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Craniofacial morphology of patients with unilateral cleft lip and palate at two stages of skeletal maturation

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Abstract: The aim of this retrospective cross-sectional investigation was to perform a 3D analysis of craniofacial morphology of patients with unilateral cleft lip and palate (UCLP) at two stages of skeletal maturation. Cone-beam computed tomography (CBCT) scans of 52 UCLP patients (34 prepubertal; 18 pubertal) were collected from an outpatient referral center for the treatment of craniofacial deformities. In total 15 multiplanar craniofacial landmarks were identified, 3D virtual surface models were created, and 13 variables were measured to assess the 3D Euclidean distances between landmarks and spatial position of the landmarks in the projected X, Y and Z components. Maxillary and mandibular pitch (clockwise, counterclockwise) rotation relative to the cranial base was also evaluated. The significance level was set at 5%. Maxillary retrusion value relative to the cranial base was higher and statistically significant greater ($p = 0.028$) in pubertal (SNA, 77.4° ± 6.2; N-ANS Y, 3.3 mm ± 3.1) than in prepubertal patients (SNA 81.0° ± 5.2; N-ANS Y, 5.8 mm ± 2.7). The posterior cranial base length (S-Ba Y) was significantly longer ($p = 0.013$) in pubertal (20.7 mm ± 3.4) than in prepubertal patients (18.4 mm ± 2.7). The upper facial height (N-ANS Z) was significantly greater ($p = 0.01$) in pubertal (46.9 mm ± 4.5) than in prepubertal patients (43.4 mm ± 3.0). Prepubertal and pubertal UCLP patients presented distinct patterns of craniofacial morphology, mainly in the sagittal component of the maxilla and in the posterior cranial base length. Pubertal patients had greater maxillary retrusion and posterior cranial base length.

Keywords: Cleft Lip; Cleft Palate; Cone-Beam Computed Tomography; Skull Base; Maxillofacial Development.

Introduction

Embryological craniofacial development is a complex and well-coordinated process,[1] with the formation of lip and palate beginning as early as jn the 6th to 12th week of gestation.[2,3] Failure in the fusion of some anatomical structures leads to the development of orofacial clefts, among which the most common is the lip and/or palatal cleft.[2,3] Children born with this condition are more prone to developing dental anomalies, types of malocclusion, speech difficulties, infections and psychosocial problems.[1,4]

Development of the maxillofacial region in UCLP patients is a delicate process, affected by hereditary and developmental factors during the embryonic period, and by postnatally acquired features. At present, there are three major theories about the maxillofacial dysplasia of cleft palate patients: teratogenic factors during the embryonic stage will interfere the development of the maxilla; early or traumatic surgeries will disturb the maxillary growth; intrinsic factors in the embryonic period are the primary causes of impaired maxillofacial development, and palatoplasty would exacerbate the maxillofacial hypoplasia to some extent.[5]

Thus, individuals with these types of maxillofacial defects frequently have maxillary constriction and hypoplasia. Moreover, patients with UCLP might also display vertical maxillary deficiency,[6] and cranial base flexure, which could lead to a compensatory change in condylar positioning causing opening of the gonial angle, clockwise mandibular rotation, and an increase in anterior inferior facial height.[6]

Previous studies on the morphological aspects and growth of cleft lip and palate individuals were conducted using two-dimensional (2D) cephalometric radiographs.[6-10] The availability of cone-beam computed tomography (CBCT) scans, acquired for the purpose of preparing surgical procedures, have opened new opportunities for upgrading the data on this topic. Concomitantly with the evolution of CBCT devices, the development of different types of post-processing software have allowed three-dimensional (3D) evaluations for assessing the facial growth and maxillo-mandibular morphology in patients with facial anomalies.[1,11-15]

Considering that older UCLP subjects had a greater chance of presenting deviation from normal growth, due to their exposure to functional and genetic components of the cleft, it has been hypothesized that pubertal UCLP patients would show a different pattern of facial growth than that of prepubertal individuals.

Therefore, the objective of the present study was to make a 3D comparison between the UCLP craniofacial morphology during prepubertal and pubertal stages of skeletal maturation.

