Arch dimensional changes in children with idiopathic short stature treated with recombinant growth hormone: a five-year study

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Through the advancement of recombinant DNA technology, biosynthetic recombinant human growth hormone (rhGH) has become available. With the commercial production of rhGH, this growth hormone is no longer in limited supply. Its metabolic effects are being studied in many new clinical situations. In addition to its use in patients with documented growth hormone deficiencies, synthetic growth hormone is now being used to treat patients with Turner syndrome, hypopituitarism, trisomy 21, and renal disease,[1] making it likely that a wide variety of medical and dental practitioners will encounter patients undergoing rhGH therapy.

In recent years, it has become apparent that some proportion of short statured children who are not GH deficient also benefit from treatment with rhGH.[2-6] Consequently, the Genentech Collaborative Growth Study is investigating the effect of rhGH in children with idiopathic short stature.[5,6] While these children are receiving rhGH primarily to increase statural growth, this type of intervention also offers a unique opportunity to study artificially induced growth of the craniofacial complex and to examine the response of developing dentoalveolar structures to rhGH administration.

In associated craniofacial studies on a subgroup of the subjects enrolled in the Genentech Growth Study, researchers have investigated the effects

Abstract

Recombinant human growth hormone (rhGH) increases stature when administered to non-GH-deficient idiopathic short statured children. The aims of this investigation were to determine pretreatment arch dimensions of short statured children (height $\geq$ 2 S.D. below mean for age) and to evaluate their response to rhGH administration by measuring arch-dimensional changes over 5 years of rhGH treatment. Dental casts of 28 short subjects (22 male, 6 female) and of age/gender-matched controls of normal stature were analyzed using a digital imaging system. Four measures of arch width and one of arch depth were calculated for each maxillary and mandibular cast. Subjects receiving orthodontic care were eliminated from the study at the initiation of treatment. Z-scores were calculated to allow for pooling of data.

Prior to rhGH treatment, all arch dimensions of the short statured subjects were smaller than the controls, with the exception of mandibular arch depth. Arch dimensions of the rhGH subjects did increase with the continued administration of rhGH. The control group also showed a significant trend for the arch dimensions to increase over time. The influence of rhGH treatment on arch dimensional changes over time remains equivocal based on the results of this investigation.

Key Words

Arch dimensional changes • Idiopathic short stature • Recombinant human growth hormone • Children • Craniofacial growth

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of rhGH therapy on craniofacial dimensions and dental development in these children with idiopathic short stature. Linear craniofacial dimensions derived from lateral cephalograms have been shown to be smaller in short statured children than in matched controls, although angular measurements do not appear to be affected prior to rhGH administration.[7] In addition, angular measurements were not affected by the administration of rhGH over the initial two years of treatment. While short statured children had smaller faces initially, the evaluation of angular measures suggested proportional growth had occurred.

Children with untreated idiopathic short stature have delayed dental development, as measured by tooth crown and root formation.[8,9] Tooth formation appears to be individually variable and shows little or no treatment response to rhGH administration over time.[8-10] Thus far, the results regarding dental development and facial size seem to be in agreement with findings for individuals with hypopituitarism.[11-13]

No prior studies have sought to characterize growth of the dental arches in short statured children who are not growth hormone deficient but who are receiving synthetic growth hormone therapy. Therefore, the present longitudinal investigation was undertaken to evaluate the developing craniofacial complex of children with idiopathic short stature by assessing their pretreatment dental arch dimensions in addition to the posttreatment response of dentoalveolar structures to rhGH administration. The specific objectives were:

1. To determine pretreatment baseline arch dimensions of the short statured subjects, as measured by arch width and arch depth; and to compare pretreatment baseline arch dimensions of these short statured subjects with those of age- and gender-matched controls and of a total reference population.

2. To compare arch dimensional changes of the treatment group, the matched controls, and the total reference population that occurred during five years of recombinant human growth hormone treatment.

It should be noted that the sample of children participating in the Genentech Study is diverse, even though the criteria for entry into the study were rigorous and well defined. While subjects were selected for short stature, many were consequently bone-age delayed as well. There was a disproportionate number of males in the study due to the increased referral of short statured males. Additionally, some of the subjects had short parents (familial short stature) while others had parents of average height (so-called constitutional short stature). Earlier studies suggested that there was little distinction between the responses of children classified as having familial short stature and those with constitutional short stature.[5] Despite the diversity of the sample, this investigation of dentoalveolar development was begun to provide initial data on the dental arch dimensions of individuals with idiopathic short stature. Furthermore, the effect of rhGH therapy on dental arch development has not been previously studied.

