en at 45°, and panoramic radiographs.[9,10] These 2D radiographs can be misleading, since complex 3-dimensional (3D) structures are projected onto flat 2D surfaces, creating distortion and magnification errors.[11,12]

Cone-beam computed tomography (CBCT), a 3D imaging technique designed specifically to create images of the maxillofacial region, allows 3D reconstructions of craniofacial structures from acquired volumetric data.[13] CBCT provides high-resolution images (i.e., with an isotropic resolution ranging between 0.125 mm and 0.4 mm) with short scanning times (10 - 70 seconds), and requires low doses of radiation (up to 15 times lower than that of medical computed tomography scans).[14] CBCTs therefore provide an opportunity for multiplanar imaging and assessment of 3D information.

However, whereas many researchers have used 2D radiographs to assess mandibular asymmetry in cleft lip and palate patients,[5-7] few have used 3D imaging to investigate this phenomenon. Indeed, we could find no published studies that have evaluated mandibular asymmetry in cleft lip and palate patients using CBCT. Therefore, we undertook this study to determine (1) whether there are any differences in mandibular measurements between the cleft and non-cleft sides of UCLP patients or the right and left sides of control patients; and (2) whether there are any significant differences in mandibular asymmetry between UCLP and control patients.

MATERIAL AND METHODS

We examined the CBCT scans of 15 patients (8 males and 7 females) with UCLP (8 right and 7 left; mean age: 21.2 ± 2.1 years, range: 17.3 - 24.4 years) and 15 control patients (mean age: 22.6 ± 3.2 years, range: 17.1 - 25.2 years) that were selected from the archives of the Oral and Maxillofacial Radiology Department of Faculty of Dentistry, Dicle University. The CBCT scans were taken as part of a set of clinically necessary radiographs. Therefore, patients were not unnecessarily subjected to additional radiation, and consequently ethical committee approval was not needed. All patients attending the dental clinic of Dicle University sign an informed consent form indicating their agreement to CBCT scans.

We used CBCT scans from patients without cleft palate as controls. These patients were matched by age and gender to the UCLP patients in the study. Selection criteria for both cleft and control patients are provided in Table 1. Only cases of complete UCLP were included in the present investigation because indivi-

Table 1. Criteria for sample selection

Inclusion criteria for non-cleft patients	Inclusion criteria for cleft lip palate patients
Angle Class I skeletal relationship, according to Steiner[16];	Patients with complete unilateral cleft lip, alveolus and palate
Less than 2 mm of crowding and normal growth and development;	Patients had undergone lip and palate reconstruction surgery;
Permanent dentition;	Permanent dentition;
Menton deviation less than 2 mm from midsagittal reference line.	Menton deviation less than 2 mm from midsagittal reference line.
Lack of orthodontic treatment and/or maxillary functional orthopedic treatment;	Lack of orthodontic treatment and/or maxillary functional orthopedic treatment;
No history of trauma and systemic disease or neuromuscular deformities;	No history of trauma and systemic disease or neuromuscular deformities;
Good facial symmetry determined clinically;	Good facial symmetry determined clinically;
No signs or symptoms of TMD.	No signs or symptoms of TMD.

TMD, Temporomandibular disorder.

duals with UCLP have unilateral malformation, allowing us to use the measurements of the contralateral non-cleft side of each individual as an internal control.[15] We included patients with non-significant facial asymmetry in order to evaluate isolated asymmetry of the mandible in UCLP individuals.

Facial asymmetry was determined by the degree of menton deviation (MD) from the midsagittal reference line, as defined by Grummons and Kappeyne van de Coppello.[17]

All CBCT images were acquired using an iCAT 3D imaging device (Imaging Sciences International, Hatfield, PA, USA), set at 5.0 mA and 120 kV. Scans with a voxel size of 0.3 mm were made with a single 360-degree rotation, 9.6-second scan. According to routine image exposure protocol, patients' heads were oriented by adjusting the Frankfort plane parallel to the horizontal plane, lateral scout radiographs were taken, and small adjustments were made. This ensures inclusion of all areas of interest and minimizes head orientation errors.

