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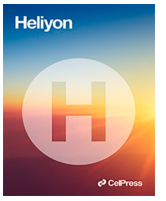

Research article

Minor physical anomalies including palatal rugae pattern and palatal dimensions in children with sickle cell disease: A cross-sectional analytical study

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ABSTRACT

Background: Sickle cell disease (SCD) is the most common hereditary hemoglobinopathy, which delays growth leading to an altered skeleton and craniofacial pattern. Palatal rugae patterning has been considered the regulator of the development of the palate. The purpose of the research work was to study the morphology of the palate, rugae pattern, and its dimensions in SCD children and compare them with healthy normal children, and to evaluate its role as minor physical anomalies (MPAs).

Methods: A cross-sectional case-control study was designed as per STROBE guidelines. The sample comprised 50 children diagnosed with sickle cell disease (Group SCD) and 50 normal healthy children as control (Group C) belonging to the same age group (10–18 years). Dental impressions were made, followed by the pouring of dental casts. The length of the palatal rugae was measured and categorized into primary (>5 mm), secondary (3 mm–5 mm), and fragmentary rugae (<3 mm). The shape of each primary palatal rugae was identified and categorized as curved, wavy, straight, circular and non-specific. Linear and angular measurements of the palatal rugae patterns and palatal dimensions (width, height, area) were measured and recorded.

Results: The total number of palatal rugae and fragmentary rugae was lesser in Group SCD than in Group C ($p < 0.05$). The depth of the palate was significantly increased, whereas the area of the palate significantly decreased in Group SCD.

Conclusions: The children with SCD showed distinctive palatal rugae patterns and dimensions when compared with normal healthy children that can be attributed as potential MPAs for sickle cell disease. Children with SCD had an under-developed palatal rugae pattern with a deep, narrow and small palate when compared to healthy children.

The dimensions of the palatal rugae pattern in SCD showed reduced distance between the incisive papilla and the first and last rugae, indicating a further decrease in the anteroposterior

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dimensions of the palate. These findings may aid in the early diagnosis and prevention of malocclusion in children with SCD by appropriate interceptive orthodontic treatment

1. Introduction

Sickle cell disease (SCD) is a homologous condition (HbSS) and an autosomal, recessive hemoglobinopathy represented by hemolytic anemia, recurrent obstruction of small blood vessels leading to acute and chronic tissue ischemia, and organ malfunction [1]. The global burden of sickle cell anemia is 111.91 per 100,000 live newborns, with 1125.49 per 100,000 in Africa, the leading continent on the list [2]. Various studies confirmed the high distribution of the *HbS* gene in Central, Southern and North-Eastern India [3,4]. Sickling is the sequelae of the genetic changes precipitated in altered environmental conditions like reduced oxygen level, 3-diphosphoglycerate (2,3-DPG), pH value, temperature, and carbon monoxide concentration [5]. Sickled hemoglobin leads to developmental disorders/growth delay [6]. As a result, the facial growth pattern is affected, including the palate and surrounding structure [7].

The compound effect of prenatal and post-natal adverse events leads to a variety of morphological and physiological alterations. The morphological variations that are usually painless and harmless are termed "minor physical anomalies" (MPAs) [8]. These are primarily present in the oral and perioral region, including palatal rugae pattern and dimensions followed by a foot and hands. MPAs are considered external marker groups with genetic-epigenetic factors that represent altered morphogenesis [9]. A close association has been established between MPAs and neurodevelopmental disorders such as Schizophrenia, bipolar disorders, autism, etc [9–12].

Changes in palatal rugae pattern and its dimension might be considered minor physical anomalies in sickle cell disease. For decades, the role of palatal rugae was limited to individual identification in forensic science [13]. Recent research suggested that patterning of rugae during development coincides with the release of many transcription factors and signalling pathways (such as *Shh - sonic hedgehog, Shox* – short stature homeobox) which further controls the anteroposterior growth of the palate [14]. It has already been assumed that the study of palatal rugae could be a marker to gain insight into the anteroposterior growth of the secondary palate [15].