Methodology

Participants, eligibility criteria, and settings

The article on this retrospective cross-sectional study was written according to the STROBE guidelines for the improvement of the quality of scientific reports.[16] It was based on evaluation of the patients' pre-treatment orthodontic records obtained from the Cleft Center of the Department of Orthodontics of the Pontifical Catholic University of Minas Gerais (Belo Horizonte, Brazil). Patients received their treatment in the period between January 2010 and December 2018. Patients were not recruited for the purpose of this study, and participants' parents or guardians provided signed, written term of informed consent for the data to be used for research. As this was a retrospective study, no priori sample size calculation was performed. All available records that met the inclusion criteria were included in the investigation. The calculated post hoc power is shown in Table.

On august 2016, the Institutional Review Board of the Pontifical Catholic University of Minas Gerais approved this investigation (CAAE: 61531416.8.0000.5137, process number 1.845.814). According to a protocol of the Graduate Program in Dentistry, all patients and/or their parents sign an informed consent before dental treatment is initiated, with three levels of authorization for the use of images and data. Patients' records included in the present study were retrieved from the files of those patients and/or their parents who had given consent. The institution is an academic referral center for patients with cleft lip and palate in a state with 21 million people. The aforementioned institution is privately owned, but the resources for the treatment of craniofacial abnormalities come from public governmental funds.

The initial sample consisted of CBCT images of 54 UCLP patients, who were selected for the present study according to the inclusion and exclusion criteria. The inclusion criteria were as follows: a) presence of complete UCLP; b) absence of previous orthodontic treatment; c) history of primary surgical interventions only, with no secondary surgical procedures such as bone grafting; d) stage of cervical vertebrae maturation between CS1 and CS4,[17] and;

e) CBCTs acquired at the beginning of treatment as part of the standard diagnostic records for patients with craniofacial abnormalities. The exclusion criteria were: a) absence of maxillary permanent first molars; b) no signs of active periodontal disease; and c) presence of any additional craniofacial disorder. After applying these criteria, two patients were excluded and 52 patients (21 females and 31 males; 33 left side cleft and 19 right side cleft), aged between 7.1 and 14.3 years (mean age of 10.7 years ± 2.1) were included in the investigation to apply the method and conduct the research.

Thirty-four patients were in the prepubertal stage (mean age of 9.7 years ± 1.5), and eighteen were in the pubertal stage (mean age of 12.7 years ± 1.5) of maturation. The prepubertal (CS1 and CS2) and pubertal (CS3 and CS4) stages were classified based on the cervical vertebrae maturation (CVM) method,[17] visualized on lateral cephalograms constructed from the CBCT's using the Dolphin software version 11.7 (Dolphin Imaging & Management Solutions, Chatsworth, USA).

Image analysis and methods of measurements

Three-dimensional virtual models constructed from the CBCT's allowed evaluation of the cranial base, maxillary, and mandibular morphological characteristics by 3D cephalometric analysis. The CBCT scans were obtained on an i-CAT machine (Imaging Sciences International, Hatfield, USA). The images were captured with a field of view (FOV) of 21 cm x 17 cm, 120 kV, 8 mA, with an exposure time of 40 seconds, and isotropic voxel of 0.3 mm. The CBCT image processing and 3D virtual models were performed with the ITK-SNAP software version 2.2 (open-source software, www.itksnap.org), and 3D Slicer software version CMF 3.0 (open-source software, www.Slicer.org) by a trained and calibrated dental maxillofacial radiology specialist. In order to evaluate the intraobserver variability and reproducibility, 3D cephalometric points were identified, plotted, and linear distances were measured twice, in 10 randomly selected CBCT's, with a 15-day interval between measurements. The intraclass correlation coefficient (ICC) ranged from 0.80 to 0.99, indicating a high level of agreement between readings, and the systematic error analysis showed no statistically significant difference (Paired t-test p-values > 0.05) between the measurements, with differences between reading ranging from 0.43 mm to 0.71 mm among the variables.

