control group, as well as considering gender as a confounding variable.

Both the left and right central incisors were not uniformly present in all cases. For example, among individuals with UCLP, the left central incisor was present in 12 (70.6 %) males and 14 (58.3 %) females, and the right central incisor was present in 12 (70.6 %) males and 16 (66.7 %) females. The same measures for the average ages of males, females, and the overall population with existing central incisors are provided for the UCLP, BCLP, and control groups in Table 1.

Initial comparisons of teeth measures for the left central incisor, including enamel thickness, dentine thickness, mesiodistal width, and enamel density, were conducted using two-way ANOVA. The results showed that all measures, i.e., mesial enamel thickness, distal enamel thickness, total enamel thickness, mesiodistal width, mesial enamel density, distal enamel density, and total enamel density, differed significantly between the three test groups with p-values <0.01, except for dentine thickness, which was not significantly different with a p-value of 0.060. Total dentine thickness and mesiodistal width were significantly higher among males (6.5 ± 0.65 mm vs 6.17 ± 0.61 mm and 8.20 ± 0.75 mm vs 7.81 ± 0.75 mm, respectively), and mesial enamel density and total enamel density were significantly higher among females (2766 ± 344 HU vs 2515 ± 510 HU and 2727 ± 250 HU vs 2570 ± 380 HU, respectively). Analysis of interaction effects showed that gender and cleft type had significant interactions for all measures with p-values <0.05, except for mesiodistal width, which was not significant (p-value = 0.703). A post-hoc test for the groups showed that mesial enamel thickness differed significantly among all three categories. Distal enamel thickness, total enamel thickness, and mesiodistal width did not

Table 1: Age and gender distributions for cases by cleft type and presence of central incisors.

Present Central incisors	Cleft type UCLP Male			BCLP			Control		
	UCLP			BCLP			Control		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
	(n = 17)	(n = 24)	(n = 41)	(n = 25)	(n = 18)	(n = 43)	(n = 19)	(n = 20)	(n = 39)
Left central incisor	12 (70.6)	14 (58.3)	26 (63.4)	6 (24.0)	10 (55.6)	16 (37.2)	17 (89.5)	20 (100.0)	37 (94.9)
Age (mean ± SD)	13.58 ± 1.51	13.14 ± 1.75	13.35 ± 1.62	14.33 ± 0.52	11.7 ± 1.49	12.69 ± 1.78	13.71 ± 1.72	14.3 ± 0.86	14.03 ± 1.34
Right central incisor	12 (70.6)	16 (66.7)	28 (68.3)	5 (20.0)	10 (55.6)	15 (34.9)	18 (94.7)	19 (95.0)	37 (94.9)
Age (mean ± SD)	13.75 ± 1.48	13.5 ± 1.9	13.61 ± 1.71	14.00 ± 0.00	11.7 ± 1.49	12.47 ± 1.64	13.72 ± 1.67	14.32 ± 0.89	14.03 ± 1.34

differ significantly between UCLP and BCLP, and both groups had significantly lower values compared with the control group. The mean values of the three enamel density measures were significantly lower in BCLP compared with both the UCLP and control groups, and the difference between the latter two groups was not significant (Table 2).

Post-hoc analysis of the six measures detected a significant interaction between gender and cleft type for the left central incisor using Tukey's test. The male BCLP group exhibited a significantly lower mean mesial enamel thickness of 0.40 ± 0.13 compared with all other groups. This trend was also observed for the total enamel thickness, although the male control group had a significantly higher mean of 2.06 ± 0.31 compared with all four CLP groups, but there was no significant difference compared with the female control group. In addition, the total dentine thickness was significantly lower, with a mean of 5.81 ± 0.37, for the female BCLP group compared with all other groups. Furthermore, the lowest mean values of all three enamel density measures were found in the male BCLP group and they differed significantly from all groups in terms of the mesial enamel density and total enamel density, but did not differ significantly from the male UCLP group in terms of the distal enamel density (Table 3).