Materials and methods

This study was part of an ongoing multi-center randomized controlled study entitled "The Efficacy and Safety of Recombinant Methionine-free Human Growth Hormone (rhGH) Treatment of the Growth Retardation of Children With Idiopathic Short Stature."[5,6] The study was conducted by the Pediatric Endocrinology Departments of the various centers and funded by Genentech, Inc, of San Francisco, Calif. Two of the centers participated in the dental portion of the research. Dental records were obtained by dental practitioners at the University of Michigan and the University of Virginia Health Science Center. Data analysis was conducted at the University of Michigan.

Children were eligible to participate in the study based on the following inclusion criteria: (1) stature greater than two standard deviations below mean for age; (2) at least one GH level ≥10 ng/ml by radioimmunoassay on provocative testing at the local center; (3) a skeletal age of <9 years (girls) or <10 years (boys); (4) minimal chronological age (CA) of 5 years; (5) weight within the 10th to 90th percentile for height, and growth rate at ≤50th percentile for age and sex for at least the 6-month period before enrollment; (6) absence of significant phenotypic abnormalities; and (7) documented 46,XX karyotype in girls.

Subjects were excluded from the study based on the following criteria: (1) any clinical sign of puberty; (2) any systemic disease; (3) chondrodystrophy, bone/cartilage dysplasia or syndrome or body disproportion; (4) nutritional or vitamin deficiency; (5) psychosocial dwarfism; (6) previous treatment with growth hormone or another experimental drug within six months before entry into the study.

Subsequent to study acceptance, medical baseline records, including stature measurement,

a hand-wrist radiograph, and laboratory tests were obtained for each subject. The dental component of the rhGH trial was approved by a review board at both of the centers participating in this study. Volunteers were recruited and informed consent was obtained.

The sample

Dentoalveolar dimensions of 28 non-GH-deficient short statured subjects (22 males, 6 females) were analyzed for this investigation. Prior to participation, Genentech, Inc, randomly assigned subjects to an immediate treatment group or a delayed treatment group. The delayed treatment group of 10 males (aged 8 years 0 months to 13 years 8 months; mean age 10 years 7 months) started treatment one year later; the intent was to create a year of control. The immediate treatment group of 12 males and 6 females (aged 5 years 9 months to 12 years 1 month; male mean age 9 years 7 months; female mean age 8 years 6 months) began growth hormone treatment immediately at a dosage of 0.10 mg/kg rhGH (weight at initial exam) subcutaneously three times per week for the first year. After the first year of the study, all subjects were randomized to receive a total weekly dose of 0.3 mg/kg rhGH at either daily or three-times-per-week intervals.

Baseline dental records included a dental examination, dental casts, lateral cephalometric radiograph, panoramic radiograph, occlusal radiographs, and intraoral photographs. Records were collected annually for six years.

As mentioned, short statured subjects receiving orthodontic therapy were excluded from the study when treatment was begun in order to eliminate the possibility of artificially induced arch dimensional changes. Consequently, one subject was excluded after the baseline year, three subjects after year one, three more subjects after year two, seven subjects after year three, and six subjects after year four. Eight subjects remained through the last year of the study.

Age- and gender-matched controls of normal stature were selected for each short statured subject from the data of the University of Michigan Elementary and Secondary Growth Study.[14] Each short statured subject was matched with an age-matched control selected on the basis of availability and quality of casts. Chronological ages were used because bone ages for the control subjects were not available.

Assessment of dental casts

Arch dimensions of the short statured subjects were determined using a modified video imaging system (ELE Imaging System, Ann Arbor, Mich) specifically developed for the routine analysis of dental casts.[15] The imaging component included a digital camera lens mounted on a copy stand with attached lighting. The dental cast was secured on a stand at a standardized distance from the lens, thus controlling magnification. The digital image of the dental cast was stored on the hard disk of a computer, displayed for analysis on the video monitor, and ultimately stored on an optical disk to allow retrieval of the image at a later time. Forty-eight specific points were digitized on the image of the cast displayed on the video monitor and the coordinates of each point were exported directly to a spreadsheet program. Cast analysis was designed to characterize, in detail, serial changes in the dimensions of the dental arches. Arch width and arch depth were calculated by the program.

