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# A longitudinal study of craniofacial growth in idiopathic short stature and growth hormone-deficient boys treated with growth hormone

H. Kjellberg* and K. Albertsson Wikland**
Departments of *Orthodontics, Faculty of Odontology and **Paediatrics, Göteborg Paediatric Growth Research Centre, Sahlgrenska Academy, Göteborg University, Sweden

SUMMARY The aim of this prospective, longitudinal, controlled study is to describe the long-term safety and efficacy of growth hormone (GH) administration on craniofacial morphology in boys with short stature.

Forty-six boys, who started GH treatment at the Department of Paediatrics Göteborg Paediatric Growth Research Centre, were consecutively included in the study. Twenty-five boys were classified as growth hormone-deficient (GHD) and 21 as idiopathic short stature (ISS). The patients were injected with 33 ($n = 31$) or 67 ($n = 15$) μg GH/kg body weight/day. The mean age at the start of treatment was 11.8 years [standard deviation (SD) 1.7]. To assess craniofacial growth, standard lateral cephalometric radiographs were obtained at the start of GH treatment, annually during 4 years, and at the end of GH treatment or when growth was less than 1 cm/year. The mean follow-up period was 6.4 years (SD 1.4). Growth changes were compared with boys from a semi-longitudinal reference group of 130 healthy subjects, 7–21 years of age. *t*-tests for independent and paired samples and multiple regression analysis were applied. Age- and gender-specific standard deviation scores for the cephalometric variables were calculated. Repeated measures analysis of variance was used to identify significant covariates over time, such as low/high GH dose and GHD/ISS and orthodontic treatment. During the study period, eight (out of 40) boys were treated with fixed orthodontic appliances, three with functional appliances (activators), and three with other appliances (plates and lingual arches).

During GH treatment period, an overall enhancement in growth of the facial skeleton was observed in boys with short stature. The changes induced by GH yielded a more prognathic growth pattern, a more anterior position of the jaws in relation to the cranial base, and increased anterior rotation of the mandible. The mandibular corpus length and anterior face height of the GH-treated boys were greater at the end of the study compared with the boys in the reference group. No differences in growth response were noted either between the GHD and ISS boys or between those treated with either 33 (low dose) or 67 (high dose) μg GH/kg body weight/day. The only change that remained significantly correlated with orthodontic treatment was the alteration in mandibular ramus height, showing a larger change in the boys who had not undergone orthodontic therapy.

The findings of this study demonstrate that GH treatment has a favourable influence on the craniofacial growth pattern of boys with short stature without acromegalic features.

## Introduction

The increased availability of growth hormone (GH) in the treatment of various types of disorders in somatic development brings with it the need for knowledge of its effects on craniofacial growth sites. Information is particularly necessary on the effect on craniofacial growth from long-term GH treatment of idiopathic short stature (ISS) children. Children with short stature [e.g. ISS or growth hormone-deficient (GHD) children, those born small for gestational age, or with syndromes or hypopituitary deficiency] display not only small facial dimensions but also bimaxillary retrognathia with the mandible mainly more deficient than the maxilla (Edler, 1979; Rongen-Westerlaken *et al.*, 1993; Midtbö *et al.*, 1996; Van Erum *et al.*, 1998b; Kjellberg *et al.*, 2000; Bergman *et al.*, 2003). Growth retardation appears to also affect the cranial base (Poole *et al.*, 1982; Midtbö *et al.*, 1996; Cantu *et al.*, 1997; Kjellberg *et al.*, 2000; Bergman *et al.*, 2003).

GH substitution therapy seems to elicit varying responses in different skeletal regions (Bevis *et al.*, 1977; Poole *et al.*, 1982; Van Erum *et al.*, 1997a, 1998a). In the facial area, all linear variables appear to be enhanced, but maxillary length and lower anterior face height growth still seem to be below the norm of healthy children (Van Erum *et al.*, 1997a). In fact, most of the variables fail to normalize completely. Poole *et al.* (1982) reported that most measurements were altered, except for the cranial base, if the variables were corrected for bone age. Neely and Rosenfeld (1994) suggested that acromegalic features could be one side-effect of GH treatment. This might indicate a different response in

skeletal units undergoing endochondral ossification as compared with bone formed intramembranously. There is evidence that GH treatment especially affects growth sites with endochondral ossification, such as the condylar cartilage (Asling and Frank, 1963; Maor *et al.*, 1993; Pirinen, 1995; Rice *et al.*, 1997; Visnapuu *et al.*, 2001; Ramirez-Yanez *et al.*, 2004).