Considering all these factors and the abnormal hard tissue development in SCD, it was hypothesized that the palatal rugae might depict a specific feature that can serve as an early identification tool for detecting SCD from a clinical perspective. Despite vast phenotypic variations in SCD, no studies have been reported regarding MPAs in sickle cell anemia. This led to the design of the present research work based on the hypothesis that the palatal rugae pattern and its dimension could be the potential MPA's in sickle cell disease.

The primary objective of the study was to study the prevalence and morphology of the palatal rugae pattern and palatal dimensions in children with SCD and compare it with healthy children.

2. Materials and methods

2.1. Study design

An Analytical Cross-Sectional Study was designed after ethical approval was obtained from Sickle Cell Institute Chhattisgarh (SCIC), Raipur (No./736/SCIC/IEC/2016). The authors have followed "Strengthening the Reporting of Observational Studies in Epidemiology" guidelines (STROBE) in reporting this research [16]. Parents were well-informed about the study, and written consent was obtained from the parents to permit their children to participate in the study.

2.2. Settings and participants

Out of 142 children diagnosed with SCD, 50 children between the ages 10–18 years belonging to the same ethnic group were selected from the Sickle Cell Institute, Raipur, Chhattisgarh, India based on the affirmative outcome of solubility tests subsequently validated by alkaline hemoglobin electrophoresis. A total of 50 healthy normal children of the same age and ethnic group were randomly selected as the control group from the Department of Pedodontics and Preventive Dentistry at Rajnandgaon, Chhattisgarh, India. Matching was done for the race, birth origin, gender, and socioeconomic status based on income levels and residence and parents' education for both groups.

Cases with a previous history of fixed orthodontics or facial orthopedics treatment or extraction of the permanent tooth; the presence of proximal caries; those who underwent hematopoietic stem cell transplantation for any systemic disease, those who have any kind of congenital or acquired conditions that hampered the development of the teeth like amelogenesis imperfect, dentinogenesis imperfect, enamel hypoplasia; any visible lesions such as torus palatinus, ulcers, and siblings were excluded.

2.3. Sample size

Sample size calculation was done using the power of the test being (0.8) and alfa error (0.05), resulting in 50 specimens per group.

The sample size was estimated using GPower 3.1.9.7. The mean and standard deviation values from the study conducted by Rajan et al. [17] projected an effect size of 0.765. For a two-tailed test with an alpha error of 5 % and power at 95 %, a sample size of 46 per group was obtained. Thus, the total sample size estimated was 92 approximating to 100.

2.4. Data measurements and variables

Two groups that were included in the present research work were:

- Group SCD (Study Group): A total of 50 children diagnosed with SCD
- Group C (Control Group): A total of 50 normal healthy children without any underlying systemic disease.

Every participant was asked to sit comfortably on the dental chair. A preliminary examination was performed, followed by recording maxillary arch impressions with perforated impression trays (GDC Standard) and alginate (Vignette chromatic Dentsply®). Casts were poured in dental stone type-IV (Dentsply®), air-dried in the natural sunlight, and made ready to measure various parameters included in the study. All the parameters were identified/measured by a single examiner under daylight using a magnifying lens. The dimensions were measured using an electronic Vernier scale (Insize 1112-200) to the accuracy of 0.01 mm. The following dimensions of the palatal and rugae patterns were studied, recorded, and tabulated in the spreadsheet for statistical analysis:

2.4.1. Length of the rugae

Both the end-points of the individual rugae were marked, then measured with the Vernier scale and categorized into primary (>5 mm), secondary (3 mm–5 mm), and fragmentary rugae (<3 mm) according to Thomas and Kotze classification [18]. The total number of palatal rugae in each category was counted and tabulated to estimate the prevalence of the palatal rugae pattern.

2.4.2. Shape of primary rugae

The shape of each primary palatal rugae (>5 mm) was identified and categorized as curved, wavy, straight, circular, and non-specific as per Kapali's classification [19].

2.4.3. Linear and angular measurements [18]

The following landmarks were recognized and marked on each dental cast using a magnifying lens (Fig. 1):

a) I: The most anterior point on incisive papilla.
b) A: The most anterior point on the rugae pattern regardless of the side and type.
c) P: The posterior-most point on the border of the last primary or secondary rugae.
d) F: The posterior-most point on the border of the last rugae (including fragmentary).

