Dental maturity in children of short stature—a two-year longitudinal study of growth hormone substitution

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The aim of this investigation was to present the 2-year follow-up results of a longitudinal study examining the influence of growth hormone (GH) substitution on dental maturity in healthy children of short stature (height <2 SD). At baseline, the children were divided into a GH-deficient group and a GH non-deficient group, and comparisons were made with healthy controls (height between −2 SD and 2 SD) and between the short stature groups. The GH-substituted group included 24 children (8 F, 16 M) with a mean chronological age of 12.20 ± 2.40 years, whereas the GH non-substituted group included 19 children (5 F, 14 M) with a mean chronological age of 11.00 ± 2.40 years. The corresponding age- and sex-matched control groups constituted 48 and 36 children, respectively. The mean dental age in the GH-substituted group was 11.60 ± 2.70 years, compared to their healthy controls 12.40 ± 2.60 years ($P < 0.05$). The dental age for the GH non-substituted children was 10.20 ± 2.60 years compared to their controls 11.90 ± 2.60 years ($P < 0.001$). GH-substituted children show an acceleration in their dental maturity in contrast to controls, whereas in non-substituted children the acceleration is less pronounced. □ *Child; dental; growth deficiency; teeth*

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Somatic growth is considered to be the result of multifactorial joint actions, evident at specific times during the growing period. Endocrinological factors play an important role in normal growth. Growth hormone (GH), insulin-like growth factor 1 (IGF-1), as well as the thyroid hormone (TH) and, finally, the sex steroids are all crucial for development during early childhood and youth (1). The capacity of tissue to accept and utilize hormones and factors via appropriate receptors as well as the amount of GH binding protein (GHBP) and IGF-1 binding protein (IGFBP) is important for the serum-concentration, and consequently for their tissue concentration, thus resulting in growth-activity (2, 3). When these hormones, factors, receptors and binding-proteins are insufficiently produced, or not coordinated correctly, various disturbances of growth may occur. Children whose arginin-insulin stimulated GH-secretion is below 10 μg/L are classified as GH-deficient (GHD) in contrast to short stature children with sufficient GH-levels, who are classified as idiopathic short stature (ISS) (4).

It is generally assumed that the oro-facial development follows the predominant growth pattern of the body, i.e. underlying the same endocrine control (1). According to Spiegel (5) and Poole (6), short stature children are prone to develop a relatively large skull and a babyish face. Independently from each other, different examiners have reported delayed dental maturity in children with impaired hormonal status or without, as part of a syndrome (6–10). Longitudinal studies on the influence of GH on dental development are usually performed using

Table 1. Chronological and dental ages according to the method of Demirjian & Goldstein ad modum Kataja et al. (12) in children of short stature, substituted or not substituted with growth hormone and respective age- and sex-matched controls; x = mean values, sd = standard deviation

	GH-substituted ($n = 24$)		Control 1 ($n = 24$)		Control 2 ($n = 24$)		Not GH-substituted ($n = 19$)		Control 1 ($n = 19$)		Control 2 ($n = 19$)	
	$\bar{x}_1$	sd_1	$\bar{x}_2$	sd_2	$\bar{x}_3$	sd_3	$\bar{x}_4$	sd_4	$\bar{x}_5$	sd_5	$\bar{x}_6$	sd_6
Chronological age	12.20	2.40	12.40	2.40 ns	12.20	2.50 ns	11.00	2.40	11.30	2.30 ns	11.30	2.20 ns
Dental age	11.60	2.70	12.20	2.60 ns	12.40	2.60*	10.20	2.60	11.90	2.60***	11.40	2.40*

inhomogeneous groups with regard to age, puberty and diagnosis (8–10). In a previous study we evaluated endocrinological factors, dental and bone maturity at baseline, for two prepubertal groups of short stature children, with or without GHD. The aim of this investigation was to study the changes in dental maturity after 2 years of GH substitution in children of short stature.

Patients and methods

The study group consisted of 43 (30 M, 13 F) healthy children, females 7.8–14.3 years of age and males 7.5–15.7 years of age. Forty children were of Swedish origin, 3 with immigrant parents from Arabic countries born in Sweden. Children with a baseline GH plasma concentration of <10 μg/L were classified as GH-deficient and were individually substituted with Genotropin® 0.1 IU/kg body-weight. For further baseline-information, see (11). The GH-deficient group included 24 children (16 M, 8 F) with a mean age of 12.3 ± 2.4 years, while the GH non-deficient group comprised 19 children (14 M, 5 F) with a mean age of 11.0 ± 2.4 years. From the baseline study, 2 patients changed their group from GH-deficient to GH non-deficient. Drop-outs from baseline included 3 patients who did not agree to further cooperation in the study. Patients were enrolled in the study after informed consent and approval by the regional ethics committee at Huddinge Hospital.