Four measures of maxillary and mandibular arch width were used in this study. From the digitized landmarks, centroid points[14] were calculated and the distance between the two centroids was taken as the arch width. Widths were measured at the maxillary and mandibular canine, first and second premolar or primary molars, and the first permanent molar.

Maxillary and mandibular arch depths were measured as the distance of a line constructed from the average of the central incisor midpoints perpendicular to a line drawn between the mesial midpoints of the permanent first molars. The distal midpoints of the second primary molars were used pending the eruption of the permanent first molars.

Data analysis

Because of the unusual sex ratio and the different ages and familial backgrounds of the short statured subjects, the Z-statistic was used to allow pooling of male and female subjects.

$$\text{Z-score} = \frac{\text{Actual measurement} - \text{Reference sample measurement}}{\text{Standard deviation of reference sample}}$$

The mean Z-score equaled the number of standard deviations that the mean for the short statured subjects lay above or below the mean for the reference population. A Z-score of zero indicated that the actual measurement equaled what was expected based on the reference population sample. A negative Z-score indicated that the subjects were below expectancy for age and sex. For example, a Z-score of -1.00 meant that the subject was one standard deviation below expectancy.[16] Since Z-scores were calculated for each individual and each measurement separately, it was possible to pool data for different

Table 1
Mean Z-scores of three of the five maxillary and mandibular arch dimensions for the two groups of subjects with idiopathic short stature (rhGH delayed and immediate treatment) and the age/sex matched controls

	BASELINE			YEAR 1			YEAR 2			YEAR 3			YEAR 4			YEAR 5		
	N	Z	SD	N	Z	SD	N	Z	SD	N	Z	SD	N	Z	SD	N	Z	SD
Maxilla	ARCH WIDTH-FIRST PERMANENT MOLAR																	
rhGH Delayed	9	-1.80	0.88	9	-1.98	0.82	9	-1.61	0.79	8	-1.47	0.69	6	-1.08	0.29	4	-1.13	0.64
rhGH Immediate	12	-2.22	1.03	16	-2.05	1.31	13	-1.74	1.44	13	-1.64	1.47	8	-1.00	1.40	4	-0.47	1.16
Controls	25	-1.06	1.14	26	-0.59	0.94	23	-0.68	1.05	21	-0.67	0.77	15	-0.66	0.94	8	-1.00	0.97
Mandible																		
rhGH Delayed	9	-1.12	0.92	9	-1.35	0.77	10	-1.43	0.79	8	-1.32	0.76	6	-1.12	0.37	4	-1.21	0.64
rhGH Immediate	14	-1.51	1.21	15	-1.40	1.15	14	-1.05	1.28	13	-1.19	1.11	8	-0.72	1.31	4	-0.19	0.85
Controls	23	-0.75	0.76	25	-0.49	0.85	22	-0.50	0.82	21	-0.77	0.73	15	-0.73	0.74	8	-0.83	0.68
Maxilla	ARCH WIDTH-CANINE																	
rhGH Delayed	8	-1.97	1.43	6	-1.52	1.40	7	-1.45	1.27	6	-1.56	0.87	4	-0.76	0.35	4	-1.07	0.68
rhGH Immediate	16	-1.62	1.01	16	-1.53	1.22	10	-1.18	1.40	6	-1.15	1.90	7	-0.75	1.79	4	-1.88	0.27
Controls	23	-1.31	1.39	21	-1.14	1.49	21	-1.08	1.12	16	-1.34	1.07	13	-1.24	0.89	7	-1.73	0.89
Mandible																		
rhGH Delayed	7	-1.87	1.18	9	-1.45	0.88	9	-1.31	0.47	7	-1.52	0.95	5	-0.96	0.39	4	-0.85	0.62
rhGH Immediate	17	-1.73	1.14	15	-1.39	1.11	10	-0.95	1.25	9	-2.00	1.15	8	-0.94	1.22	2	-0.76	0.20
Controls	25	-1.08	1.06	22	-0.90	0.98	20	-0.95	0.93	21	-0.97	0.95	12	-0.83	0.68	8	-1.13	0.75
Maxilla	ARCH DEPTH																	
rhGH Delayed	10	-1.80	0.69	8	-1.66	0.89	9	-1.77	0.99	8	-1.41	0.64	6	-1.26	0.99	4	-1.58	0.65
rhGH Immediate	11	-2.64	1.34	15	-2.22	1.65	13	-2.19	1.48	13	-1.82	1.53	8	-1.23	1.23	4	-1.72	0.86
Controls	24	-1.32	0.79	25	-1.11	1.06	23	-1.00	1.05	21	-1.21	0.92	15	-1.07	1.05	8	-1.14	1.22
Mandible																		
rhGH Delayed	9	-3.12	1.84	8	-1.73	1.22	9	0.26	2.26	7	1.21	2.48	6	2.51	0.80	4	3.63	0.84
rhGH Immediate	12	-1.80	1.37	15	-1.43	1.55	14	-1.13	2.83	13	-0.04	2.34	8	-0.09	2.24	4	-0.36	3.44
Controls	23	-3.12	2.37	25	-2.86	2.18	22	-1.75	2.35	21	-0.43	2.77	15	-0.27	2.60	8	-1.02	3.48