The linear distance between I and A (IA), I and P (IP), and I and F (IF); angular measurement angle of divergence (AD) formed by the midline of the medial palatal raphe and the line joining incisive papilla with the origin of most posterior primary or secondary rugae on one side of the palate were measured and recorded.

2.4.4. Palatal dimensions [18]

To measure the palatal dimensions, the following landmarks were recognized (Fig. 2):

a) W_1 and W_2: The mesio-palatal cusp tips of left and right permanent maxillary 1st molar, respectively.
b) C_1 and C_2: The line drawn perpendicular to the line W_1W_2 intersecting W_1W_2 at C_1 and mid-palatal raphe at C_2.

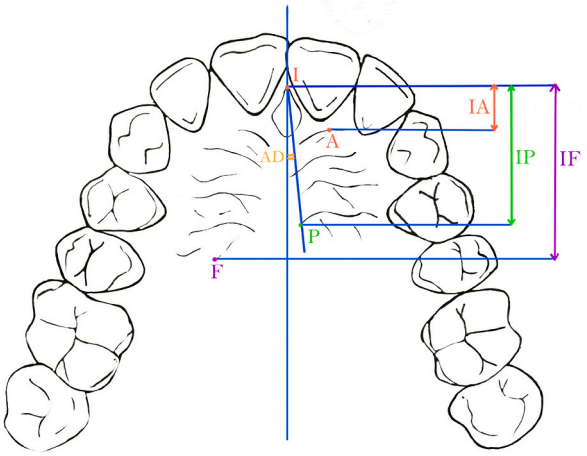


Fig. 1. Dimensions including width (W), Depth (D), and the area of the palate.

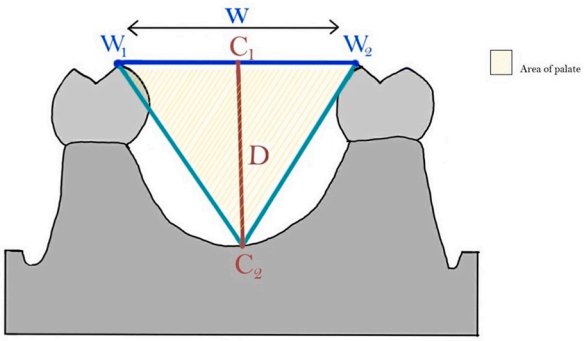


Fig. 2. Palatal rugae dimensions including linear measurements and angular measurements.

The width of the palatal arch (W) was measured from point W_1 to point W_2. The depth (D) of the palatal arch was measured from the distance between points C_1 and C_2. The area of the palate was calculated by multiplying base and height divided by 2 represented as $(W \times D)/2$; in which base is the width of the palate (W) and height is the depth of the palate (D). The width and depth were measured, and the area of the palate was calculated.

2.5. Statistical analysis

For measuring the intra-examiner agreement, the PR pattern ($n = 22$, 22 % of the total sample) was reclassified within 30 days after the initial categorization by the same examiner. The same examiner remeasured the rugae. The palate dimensions ($n = 10$, 10 % of the total sample) were also remeasured within 30 days by the same examiner. Kappa statistics were found to be 0.95 (Near Perfect agreement). While the inter-rater agreement was found to be (0.85) (Near Perfect agreement) between 3 investigators (AP, HM, RMS).

A Chi-square test was used to analyze the distribution of children as per the type of dentition. Unpaired Student's t-test was used to compare the palatal rugae pattern and its dimensions between the two groups. The threshold for results to be considered significant was set at $p \leq 0.05$ and the confidence interval as 95 %. The analysis was performed using the Statistical Package for the Social Sciences (SPSS) 24.0 (IBM Corp., Armonk, NY, USA) software.

3. Results

All 100 participants were included in the study. The ratio of females and males in both groups was approximately 1:1. The mean age was 14.6 ± 2.33 years and 14.74 ± 2.03 years in Group SCD group (26 females and 24 males) and Group C (25 females and 25 males) respectively. No significant difference was found in age and gender distribution ($p > 0.05$).