For better evaluation and a precise 1-to-1 ratio, measurements of anatomic surface landmarks and reconstructed 3D models of UCLP patients were used in this study. DICOM files obtained from the CBCT scans were reconstructed using Mimics 10.0 (Materialise NV, Leuven, Belgium). This software allows the use of both Hounsfield and gray values to separate the area of interest from its surrounding structures, enabling the visualization of areas that are superimposed by other structures in the intact model. One important structure in the diagnosis of facial asymmetry, the condyle, can be evaluated separately after the mandible has been isolated from the rest of the image.[11] We used the auto-segmentation function of the software to isolate the mandibles from the images and removed the teeth above the alveolar bone of the mandibles. All landmark identifications and measurements were made using the Mimics 10.0 software. We used the landmarks described by You et al.[18] in their examination of asymmetric mandibles based on condylar, coronoid, angular, body, and chin units (Table 2). These authors used the mandibular and mental foramina as important reference points at the junction of the skeletal units. Point F was proposed as a good reference point for the mandibular and mental foramina in 3D images of the mandible[19]

Table 2. Description of mandibular landmarks used in the study

Landmark	Definition
Con_{sup} (condylion superius)	The most superior point of the condylar head
Con_{med} (condylion medialis)	The most medial point of the condylar head
Con_{lat} (condylion lateralis)	The most lateral point of the condylar head
Cor_{sup} (coronoid superius)	The most superior point of the coronoid process
F (fossa of mandibular foramen)	The most inferior point on the fossa of the mandibular foramen
J_{lat}	The most lateral and deepest point of the curvature formed at the junction of the mandibular ramus and body
J_{med}	The most medial and deepest point of the curvature formed at the junction of the mandibular ramus and body
Go_{post} (gonion posterius)	The most posterior point on the mandibular angle
Go_{mid} (gonion midpoint)	The midpoint between Go_{post} and Go_{inf} on the mandibular angle
Go_{inf} (gonion inferius)	The most inferior point on the mandibular angle
MF (mental foramen)	The entrance of the mental foramen
Me (menton)	The most inferior midpoint on the symphysis
Pog (pogonion)	The most anterior midpoint on the symphysis
B (supramentale)	The midpoint of the greatest concavity on the anterior border of the symphysis
G (genial tubercle)	The midpoint on genial tubercle

(Fig 1). Because primary intramembranous ossification begins in the mental foramen, it is generally accepted as a good point for the division of the mandibular corpus into body and chin units.[18] Therefore, we used point F as a guide to measure the skeletal unit lengths.

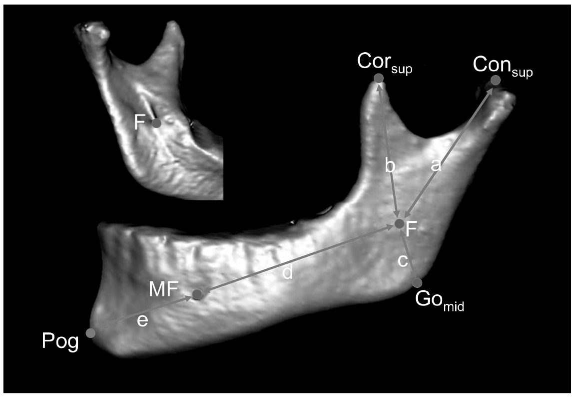

Fig 1. Landmarks and measurements used in this study. A, condylar unit length; b, coronoid unit length; c, angular unit length; d, body unit length; e, chin unit length; Cor_{sup}, coronoid superius; Con_{sup}, condylion superius; F, fossa of mandibular foramen; Go_{mid}, gonion midpoint; MF, mental foramen; Pog, pogonion.

All linear measurements were performed by controlling the localization of the landmarks in all dimensions

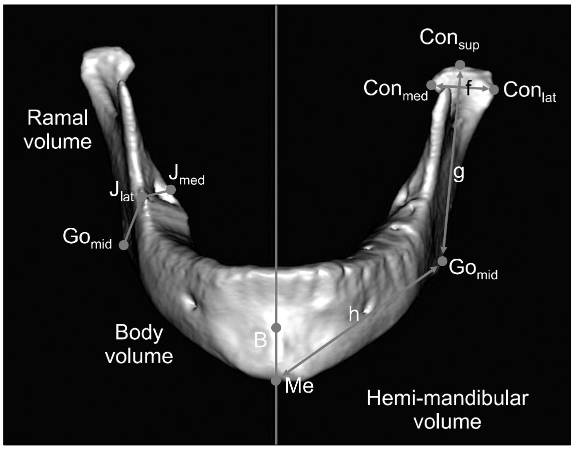

Fig 2. Landmarks and measurements used in this study. f, Condylar width; g, ramal height; h, body length; J_{lat}, the most lateral and deepest point of the curvature formed at the junction of the mandibular ramus and body; J_{med}, The most medial and deepest point of the curvature formed at the junction of the mandibular ramus and body; Go_{mid}, gonion midpoint; Con_{sup}, condylion superius; Con_{med}, condylion medialis; Con_{lat}, condylion lateralis; Me, menton.