CBCT processing steps were based on a previous study,[18] and are described below:

a. The tomographic scans were imported into the ITK-SNAP 2.2 software for the conversion of DICOM files into gipl.gz format (Figure 1A-C);
b. For segmentation and construction of 3D virtual models in the 3D Slicer CMF 3.0 software, the "intensity segmenter" tool was used. Subsequently, unnecessary noises were removed using ITK-SNAP 2.2 software. The 3D virtual models in .vtk files were built using the "model maker" tool of 3D Slicer CMF 3.0 software;
c. Orientation of the 3D virtual model in the 3D Slicer CMF 3.0 software was carried out in the Cartesian plane using the "transforms" tool as previously described[19] (Figure 1D-F). After orientation of the 3D virtual model, the orientation matrix was created and then applied to the tomographic scan and segmentation using the "apply matrix" tool;
d. Landmarks were identified in the greyscale CBTC images with the ITK-SNAP 2.2 software and cephalometric measurements were performed in the 3D virtual models with the 3D Slicer CMF software. The landmarks were marked at the cephalometric points: S, Ba, N, ANS, PNS, A, B, Pog, Gn, Me, Po (right and left), Co (right and left) and Go (right and left) using the "paintbrush" tool, using a landmark with the size of three voxels. The cephalometric points were located in the multiplanar sections (axial, coronal and sagittal) (Figure 1G-I).

After marking the landmarks, a 3D virtual model for each landmark was created in the 3D Slicer CMF 3.0 software. Subsequently, fiducial points were marked on the virtual models of these landmarks, allowing the measurement of 13 variables (angles SNA, SNB, SNPog, NSBa, MeGoCo right and left, SNPP; and linear distances: N-ANS, ANS-Me, NS, S-Ba, N-Ba and Po-Po) with use of the "Q3DC" tool