Similar comparisons were conducted for the right central incisor, and the group differences were significant for the same measures as observed for the left central incisor (all except the total dentine thickness). Gender-wise differences were significant only for the mesial enamel density and total enamel density, with higher means for females (2654 ± 318 vs 2508 ± 281 and 2637 ± 366 vs 2504 ± 344, respectively). In particular, the interaction effect of gender and cleft type was significant for mesial enamel thickness, total enamel thickness, and distal enamel density, with *p*-values of 0.027, 0.040, and 0.006, respectively. For the total enamel density, the *p*-value of 0.052 was considered close to significant. Post-hoc Tukey's test results indicated no significant differences in most measures in the two CLP groups, except for the distal and total enamel density. However, both CLP groups had significantly lower mean values for all measures compared with the control group, except for mesial enamel density and total enamel density, which did not differ significantly between the UCLP and control groups (Table 4).

For the right central incisor, post-hoc analysis was performed based on four measures to examine the differences among groups based on the significant interaction effect. The male BCLP group had the lowest mean mesial enamel thickness and total enamel thickness, which were significantly lower than those in the two control groups. The female BCLP group had the lowest mean distal enamel density, and the male BCLP group had the lowest total enamel density (Table 5).

The intra-rater and inter-rater reliability results for the left central incisor were determined as 95 % confidence intervals (CIs): total enamel thickness, 0.92 (CI = 0.69−0.98); dentine thickness, 0.92 (CI = 0.80−0.97); total enamel density, 0.97 (CI = 0.90−0.99); and mesiodistal width, 0.95 (CI = 0.88−0.98). The inter-rater reliability results for the left central incisor were: total enamel thickness, 0.93 (CI = 0.81−0.97); dentine thickness, 0.92 (CI = 0.80−0.97); total enamel density, 0.96 (CI = 0.89−0.98); and mesiodistal

Table 2: Average measures and post hoc Tukey's results with *p*-values based on two-way ANOVA for two factors and interaction (left central incisor).

		Mesial enamel thickness	Distal enamel thickness	Total enamel thickness	Total dentine Thickness	Mesiodistal width	Mesial enamel density	Distal enamel density	Total enamel density
Cleft type	UCLP	0.76 ± 0.18^{a}	0.76 ± 0.13^{a}	1.52 ± 0.25^{a}	6.13 ± 0.63	7.65 ± 0.63^{a}	2690 ± 386^{a}	2655 ± 282^{a}	2673 ± 264^{a}
	BCLP	0.59 ± 0.22^{b}	0.73 ± 0.20^{ab}	1.32 ± 0.34^{ab}	6.17 ± 0.85	7.48 ± 0.87^{ab}	2256 ± 559^{b}	2419 ± 318^{b}	2337 ± 364^{b}
	Control	0.88 ± 0.20^{c}	1.05 ± 0.22^{c}	1.94 ± 0.32^{c}	6.51 ± 0.50	8.44 ± 0.54^{c}	2803 ± 305^{ac}	2769 ± 278^{ac}	2786 ± 241^{ac}
p-values based on two-way ANOVA with interaction									
Factors	Cleft type	**< 0.001**	**< 0.001**	**< 0.001**	0.060	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
	Gender	0.138	0.806	0.408	**< 0.002**^{M}	**0.011**^{M}	**< 0.001**^{F}	**0.024**^{F}	**< 0.001**^{F}
	Cleft type x Gender	**0.007**	**0.028**	**0.002**	**0.040**	0.703	**0.001**	**0.003**	**< 0.001**

Averages with different letters (a—c) are significantly different at the 5 % level of significance.
"M" indicates that males have a significantly higher average at the 5 % level of significance.
"F" indicates that females have a significantly higher average at the 5 % level of significance.
Enamel thickness, dentine thickness, and mesiodistal width (in mm); and enamel density (HU).

Table 3: Post-hoc analysis for measures with significant cleft type * gender interaction (left central incisor).

