Long-term facial changes and clinical correlations in patients with treated acromegaly: a cohort study

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Abstract

Background: Facial abnormality is the most significant feature in acromegaly patients. However, it is unclear whether and how patient facial appearance improves after treatment. This study aimed to identify 3D facial changes in acromegaly patients after surgical treatment.

Methods: This study included 30 acromegaly patients who underwent resection of a pituitary GH adenoma. The location and extent of facial changes were identified by comparing baseline and 2-year follow-up 3D images of the face. Relationships between facial changes and GH and IGF-1 were evaluated with simple or multivariable linear regression models.

Results: Significant soft tissue improvements were observed in acromegaly patients with complete remission, especially in the nose and lip region. Significant reductions in nasal width (3.46 mm, $P < 0.001$), tip protrusion (1.18 mm, $P = 0.003$), face curve length (3.89 mm, $P = 0.004$) and vermilion area (1.42 cm³, $P = 0.001$) were observed at the 2-year follow-up. Further, changes in nasal width were associated with decreases in GH ($\beta = 4.440$, $P = 0.017$), the GH nadir ($\beta = 4.393$, $P = 0.011$) and IGF-1 ($\beta = 5.263$, $P = 0.002$). The associations were maintained after adjusting for confounders.

Conclusions: Acromegaly patients achieved considerable facial improvements after surgical treatment. The change in nose width was associated with GH and IGF-1 decrease. Better control of patient hormone levels after surgery improves patient facial recovery.

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Introduction

Acromegaly is a chronic progressive endocrine disease with an occult onset. Approximately 95% of patients with acromegaly suffer from pituitary growth hormone (GH) adenomas (1). Long-term, excessive secretion of GH and IGF-1 leads to excessive hyperplasia of soft tissues, bones and cartilage throughout the body, causing changes in the face, hypertrophy of the hands and feet, thick skin, and enlarged internal organs, bones and joints. Facial abnormalities can cause patients to lack self-confidence and suffer from psychological trauma. Furthermore,

abnormalities can cause abnormal maxillofacial function and significantly reduce patient quality of life (QoL) (2, 3).

Acromegaly can be effectively treated after diagnosis. Studies have shown that successful treatment may partially reverse thickening of articular cartilage and symptoms of sleep apnoea (4, 5). Understanding the quantitative changes in patient appearance after treatment are greatly significant for assessing disease prognosis and studying the pathophysiological characteristics of this disease. However, there are currently no prospective studies that

quantitatively analyse facial changes in patients. Although patients are very concerned about facial changes after treatment, it is often difficult for doctors to accurately answer their questions.

Two-dimensional photos are often used for facial analysis of acromegaly patients. With the advancement of computer-aided diagnostic technology, artificial intelligence can improve the diagnostic efficiency of acromegaly by comparing differences in the face between normal people and acromegaly patients (6, 7). However, 2D photographs are difficult to quantitatively analyse, and a substantial amount of spatial information is lost. Recently, 3D stereo photography has gradually advanced and been applied in the medical field. This method can obtain detailed information, including length, depth, and volume, to comprehensively evaluate changes in the face or limbs (8). In our previous studies, 3D stereo photography was used to describe the face of acromegaly patients and quantitatively evaluate structural abnormalities such as nose width, length, and height; upper and lower lip thickness; nasolabial angle and nasofrontal angle (9).

The study utilized 3D imaging technology to collect 3D facial images of acromegaly patients before and after transnasal sphenoid pituitary adenoma resection. This study aimed to quantitatively analyse preoperative and postoperative facial changes in acromegaly patients and further explore relationships between these changes and GH and IGF-1 levels.

Methods

Participants

This is the first prospective cohort study focusing on postoperative facial changes in Chinese acromegaly patients (chictr.org, ChiCTR1900021359). This study prospectively enrolled acromegaly patients who were admitted to the Department of Neurosurgery, Peking Union Medical College Hospital (PUMCH), China from January 2017 to August 2017. The inclusion criteria were (i) patients of both sexes who were 18 years or older and had clinical manifestations of acromegaly (10); (ii) patients with IGF-1 levels greater than sex- and age-matched normal levels (age-related reference range of IGF-1 levels at PUMCH were defined as follows: 18–20 years, 127–584 ng/mL; 21–25 years, 116–358 ng/mL; 26–30 years, 117–329 ng/mL; 31–35 years, 115–307 ng/mL; 36–40 years, 109–284 ng/mL; 41–45 years, 101–267 ng/mL; 46–50 years, 94–252 ng/mL; 51–55 years, 87–238 ng/mL; 56–60 years, 81–225 ng/mL; 61–65 years,

75–12 ng/mL) and GH nadir glucose inhibition test values > 0.4 ng/mL (1); (iii) patients who were newly diagnosed with the disease and received initial treatment (i.e. patients who had never received pituitary surgery, drug therapy, or radiation therapy before enrolment); (iv) patients with a pituitary adenoma based on enhanced MRI of the pituitary gland; (v) other pituitary-related hormones at normal reference levels. The exclusion criteria were (i) patients with elevated GH and IGF-1 levels caused by non-pituitary GH adenomas; (ii) patients who did not undergo surgery and (iii) patients who could not complete a facial evaluation after surgery.