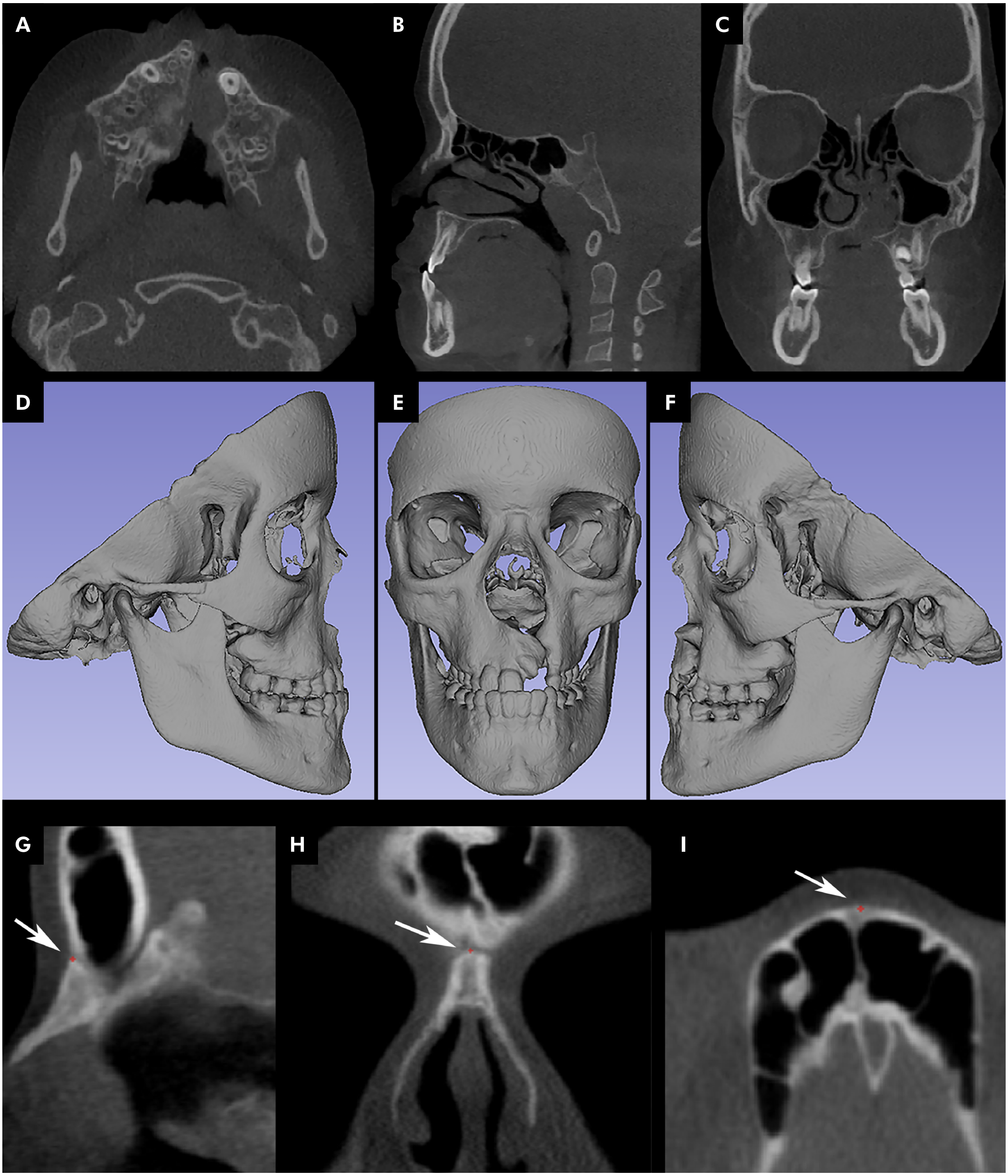

Figure 1. Multiplanar reconstructions of CBCT images and oriented three-dimensional virtual model. Axial (A), sagittal (B) and coronal (C) slices of CBCT after orientation of the head. Right side (D), frontal (E) and left side (F) views after orientation of 3D virtual model. Landmark at the nasio (N) point in the sagittal (G) coronal (H) and axial (I) sections.