	Mesial enamel thickness	Distal enamel thickness	Total enamel thickness	Total dentine thickness	Mesial enamel density	Distal enamel density	Total enamel density
Male + UCLP	0.78 ± 0.16^{a}	0.74 ± 0.09^{a}	1.52 ± 0.18^{a}	6.33 ± 0.58^{a}	2596 ± 368^{a}	2525 ± 229^{a}	2561 ± 156^{a}
Female + UCLP	0.74 ± 0.20^{ab}	0.77 ± 0.15^{ab}	1.51 ± 0.30^{ab}	5.96 ± 0.64^{ab}	2771 ± 397^{ab}	2767 ± 282^{ab}	2769 ± 303^{ab}
Male + BCLP	0.40 ± 0.13^{c}	0.67 ± 0.21^{abc}	1.07 ± 0.24^{c}	6.77 ± 1.11^{ac}	1694 ± 200^{c}	2197 ± 307^{ac}	1945 ± 220^{c}
Female + BCLP	0.70 ± 0.19^{abd}	0.77 ± 0.19^{abcd}	1.47 ± 0.31^{abd}	5.81 ± 0.37^{abd}	2593 ± 402^{abd}	2552 ± 252^{abd}	2573 ± 175^{abd}
Male + control	0.92 ± 0.17^{abde}	1.14 ± 0.18^{e}	2.06 ± 0.31^{e}	6.52 ± 0.50^{abce}	2748 ± 363^{abde}	2848 ± 193^{abde}	2798 ± 271^{abde}
Female + control	0.86 ± 0.22^{abdef}	0.98 ± 0.23^{ef}	1.83 ± 0.29^{abef}	6.50 ± 0.52^{abcf}	2850 ± 246^{abdef}	2702 ± 324^{abdef}	2776 ± 219^{abdef}

In the post-hoc analysis, each group was given a unique letter label (a—f). Next, when comparing subsequent groups, if the difference in means between the current and previous group was not statistically significant, the letter assigned to the previous group/s was prefixed to the new letter for the current group. However, if the difference was statistically significant, the prefix was disregarded. *p*-value ≤0.05 was considered to indicate a statistically significant difference. Enamel thickness, dentine thickness, and mesiodistal width (in mm); and enamel density (HU).

Table 4: Average measures and post hoc Tukey's results with *p*-values based on two-way ANOVA for two factors and interaction (right central incisor).

		Mesial enamel thickness	Distal enamel thickness	Total enamel thickness	Total dentine thickness	Mesiodistal width	Mesial enamel density	Distal enamel density	Total enamel density
Cleft type	UCLP	0.60 ± 0.19^{a}	0.68 ± 0.18^{a}	1.28 ± 0.33^{a}	6.21 ± 0.68	7.49 ± 0.67^{a}	2567 ± 280^{a}	2437 ± 390^{a}	2502 ± 304^{a}
	BCLP	0.55 ± 0.14^{ab}	0.51 ± 0.28^{ab}	1.05 ± 0.40^{ab}	6.12 ± 0.28	7.18 ± 0.58^{ab}	2390 ± 336^{ab}	2020 ± 608^{b}	2205 ± 414^{b}
	Control	0.84 ± 0.16^{c}	1.04 ± 0.27^{c}	1.88 ± 0.36^{c}	6.52 ± 0.63	8.41 ± 0.58^{c}	2689 ± 281^{ac}	2887 ± 240^{c}	2789 ± 202^{ac}
p-values based on two-way ANOVA with interaction									
Factors	Cleft type	**< 0.001**	**< 0.001**	**< 0.001**	0.082	**< 0.001**	**0.001**	**< 0.001**	**< 0.001**
	Gender	0.075	0.251	0.089	0.059	0.356	**0.004**^{F}	0.086	**0.008**^{F}
	Cleft type x gender	**0.027**	0.166	**0.040**	0.795	0.608	0.317	**0.006**	**0.052**

Averages with different letters are significantly different at the 5 % level of significance.
"F" indicates that females have a significantly higher average at the 5 % level of significance.
Enamel thickness, dentine thickness, and mesiodistal width (in mm); and enamel density (HU).

Table 5: Post-hoc analysis for measures with significant cleft type * gender interaction (right central incisor).