In Group SCD, 40 (80.0 %) had permanent dentition, while in Group C, 49 (98.0 %) children had permanent dentition, and only one (2.0 %) had mixed dentition. When the malocclusion distribution was compared, it was statistically significant ($p < 0.05$, Table 1).

The prevalence of fragmentary rugae was less in Group SCD when compared to Group C, with a statistically significant difference between the two groups. A total of 463 rugae were observed in Group SCD and 530 in Group C, with the difference, found to be statistically significant. However, the prevalence of primary and secondary rugae was lower in the Group SCD but was statistically non-significant (Tables 2 and 3).

The number of curved, wavy, circular, and non-specific shaped primary rugae was lesser in Group SCD, whereas straight-shaped primary palatal rugae were lesser in Group C. However, there was a statistically non-significant difference in the shapes of primary palatal rugae when compared across the groups (Tables 4 and 5).

The width and the area of the palatal arch were found to be lesser in Group SCD and statistically significant for the area of the palate ($p < 0.05$), whereas the depth of the palatal arch was lower in Group SCD and was not statistically significant when compared with Group C (Table 6). From our analysis, we could observe that the area and center of the palatal arch depicted to have statistical Significance where both the values were less for the SCD Group.

When the distance between incisive papilla and most anterior rugae (IA) was compared among the two groups, it was found to be lesser in Group SCD, and the difference was found to be statistically significant. Similarly, a significant difference was seen when the distance between incisive papilla and last rugae (IF) was compared with lesser values in Group SCD. However, there was no statistically

Table 1
Distribution of children as per the type of dentition in the study groups.

Type of Dentition	Group SCD	Group C	χ^2value	p-value
Mixed	10 (20.0 %)	1 (2.0 %)	8.274	0.004[a]
Permanent	40 (80.0 %)	49 (98.0 %)		

[a] Significant.

Table 2
Prevalence of rugae type between the groups.

Rugae Type	Group SCD No. (%)	Group C No. (%)
Primary	295 (63.71)	323 (60.93)
Secondary	127 (27.42)	147 (27.73)
Fragmentary	41 (8.87)	60 (11.34)
Total	463 (100)	530 (100)

Table 3
Comparison of rugae between the study groups.

Rugae Type	Group SCD (Mean ± SD)	Group C (Mean ± SD)	t -value	p-value
Primary	5.9 ± 1.62	6.46 ± 1.81	1.631	0.106 (NS)
Secondary	2.54 ± 1.37	2.94 ± 1.13	1.589	0.115 (NS)
Fragmentary	0.82 ± 0.92	1.2 ± 0.97	2.012	0.047[a]
Total	9.26 ± 2.18	10.6 ± 2.36	−2.950	0.004[a]

[a] Significant NS Non-Significant.

Table 4
Prevalence of primary rugae as per shapes between the study groups.

Rugae Type	Group SCD No. (%)	Group C No. (%)
Curved	120 (40.68)	134 (41.49)
Wavy	73 (24.75)	84 (26.01)
Straight	59 (20.0)	53 (16.41)
Circular	0 (0)	2 (0.62)
Non-specific	43 (14.58)	50 (15.48)
Total	**295 (100)**	**323 (100)**

Table 5
Comparison of primary rugae as per shapes between the study groups.

Primary Rugae Shape	Group SCD (Mean ± SD)	Group C (Mean ± SD)	t -value	p-value
Curved	2.4 ± 1.325	2.72 ± 1.356	−1.194	0.235 (NS)
Wavy	1.46 ± 1.147	1.68 ± 1.168	−0.95	0.344 (NS)
Straight	1.32 ± 0.957	1.06 ± 1.15	1.229	0.222 (NS)
Circular	0	0.04 ± 0.198	−1.429	0.156 (NS)
Non-specific	0.86 ± 1.03	1 ± 1.125	−0.649	0.518 (NS)

NS Non-Significant.

Table 6
Comparison of dental arch and palate dimensions across the study groups.