ages, different teeth, and different arch dimensions. The use of Z-scores also facilitated comparison with the findings of previous investigators who had used Z-scores in their analyses.[7-10]

Because initial review of the data indicated a departure from a normal distribution, nonparametric techniques were used to test for correlations and differences throughout this investigation. Binomial probability tests also were performed to test for significant trends. A P-value of less than 0.05 was considered statistically significant.

Arch dimensions were transformed to Z-scores using raw data from a reference sample of 208 children from the Michigan Growth Study whose serial dental casts had been digitized previously.[14] Delta Z-scores (Δ Z) were calculated to measure the changes in arch dimensions between annual visits. Negative Z-scores that approached the reference population Z-score of zero longitudinally were considered to represent "catch-up" growth.

Results

The mean arch dimension Z-scores were calculated for the 5 years of the study. Z-scores for several of the arch dimensions are shown in Table 1. Prior to rhGH administration, arch dimensions of the short statured subjects were smaller than the matched controls in all but one arch dimension, namely arch depth at the mandibular first molar, as revealed by their negative Z-scores at the baseline measurement. Likewise, baseline arch dimension Z-scores of the short statured subjects fell below expectancy (i.e., Z=0.0) when compared with the Michigan Growth Study reference population.

The Z-scores of the controls also were below expectations at baseline, even though the controls were a subset of the reference population. For example, baseline Z-scores for both of the rhGH treatment groups and the controls were

negative for arch width measured at the maxillary permanent first molar (Figure 1). During subsequent years, the arch width Z-scores of the two rhGH treatment groups remained negative for this measurement, but appeared to be approaching expectancy as the study continued. In fact, almost all of the individual arch dimension Z-scores seemed to be "catching up" over the course of the study.

Results from pooling both the maxillary and mandibular arch dimensions further suggested that, although baseline arch dimensions were below those of the reference population, the short statured subjects were "catching up" while the controls, although below expectation as well, remained fairly stable over time. The results of pooling both the maxillary and mandibular arch dimension Z-scores are shown in Figure 2. As mentioned, the number of individuals and the number of measurements decreased with the elimination of orthodontic patients from the study.

Within-group arch dimensional changes

To determine if there were statistically significant within-group differences in arch dimensions between annual visits for the rhGH delayed treatment group, the rhGH immediate treatment group, and the matched controls, Wilcoxon signed rank sum tests were performed. Despite the apparent tendency for the arch dimensions of the short statured subjects to approach the reference population mean over time, few of the arch dimensional changes of the rhGH groups or the controls were statistically significant between annual visits.

Between-group arch dimensional changes

Between-group differences in arch dimension Z-scores were analyzed using Mann-Whitney *U* tests. At baseline, none of the arch dimensions of the rhGH delayed treatment subjects were significantly different from the arch dimensions of the rhGH immediate treatment group, with the exception of mandibular arch depth. Even after one year of synthetic growth hormone therapy, the arch dimensions of the immediate treatment subjects were still not significantly different from the arch dimensions of those in the delayed treatment group. Furthermore, during subsequent years, no statistically significant differences existed between the two rhGH treatment groups, with the exception of mandibular arch depth at baseline and year four.