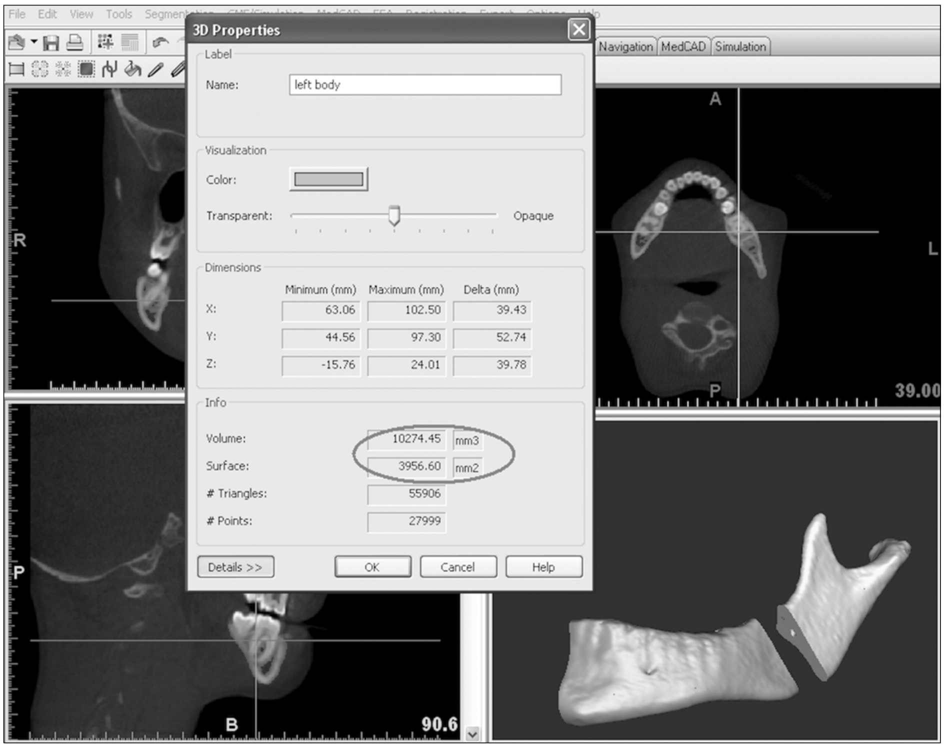

Fig 3. An example of surface and volumetric measurements.

on the reconstructed 3D surface models. The following bilateral measurements were made (Figs 1 - 3, Table 2): (1) condylar unit length: Con_{sup} - F; (2) coronoid unit length: Cor_{sup} - F; (3) angular unit length: F - Go_{mid}; (4) body unit length: F - MF; (5) chin unit length: MF - Pog; (6) condylar width: Con_{med} - Con_{lat}; (7) ramal height: Con_{sup} - Go_{mid}; (8) body length: Go_{mid} - Me; (9) hemi-mandibular volume: the mandibular volume was divided into 2 hemi-mandibular volumes by the plane connecting Me, B, and G; and (10) ramal and body volumes: hemi-mandibular volume was divided into ramal and body volumes by the plane connecting Gomid, J_{lat} and J_{med}. In addition, the surface area of all mandibular parts was calculated. All data

Table 3. Bland and Altman Plot to assess the repeatability

Measurements	Correlation	Bias	95% CI	SE	SD
Condylar width	0.04	0.05	0.011 – 0.079	0.0151	0.048
Ramal height	−0.17	0.01	−0.033 – 0.059	0.0206	0.065
Body length	−0.19	0.01	−0.070 – 0.056	0.0279	0.088
Hemi-mandibular volume	−0.36	−16.00	−41.055 – 9.055	110,755.0	35,024.0
Hemi-mandibular surface	−0.05	12,601.00	−15,904 – 41,106.44	12,601,005.0	39,847,862.0
Ramal volume	−0.01	4.00	−0.266 – 8.266	18,856.0	5,963.0
Ramal surface	−0.14	−3.70	−7.022 – −0.378	14,686.0	4,644.0
Body volume	−0.18	−1.00	−9.564 – 7.654	37,859.0	11,972.0
Body surface	0.30	9.00	2.736 – 15.264	27,689.0	8,756.0

CI, Confidence interval; SE, standard error; SD, standard deviation.