The growth changes appear to be age-dependent, i.e. younger patients show a more pronounced response of the variables measured (Van Erum *et al.*, 1997a). Furthermore, those authors suggest that GH increases the effect on the facial structures in a dose-dependent manner (100 μg/kg/day compared with 67 μg/kg/day). However, the children in the above-mentioned studies were followed for short periods of time, and none until adulthood, making it difficult to draw conclusions as to their facial appearance as adults.

The aim of the present study is therefore to describe the long-term effects of GH administration on craniofacial morphology in boys with short stature.

## Subjects

The study was approved by the Ethical Committee of the Medical Faculty of Göteborg University (R 057–99). Informed consent was obtained from each boy and at least one parent. The study was performed in accordance with the Declaration of Helsinki.

### *Study group*

Forty-eight boys were examined for short stature [greater than 2 standard deviations (SD) below the normal mean height for subjects of a similar age and gender or slow postnatal growth rate i.e. growth velocity below the mean for the Swedish population (Karlberg *et al.*, 1976)]. The participants were referred for treatment with GH to the Göteborg Paediatric Growth Research Centre, The Queen Silvia Children's Hospital Sahlgrenska, Göteborg University, Sweden. To be included in the investigation, the children had to display satisfactory general paediatric, auxological, and endocrine features to exclude any complicating factors. Most of the boys (93%) had not started their pubertal growth spurt. The boys have been described in detail in an earlier study (Kjellberg *et al.*, 2000). Of the 48 boys, two were excluded, one because GH treatment was discontinued after 2 months and one because he suffered from foetal alcohol syndrome. Twenty-one ISS boys had participated in two randomized clinical trials to study the influence of GH treatment on the outcome of final height (kb10 TRN 88–080, $n = 20$ and kb5 TRN 87–010, $n = 1$). Twenty-five boys were classified as GHD while 21 ISS showed a slow postnatal growth rate or short stature, defined as below –2 SD. The patients were injected daily with 33 ($n = 31$) or 67($n = 15$) μg GH/kg body weight/day (Genotropin Pharmacia, Pfizer, New York, USA) for a mean of 5.7 years (range 3.0–9.5 years, SD 1.2). Three boys were still receiving GH treatment at the end of the study period.

At the start of the examination, which was equal to the start of GH treatment, the boys had a mean age of 11.8 years (range 6.2–15.0 years, SD 1.7). They were followed for a mean of 6.4 years (range 3.1–10.0 years, SD 1.4). Their mean age at the last examination was 18.2 years (range 14.8–21.6 years, SD 1.7).

The mean height standard deviation score (SDS) increased from –2.19 (range –3.27 to –1.30) to –0.85 (range –2.89 to +0.70) during the study period. The mean change in body height during the same period was 37.7 cm (range 18.0–59.4 cm, SD 8.5).

The criteria for ending the study were when the boys grew less than 1 cm/year. At the last examination, 33 boys had no growth left or grew less than 1 cm/year. The mean predicted growth in the remaining 13 boys, who did not wish to participate further in the study for different reasons (3 boys moved from the city and 10 failed to attend the last examination), was 4.5 cm/year (range 2–9 cm, SD 2.7).

During the study period, eight (out of 40) boys were treated with fixed orthodontic appliances, three with functional appliances (activators), and three with other appliances (plates and lingual arches). Data concerning orthodontic treatment were missing for six boys.

### *Reference group*

The reference control group, for comparing the sagittal cephalograms, consisted of 130 healthy boys with a mean age of 12.0 years (range 7–21 years, SD 4.0) who took part in a semi-longitudinal growth study to establish cephalometric standards for Swedish children and young adults (Thilander *et al.*, 1982; Persson and Thilander, 1988). All boys showed a Class I molar relationship, normal transverse and vertical relationships, no crowding and a normal profile without any obvious asymmetry, and no history of orthodontic treatment.

## Methods

Standard lateral cephalometric radiographs were taken at the start of GH treatment and then annually during the 4-year growth period. Thereafter, radiographs were taken at the end of GH treatment or when growth was less than 1 cm/year. The tracings were digitized and analysis was performed using a computer program (Quick Ceph Image Pro version 2.5 for Macintosh, Orthodontic Processing, San Diego, California, USA). The enlargement factor of 5.15 per cent in the GH group and 10.0 per cent in the reference group was adjusted to zero for all linear measurements.