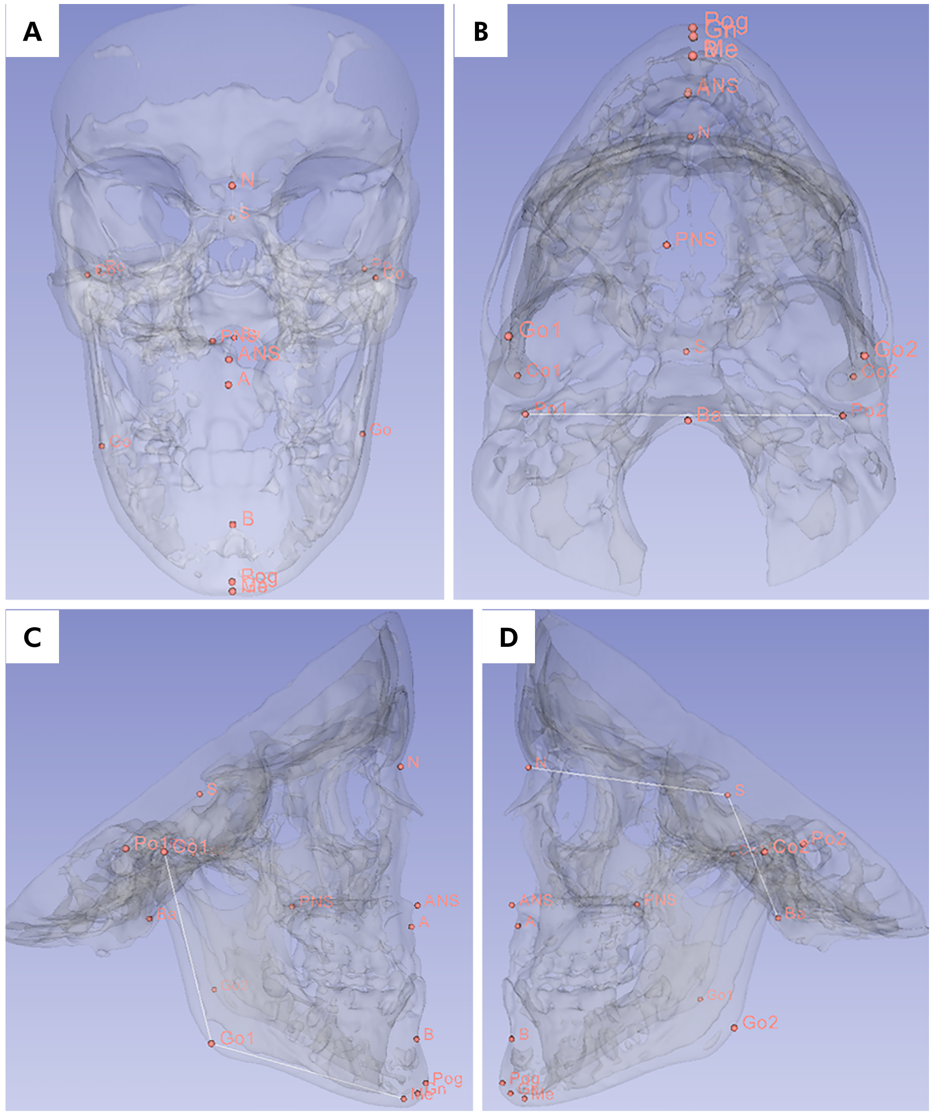

Figure 2. Fiducial points applied to the three-dimensional virtual models of landmarks. Frontal view (A), upper view showing the Po-Po linear distance (B), right side view showing the gonial angle (C) and left side view showing the NSBa angle (D).

of the 3D Slicer CMF 3.0 (Figure 2). Pitch rotation[20] of the cephalometric landmarks in the sagittal view and linear distances were measured to assess the 3D Euclidean distances between landmarks, and the spatial displacement of the landmarks in the projected X (right-left), Y (anterior-posterior) and Z (superior-inferior) components.

Statistical analysis

The chi-square test was performed to verify the homogeneity of the independent variables (gender and growth stage). The assumptions of normal distribution (Kolmogorov-Smirnov's test) and the same variance (Levene's test) were performed for the continuous and dependent variables. Comparison between groups was carried out with the Student's-*t* test considering a significance level of 5%. Statistical analysis was conducted using SPSS 21.0 software (SPSS Inc., Armonk, USA).

Results

Table presents the comparison of the means of angular and linear measurements of prepubertal

Table. Angular and linear measurements according to the stages of biological maturation of the UCLP patients.

Measures	Component	Prepubertal (n = 34) / Pubertal (n= 18)	Mean	SD	p-value
SNA	Pitch	Pre	81.09	5.25	0.028*
		Pub	77.40	6.21	
SNB	Pitch	Pre	77.74	4.66	0.761
		Pub	77.28	6.10	
NSGn	Pitch	Pre	67.27	3.97	0.375
		Pub	68.75	6.33	
NSBa	Pitch	Pre	129.37	5.64	0.065
		Pub	132.70	6.74	
MeGoCo[a]	Pitch	Pre	124.47	4.43	0.335
		Pub	125.92	6.20	
MeGoCo[b]	Pitch	Pre	125.62	4.66	0.687
		Pub	125.05	5.14	
SNPP	Pitch	Pre	8.59	3.99	0.088
		Pub	10.91	5.50	
N-ANS	X	Pre	2.35	1.55	0.926
		Pub	2.30	2.15	
	Y	Pre	5.84	2.71	0.003*
		Pub	3.28	3.13	
	Z	Pre	43.38	3.03	0.001*
		Pub	46.91	4.48	
	3D	Pre	43.94	2.96	0.003*
		Pub	47.22	4.46	
ANS-Me	X	Pre	4.09	1.86	0.666
		Pub	3.86	1.81	
	Y	Pre	10.55	4.87	0.122
		Pub	8.42	4.17	
	Z	Pre	56.99	4.43	0.117
		Pub	59.95	6.99	
	3D	Pre	58.35	4.19	0.194
		Pub	60.80	7.149	
S-Ba	X	Pre	1.01	1.04	0.151
		Pub	0.62	0.54	
	Y	Pre	18.46	2.71	0.013*
		Pub	20.69	3.41	
	Z	Pre	35.18	2.70	0.923*
		Pub	35.09	3.53	
	3D	Pre	39.85	2.55	0.273
		Pub	40.85	3.90	

Continue

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N-S	X	Pre	0.85	0.97	0.913
		Pub	0.82	0.63	
	Y	Pre	60.52	2.81	0.259
		Pub	61.45	2.77	
	Z	Pre	12.65	3.15	0.519
		Pub	13.36	4.67	
	3D	Pre	61.92	2.81	0.177
		Pub	63.06	2.89	
N-Ba	X	Pre	1.17	0.83	0.168
		Pub	0.86	0.61	
	Y	Pre	78.90	3.92	0.191
		Pub	80.88	6.93	
	Z	Pre	47.83	3.67	0.484
		Pub	46.61	8.79	
	3D	Pre	92.42	3.97	0.627
		Pub	93.55	9.33	
Po-Po	X	Pre	86.62	4.96	0.186
		Pub	88.65	5.56	
	Y	Pre	1.97	1.63	0.559
		Pub	2.26	1.72	
	Z	Pre	1.12	0.92	0.608
		Pub	1.26	1.01	
	3D	Pre	86.65	4.91	0.177
		Pub	88.70	5.55	