Table 4. Side-to-side comparison of the linear, surface and volumetric measurements between the cleft and non-cleft sides in UCLP patients and right and left sides in non-cleft patients

Measurements	UCLP patients					Control patients				
	Cleft side		Non-cleft side		p-value	Left side		Right side		p-value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Condylar unit length (mm)	41.50	5.41	40.70	5.02	0.247	41.98	3.84	43.53.	6.68	0.130
Body unit length (mm)	54.21	5.54	57.67	8.95	0.054	56.80	4.92	55.76	4.47	0.359
Coronoid unit length (mm)	39.10	6.43	37.00	5.85	0.046*	37.72	8.03	38.80	5.06	0.685
Angular unit length (mm)	19.64	4.90	20.01	3.92	0.645	22.81	9.58	20.79	2.90	0.487
Chin unit length (mm)	27.48	5.17	28.43	5.42	0.472	27.49	4.87	26.64	2.92	0.538
Condylar width (mm)	17.35	3.19	18.28	4.97	0.372	17.28	2.02	17.24	1.83	0.885
Ramal height (mm)	58.47	8.66	57.04	8.51	0.065	58.77	5.16	61.11	5.09	0.024*
Body length (mm)	78.26	7.33	79.71	7.85	0.088	77.67	9.34	72.12	11.83	0.021*
Hemi-mand volume (cm^3)	23.77	8.16	24.54	7.58	0.632	28.16	4.46	28.42	4.72	0.743
Hemi-mand surface (cm^2)	12.57	4.25	13.03	4.63	0.535	14.48	4.07	13.93	2.43	0.288
Ramal volume (cm^3)	8.08	3.36	7.33	2.53	0.323	8.04	1.72	7.95	1.60	0.598
Ramal surface (cm^2)	5.21	1.83	5.09	1.60	0.702	4.98	1.19	5.11	1.07	0.425
Body volume (cm^3)	16.06	6.65	16.10	4.70	0.978	20.73	3.53	20.39	3.37	0.263
Body surface (cm^2)	7.82	3.29	8.07	2.47	0.738	9.45	1.49	9.23	1.64	0.215

UCLP, Unilateral cleft lip and palate; SD, standard deviation. $^*p < 0.05$.

were measured in cm^2 or cm^3, and all landmark identifications and measurements were made by one individual to prevent interobserver variability.

To determine the errors associated with CBCT measurements, 15 of the CBCT images were randomly selected and re-measured 4 weeks after the initial measurements.

Statistical analysis

All statistical analyses were performed using the statistical package for social sciences, 13.0 (SPSS for Windows; SPSS Inc., Chicago, IL, USA). Normality of the data was tested using Shapiro-Wilks tests, and the homogeneity of variances was verified using Levene's test. All UCLP and control patient asymmetry data was normally distributed with homogeneous variance, except for gender data. Therefore, we used parametric tests to evaluate the asymmetry data.

Wilcoxon tests were used to compare genders. To compare the measurements between the cleft and non-cleft sides in UCLP patients, and the right and left sides in control patients, we used paired-sample t-tests. We performed independent *t*-tests to evaluate side-to-side differences and differences between cleft and control patients. To evaluate the differences in asymmetry between control and UCLP patients, we compared the right-left differences of controls with the cleft-non-cleft differences of UCLP patients. *p*-values less than 0.05 were considered significant. Results are reported as the means ± standard deviations.

RESULTS

A Bland and Altman plot revealed no significant differences between repeated measurements of the same radiograph (Table 3). There were also no significant differences between any of the median measurement values for male and female subjects ($p > 0.05$ for all). Therefore, data for both genders were pooled for further analyses.