Ten linear, 12 angular measurements and two ratios, were calculated (Figure 1 and Table 1). All measurements that have been described previously (Kjellberg *et al.*, 2000) are presented at the start of GH treatment and at the end of the

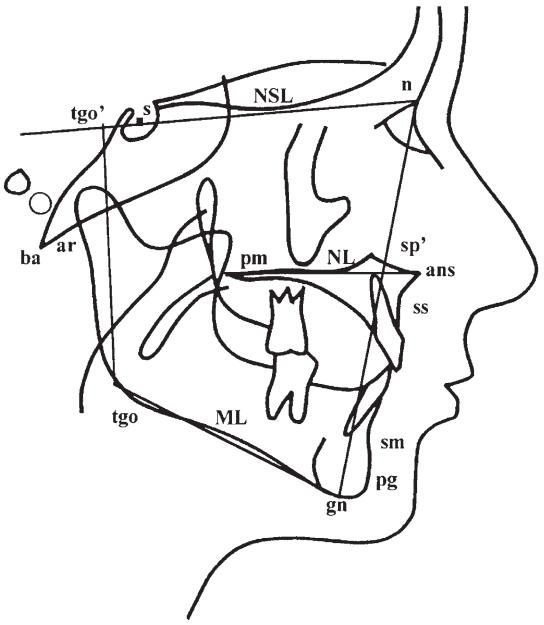


**Figure 1** Landmarks and reference lines used for linear and angular measurements on the lateral cephalogram. The reference points and lines used are in accordance with those of Björk (1947). In addition, the following landmarks were used: tgo′ = the projection of tgo on the nasion–sella line (NSL), sp′ = the intersection between the nasal line (NL) and a line between nasion and gnathion.

follow-up period. All variables were converted into age- and gender-specific SDS using the reference group of healthy boys (Thilander *et al.*, 1982; Persson and Thilander, 1988). A longitudinal change in SDS towards zero was considered to represent catch-up growth.

*Statistical analysis*

Paired and unpaired *t*-tests were used for within- and between-subject comparisons. A repeated measures analysis of variance (ANOVA) was used to identify significant covariates over time, such as GH dose, GHD/ISS, and orthodontic treatment. Pearson correlation analyses were performed. *P* values less than 0.05 were considered statistically significant.

SDS was calculated using data from the reference group previously described (Thilander *et al.*, 1982; Persson and Thilander, 1988).

As the outcome variables were possibly influenced by the age of the subjects, curve-fit analyses were performed using powers of age. The criterion for best fit was the highest $R^2$, the coefficient of multiple determination. Outliers greater than 3 SD or smaller than –3 SD were deleted in the curve-fit analyses. Most variables were best fitted to age by a linear transformation, but some by a transformation including both age and squared age.

Accordingly, the transformations were

Linear: $V_t = b_0 + b_1 \times \text{age}$ or

Quadratic: $V_t = b_0 + b_1 \times \text{age} + b_2 \times \text{age}^2$,

where *b*0, *b*1, and *b*2 were estimated in the reference sample.

SDS was computed as SDS = (observed value – *V*t)/$SD_{res}$, where $SD_{res}$ is the residual standard deviation in the reference sample.

Two variables did not have any correlation with age. For these variables, SDS was calculated as (observed value – reference mean value)/reference SD.

Linear input, i.e. calculating missing values between two recordings by taking the mean between two recordings, was performed on eight occasions (eight missing radiographs out of 256, 3.1 per cent).

To test the reproducibility of the cephalometric method, duplicate determinations were made of 15 cephalograms. The measurement error is given in terms of SD and calculated according to the formula: $S_e = \sqrt{\sum (a_2 - a_1)^2 / 2n}$, where $a_2 - a_1$ is the difference between two measurements and $n$ the number of pairs of measurements. The measurement error ($S_e$) between two sets of records ranged from 0.4–1.5 mm for linear and 1.0–1.1 degrees for angular measurements. The Statistical Package for Social Sciences, version 11 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis.

## Results

Pre-treatment craniofacial morphology showed smaller linear measurements for all facial structures, as well as a retrognathic facial type and a skeletal Class II tendency compared with the reference group (Table l). The jaw (gn–tgo–ar) and cranial base (n–s–ba, n–s–ar) angles were increased in the children with short stature, while the angles between the anterior cranial base and the mandibular plane (ML/NSL) and between the maxilla and mandible (ML/NL) were larger than normal. The proportions between anterior and posterior face heights and between upper and lower anterior face heights were also smaller than those of the reference group.

Forty-six per cent (11 out of 24) of the measured variables normalized completely during the study period (Table 1, Figure 2). Improvement towards the norm, influenced by GH treatment, was additionally seen in 25 per cent (six out of 24) of the variables. A significantly accelerated growth rate beyond the norm was observed in the GH-treated children for mandibular corpus length (gn–tgo and ar–gn) and total and lower anterior face height (n–gn, sp′–gn).