Determination of dental maturity was made according to Demirjian and Goldstein ad modum Kataja (12), based on dental maturity scores (13) using panoramic radiographs. A second radiograph was taken 2 years after the baseline study. One dentist evaluated dental maturity and dental age. Prior to the assessment, the dentist was calibrated to a co-worker. For each child included in the study groups, panoramic radiographs were obtained from 2 age- and sex-matched healthy controls from patient files (Control 1 and Control 2), altogether 86 individuals. None of the controls had any record of systemic diseases. Radiographs from children exhibiting major deviations from normal occlusion or aplasia were excluded.

Tooth size was determined by measuring the length of the left lower first molar, the distance between mesial cusp and apex, with vernier callipers (Gansel®). The distance was measured to the nearest 0.01 mm.

Statistical analyses

In order to analyze the differences between the two short-stature groups and their controls, Student's *t*-test was used. When comparing differences between the two short-stature groups and their respective controls a contrast was formed $C = \sqrt{(\bar{x}_1 + \bar{x}_2) - (\bar{x}_3 - \bar{x}_4)}$ with standard error $\sqrt{(se_1{}^2 + se_2{}^2) - (se_3{}^2 + se_4{}^2)}$. The mean value for

Table 2. Differences between dental ages according to Kataja et al. (12) and chronological ages in children of short stature, substituted or not GH-substituted, and respective age- and sex-matched controls; d = mean difference between dental age and chronological age, sd = standard deviations

	GH-substituted ($n = 24$)		Control 1 ($n = 24$)		Control 2 ($n = 24$)		Not GH-substituted ($n = 19$)		Control 1 ($n = 19$)		Control 2 ($n = 19$)	
	d_1	sd_1	d_2	sd_2	d_3	sd_3	d_4	sd_4	d_5	sd_5	d_6	sd_6
Differences dental-chronological age	-0.60 ± 1.00		0.10 ± 1.20 ns		0.25 ± 0.85*		-0.80 ± 0.80		0.50 ± 0.80***		0.02 ± 0.93*	

Student's *t*-test, level of significance: *$P < 0.05$, ***$P < 0.001$, ns = non-significant. Control 1 = the first control group. Control 2 = the second control group.

Table 3. Contrast* formed for the GH-substituted and not GH-substituted short-stature children regarding dental age–chronological age

		Not GH-substituted	GH-substituted	
	Control group	x sd	x sd	Contrast *t*-value *P*
Δ dental-chron age	1	-1.29 ± 1.17	-0.47 ± 1.77	0.075 ns
Δ dental-chron age	2	-0.86 ± 1.39	-0.81 ± 1.47	0.921 ns

* Contrast: see explanation in statistical analyses.

each group is represented by $\bar{x}_1$, $\bar{x}_2$, $\bar{x}_3$, $\bar{x}_4$, whereas standard error for the respectively studied group is represented by se_1, se_2, se_3, se_4. Student's *t*-test was also performed in order to evaluate the differences regarding tooth length. The studied groups and their controls were sex- and age-matched, and therefore treated as dependent on each other. In order to follow the matched design in the statistical evaluation the 2 control groups were analysed separately.

Results

The estimated dental age after 2 years of GH treatment compared to chronological age is presented in Table 1. The dental age in the GH-substituted group was 11.6 ± 2.7 years, whereas the corresponding dental age for the GH non-substituted children was 10.20 ± 2.6 years. Compared to their controls, the children not receiving GH-substitution exhibited a significantly reduced ($P < 0.05$) dental maturity scores and subsequently reduced dental ages. As can be seen in Table 2, the mean difference between dental and chronological age, as determined using the method Demirjian and Goldstein ad modum Kataja et al. (12), was -0.6 ± 1.0 years for the GH-substituted children of short stature and 0.25 ± 0.85 years in the healthy controls ($P < 0.05$). In children not receiving GH-substitution, the mean difference between dental and chronological age was -0.80 ± 0.80 years compared to 0.50 ± 0.80 years in healthy controls ($P < 0.001$). A contrast was formed to compare the differences between GH-substituted and GH non-substituted children and their respective controls (Table 3). The difference between the studied groups and their first control groups, expressed as difference between dental and chronological age, was -1.29 ± 1.17 years for the GH non-substituted and -0.47 ± 1.77 years for the GH substituted children. The corresponding difference for the second control group was -0.86 ± 1.39 years respectively -0.81 ± 1.47 years, both non-significant differences. When comparing the mean difference between dental maturity at baseline and 2 years later, no differences were seen between the GH-substituted and non-substituted group. As can be seen in Table 4, only one comparison between GH not-substituted children and controls showed a significant reduction ($P < 0.05$). No further significant differences were seen in either of the studied groups concerning tooth-length.