	Mesial enamel thickness	Total enamel thickness	Distal enamel density	Total enamel density
Male + UCLP	0.51 ± 0.10^{a}	1.05 ± 0.24^{a}	2127 ± 184^{a}	2279 ± 111^{a}
Female + UCLP	0.67 ± 0.20^{ab}	1.45 ± 0.29^{ab}	2669 ± 338^{b}	2669 ± 297^{b}
Male + BCLP	0.48 ± 0.11^{abc}	1.00 ± 0.37^{ac}	2128 ± 778^{ac}	2154 ± 428^{ac}
Female + BCLP	0.58 ± 0.15^{abcd}	1.08 ± 0.42^{abd}	1966 ± 545^{acd}	2230 ± 428^{acd}
Male + control	0.87 ± 0.15^{be}	1.91 ± 0.32^{e}	2848 ± 280^{be}	2751 ± 223^{be}
Female + control	0.82 ± 0.17^{bef}	1.86 ± 0.39^{bef}	2924 ± 196^{bef}	2825 ± 179^{bef}

In the post-hoc analysis, each group was given a unique letter label (a−f). Next, when comparing subsequent groups, if the difference in means between the current and previous group was not statistically significant, the letter assigned to the previous group was prefixed to the new letter for the current group. However, if the difference was statistically significant, the prefix was disregarded. *p*-value ≤ 0.05 was considered to indicate a statistically significant difference. Enamel thickness, dentine thickness, and mesiodistal width (in mm); and enamel density (HU).

width, 0.96 (CI = 0.90−0.99). Hence, the ICC results showed that the reliability was excellent.

The intra-rater and inter-rater reliability results for the right central incisor were determined as 95 % CIs: total enamel thickness, 0.96 (CI = 0.90−0.98); dentine thickness, 0.93 (CI = 0.82−0.97); total enamel density, 0.99 (CI = 0.97−0.99); and mesiodistal width, 0.93 (CI = 0.83−0.97). The inter-rater reliability results for the right central incisor were: total enamel thickness, 0.96 (CI = 0.90−0.98); dentine thickness, 0.95 (CI = 0.87−0.98); total average enamel density, 0.98 (CI = 0.94−0.99); and mesiodistal width, 0.92 (CI = 0.81−0.97). Hence, the ICC results showed that the reliabilities of the methods used for measuring the right central incisor in this study were good to excellent.

Discussion

Previous studies used periapical and panoramic radiographs to assess tooth structure, but these conventional methods may produce inaccurate measurements due to potential image distortion or blurriness.[16,17] By contrast, CBCT provides high-quality three-dimensional images with detailed views from any angle, eliminating structural overlap. As a result, CBCT allows more precise and reproducible linear measurements to be acquired.[32] The findings obtained in the present study regarding tooth size, enamel thickness, and enamel density in the permanent central incisors of individuals with CLP agree with those reported in previous research.[33,34] Tooth defects, including abnormalities and structural variations, are frequently observed in children with CLP.[35,36] We also included a control group to better understand tooth structural changes and explore potential correlations with different categories of clefts.

Previous studies have demonstrated that the most common enamel defects are hypoplasia, opacity, and hypomineralisation.[9,37,38] Enamel hypoplasia and opacities have also been reported in individuals with cleft.[34,39] Moreover, a study found a combination of defects, with hypoplasia characterised by reduced enamel thickness and some opacities on the same tooth surface.[40] An animal study conducted on a mouse model of cleft found thinner enamel with lower enamel density compared with normal teeth.[25] In our study, we observed significantly reduced enamel thickness in the central incisors. In particular, the mean enamel thicknesses in the left central incisors were 1.52 mm in UCLP individuals, 1.32 mm in BCLP individuals, and 1.94 mm in non-cleft individuals. In the right central incisors, the mean enamel thicknesses were 1.28 mm in UCLP, 1.05 mm in BCLP, and 1.88 mm in the non-cleft population. Interestingly, there were no significant differences in dentine in the central incisors.

Furthermore, we found that the enamel density of the thin enamel surface was lower in children with CLP. However, few previous studies have investigated enamel thickness and density defects, making it challenging to conduct comparisons and establish representative findings.[34,41] A previous study of molar incisor hypomineralisation in permanent teeth demonstrated that CLP children were more susceptible to enamel hypomineralisation defects than the control group, highlighting their increased risk compared with non-cleft individuals.[41] In the present study, we also identified differences in enamel density among the control group and UCLP and BCLP groups. In particular, areas with thin enamel were characterised by lower enamel density than regions with normal thickness. Consequently, both cleft groups exhibited thin enamel and reduced enamel density in the central incisors compared with the control group. These results suggest that infants with CLP may experience more decayed teeth and filled carious lesions than their non-cleft counterparts, as also described in other studies.[42,43] Several studies detected moderate to severe enamel alterations in UCLP and BCLP.[34,41] In the present study, among the sample of children with CLP, those with BCLP exhibited more severe enamel defects, suggesting a stronger association with bilateral clefts.