In contrast, the arch dimensions of the short statured subjects were found to be significantly smaller when compared with the matched controls, particularly in the earlier years of the in-

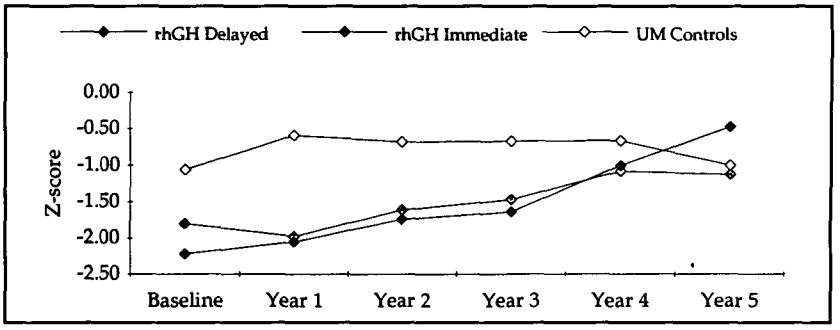

Figure 1

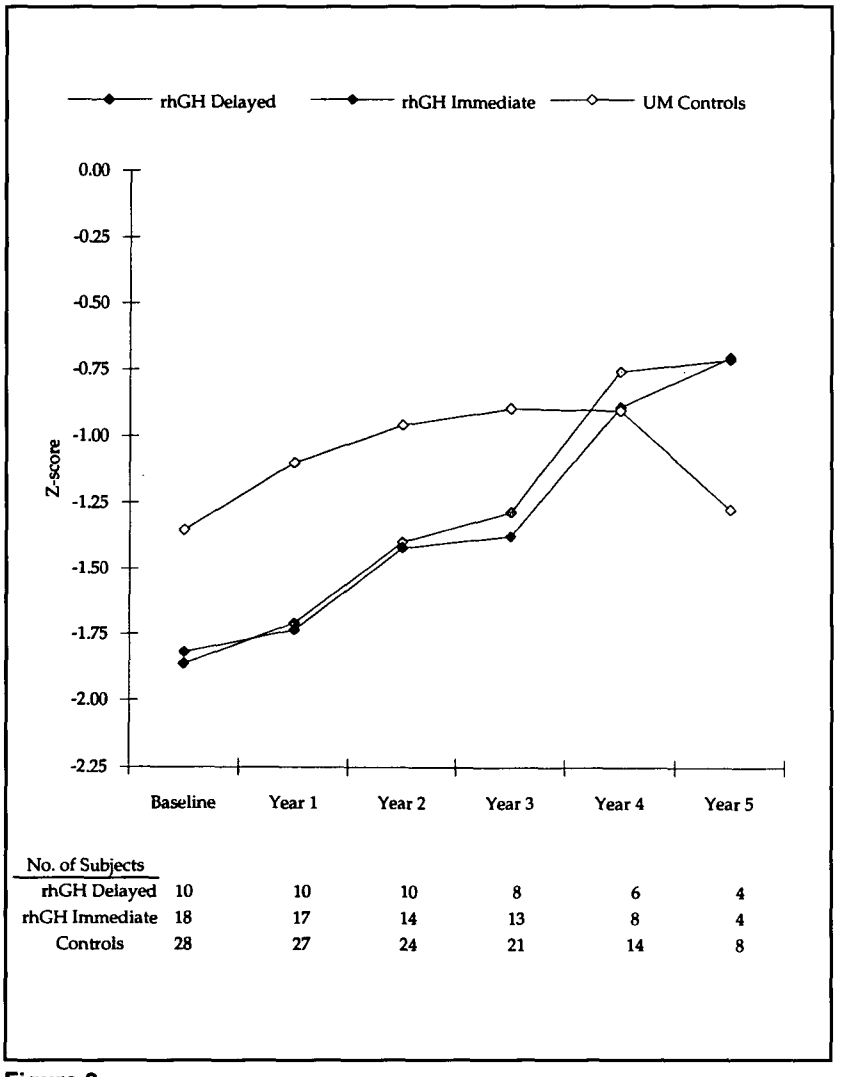

Figure 2

Figure 1
Z-scores of the centroid arch width at the maxillary first molar (M1). M1 arch width of the two rhGH groups fell below expectancy but appeared to be "catching up" over time, while arch width of the controls remained fairly stable.