Pitch: angular measurements following the rotation in the right-left axis; [a]Comparison between MeGoCo angle of prepubertal and pubertal patients on the CLP side; [b]Comparison between MeGoCo angle of Prepubertal and Pubertal Patients on the non-CLP side; * Student's-*t* test. Statistically significant difference ($p < 0.05$).

and pubertal UCLP patients. The results showed that maxillary retrusion relative to the cranial base was evident in the Pubertal (SNA, 77.4° ± 6.2; N-ANS Y, 3.3 mm ± 3.1) but not in the Prepubertal Group (SNA, 81.0° ± 5.2; N-ANS Y, 5.8 mm ± 2.7), with statistically significant difference between Groups (p = 0.028). Analysis of mandibular position relative to the cranial base (SNB), and of cranial base length and cranial base angle revealed no statistically significant differences between groups; while the posterior cranial base length of UCLP patients (S-Ba Y) was significantly longer in puberty (20.7 mm ± 3.4 vs. 18.4 mm ± 2.7, *P* = 0.013). Similarly, the inter Porion distance and the vertical components of the skeletal morphology represented by mandibular gonial angle and palatal plane exhibited no statistically significant differences between Groups, except for the upper facial height (N-ANS Z), which was significantly greater (p = 0.01) in the Pubertal Group (46.9 mm ± 4.5 vs. 43.4 mm ± 3.0).

Discussion

A significantly higher value of maxillary retrusion was observed in older, pubertal UCLP patients, in comparison with younger, less mature individuals. The abnormal and impaired maxillary growth pattern in UCLP patients may result from intrinsic tissue defects and/or negative environmental factors.[21,22] Intrinsic tissue anomalies can be interpreted as abnormal growth factors affecting the midface and even the cranial base.[21] Anatomically, this structure connects the neurocranium to the facial skeleton. However, the relationship between the cranial base and maxilla in UCLP patients might be different, so that the skeletal Class III population might have smaller anterior cranial base length, and thus the cranial base angle could be associated with maxillary retrognathism.[9,22]

Although differences in the cranial base, mandibular morphology, and maxillary transverse dimension of UCLP patients have been previously described,[5] these findings have been controversial.[6,7-9,21] The lack of consensus between studies might be associated with the reduced sample size,[15] use of chronological age rather than the skeletal maturation stages,[7,8] and lack of standardization in the acquisition of radiographic examinations.[7,8,21]

Moreover, the cephalographs used in past times allowed only 2D analysis, with all the limitations inherent to the method, such as the overlapping of anatomical references, inaccurate identification of the structures, and difficulty with standardizing the geometric and energetic factors. To overcome these limitations, few studies have evaluated craniofacial morphology with the aid of CBCT scans.[1,15,23-25] However, to the best of our knowledge, to this date, only two studies have used CBCT's to evaluate the cranial base morphology of UCLP patients.[15,25] Furthermore, none of these studies that have performed 3D analysis of cranial base and/or maxillo-mandibular morphology in patients with cleft lip and palate, by means of CBCT,[1,15,23-25] compared the prepubertal and pubertal stages of skeletal maturation.

In the present sample of UCLP patients, the values of the cranial base angle (NSBa), total cranial base length (N-Ba Y), anterior cranial base length (N-S Y), and the posterior cranial base length (S-Ba Y) were greater in the Pubertal than in the Prepubertal Group, but only S-Ba Y showed statistically significant difference. These results were similar to those reported in previous cephalometric studies.[8,21] Differences in the method used to evaluate the growth stages and the use of 2D cephalograms in the previous studies might be the explanation for the minor divergences in findings between our investigation and those previously mentioned. Some components of the anterior cranial base are the earliest structures to reach maturity in shape and size, at around 7-8 years of age.[26] However, growth of the posterior cranial base (S-Ba) is closely related to skeletal age.[27-29] In this regard, a previous study has described that growth in the distance of S-Ba was constant, with significant differences between all stages CS1/2 (prepubertal), CS2/3 (pubertal) and CS4/5 (postpubertal) of skeletal maturation, in both sexes.[28] Therefore, the significantly greater posterior cranial base length observed in pubertal UCLP patients in the present study, was derived from the characteristic development of this anatomical structure during the normal growth.