Increase in mean body height during the 2-year period showed no significant difference for the 2 groups of short-stature children, 12.93 ± 4.35 cm in the GH non-substituted children and 16.00 ± 5.50 cm for the GH-substituted children.

Discussion

The results from the baseline study (11) indicated that the best method for examining dental age in Swedish children is that devised by Demirjian and Goldstein ad modum Kataja et al. (12). Methods designed for dental maturity determination in Scandinavian children, Haavikko (14), Gustavsson & Koch (15) and Liljeqvist & Lundberg (16) and Kataja et al. (12), overestimate dental age to chronological age by 12–20 months (17). The baseline study also showed that GH-deficient and GH non-deficient children of short stature exhibited delayed dental age compared to age- and sex-matched controls. Our previous results revealed that the delay was independent of the degree of GH-deficiency, which might be interpreted as an inability to estimate the disturbances of the GH-axis. Data from this 2-year follow-up suggest that the delayed dental maturity at baseline, in GH-deficient children, was

Table 4. Comparison of tooth size (left permanent molar) between children of short stature, substituted or not GH-substituted and respective age- and sex-matched controls. Mean values (x), and standard deviations (sd)

	GH-substituted ($n = 24$)	Control 1 ($n = 24$)	Control 2 ($n = 24$)	Not GH-substituted ($n = 19$)	Control 1 ($n = 19$)	Control 2 ($n = 19$)
Toothsize (mm)	x_1 sd_1	x_2 sd_2	x_3 sd_3	x_4 sd_4	x_5 sd_5	x_6 sd_6
Length	28.80 ± 2.39	28.80 ± 2.45 ns	29.00 ± 2.44 ns	27.21 ± 3.58	28.90 ± 2.32 ns	29.70 ± 2.60*

Student's *t*-test, level of significance: *$P < 0.05$, ***$P < 0.001$, ns = non-significant, Control 1 = the first control group. Control 2 = the second control group.

normalized compared to controls after 2 years of GH-substitution. In the GH non-substituted children, the difference compared to the controls still remained after 2 years. The results suggest that 2 years of GH-substitution accelerates dental maturity in short-stature children with GH-deficiency.

This finding is partly confirmed by Myllerniemi (8), who assessed dental maturity during 2–4 years of GH-substitution in children with the diagnosis hypopituitarism, ages ranging between 4.4 and 16.7 years. The cut-off point was set to <7 μg /L (17). Changes in dental delay were variable, but mostly parallel to the skeletal delay. During GH-substitution the lag in dental development diminished slowly. In contrast, Ito (18) found that GH-substitution in idiopathic short-stature children for 2 years did not have a significant influence on the tooth formation and consequently dental maturation.

There are indications that the growth rates achieved following GH-treatment (with the same therapeutic doses) in extreme GH-deficiency may be higher than in children with moderate GH-deficiency (19). Thus some children with significant short stature may be less sensitive to GH-treatment as those with severe GH-deficiency. It could be speculated that dental maturity may follow the same pattern. Pretreatment height velocity appears to explain only about 50% of the response to GH-substitution (20). Age has likewise been suggested as one of the predictive factors for GH-treatment response (20). These factors could not be excluded as significant during dental maturation.

Concerning tooth size at baseline there were significant differences between the groups of short-stature children with or without GH-deficiency. In the follow-up, the results revealed that the differences in length of the first left lower molar compared to controls were diminishing in both the GH-substituted and GH non-substituted children. This result might also have been influenced by the fact that there was a difference between the chronological ages regarding the short-stature groups.

In conclusion, the results of this study suggest that GH-deficient children after GH-substitution show signs of an accelerated dental maturity and thus dental age.

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