Genetic alterations are known to contribute to the development of clefts and tooth structural abnormalities. Enamel formation is regulated by various proteins, including enamelin (ENAM), amelogenin (AMEL), kallikrein-4, and matrix metalloprotease-20 (MMP-20),[44] DLX3,[45] FAM83H, WDR72,[46] and SLC4A4.[47] Enamel defects may result from alterations in the secretion or function of these proteins. Genetic modifications in the ENAM and AMEL proteins are likely to cause enamel defects, such as thin enamel and surface pits.[44] A study showed that AMEL, encoded by the AMELX gene, plays a crucial role in dental enamel formation and may also be associated with CLP, highlighting a genetic link between enamel defects and CLP.[48] Further research may be needed in humans to elucidate the genetic link between clefts and defects affecting enamel.

The proposed inheritance patterns for cleft palate include X-linked recessive or autosomal dominant inheritance.[49] The Y chromosome enhances enamel and dentine growth, but the role of the X chromosome in tooth crown development may be limited to enamel formation.[31] Various studies of tooth size and morphology have shown that enamel and root formation are directly influenced by genes on the X chromosome.[30,50,51] In the present study, we found thin enamel with a low enamel density in both central incisors, but there was no difference in the dentine thickness between CLP and non-cleft patients. Based on this study, the variations in tooth morphology and size suggest that interactions between epithelium and mesenchyme during tooth morphogenesis may be influenced by genes on the X chromosome. Alvesalo and colleagues (1991) found thicker enamel in females compared with males. Their findings also indicated that the enamel thicknesses in the central incisors and canines were higher in females, although the differences were small.[30] In the present study, the overall enamel thickness in the male control group was significantly higher than in all four CLP groups but did not differ significantly compared with female control individuals. In general, the dentine thickness was significantly greater in males than in females. In addition, compared with all other groups, the dentine thickness in the left central incisor was significantly lower in the female BCLP group, with a mean of 5.81 ± 0.37. As discussed earlier, the Y chromosome enhances the mitotic capacity of developing tooth germs and accelerates dentine development, while the amelogenesis process appears to be influenced by the X chromosomes.[50] A previous study demonstrated that male patients with Klinefelter (XXY) syndrome exhibited larger tooth size and thicker enamel compared with control males or females. However, the dentine in Klinefelter males was thicker than that in female controls but thinner than that in male controls.[30] By contrast, female patients with Turner (XO) syndrome have smaller teeth with normal dentine thickness and reduced enamel thickness.[52] It has also been demonstrated that males possess specific amelogenin proteins, whereas females lack these proteins.[53]

CLP defects can originate from the ectoderm. Specific genes responsible for causing CLP may be present throughout the oral epithelium, leading to the continued expression of CLP genes in this tissue. Consequently, genes involved in labiopalatine development may also be involved in tooth patterning as well as in amelogenesis.[25] Genetic studies have shown that amelogenin (encoded by the AMELX gene), which is involved in enamel formation, is also a candidate gene for CLP, suggesting a genetic link between clefts and enamel defects.[48] This association appears to be absent in dentine formation. Interestingly, a recent study found a reduced enamel thickness and lower enamel density in individuals with CLP compared with non-cleft individuals, but dentine appeared to be less affected. Dentine formation by odontoblasts begins before amelogenesis and follows a different regulatory pathway. Odontoblasts originate from neural crest cells and initiate dentine deposition before enamel formation.[54] The processes leading to CLP involve tissues derived from the frontonasal and maxillary prominences, which influence lip and palate formation,[55] but not the neural crest cells that are directly responsible for dentinogenesis. Thus, dentine formation may proceed normally despite enamel defects. This observation supports the fact that enamel is derived from the ectodermal epithelium whereas dentine comes from mesenchymal tissue. Therefore, enamel can be more prone to defects in CLP patients. Further genetic studies could be useful to provide some important insights that may complement the findings obtained in the present study. Various factors, such as trauma, nutritional deficiencies, diseases, and metabolic conditions in CLP, may contribute to enamel defects. In addition, rehabilitation processes in CLP patients, including primary and secondary surgeries, are essential in early childhood. Recurrent infections in CLP children during this period may also disrupt hard tissue matrices and the mineralisation process in odontogenesis, leading to enamel defects.[34]