This study was approved by the PUMCH Clinical Ethics Committee (approval ID: ZS-1324). Written informed consent was obtained from all participants. The researchers were authorized to use the participant photos and clinical data for the clinical study and for academic publication.

Study design

This was a prospective cohort study. We recorded clinical data from patients before surgery (age; sex; height weight; BMI; disease course; random GH, GH nadir, and IGF-1 levels). The random GH, GH nadir, and IGF-1 levels were measured 1–2 weeks preoperatively. All patients underwent 3D facial imaging before surgery. After excluding surgical contraindications, all of the patients underwent transsphenoidal pituitary tumour resection. If there were no surgical complications, patients were discharged 3 days after the operation. The patients were then followed up in the outpatient service. At the 2-year follow-up, facial 3D imaging was performed. If the patients did not meet the biochemical cure standard, including the presence of residual tumours or recurrent tumours, and had high GH and IGF-1 levels, we re-evaluated their conditions and prepared an optimized treatment. The complete remission criteria included normal postoperative IGF-1 levels and GH nadir values (based on a glucose tolerance test) below 0.4 ng/mL (11).

The disease course refers to the time period between acromegaly symptom presentation and diagnosis. The GH nadir value was obtained by an oral glucose tolerance test (OGTT). GH and IGF-1 were measured by chemiluminescence assays using an IMMULITE 2000 analyser (Siemens Healthcare Diagnostics) in a clinical laboratory at PUMCH. The assay procedure was described in a previously published study (12). The percent decrease in GH and IGF-1 was calculated as follows: percentage decrease = $(\text{value}_{\text{baseline}} - \text{value}_{\text{follow-up}}) / \text{value}_{\text{baseline}} \times 100\%$.

Three-dimensional imaging and analysis

A VECTRA H1-270 camera (Canfield Scientific, Parsippany, NJ) was used for 3D imaging. Facial 3D imaging was performed by a plastic surgeon with more than 5 years of imaging experience. Each patient sat in front of a well-lit white background. Patients shaved their beard or moustache, removed their hats and glasses, their ears were visible, and patients with long hair used a headband to keep their hair out of their face. Each patient stood against the wall, relaxed their face, opened their eyes, closed their mouth, and looked ahead in a natural manner. Based on the instruction manual for the 3D camera, photos were taken that included antero-posterior and lateral (45°) views of both sides of the face.

Face measurements were performed using Mirror software (Canfield Scientific, Parsippany, NJ); each measurement was performed in duplicate, and the mean was calculated. According to a standard procedure reported by Farkas *et al.* (13), surface landmarks (Fig. 1) were first marked on each patient's face, including the glabella (g); nasion (n); pronasale (prn); subnasale (sn); alare (al); labiale superius (ls); labiale inferius (li); stomion (sto); cheilion (ch); gnathion (gn); zygon (zy); endocanthion (en) and exocanthion (ex). The definition of each landmark is provided in Table 1.

The following measurements were performed:

1. Nose: nasal width (al-al), nasal length (n-prn), nasal curve length (n-prn-sn), tip protrusion (sn-prn),

nasofrontal angle (g-n-prn) and columella-labial angle (prn-sn-ls).

2. Labio-oral region: mouth width (ch-ch), height of the upper lip vermilion (ls-sto), height of the lower lip vermilion (sto-li), and vermilion area.
3. Orbits: biocular diameter (ex-ex) and intercanthal distance (en-en).
4. Face: face length (n-gn), height of the upper face (n-sto), height of the lower face (sto-gn), face curve length (n-gn) and face width (zy-zy).

Statistical analysis

Descriptive results are expressed as the mean $\pm$ standard deviation (s.d) for continuous variables or as the number of participants (percentages) for categorical variables. The facial parameters were tested for normality by Shapiro-Wilk test. The significance of facial changes between baseline and the 2-year follow-up were evaluated using paired *t*-tests. To investigate the relations between facial changes and GH, the GH nadir and IGF-1, simple and multivariable linear regression analyses were conducted. In model 1, simple linear regression analyses were performed without adjustments. In model 2, multivariable linear regression analyses were conducted after adjusting for sex, age and BMI. In model 3, adjustments were made for sex, age, BMI and disease course. Results are expressed as the regression coefficient (β) with the 95% CI. *P*-values (two-tailed) <0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS statistics for Windows (version 21.0; IBM Corp).