The positional relationship between the maxilla and mandible were expressed as angular changes during the study period. All sagittal angles (s–n–ss, s–n–sm, s–n–pg, n–ss–pg) improved significantly during the growth period. The overall growth change in the vertical positions of the mandible (ML/NSL, ML/NL) improved similarly. Improvement was also observed in the slight convex profile (n–ss–pg) in the boys.

**Table 1** Mean and standard deviation (SD) of standard deviation scores of transformed outcome variables at start and end of study and changes during study.

| | At start | | | End | | Change | | Start | End | Change |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | *n* | SD | Mean | SD | Delta | SD | *P*1 | *P*2 | *P*3 |
| Cranial | | | | | | | | | | |
| n–s–ba(°) | 0.63 | 46 | 1.04 | 0.53 | 0.98 | 0.10 | 0.55 | <0.001 | <0.001 | NS |
| n–s–ar(°) | 0.53 | 46 | 1.00 | 0.68 | 0.99 | −0.15 | 0.50 | <0.001 | <0.001 | <0.042 |
| s–n (mm) | −2.47 | 46 | 0.77 | −2.11 | 1.10 | −0.36 | 0.54 | <0.001 | <0.001 | <0.001 |
| s–ba (mm) | −1.70 | 46 | 0.52 | −1.17 | 0.67 | −0.54 | 0.55 | <0.001 | <0.001 | <0.001 |
| Facial upper | | | | | | | | | | |
| s–n–ss (°) | −0.59 | 46 | 1.07 | −0.10 | 1.22 | −0.49 | 0.67 | <0.001 | NS | <0.001 |
| NL/NSL (°) | 0.16 | 46 | 1.02 | 0.48 | 1.08 | −0.32 | 0.66 | NS | <0.004 | <0.002 |
| n–sp′ (mm) | −1.03 | 46 | 0.77 | 4 | 1.19 | −1.17 | 0.84 | <0.001 | NS | <0.001 |
| pm–ans (mm) | −0.56 | 46 | 1.02 | −0.14 | 1.54 | −0.42 | 1.06 | <0.001 | NS | <0.010 |
| Facial lower | | | | | | | | | | |
| s–n–sm (°) | −1.11 | 46 | 1.06 | −0.34 | 1.31 | −0.78 | 0.70 | <0.001 | NS | <0.001 |
| s–n–pg (°) | −1.49 | 46 | 1.03 | −0.48 | 1.25 | −1.01 | 0.72 | <0.001 | <0.012 | <0.001 |
| ML/NSL (°) | 1.21 | 46 | 1.07 | 0.15 | 1.28 | 1.06 | 0.63 | <0.001 | NS | <0.001 |
| ML/NL (°) | 1.00 | 46 | 1.14 | −0.19 | 1.25 | 1.19 | 0.51 | <0.001 | NS | <0.001 |
| gn–tgo–ar (°) | 0.50 | 46 | 1.03 | −0.16 | 1.02 | 0.66 | 0.61 | <0.002 | NS | <0.001 |
| sp′–gn (mm) | −0.53 | 46 | 0.93 | 0.42 | 1.36 | −0.95 | 0.69 | <0.001 | <0.041 | <0.001 |
| tgo–ar (mm) | −1.39 | 46 | 0.82 | 0.23 | 1.35 | −1.62 | 0.84 | 0.001 | NS | <0.001 |
| gn–tgo (mm) | −0.24 | 46 | 0.64 | 0.64 | 1.02 | −0.88 | 0.70 | <0.014 | <0.001 | <0.001 |
| ar–gn (mm) | −0.84 | 45 | 0.74 | 0.72 | 1.25 | −1.56 | 0.81 | <0.001 | <0.001 | <0.001 |
| Facial upper and lower | | | | | | | | | | |
| ss–n–sm (°) | 0.57 | 46 | 1.16 | 0.45 | 1.36 | 0.12 | 0.74 | <0.002 | <0.028 | NS |
| s–ar–tgo (°) | −0.04 | 45 | 0.92 | −0.09 | 0.96 | 0.05 | 0.70 | NS | NS | NS |
| n–ss–pg (°) | −0.70 | 45 | 1.17 | −0.07 | 1.48 | −0.63 | 0.76 | <0.001 | NS | <0.001 |
| n–gn (mm) | −0.51 | 46 | 0.94 | 0.64 | 1.38 | −1.15 | 0.79 | <0.001 | <0.003 | <0.001 |
| tgo′–tgo (mm) | −1.95 | 46 | 0.80 | −0.11 | 1.34 | −1.84 | 0.88 | <0.001 | NS | <0.001 |
| n–sp′/sp′–gn (%) | −0.52 | 46 | 1.02 | −0.18 | 1.24 | −0.34 | 0.71 | <0.001 | NS | <0.002 |
| tgo′–tgo/n–gn (%) | −1.64 | 46 | 1.01 | −0.38 | 1.26 | −1.26 | 0.79 | <0.001 | <0.047 | <0.001 |