Palatal arch dimensions	Group SCD (Mean ± SD)	Group C (Mean ± SD)	t -value	p-value
Width of palatal arch	2.4 ± 1.325	2.72 ± 1.356	−1.194	0.235 (NS)
Depth of palatal arch	1.46 ± 1.147	1.68 ± 1.168	−0.95	0.344 (NS)
Center of palatal arch	1.32 ± 0.957	1.06 ± 1.15	1.229	0.222 (NS)
Area of palatal arch	0.86 ± 1.03	1 ± 1.125	−0.649	0.518 (NS)

NS Non-Significant.

Table 7
Comparison of rugae dimensions across the study group.

Palatal dimensions	Group SCD (Mean ± SD)	Group C (Mean ± SD)	t -value	p-value
IA	7.56 ± 1.99	8.6 ± 1.29	−3.09	0.003[a]
IP	25.3 ± 4.71	26.68 ± 3.34	−1.69	0.094
IF	25.4 ± 4.06	27.9 ± 3.75	−3.22	0.002[a]
Angle of Divergence	13.52 ± 9.73	16.16 ± 8.85	−1.42	0.159

[a] Significant.

significant difference when IP and angle of divergence (AD) were compared between the groups (Table 7).

4. Discussion

Sickle-cell disease (SCD) is an inherited hemoglobin disorder resulting from the point mutation (Adenine to Thymine) of the 6th amino acid (valine-GAG replaces glutamic acid-GTG) of the β-globin chain on the 11th chromosome [20]. Valine being hydrophobic causes the production of polymerized sickle hemoglobin (Hb-S) [15]. In the recent past, tremendous research work is being done in the field of sickle cell anemia [21–23]. However, despite vast contemporary scientific data, still, little knowledge is gathered on MPA, including palatal dimensions or rugae patterns in children with SCD. Proper research will help track down the prone children and provide early interceptive orthodontic treatment to prevent the deleterious effect.

In the present study, all the subjects belonged to the same ethnic origin to avoid any bias. The subjects for the case study group included children who tested positive for sickle cell disease (HbSS) as the severity of symptoms is more pronounced due to homozygous conditions [24]. The variables selected for the present research work were as per Thomas and Kotze's classification, which includes a wide variety of categories such as palatal rugae pattern with subcategories of prevalence and dimensions of rugae, the shape of palatal rugae, dimensions of the palatal arch and rugae dimensions providing comprehensive data to study palatal rugae pattern [18]. Any specific feature pertaining to the above categories could serve as a potential MPA and be a presumptive diagnostic marker to intercept developing systemic and local complications effectively and efficiently.

The first set of data included the prevalence of different types of rugae patterns. In children with sickle cell disease, it was observed that primary rugae are the most prevalent type, followed by secondary and fragmentary rugae. Similar findings were found in normal children; however, fragmentary rugae were much lesser in SCD children comparatively. Similar observations have been reported in normal healthy children with a higher number of primary rugae and a lesser number of secondary and fragmentary rugae [19,25]. In the present study, the total number of rugae and fragmentary rugae were lesser in number in the children with SCD suggesting under-development, which can be attributed to two factors. Delayed growth is one of the common findings in SCD, which could have resulted in underdeveloped palatal rugae [26]. The second reason could be excessive growth of the midface in SCD patients due to bone marrow hyperplasia, which is compensation for the short life span of erythrocytes [27]. Both reasons contradict each other, which exhibits the scope for further research.

The second set of variables included the distribution of primary palatal rugae, classified as curved, straight, wavy, circular, and non-specific based on the shape. The most commonly observed shape is curved, followed by wavy, straight, non-specific, and circular. Various studies have been done on a population of different origins, and wide variation has been observed (Table 8).

The third set of variables included dimensions of the palate, and it was observed that the width and area of the palate were significantly lesser. In contrast, the depth of the palate was significantly higher in SCD children. Deep palate might be attributed to Angle's class II tendency in SCD children. On the other hand, the width and area of the palate were decreased, indicating delayed/retarded growth [24–27,33–35]. It has already been proven that angle's class II showed the narrowest transverse arch dimension contributing to the narrow maxillary arch [36]. Moreover, the increase in palatal width and area occurs during the transition from mixed to permanent dentition, which is further delayed in the case of SCD [37].