Results

Participant characteristics

Patients were carefully screened for the inclusion and exclusion criteria. A total of 53 acromegaly patients were included in the study. The patients underwent 3D facial appearance evaluations and random GH, GH nadir, and IGF-1 tests before surgery. Among these patients, 23 were unable to complete the 2-year follow-up and were excluded from the study. Finally, data from 30 patients were available for analysis.

The clinical features of patients are summarized in Table 2. The mean age of these patients was 41.3 years, and 1/3 of patients were women. The mean BMI was 25.94 kg/m², and the mean disease course was 69.77 months. According to the tumour diameter, the patients

Figure 1

Landmarks used in face measurements. g, glabella; n, nasion; prn, pronasale; sn, subnasale; al, alare; ls, labiale superius; li, labiale inferius; sto, stomion; ch, cheilion; gn, gnathion; zy, zygon; en, endocanthion and ex, exocanthion. A full colour version of this figure is available at <https://doi.org/10.1530/EJE-20-0962>.

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Table 1 Analysed anthropometric landmarks.

Landmark	Abbreviation	Definition
glabella	g	The most prominent midline point between the eyebrows
endocanthion	en	The point at the inner commissure of the eye fissure
exocanthion	ex	The point at the outer commissure of the eye fissure
nasion	n	The point in the midline of both the nasal root and the nasofrontal suture
pronasale	prn	The most anterior midpoint of the nasal tip
subnasale	sn	The midpoint on the nasolabial soft tissue contour between the columella crest and the upper lip
alare	al	The most lateral point on each alar contour
labiale superius	ls	The midpoint of the upper vermilion line
labiale inferius	li	The midpoint of the lower vermilion line
stomion	sto	The imaginary point at the crossing of the vertical facial midline and the horizontal labial fissure between gently closed lips, with teeth shut in natural position
cheilion	ch	The point located at each labial commissure
gnathion	gn	The lowest median landmark on the lower border of the mandible
zygion	zy	The most lateral point of each zygomatic arch

were divided into the micro-adenoma (less than 10 mm), macro-adenoma (10 and 30 mm), and giant adenoma (larger than 30 mm). As a result, 5 patients had micro-adenoma, 22 patients had macro-adenoma, and 3 patients had giant adenoma. The baseline GH level was 22.79 ng/mL (s.d.=25.25), the GH nadir level was 15.18 ng/mL (s.d.=18.55), and the mean IGF-1 level was 854.07 ng/mL (s.d.=264.88). At the 2-year follow-up, the mean GH level was 2.61 ng/mL (s.d.=4.01), the mean GH nadir level was 1.29 ng/mL (s.d.=2.63), and the mean IGF-1 level was 360.70 ng/mL (s.d.=243.08). According to the criteria for complete remission, 12 patients had not achieved complete remission 2 years after surgery, while 18 patients

achieved complete remission. The characteristics of the nose, labio-oral region, orbits and face of the 30 patients at baseline and the 2-year follow-up are described in Supplementary Table 1 (see section on [supplementary materials](#) given at the end of this article).

Identification of 3D facial changes

We compared 3D changes in patient facial appearance at baseline and the 2-year follow-up. All of the facial parameters in this study were continuous data, and the difference values were normally distributed. The heat map shows that significant facial improvement occurred in the nose and lip region. The overlay view clearly shows the restoration of side contours and shrinkage of the alae nasi. Typical cases are presented in [Figs 2](#) and [3](#).

According to the remission criteria, patients were divided into an incomplete remission group and a complete remission group. Further quantitative analysis was performed to examine the facial, orbital, nasal and labio-oral areas in both groups ([Tables 3](#) and [4](#)).

Nose parameters

In the complete remission group, significant improvements in all nose parameters except nasal length were observed at the 2-year follow-up. There was a significant decrease in nasal width (3.46 mm, $P < 0.001$), nasal curve length (1.86 mm, $P = 0.002$) and a reduction in tip protrusion (1.18 mm, $P = 0.003$). The nasofrontal angle (3.23°, $P = 0.002$) and columella-labial angle (2.71°, $P = 0.044$) increased, making the face flatter. In the incomplete remission group, nasal width also decreased significantly (2.06 mm, $P = 0.002$), although other parameters were not significantly different.

Table 2 Clinical characteristics of the study participants.