$P_1$ and $P_2$ indicate significant deviation from normal at the start and end of the study, respectively, and $P_3$ the significance of changes. NS, not significant.

The relationship between anterior and posterior face height improved but failed to normalize completely during the growth period, mainly because of anterior face height, which was greater than the norms at the end of the study. Worsening during the follow-up period was seen for n–s–ar and NL/NSL.

Repeated measures ANOVA did not reveal significant differences for any of the variables due to the different doses or if the boys were GHD or ISS. The only change that was significantly correlated with orthodontic treatment was in mandibular ramus height (tgo–ar SDS), showing a larger change in the boys who had not undergone orthodontic treatment ($P < 0.005$, Figure 3). However, repeated measures ANOVA did not reveal a significant difference between the two groups.

The age at the start of GH treatment was found to influence several variables (Table 2). The SDS for the linear variables, mandibular length (ar–gn), posterior cranial base length (s–ba), and anterior face height (n–sp′, sp′–gn, n–gn), and for the angular variables, cranial base angles (n–s–ar, n–s–ba) and vertical inclination of the jaws (NL/NSL, ML/NSL, ML/NL), increased more if GH treatment was started at an early age. The sagittal position of the maxilla and mandible (s–n–ss, s–n–sm, s–n–pg) changed less when GH treatment was started early. The remaining variables were not significantly affected by age at the start of treatment.

## Discussion

The pre-treatment data indicated that boys with short stature with or without GHD had a retrognathic type of face with overall smaller dimensions. The facial skeletal growth increase was, in certain areas, stimulated by GH therapy to a rate beyond normal limits, indicating that the craniofacial growth sites respond to treatment similar to those involved in the increase in body height. During GH treatment, an increase in growth was detected, especially enhancing facial growth in an anterior direction and without apparent signs of disproportional growth.

Almost all boys in the present study were followed until the end of their growth period and all had been treated with GH supplementary therapy until then, with the exception of those who reached normal height before the end of the growth period. Some boys still had not reached adulthood at