The dimensions of the palatal arch were studied in various anomalies except for SCD patients, which makes this a pioneer study. In patients with Turner's syndrome (6–50 years), the maxillary dental arch was narrower and shorter with normal palatal height [38]. Dimensions of the dental arches of children affected with hypophosphatemic vitamin-D-resistant rickets suggested maxillary arch depth and arch perimeter were significantly reduced [39]. Hattab et al. reported that the dimensions of maxillary and mandibular arches are significantly less in children with thalassemia major [40]. Few other studies done among adult groups of Down's syndrome observed a narrower and deeper hard palate, while in schizophrenic patients, the palatal area was smaller [41,42]. Hence, it can be suggested from the present research work that children with SCD have increased depth and decreased width of the palate with a smaller area. As the changes in the size of dental arches can impact the occlusal relationships, these changes should be considered when planning orthodontic treatment and orthognathic surgery.

The last set of data compared in the present study was the rugae dimensions. It was found that the distance between the most anterior point on the incisive papilla and the most anterior point on the rugae pattern regardless of the side (IA) and distance between the incisive papilla to the posterior border of the last rugae (including fragmentary) regardless of the side (IF) was significantly less in case of SCD children. This further explains the influence of patterning of the palatal rugae pattern and its effect on the anteroposterior

Table 8
Studies on shapes of palatal rugae in various population.

Origin	Straight/Line No. (%)	Curved No. (%)	Wavy/Sinuous No. (%)	Circular No. (%)	Others No. (%)
Aborigines [19]	34 (3.6)	221 (23.1)	531 (55.8)	34 (3.6)	132 (13.9)[a]
Caucasians [19]	17.6 (15.2)	298 (25.8)	469 (40.6)	33 (2.9)	180 (15.6)[a]
Nepalese [28]	339 (22.1)	342 (22.3)	599 (39.0)	43 (2.8)	211 (13.75)[b]
Egyptian [29]	117 (20.7)	200 (35.39)	166 (29.38)	14 (2.48)	68 (12.04)[c]
Saudi [29]	110 (19.71)	158 (28.31)	248 (44.44)	7 (1.25)	35 (6.27)[c]
Portuguese [30]	77 (38.5)	35 (17.5)	79 (39.5)	3 (1.5)	6 (3.0)
Indonesian [31]	278 (29.17)	243 (25.5)	273 (28.65)	7 (0.73)	152 (15.95)[d]
Indian [32]	123 (25.63)	208 (43.33)	111 (23.13)	0.0	38 (7.91)[e]

Others include [a]unification; [b]branched; [c]unification and crosslink; [d]unification and non-specific; [e]unification and non-specific.

axis of the palate [15]. The temporal sequence of rugae formation in mice is 8-(2,9)-(1,3)-4-5-6-7-7b where '1′ is the anterior-most, and '9′ is the posterior-most rugae under the influence of Shh expression [15]. That same patterning mechanism is likely to be present in mammals [43]. The altered craniofacial features frequently observed in SCD also might have led to the changes in dimensions of the palatal rugae pattern [35]. Hence, all these contribute to altered rugae dimensions in SCD.

Considering the findings of the present study, it can be concluded that there is reduced growth of palate and palatal rugae in children with sickle cell disease. To explain this on a molecular level, the influence of signalling pathways and various transcription factors such as shh and shox2 might contribute to differential patterning of palatal rugae patterns in SCD. The exogenous protein Shh expression is restricted to palatal rugae, which regulates *Fgf10* and *Fgf7* (Fibroblast growth factor 10 and 7) along the oral and nasal side, respectively, guiding the anteroposterior development of the palate [44,45]. In addition to this, the expression of Shox2 (short stature homeobox-2) in the anterior region specifically forms the first palatal rugae further establishes the oronasal axis [15,46,47]. Transforming growth factors – beta (*TGF-B*) and *Shh* play a key role in epithelial proliferation during development [48–50]. In addition to this, a few genes such as *BMP6, TGFBR2, TGFBR3, EDN1* (Endothelin-1), *ERG* (v-ets erythroblastosis virus E26 oncogene-like), and *ECE1* (Endothelin converting enzyme 1) have been identified in association with avascular necrosis in SCD [51]. All these genetic signalling pathways and epigenetic factors might have resulted in reduced growth of palate and palatal rugae pattern (Fig. 3).