	Mean (s.d.) or n (%)
Gender	
Male	20 (66.7%)
Female	10 (33.3%)
Age (years)	41.30 (10.41)
Height (cm)	171.47 (7.39)
Weight (kg)	76.81 (14.14)
BMI (kg/m ²)	25.94 (3.25)
Disease duration (months)	69.77 (58.62)
Adenoma size	
Micro-adenoma (< 10 mm)	5 (16.7%)
Macro-adenoma (10–30 mm)	22 (73.3%)
Giant adenoma (> 30 mm)	3 (10.0%)
GH (ng/mL)	
Baseline	22.79 (25.25)
2-year follow-up	2.61 (4.01)
GH nadir (ng/mL)	
Baseline	15.18 (18.55)
2-year follow-up	1.29 (2.63)
IGF-1 (ng/mL)	
Baseline	854.07 (264.88)
2-year follow-up	360.70 (243.08)

GH, growth hormone; IGF-1, insulin-like growth factor 1.

Figure 2

Typical case 1. A 34-year-old female acromegaly patient had random GH, GH nadir and IGF-1 levels of 25.6 , 17 and 605 ng/mL, respectively, before surgery and underwent transsphenoidal pituitary tumour resection. Two years after surgery, her random GH, GH nadir and IGF-1 levels decreased to 2.0 , 0.37 , and 206 ng/mL, respectively. Panels A and B show 3D frontal and lateral images of her face before and 2 years after surgery, respectively. Panel C shows the location and extent of facial changes with a heat map (green indicates that the difference is close to zero, and red indicates a decrease). Panel D shows significant improvements in lateral face contour and alae nasi in the overlay view. A full colour version of this figure is available at <https://doi.org/10.1530/EJE-20-0962>.

Labio-oral parameters

All labio-oral parameters, including mouth width (0.96 mm, $P = 0.034$), height of the upper lip vermillion (0.46 mm, $P = 0.031$), height of the lower lip vermillion (1.26 mm, $P = 0.001$) and vermillion area (1.42 cm³, $P = 0.001$), significantly decreased at the 2-year follow-up in the complete remission group. In the incomplete remission group, only the height of the lower lip vermillion (1.18 mm, $P = 0.001$) and vermillion area (0.60 cm³, $P = 0.034$) significantly decreased.

Orbit parameters

Biocular diameters significantly decreased in both the complete remission group (1.52 mm, $P = 0.003$) and the incomplete remission group (1.81 mm, $P = 0.046$). Inter-canthal distances did not significantly change in either group.

Face parameters

In the complete remission group, face length (1.60 mm, $P = 0.023$), height of the lower face (1.68 mm, $P = 0.023$), and face curve length (3.89 mm, $P = 0.004$) were significantly reduced at the follow-up compared with before surgery. In the incomplete remission group, only face curve length significantly changed (3.15 mm, $P = 0.009$). The height of the upper face and face width at baseline and the 2-year follow-up in either group.

Associations between GH, IGF-1 and facial improvements

Table 5 shows the results of simple and multivariable linear regression analyses between GH or IGF-1 and changes in nasal width, vermillion area and face curve length. Although significant improvements were found

Figure 3

Typical case 2. A 27-year-old male acromegaly patient had random GH, GH nadir and IGF-1 levels of 34.6, 31.5 and 1122 ng/mL, respectively, before surgery and underwent transsphenoidal pituitary tumour resection. Two years after surgery, his random GH, GH nadir and IGF-1 levels decreased to 0.1, 0.05, and 208 ng/mL, respectively. Panels A and B show 3D frontal and lateral images of his face before and 2 years after surgery, respectively. Panel C shows the location and extent of facial changes with a heat map. Panel D shows significant improvements in lateral contour and alae nasi. A full colour version of this figure is available at <https://doi.org/10.1530/EJE-20-0962>.

at the 2-year follow-up for other facial parameters, these parameters were not significantly associated with GH or IGF-1 (data not shown).

The change in nasal width was inversely associated with postoperative GH ($\beta = -0.266$, $P = 0.028$) and GH nadir levels ($\beta = -0.378$, $P = 0.028$) after adjusting for sex, age and BMI or further adjusting for disease course. A significant correlation was observed between nasal width improvements and GH decreases ($\beta = 4.440$, $P = 0.017$) as well as between nasal width improvements and GH nadir decreases ($\beta = 4.393$, $P = 0.011$). These associations were maintained when adjusting for covariates in model 2 and model 3. Moreover, nasal width improvements were correlated with postoperative IGF-1 levels ($\beta = -0.004$, $P = 0.019$) and IGF-1 decreases ($\beta = 5.263$, $P = 0.002$) in the unadjusted model. Notably, the results remained

significant in the partially and completely adjusted models ($P < 0.001$).