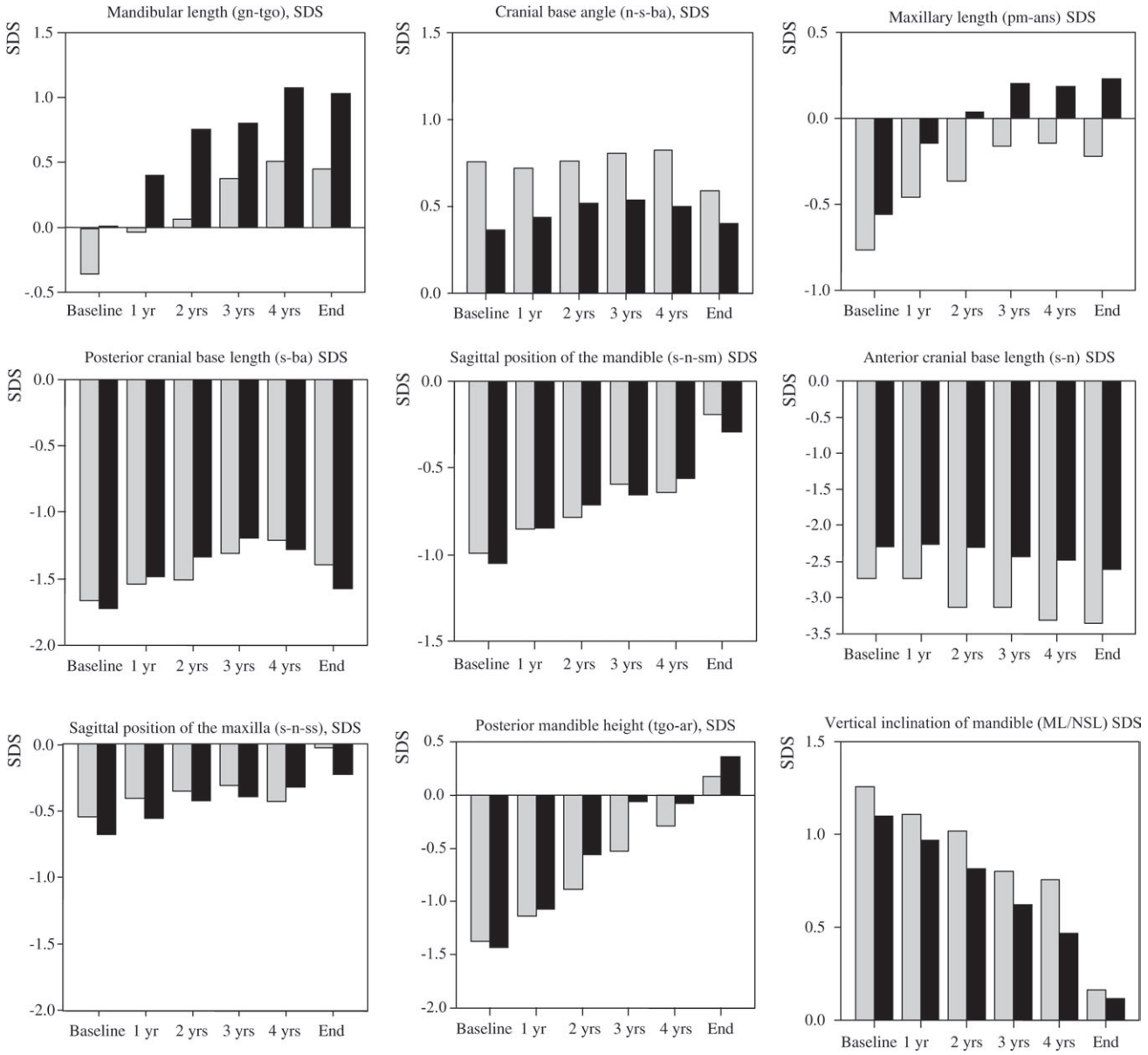


**Figure 2** Mean changes during the period from the start of growth hormone treatment until the end of the growth period measured as standard deviation scores for nine linear and angular measurements. Grey bar, dose 33 μg/kg/d, $n = 31$; black bar, dose 67 μg/kg/d, $n = 15$.

the end of the study. However, it is not believed that the remaining growth in these individuals will change the results of the study as all were beyond the pubertal growth spurt with only minor growth remaining.

The advantage of continuing with GH treatment until growth has ceased has been emphasized by Van Erum *et al.* (1997b). Those authors found that withdrawal of GH before completion of growth resulted in 'catch-down' growth of the craniofacial components, even for those who had not shown accelerated growth during GH treatment. The angular measurements in their study, however, were unaffected 2 years after the cessation of GH administration.

The reason for limiting the study to boys was that most children seeking GH treatment were boys. In the clinical trial, from which the boys were selected, only one-third of the participants were girls. This made it difficult to find a sufficiently large group of girls for comparison. Another reason for including only boys was to reduce the variability, as it is known that healthy girls show a different craniofacial growth pattern to healthy boys. Most of the craniofacial distances are larger in boys than in girls, especially after puberty (Thilander *et al.*, 2005). As females might react differently with regard to craniofacial morphology when undergoing GH treatment, the findings of the present study cannot be directly extrapolated to girls. In previous

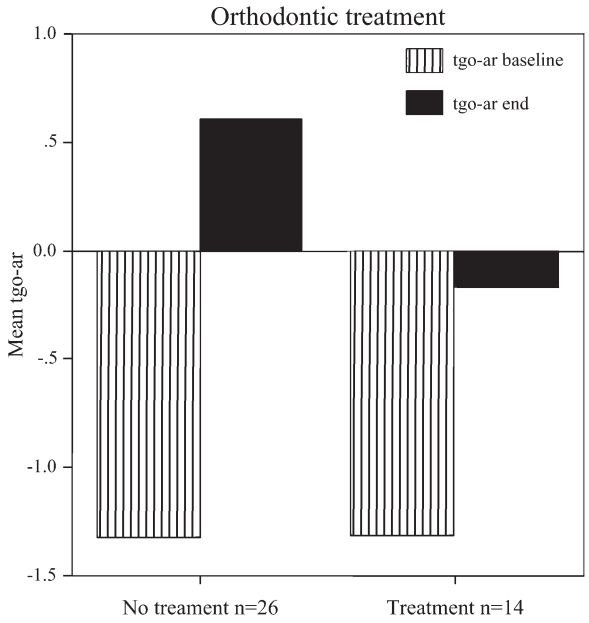


**Figure 3** The mean change in the standard deviation scores for mandibular ramus height (tgo–ar) during the growth period was significantly correlated with orthodontic treatment, showing a larger change in the boys without orthodontic treatment ($P < 0.005$).

investigations (Poole *et al.*, 1982; Cantu *et al.*, 1997; Van Erum *et al.*, 1997a), the results from boys and girls were not separated making it difficult to draw any conclusions concerning differences in the response to GH treatment. This has still to be investigated.