The association between the cleft palate and abnormal morphology of the cranial base can be justified anatomically and functionally.[30] As the spheno-occipital synchondrosis represents remnants of the early chondrocranium, a congenital alteration, an aberrant growth or a late maturation of the cartilage tissue may affect the morphology of the cranial base.[31] Functionally, factors such as extended head posture, caused by the reduced airway size, may also affect the postnatal growth pattern of the cranial base in individuals with isolated cleft palate.[32]

As regards changes in the maxilla, maxillary retrusion relative to the cranial base (SNA and N-ANS Y) was observed to be more evident in Pubertal than Prepubertal patients. The significantly greater upper facial height (N-ANS Z) of Pubertal patients could be explained by normal facial growth. Similarly, in a study with bilateral cleft lip and palate patients, submitted only to primary surgical procedures and without orthodontic treatment, a statistically significant reduction in the SNA angle was reported between the Prepubertal and Pubertal growth stages.[17] In a recent study, UCLP patients who had been treated with the surgical lip approach, whether the palate had been operated or not, showed a smaller maxillary length, and this sagittal discrepancy increased with age.[22]

The position of the mandible relative to the cranial base (SNB), mandibular rotational pattern, and gonial angle (MeGoCo) showed no statistically significant difference between the Prepuberal and Pubertal Stages. Similar findings have also been reported in a previous study.[21] However, they reported a significantly greater anterior inferior facial height (ANS-Me) in the Pubertal Stage, whereas in our sample, despite the pubertal group having had a longer vertical ANS-Me distance (59.95 mm vs. 56.99 mm) there was no statistically significant difference between Groups.

The strength of the present study relies on the fact that all CBCT scans had been acquired and evaluated after primary surgeries for lip and palate closure and before secondary procedures (*e.g.* alveolar bone graft; orthognathic surgery). Moreover, orthodontic treatments had not been performed up to that point. Therefore, all patients in the UCLP groups had only been submitted to labioplasty and palatoplasty up to that time. Due to the retrospective cross-sectional design with use of a convenience sample, one of the limitations of the present study was the impossibility of organizing the UCLP groups (prepubertal and pubertal) according to Angle's classification. However, as there were no differences between the two groups in the distribution of types of malocclusion (Angle's classification) and gender, this limitation should have no impact on the results observed.

A better understanding of the impact of distinct patterns of craniofacial morphology, mainly in the sagittal component of the maxilla and in the posterior cranial base length could be obtained by conducting a study that included a third Group for the purpose of comparison consisting of patients with UCLP who had been submitted to secondary surgical procedures (*e.g.* alveolar bone graft; orthognathic surgery) and orthodontic treatment, and a fourth group consisting of individuals without UCLP. Therefore, further investigations are recommended since the recognition that UCLP patients could present an authentic maxillary growth pattern should guide professionals to adopt more pragmatic early dentofacial treatment protocols. These should be focused on the maxillary sagittal perspective, enabling gains in functional and esthetic aspects, consequently improving the quality of life of these individuals.

This study did not aim to evaluate facial asymmetry in patients with UCLP in the Pepubertal and Pubertal Stages of skeletal maturation. However, since we observed that the maxillary retrusion relative to the cranial base was significantly greater in the Pubertal than in Prepubertal Group, and because there are no previous studies that have performed 3D evaluation in different stages of skeletal maturation, future CBCT studies should be conducted to investigate the craniofacial morphology and asymmetry in patients with UCLP at different stages of growth.

Conclusions

Prepubertal and Pubertal UCLP patients presented distinct patterns of craniofacial morphology, mainly in the sagittal component of the maxilla and in the posterior cranial base. Pubertal UCLP patients showed greater maxillary retrusion and posterior cranial base length.

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