A reduction in vermilion area was associated with GH decreases in both the unadjusted and adjusted models (model 1: $\beta = 2.772$, $P = 0.014$; model 2: $\beta = 2.705$, $P = 0.024$; model 3: $\beta = 2.414$, $P = 0.041$); GH nadir decreases after adjustment in model 3 ($\beta = 2.307$, $P = 0.037$); IGF-1 decreases in the unadjusted ($\beta = 2.114$, $P = 0.048$) and adjusted models.

A change in face curve length was significantly associated with GH decreases in the unadjusted simple linear regression analysis ($\beta = 7.970$, $P = 0.030$) and fully adjusted multivariable linear regression analyses ($\beta = 7.510$, $P = 0.033$). No correlations were found between face curve length reductions and postoperative GH, GH nadir or IGF-1 levels.

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Table 3 Quantitative facial changes of patients with complete remission at baseline and 2 years after surgical treatment. Results are expressed as mean $\pm$ s.e., or as mean (95% CI). Comparison between baseline and 2-year follow-up measurements was performed using paired *t*-test.

	Complete remission (n = 18)			
	Baseline	Follow-up	Changes	p
GH (ng/mL)	20.82 $\pm$ 23.46	1.17 $\pm$ 2.30	−19.66 (−31.49, −7.83)	0.003
GH nadir (ng/mL)	13.25 $\pm$ 13.95	0.21 $\pm$ 0.10	−13.04 (−20.00, −6.09)	0.001
IGF-1(ng/mL)	869.72 $\pm$ 258.48	251.56 $\pm$ 91.88	−618.17 (−750.43, −485.91)	<0.001
Nose parameters				
Nasal width (mm)	46.37 $\pm$ 4.06	42.91 $\pm$ 4.17	−3.46 (−4.62, −2.30)	<0.001
Nasal length (mm)	50.21 $\pm$ 5.60	49.72 $\pm$ 5.22	−0.49 (−1.20, 0.22)	0.164
Nasal curve length (mm)	73.20 $\pm$ 7.41	71.34 $\pm$ 7.25	−1.86 (−2.97, −0.76)	0.002
Nasal tip protrusion (mm)	19.69 $\pm$ 2.85	18.51 $\pm$ 3.04	−1.18 (−1.89, −0.48)	0.003
NFA (degree)	140.77 $\pm$ 7.82	144.00 $\pm$ 8.87	3.23 (1.35, 5.11)	0.002
CLA (degree)	103.92 $\pm$ 14.81	106.64 $\pm$ 13.85	2.71 (0.09, 5.34)	0.044
Labio-oral parameters				
Mouth width (mm)	53.98 $\pm$ 3.18	53.02 $\pm$ 3.56	−0.96 (−1.83, −0.08)	0.034
Height of the upper lip vermillion (mm)	11.58 $\pm$ 1.58	11.13 $\pm$ 1.50	−0.46 (−0.86, −0.05)	0.031
Height of the lower lip vermillion (mm)	12.65 $\pm$ 2.39	11.38 $\pm$ 2.68	−1.26 (−1.92, −0.62)	0.001
Area of the vermillion (cm ³)	12.80 $\pm$ 2.43	11.38 $\pm$ 1.95	−1.42 (−2.17, −0.67)	0.001
Orbits parameters				
Biocular diameter (mm)	100.19 $\pm$ 4.94	98.66 $\pm$ 5.17	−1.52 (−2.45, −0.59)	0.003
Intercanthal distance (mm)	36.87 $\pm$ 2.97	36.68 $\pm$ 3.23	−0.19 (−0.79, 0.40)	0.500
Face parameters				
Face length (mm)	132.29 $\pm$ 8.68	130.69 $\pm$ 8.76	−1.60 (−2.94, −0.25)	0.023
Height of the upper face (mm)	82.71 $\pm$ 4.00	81.78 $\pm$ 3.86	−0.93 (−1.96, 0.10)	0.074
Height of the lower face (mm)	52.84 $\pm$ 5.75	51.16 $\pm$ 5.29	−1.68 (−3.09, −0.26)	0.023
Face curve length (mm)	166.29 $\pm$ 14.48	162.4 $\pm$ 13.20	−3.89 (−6.32, −1.46)	0.004
Face width (mm)	131.62 $\pm$ 12.34	129.8 $\pm$ 12.68	−1.82 (−3.88, 0.24)	0.079

CLA, columella-labial angle; NFA, nasofrontal angle .

Discussion

Facial abnormality is the most significant feature in acromegaly patients, and acromegaly patients frequently want to know whether their facial appearance will improve after treatment. However, it was previously unclear whether facial appearance improves after treatment. This study is the first long-term cohort study to use 3D imaging to examine facial changes in acromegaly patients 2 years after surgery. Two-dimensional imaging was used in most previous studies that addressed facial changes in acromegaly patients (14, 15). However, the face is a complex 3D structure. Two-dimensional imaging cannot obtain all facial information; thus, changes in area, depth, and angle are often ignored (16, 17). After 3D image registration, the main areas of facial improvement can be directly visualized through overlay views and heat maps.