Thirty-five per cent of the boys were treated with orthodontic appliances during the follow-up period. The only significant change correlated with orthodontic treatment was in mandibular ramus height, showing a larger change in the boys without orthodontic treatment. However, when repeated measures ANOVA was used to test for significant differences between the two groups instead of correlation analysis, no significant difference was observed. Furthermore, there is no scientific evidence that orthodontic treatment can significantly alter the inherited complex craniofacial skeleton of the growing child on a permanent basis. The rather high percentage of orthodontically treated boys points to the fact that short stature boys have a greater need for orthodontic treatment, either because of increased crowding caused by small jaws or because of a higher frequency of Class II malocclusions. However, this observation has to be studied further before any conclusions can be reached.

All linear variables showed catch-up towards norm values at the final examination. This is in contrast to the findings of Van Erum *et al.* (1997a) where none of the treated children reached the norm values, except for lower and total anterior face height. The younger children, the short treatment period, and the fact that the children in that study were not followed until the end of growth might explain this finding.

**Table 2** Pearson correlation coefficients ($r$) showing the correlation between age at baseline and changes (standard deviation scores, final − baseline value) of outcome variables.

| Cranial | $r$ | $P$ |
|---|---|---|
| Delta, n–s–ba | −0.48 | <0.001 |
| Delta, n–s–ar | −0.30 | <0.040 |
| Delta, s–n | −0.10 | NS |
| Delta, s–ba | −0.29 | <0.048 |
| Facial upper | | |
| Delta, s–n–ss | 0.42 | <0.003 |
| Delta, NL/NSL | −0.31 | <0.034 |
| Delta, n–sp’ | −0.51 | <0.000 |
| Delta, pm–ans | −0.05 | NS |
| Facial lower | | |
| Delta, s–n–sm, | 0.37 | <0.012 |
| Delta, s–n–pg | 0.47 | <0.001 |
| Delta, ML/NSL | −0.48 | <0.001 |
| Delta, ML/NL | −0.45 | <0.002 |
| Delta, gn–tgo–ar | 0.02 | NS |
| Delta, sp’–gn | −0.44 | <0.002 |
| Delta, tgo–ar | −0.10 | NS |
| Delta, gn–tgo | −0.25 | NS |
| Delta, ar–gn | −0.36 | <0.015 |
| Facial upper and lower | | |
| Delta, ss–n–sm | 0.19 | NS |
| Delta, s–ar–tgo | 0.07 | NS |
| Delta, n–ss–pg | −0.23 | NS |
| Delta, n–gn | −0.53 | <0.000 |
| Delta, tgo’–tgo | −0.26 | NS |
| Delta, n–sp’/sp’–gn | 0.56 | <0.000 |
| Delta, tgo’–tgo/n–gn | 0.37 | <0.012 |

NS, not significant.

The boys in the present study showed increased maxillary growth, which was beyond the catch-up growth in the mandible. This was not found in previous studies (Poole *et al.*, 1982; Cantu, 1997; Van Erum *et al.*, 1997a). The improved growth in maxillary length might be explained by a similar stimulative effect on membranous as on endochondral bone formation by GH, as demonstrated in animal experiments (Kurtz *et al.*, 1970; Maor *et al.*, 1989a,b).

In a recent study, Carvalho *et al.* (2003) concluded that long-term GH treatment with standard doses in patients with GH deficiency might be associated with acromegalic features, such as increased foot and mandibular size, particularly in girls. However, they emphasized that this was just a preliminary study and in only four out of 21 patients was the lower jaw length greater than +2 SD. In contrast to these findings, Segal *et al.* (2004) noted no adverse effects on growth of the hands and feet but did find excessive growth of head circumference.

Almost all linear measurements were normalized, except mandibular and cranial base lengths and anterior face height. Although mandibular length and anterior face height values exceeded the norms at the end of treatment, the increase did not result in the development of a Class III skeletal or dental relationship, nor was the increase of clinical importance for facial appearance. Furthermore, as

the majority of the GH-treated boys had reached their final height or had only minor growth left, the risk of developing acromegalic features was minimal. Only one boy showed an ss–n–sm angle less than 0 degrees (−0.2 degrees), indicating a Class III skeletal relationship. This observation should be compared with the frequency of a Class III malocclusion of approximately 4 per cent normally seen in a Swedish population (Thilander and Myrberg, 1973).