Descriptive statistics and comparisons of the linear, surface, and volumetric measurements between the cleft and non-cleft sides of UCLP patients are presented in Table 4. In UCLP patients, the coronoid unit was longer on the cleft side than on the non-cleft side

Table 5. Comparison of the linear, surface and volumetric measurements between cleft lip palate and non-cleft patients

Measurements	UCLP		Control		*p*-value
	Mean	SD	Mean	SD	
Condylar unit length (mm)	41.10	5.06	42.75	5.12	0.382
Body unit length (mm)	55.94	6.73	56.28	4.19	0.867
Coronoid unit length (mm)	38.05	5.86	38.26	4.41	0.913
Angular unit length (mm)	19.83	4.17	21.80	4.50	0.223
Chin unit length (mm)	27.95	4.67	27.07	3.06	0.544
Condylar width (mm)	17.81	3.70	17.26	1.86	0.610
Ramal height (mm)	57.75	8.47	59.94	4.81	0.393
Body length (mm)	78.98	7.44	74.89	9.82	0.209
Hemi-mand volume (cm^3)	24.15	7.27	28.29	4.33	0.069
Hemi-mand surface (cm^2)	12.80	4.22	14.20	3.21	0.316
Ramal volume (cm^3)	7.70	2.62	7.99	1.63	0.719
Ramal surface (cm^2)	5.15	1.61	5.05	1.11	0.839
Body volume (cm^3)	16.08	4.99	20.56	3.35	0.008*
Body surface (cm^2)	7.94	2.53	9.33	1.52	0.082

UCLP, Unilateral cleft lip and palate; SD, standard deviation. $^*p < 0.01$.

Table 6. Intergroup comparison of side-to-side differences

Measurements	UCLP		Control		*p*-value
	Mean	SD	Mean	SD	
Condylar unit length (mm)	1.34	2.31	1.55	3.73	0.858
Body unit length (mm)	−3.12	6.55	−1.04	4.26	0.313
Coronoid unit length (mm)	1.04	4.16	1.08	10.13	0.990
Angular unit length (mm)	−0.40	3.00	−2.01	10.92	0.586
Chin unit length (mm)	3.30	3.79	−0.84	5.20	0.019*
Condylar width (mm)	−0.75	3.92	−0.04	1.05	0.504
Ramal height (mm)	2.00	2.34	2.33	3.56	0.761
Body length (mm)	−0.31	3.40	−5.54	8.28	0.032*
Hemi-mand volume (cm^3)	2,518.59	5,545.97	262.14	3,031.91	0.178
Hemi-mand surface (cm^2)	1,193.81	2,550.72	552.61	1,936.96	0.044*
Ramal volume (cm^3)	563.39	2,867.08	−92.18	661.06	0.396
Ramal surface (cm^2)	394.43	1,168.91	134.97	402.47	0.507
Body volume (cm^3)	809.00	566.26	−342.52	1,613.37	0.455
Body surface (cm^2)	305.60	2,884.58	−215.36	715.20	0.503

UCLP, Unilateral cleft lip and palate; SD, standard deviation. $^*p < 0.05$.

(p = 0.046). This was the only significant difference between the cleft and non-cleft sides of these patients. Only the ramal height (p = 0.024) and body length (p = 0.021) were significantly different on the right and left sides of control patients (Table 4). Therefore, the data for both sides in each group were pooled for further statistical analysis.

Comparison of measurements between groups indicated that the body volume was significantly lower in UCLP patients than in controls (16.08 ± 4.99 cm^3 vs. 20.56 ± 3.35 cm^3; p = 0.008; Table 5). Comparison of the differences between the cleft and non-cleft sides of UCLP patients with the differences between the left and right sides of control patients indicated that side-to-side body length differences were greater in the control group than in the UCLP group (p = 0.032), whereas side-to-side differences in chin unit length and hemi-mandibular surface area were greater in the UCLP group than in the control group (p = 0.019 and p = 0.044, respectively; Table 6).

DISCUSSION

In UCLP patients, facial and nasomaxillary skeletal asymmetries are commonly present with the nasomaxillary complex being more asymmetric in affected individuals than in non-cleft controls.[20] Previous 2D studies on facial asymmetry have reported that the mandible appears to be the leading factor in facial asymmetry.[21,22] Because quantitative measurement is a key element in the diagnosis of asymmetry, 3D structures cannot be properly analyzed with 2D radiographs.[11] We therefore used 3D images to assess mandibular asymmetry in cleft lip and palate patients.