Previous cross-sectional studies indicated that there are significant differences between acromegaly patients after treatment and the normal population. In 2015, Wagenmakers *et al.* evaluated facial changes in 16 acromegaly patients in long-term remission and compared

those changes with facial features of 16 normal people. The results showed that compared with faces of individuals in the control group, faces of acromegaly patients were significantly wider, and in some acromegaly patients, typical skin soft tissue abnormalities were also observed (18). In 2016, a multi-centre study compared the hands of acromegaly patients who underwent surgery over 2 years ago with the hands of matched normal people. The results showed that even after a recovery period of at least 2 years, the finger length and width of acromegaly patients remained significantly different from those of individuals in the normal group (19). However, these studies could not answer questions about how patients changed after surgery. In addition, facial abnormalities between different patients have significant individual differences; therefore, the longitudinal comparison of individual images before and after treatment is more meaningful. This study was a prospective cohort study that addressed these important issues through a 2-year follow-up.

Our study, for the first time, quantified the reverse of soft tissue hypertrophy after elimination of the effects of high GH and IGF-1 levels via surgery. We found that

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Table 4 Quantitative facial changes of patients with incomplete remission at baseline and 2 years after surgical treatment. Results are expressed as mean $\pm$ s.e., or as mean (95% CI). Comparison between baseline and 2-year follow-up measurements was performed using paired *t*-test.

	Incomplete remission (n = 12)			
	Baseline	Follow-up	Changes	p
GH (ng/mL)	25.73 $\pm$ 28.54	4.79 $\pm$ 5.07	-20.94 (-36.51, -5.37)	0.013
GH nadir (ng/mL)	18.08 $\pm$ 2.32	2.93 $\pm$ 3.65	-15.15 (-28.82, -1.48)	0.033
IGF-1 (ng/mL)	830.58 $\pm$ 284.12	524.42 $\pm$ 306.60	-306.17 (-430.85, -181.48)	<0.001
Nose parameters				
Nasal width (mm)	45.37 $\pm$ 3.91	43.31 $\pm$ 4.26	-2.06 (-3.17, -0.94)	0.002
Nasal length (mm)	50.01 $\pm$ 6.85	50.67 $\pm$ 7.16	0.66 (-0.42, 1.75)	0.206
Nasal curve length (mm)	71.36 $\pm$ 8.74	71.11 $\pm$ 9.12	-0.25 (-1.57, 1.06)	0.682
Nasal tip protrusion (mm)	18.29 $\pm$ 1.85	17.44 $\pm$ 2.15	-0.85 (-1.70, 0.01)	0.052
NFA (degree)	141.13 $\pm$ 7.68	142.24 $\pm$ 8.62	1.11 (-1.44, 3.66)	0.358
CLA (degree)	107.67 $\pm$ 13.31	106.23 $\pm$ 13.17	-1.44 (-4.99, 2.11)	0.391
Labio-oral parameters				
Mouth width (mm)	54.60 $\pm$ 3.54	52.96 $\pm$ 3.59	-1.64 (-3.82, 0.54)	0.126
Height of the upper lip vermillion (mm)	11.99 $\pm$ 2.25	11.30 $\pm$ 2.30	-0.68 (-1.64, 0.27)	0.145
Height of the lower lip vermillion (mm)	11.79 $\pm$ 2.54	10.61 $\pm$ 2.49	-1.18 (-1.99, -0.36)	0.009
Area of the vermillion (cm ³)	12.42 $\pm$ 2.86	11.82 $\pm$ 3.03	-0.60 (-1.14, -0.05)	0.034
Orbits parameters				
Biocular diameter (mm)	102.11 $\pm$ 8.99	100.31 $\pm$ 8.36	-1.81 (-3.58, -0.03)	0.046
Intercanthal distance (mm)	36.58 $\pm$ 3.30	36.70 $\pm$ 3.27	0.12 (-0.77, 1.01)	0.771
Face parameters				
Face length (mm)	128.32 $\pm$ 11.23	127.07 $\pm$ 10.7	-1.24 (-2.70, 0.21)	0.087
Height of the upper face (mm)	80.44 $\pm$ 7.43	80.16 $\pm$ 7.58	-0.27 (-1.46, 0.92)	0.624
Height of the lower face (mm)	49.29 $\pm$ 5.59	47.90 $\pm$ 5.18	-1.40 (-3.24, 0.45)	0.124
Face curve length (mm)	159.90 $\pm$ 16.86	156.75 $\pm$ 15.58	-3.15 (-5.34, -0.96)	0.009
Face width (mm)	129.09 $\pm$ 10.09	127.02 $\pm$ 8.56	-2.07 (-4.42, 0.29)	0.080