This research can be considered innovative data for the study of MPAs in sickle cell disease. However, the results warrant future research work related to genetic studies about the patterning of rugae in SCD. Also, research in the past has established the dimensional stability of alginate to be dependent on various factors like storage time, materials, etc. Hence, replacing alginate with digital impressions in the future might lead to improved and more accurate data [52]. There is a need to further investigate other sickle cell traits such as palatal dimensions, formulating a universally accepted method to calculate surface area and an improved version of palatal rugae classification. This novel study provides exciting data that needs further embellishment with the following substantive points:

- The palatal rugae pattern and its dimensions can be a presumptive diagnostic marker to intercept developing systemic and local complications effectively and efficiently.
- The study of palatal morphology and its dimensions can aid in a proper diagnosis of the developing malocclusions in children with sickle cell disease.
- Children with under-developed palatal rugae and collapsed palatal arch can be an indication to rule out sickle cell disease with further investigations.

Even though few parameters are depicted to showcase statistical significance the sample size of the study limits us to extrapolate them. Another limitation which was profoundly observed was that these participants belonged to a single geographic distribution providing a better understanding of the condition including a large geographic domain with more number of cases and controls with 1:1 matching can provide us with a better understanding of the differences observed in palatal rugae pattern and palatal dimensions in children with sickle cell disease when compared to healthy individuals.

5. Conclusions

In the present study, it can be concluded that children with SCD have an under-developed palatal rugae pattern with a deep, narrow, and small palate. The children with SCD showed distinctive palatal rugae patterns and dimensions when compared with normal healthy children that can be attributed as potential minor physical anomalies for sickle cell disease.

Data availability statement

The data associated with the study has not been deposited into any of the publicly available repositories. However, the data will be made available on request.

Additional information

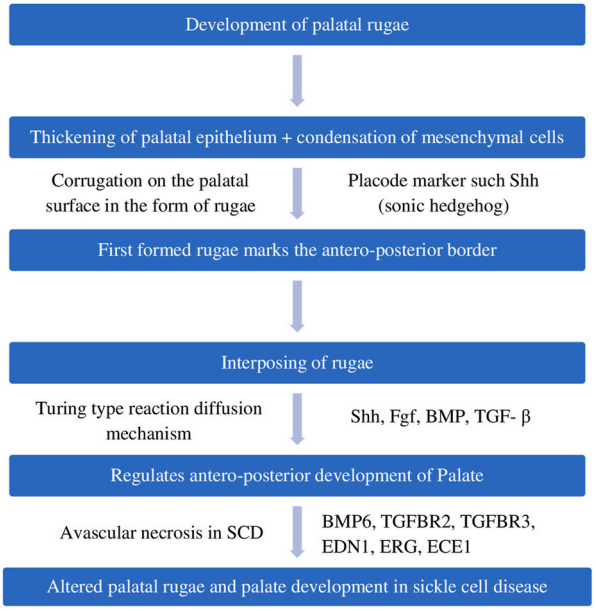
No additional information is available for this paper.

CRediT authorship contribution statement

Raghavendra M. Shetty: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Aditi Pashine:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Sunaina Shetty:** Writing – review & editing, Methodology, Formal analysis. **Hrishikesh Mishra:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation. **Tarun Walia:** Writing – review & editing, Formal analysis. **Shishir Ram Shetty:** Writing – review & editing, Formal analysis. **Vijay Desai:** Writing – review & editing, Formal analysis. **Nilima Thosar:** Writing – review & editing, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to



Shh - sonic hedgehog; FGF - Fibroblast growth factor; BMP - Bone morphogenic protein; TGF- β – Transforming growth factor – Beta; EDN1 - Endothelin-1; ERG - v-ets erythroblastosis virus E26 oncogene like; ECE1 - Endothelin converting enzyme 1

Fig. 3. Flow chart representing the regulation of patterning of palatal rugae and palatal development.

influence the work reported in this paper.

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