Previous studies have shown that UCLP patients reach the postpubertal growth spurt at a later age than do non-cleft patients.[23] da Silva Filho et al.[24] reported that cleft patients, irrespective of the type of cleft, have smaller mandibles than non-cleft patients at adulthood. Krogman et al.[25] used postero-anterior cephalometric radiographs to assess craniofacial growth and noted a significantly larger gonial height in the UCLP group and bilateral CLP group during early and late childhood. Further, Laspos et al.[26] studied postero-anterior radiographs of children and reported that UCLP patients had mandibles that were more asymmetric than those of controls. In contrast, Athanasiou et al.[27] found that those children with cleft palates who have undergone corrective surgery may have normal growth rates. In the current study, only post-adolescent patients were included to eliminate possible growth rate differences. We are therefore unable to discuss the cause-and-effect relationship between mandibular asymmetry and growth.

Liukkonen et al.[1] reported that facial asymmetry is a natural phenomenon often due to differences in mandibular dimensions on the right and left sides. They also concluded that healthy young subjects generally have some degree of mandibular asymmetry. In the present study, side-to-side comparisons of control patients revealed statistically significant differences in ramal height and body length. We attribute the differences in these measurements to natural asymmetry. On the other the hand, the side-to-side comparison in the UCLP group revealed that the coronoid unit length was significantly longer on the cleft side. The coronoid unit is affected by the temporalis muscle[28]; however, side-to-side comparison of temporalis muscle volume revealed no statistical difference in patients with facial asymmetry.[29] It is difficult to attribute the difference in coronoid unit length directly to muscular activity because the muscles and other soft tissues were not considered in the current study.

Side-to-side differences in chin unit length, body unit length, and hemi-mandibular surface measurements were significantly different between the groups in this study. However, no statistically significant differences were found in any of the other measurements considered. These differences may be related to genetic factors or to functional activity of the skeletal muscular system, particularly in the masticatory apparatus.

According to Laspos et al.,[5] UCLP patients may have cranial base/temporal region anomalies that are responsible for asymmetry of the lower facial skeleton. Smahel and Brejcha[6] studied the lateral and PA radiographs of 58 UCLP patients (32 complete CLP and 26 incomplete clefts of the palate) and found no significant differences between the two cleft groups, except for a shorter mandibular ramus in complete UCLP patients. Smahel and Müllerová[30] used lateral and posteroanterior radiographs to study the craniofacial morphology in UCLP patients prior to palatoplasty and detected significant shortening of the mandibular body and ramus. In contrast, Horswell and Levant investigated 16 complete UCLP patients and found that the mandible was normal in every dimension.[31] Kurt et al.[7] compared the condylar, ramal, and condylar plus ramal height values on panoramic radiographs and found no statistically significant differences except gonial angle, and they considered that this difference might result from a compensation mechanism of the mandible on the cleft side. In the current study, only body volume was significantly different between cleft and non-cleft patients. We attribute the differences between our results and those of earlier studies to the use of different research methods and landmarks used for assessment. Additionally, differences in body volume may result from muscular activity and functional adaptation to soft tissue disharmonies. However, these were not considered in the present study. Further study is needed to understand the role of soft tissues, including muscle volume and muscle activity, in the observed mandibular asymmetry in UCLP patients.

One limitation of this study is the small sample size. To overcome this limitation, patients' age and gender were homogenized, and the same author carefully performed all measurements. The high precision of CBCT quantitative analyses contributes to the reliability of the measurements rendering small sample sizes acceptable.[32] Future studies with large sample sizes are needed for further explore facial asymmetry in UCLP patients.

CONCLUSION

Mandibular asymmetry was evaluated 3-dimensionally using the CBCT data of UCLP patients. From this evaluation, we conclude the following:

1. There is no statistically significant difference between genders in mandibular asymmetry measurements in either group.
2. In the UCLP group, coronoid unit length was significantly longer on the cleft side than on the non-cleft side. Only ramal height and body length were significantly different between the left and right sides of non-cleft control subjects.
3. Although body volume was larger in UCLP patients

than in controls, both groups had similarly symmetrical mandibles.

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