CLA, columella-labial angle; NFA, nasofrontal angle.

there were several important facial changes, mainly in the nose and lip region, in the complete remission group at the 2-year follow-up. Interestingly, our previous 3D study revealed that there are significantly abnormal areas of soft tissue in the lips and nose of acromegaly patients (9). In the present study, the patients with complete remission showed significantly reduced nasal width and tip protrusion and increased nasofrontal and columella-labial angles. The patients' lips also significantly changed after treatment; patients with complete remission exhibited reduced mouth width, thinner upper and lower lips and smaller vermillion areas. Most of these changes were in soft tissue rather than skeletal structure. These results are consistent with the cephalometric assessment reported by Dostalova *et al.* Their study found that there was no significant difference in bone parameters between a treated group and an untreated group (14).

Nose length (g-prn) is the only nasal parameter that did not significantly change because it is mainly determined by the nasal bone and septal cartilage. Similarly, face width (zy-zy), calculated by the distance between the bilateral zygomatic processes, did not significantly change. In the

orbital area, the biocular diameter (ex-ex) decreased, while the intercanthal distance (en-en) did not significantly change. This may be due to the fact that the lateral canthal tendon (LCT) is more likely to deform horizontally (20). In the lower face, although the chin is supported by the mental protuberance of the mandible, the skin overlying the chin is thick and measures between 2.00 and 2.50 mm in most adults (21). Moreover, there are dense s.c. fat pads and musculature over the bony structure (22). As a result, the patients' pogonion (gn) moved up, causing the height of the lower face to decrease.

These 'minor' changes may be one of the keys to improving patient QoL. Many studies have shown that surgical treatments significantly improved the QoL of patients (2, 23, 24). Furthermore, Sardella *et al.* showed that the improvements were mainly in their psychological and appearance domains rather than physical domains by using the acromegaly quality of life questionnaire (AcroQoL) (25). Although patient faces improved at the millimetre level in the current study, it had great aesthetic significance. The nose width (al-al) of patients with complete remission decreased by an average of 3.46 mm

Clinical Study	F Du and others	Facial changes of treated acromegaly patients	184:2	239
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Table 5 Relationships between GH or IGF-1 and facial changes.

	Model 1		Model 2		Model 3	
	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
Postoperative GH						
Nasal width	-0.126 (0.332, 0.081)	0.223	-0.266 (-0.500, -0.032)	0.028	-0.255 (-0.486, -0.025)	0.031
Vermilion area	-0.032 (-0.160, 0.096)	0.612	-0.038 (-0.197, .0120)	0.622	-0.030 (-0.183, .0123)	0.690
Face curve length	-0.194 (-0.603, 0.215)	0.340	-0.182 (-0.644, 0.281)	0.426	-0.201 (-0.659, 0.259)	0.373
GH decrease (%)						
Nasal width	4.440 (0.864, 8.031)	0.017	4.680 (0.994, 8.381)	0.015	4.310 (0.582, 8.054)	0.025
Vermilion area	2.772 (0.611, 4.934)	0.014	2.705 (0.393, 5.016)	0.024	2.414 (0.113, 4.714)	0.041
Face curve length	7.970 (0.821, 15.128)	0.030	6.779 (-0.235, 13.794)	0.058	7.510 (0.649, 14.375)	0.033
Postoperative GH nadir						
Nasal width	-0.213 (-0.527, 0.101)	0.175	-0.378 (-0.718, -0.039)	0.030	-0.392 (-0.719, -0.064)	0.021
Vermilion area	-0.026 (-0.223, 0.171)	0.787	-0.043 (-0.273, 0.186)	0.700	-0.053 (0.273, 0.168)	0.628
Face curve length	-0.009 (-0.646, 0.627)	0.976	-0.072 (-0.748, 0.604)	0.827	-0.053 (-0.724, 0.618)	0.873
GH nadir decrease (%)						
Nasal width	4.393 (0.965, 7.642)	0.013	4.650 (1.173, 8.136)	0.011	4.800 (1.459, 8.141)	0.007
Vermilion area	2.034 (-0.090, 4.157)	0.060	2.205 (-0.068, 4.477)	0.057	2.307 (0.153, 4.462)	0.037
Face curve length	1.555 (-5.736, 8.847)	0.665	3.646 (-3.396, 10.688)	0.296	3.443 (-3.554, 10.439)	0.320
Postoperative IGF-1						
Nasal width	-0.004 (-0.007, 0.001)	0.019	-0.097 (-0.009, -0.002)	0.003	-0.006 (-0.009, -0.002)	0.002
Vermilion area	-0.001 (-0.003, 0.001)	0.350	-0.001 (-0.004, 0.001)	0.311	-0.001 (-0.004, 0.001)	0.267
Face curve length	0.003 (-0.004, 0.009)	0.451	0.000 (-0.008, 0.007)	0.959	0.001 (-0.007, 0.007)	0.990
IGF-1 decreased (%)						
Nasal width	5.263 (2.172, 8.354)	0.002	6.971 (3.987, 9.956)	<0.001	6.752 (3.819, 9.685)	<0.001
Vermilion area	2.114 (0.020, 4.207)	0.048	2.518 (0.189, 4.848)	0.035	2.332 (0.062, 4.601)	0.044
Face curve length	-1.795 (-9.021, 5.430)	0.615	-0.105 (-7.607, 7.398)	0.977	0.360 (-7.114, 7.835)	0.922