The greater increases in growth in mandibular length and anterior face height indicate that the interstitial cartilage growth of the condyles is influenced more by GH treatment than the periosteal and sutural growth sites. A few authors (Poole *et al.*, 1982; Van Erum *et al.*, 1997a; Segal *et al.*, 2004) have also reported this finding, although Cantu *et al.* (1997) found that ramus height was the least affected of the individual measurements and antero-posterior growth of the mandible was likewise unaffected.

The enhanced growth of the posterior cranial base was in agreement with clinical and experimental findings of the positive effect of GH on cranial base endochondral ossification centres, such as the spheno-occipital synchondrosis (Petrovic and Stutzmann, 1980; Cantu *et al.*, 1997; van Erum *et al.*, 1998b). The findings of the present study demonstrate that boys who start GH treatment at younger ages exhibit a larger posterior cranial base length (s–ba) at the end of the study. In older children (14–15 years of age), this synchondrosis is fused and thereafter could not be influenced by GH treatment.

In the present investigation, the age of the patients at the start of treatment did not influence the final length of the anterior cranial base (s–n). This may indicate that increased GH administration does not have any impact on growth of the anterior cranial base in the age group examined. The anterior cranial base is fused after 7 years of age, and from that time onward, will increase in length only by apposition at nasion. This could also be an explanation as to why cranial base length failed to catch up to normal values during the study period. In very young children, however, GH treatment might have resulted in a different outcome and thus affected cranial length, which, in fact, has been shown to occur (Van Erum *et al.*, 1997a).

The age at the start of treatment affected the result of some variables measured, whereas GH deficiency or high or low dose GH did not. In this respect, the findings of Van Erum *et al.* (1997a) and of the present study have shown that the younger the child at the start of GH treatment, the larger the positive effect on craniofacial structures. Moreover, experimental studies on rats have shown that the timing of GH treatment affects the craniofacial complex (Vandeberg *et al.*, 2004). The finding in the present study of a greater positive effect in young children for growth of the mandible is in agreement with Vandeberg *et al.* (2004). Contradictory results were found by Cantu *et al.* (1997) who observed no effects of starting age on posterior cranial base or anterior face height. This could partly be explained by the differences in the age groups studied. Surprisingly, several angular measurements (s–n–sm, s–n–ss, s–n–pg) improved less when GH treatment started earlier. One might have expected that these angular measurements, representing forward growth of the mandible and maxilla, would improve to a larger extent in younger patients e.g. in boys who were GH treated for a longer period of time. However, this was not the case and this observation might be explained, in part, by individual variations.

It is well known that high GH dose administration (up to 100 mg/kg/day) results in pronounced growth in body height (de Zegher *et al.*, 1996; Wilton *et al.*, 1997). For facial growth, Van Erum *et al.* (1998a) found that higher GH doses accelerated the growth rate even more, especially in regions where cartilage-mediated growth occurs, i.e. in the mandible and spheno-occipital synchondrosis. Higher doses of GH produce a more pronounced growth response for both total posterior (Van Erum *et al.*, 1997a, 1998a) and anterior (Segal *et al.*, 2004) face heights.

The present study could not demonstrate any differences in treatment response, either between GHD and ISS boys or between those treated with high or low doses of GH, a finding consistent with that of de Zegher *et al.* (1996).

## Conclusions

GH treatment resulted in an overall increase in growth of the craniofacial skeleton, to or towards normal levels for 71 per cent of the measured variables. A more prognathic growth pattern and anterior rotation of the mandible was seen. Age at the start of GH treatment influenced the effect of GH on several variables. No differences in growth response were observed between boys treated with either a low (33 μg/kg/day) or high (67 μg/kg/day) dose of GH. In addition, there was no difference in growth response between GHD and ISS boys. The change in mandibular ramus height (tgo–ar SDS) was significantly influenced by orthodontic treatment, showing a larger change in boys without treatment. The findings indicate that GH treatment, in boys with short stature, has a favourable influence on the craniofacial growth pattern without acromegalic features.

## Address for correspondence

Heidrun Kjellberg
Department of Orthodontics
Sahlgrenska Academy
Göteborg University
Medicinaregatan 12A
SE-413 90 Göteborg
Sweden
E-mail: heidrun.kjellberg@vgregion.se

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