Moreover, studies have investigated differences in the mesiodistal tooth dimensions between CLP patients and non-cleft individuals. These studies consistently showed that the anterior mesiodistal tooth dimensions of CLP children were smaller than those in the control group, which agree with the findings obtained in the present study.[1,33,56,57] In addition, previous research has shown that mutations in the Pax9 and MSX1 genes result in smaller teeth throughout the dentition.[58] Furthermore, unaffected siblings and parents of cleft patients exhibit a higher occurrence of dental defects, suggesting that smaller tooth size represents subclinical phenotypes within the CLP spectrum, sharing a common underlying aetiology.[59–61] The present study did not specifically investigate the genetic link between tooth abnormalities and different cleft phenotypes, but the smaller tooth size observed among CLP patients may warrant further genetic research in the future to correlate these findings.

Patients with amelogenesis imperfecta face dental restoration challenges due to weak enamel-resin bonding from altered enamel composition.[62] Similarly, CLP patients, with reduced enamel thickness and density, may experience adhesion issues affecting composite restorations, crowns, and veneers. Minimally invasive dentistry can help preserve tooth structure, while stronger bonding systems and materials like composite resin and glass ionomer cement may improve durability and reduce microleakage.[63] Early fluoride applications and calcium phosphate remineralising substitutes[63] may also help to protect CLP teeth. Interproximal stripping, a common orthodontic technique, may increase plaque retention and caries risk,[64] while compromised enamel adhesion can lead to microleakage and demineralisation beneath orthodontic brackets.[65] To prevent further enamel damage in CLP patients, clinicians may use fluoride-releasing agents and implement protective measures such as chlorhexidine or benzydamine mouth rinses, triclosan benzydamine varnishes, and xylitol.[64,65]

One of the limitations of the current study was the small sample size. This research was retrospective in nature and only CLP patients who underwent CBCT scans were recruited as the cost of CBCT scanning meant that not all CLP patients received this procedure. Hence, future studies involving larger cohorts as well as bilateral cleft palate patients or other types of cleft palate patients in higher age groups would provide greater insights into this condition.

Conclusion

According to the results obtained in the present study, tooth abnormalities were strongly associated with CLP. In CLP patients, the tooth size was smaller, and the enamel thickness and enamel density were lower compared with the control group, but dentine remained largely unaffected. The clinical significance of our study is the recommendation that dental rehabilitation for CLP children should prioritise a conservative management approach when restoring teeth. Understanding the thickness of enamel and dentine in cleft patients is crucial during restorative procedures and orthodontic therapy. Furthermore, teeth with a lower enamel density are more susceptible to decay. Implementing and modifying oral health care strategies at an early stage of life can be beneficial for reducing the risk of tooth caries in children with cleft.

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Conflict of interest

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Ethical approval

The study received approval from the Human Research Ethics Committee (JEPeM) at Universiti Sains Malaysia

(Malaysia) [USM/JEPeM/17070341], 15/11/2017 and the Ethical Review Committee at CMH-Lahore Medical College and Institute of Dentistry (Pakistan) [29/ERC/CMH/LMC], 31/01/2017.

Authors contributions

Conceptualisation, S.J., M.F.K., and M.Q.; Methodology, S.J., M.F.K., and M.Q; Software, M.Q. and H.K.; Validation, S.J. and M.F.K.; Formal analysis, A.I.A. and M.Q.; Investigation, A.I.A and M.Q; Resources, M.Q.S. and H.K.; Data curation, M.F.K. and M.Q; Writing – original draft preparation, S.J. and M.Q.; Writing – review & editing, S.J., M.F.K., A.I.A., M.Q.S., and H.K. All authors have read and agree with the submitted version of the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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