Model 1: simple linear regression analyses with no adjustment. Model 2: multivariable linear regression analyses adjusted for gender, age and BMI.

Model 3: multivariable linear regression analyses adjusted for gender, age, BMI and disease course.

(2.30 to 4.62), while the nasofrontal angle increased by an average of 3.23° (1.35 to 5.11), which is a considerable improvement even for rhinoplasty (26). In facial morphology, there are significant differences between male and female faces, but the range of the difference is also within a few millimetres. For example, a study of the Han Chinese faces showed that the sex difference in the lower vermilion height was only 0.34 mm, which is one-third of the lower lip change in this study (27). These changes in facial features, which mainly involve soft tissue, have not been found in previous studies due to their small absolute values but were observed in our prospective study. These changes are important reasons for the improvements in patient mental health and QoL after surgery.

The degree of improvement from the treatment of acromegaly patients is significantly related to disease control. Patients with complete remission after treatment had more significant improvements than those without complete remission. However, multivariable linear regression analysis showed that not all improvements in the face index were linearly correlated with changes in GH or IGF-1. Among the parameters, the width of the nose has the strongest linear correlation with GH and IGF-1. Regardless of whether simple or multivariable linear regression models were employed, the decreases in GH,

the GH nadir and IGF-1 were significantly linearly related to the change in nose width. Although postoperative GH and the GH nadir were not significantly associated with nasal width in the simple linear regression model, significant negative associations were found when adjustments were made for possible confounders such as sex, age, BMI and disease course.

Facial abnormalities in acromegaly patients are caused by the long-term, chronic effects of GH and IGF-1 on bone, cartilage, and soft tissue (28). In 2018, Xie *et al.* found that decreased GH levels after surgery led to a redistribution of adipose tissue, with increased abdominal fat and reduced facial fat (29). As hormone levels decrease, cells of the cartilage and soft tissue divide faster than those of bone tissue (30, 31). These studies provide a theoretical basis for improvements in soft tissue in acromegaly patients, but the mechanism of facial improvements requires further study.

Our study has some limitations. This study examined patient facial changes 2 years after surgery and found that changes predominantly occurred in soft tissue. However, facial changes in acromegaly patients involve long-term processes, and processes related to bone tissue reconstruction may continue throughout life (32). Another limitation of our study is the small sample size. We did not have enough equipment or 3D images

to examine more patients. Furthermore, only a few acromegaly patients underwent preoperative 3D imaging and long-term follow-up after surgery. In the future study, we would consider to involve more patients and to collect both short-term and long-term data in order to better understand the kinetics of facial changes after surgery.

In conclusion, this prospective study identified facial changes in acromegaly patients after treatment with 3D imaging. Patients who achieved complete remission showed considerable improvements in facial soft tissue 2 years after surgery, with significant changes in the nose and lips. This study found negative linear associations between postoperative GH, the GH nadir and IGF-1 levels and nasal width reductions after adjusting for confounders. GH, the GH nadir and IGF-1 decreases after treatment were positively associated with nasal width and vermilion improvements. Thus, better control of patient hormone levels after surgery will improve patient facial recovery. Based on the current study, we suggested that facial measurement be used as a complementary assessment tool before treatment and in the follow-up clinic. Future large-scale and longer-term prospective studies may reveal patterns of change in facial soft tissue and bone tissue in acromegaly patients after treatment.

Supplementary materials

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-20-0962>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Author contribution statement

Fengzhou Du conducted the study and wrote the manuscript. Qiao Chen helped with 3D photography. Xiaojun Wang and Xiaopeng Guo assisted with the patient follow-up. Zihao Wang and Lu Gao helped to analyse data. Xiao Long and Bing Xing conceived and designed the project, oversaw the collection of results and data interpretation.

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