Figure 2
Mean Z-scores of five combined maxillary and mandibular arch dimensions for the two groups of subjects with idiopathic short stature (rhGH delayed treatment and rhGH immediate treatment) and the age/sex matched controls. Note that the short statured subjects appeared to be "catching up" over time.

vestigation. As the investigation continued, there were fewer significant differences between the short statured subjects and the controls. At years four and five, there were no significant differences for any of the arch dimensions. However, interpretation of these results must be made cautiously due to the reduction in the number of arch dimensions measured subsequent to the exclusion of those receiving orthodontic treatment.

Although within-group arch dimensional changes were not statistically significant between annual visits, tests for trends were performed to clarify if there was nevertheless a tendency for the arch dimensions to "catch up" over time. Binomial probability tests for trend revealed that there was a significant tendency for each group's arch dimensions to approach those of the reference population. Thus, although the arch dimension Z-scores were not statistically different between years, there was a significant trend towards "catch up" growth in all three groups (rhGH delayed treatment, rhGH immediate treatment, and controls) over time.

Discussion

Because of the negative social and societal implications of being short, many parents aggressively seek treatment for their children. However, any group of children with idiopathic short stature is, by nature, heterogeneous. As mentioned earlier, some are constitutionally delayed while others are familially delayed. Though the number of short statured children participating in this study was fairly low (n=28), because the subjects were selected for short statured height greater than two standard deviation below mean for age, the sample was theoretically the bottom 3% of a potentially much larger sample.

At baseline, all pretreatment arch dimensions of the short statured children were smaller compared to the matched controls, with the exception of mandibular arch depth. The arch dimensions of the short statured subjects were also smaller than the normative reference population. This was an expected finding given the developmental delay and overall body-size reduction of the short children. However, arch dimensions of the age and gender matched control group were also reduced compared to the reference population. Given that the controls were a subset of the reference population, this was not expected.

The Genentech Collaborative Growth Study[5,6] was designed to include one year of control at the beginning of the study, during which a portion of the subjects with idiopathic short stature received recombinant human growth hormone while the other portion of the subjects remained untreated. After one year of synthetic growth hormone administration, there continued to be no significant differences in arch dimensions between the delayed treatment group and the immediate treatment group. Ideally, the study design would have included a matched pair design of untreated short statured individuals as a true control group. Ethical considerations precluded withholding treatment for a longer period of time as the enhanced growth response under rhGH administration was already well known. Nevertheless, lack of a true control population was a limitation. During the five years of this study, with the exception of mandibular arch depth at baseline and again at year four, there were no significant differences between the two rhGH treatment groups in any of the maxillary or mandibular arch dimension measurements.

This finding parallels the previously reported results of other craniofacial studies from the Genentech Collaborative Growth Study. While stature increased significantly after only one year of rhGH treatment, rhGH did not appear to have an appreciable affect on tooth formation or cephalometric dimensions over the short term.[5-9]

There was a significant trend for the relative dimensions of the short statured subjects to increase with time. This trend was evident not only for the rhGH subjects, but for the matched controls as well. All groups showed a tendency to "catch-up" to the mean arch dimensions of the reference population. Thus, it was not clear if the short statured children were showing arch dimensional changes in response to rhGH administration, or in spite of it. These children were greater than or equal to two standard deviations below the mean height for age, but they had not yet stopped growing. An increase in arch dimensions may have occurred even if the short statured subjects had remained untreated, just as their stature would likely have increased even without rhGH therapy. Therefore, there is a need to characterize the "normal" arch dimensional changes of untreated short statured subjects to help elucidate if rhGH administration contributed to the arch dimensional changes seen in the treated short statured children.

The magnitudes of arch dimensional changes from infancy to late adolescence normally are about 5 mm or less, with the changes occurring gradually during the growth period. Moreover, there are great individual variations in arch dimensional changes.[17] The Genentech Study has

proposed that approximately half of the short statured children will respond to rhGH therapy. Future studies may reveal that the children who show the greatest increase in stature also experience the greatest increase in arch dimensions.

Exclusion of the subjects with malocclusions, particularly those with crowding, may have explained the tendency for the arch dimensions of the short statured children to increase over time. As shown by Howe and co-workers[18] and others, the dimensions of crowded arches are significantly smaller than the dimensions of uncrowded arches. The exclusion of the subjects with malocclusions, particularly those with crowding, may explain the tendency for the arch dimensions of the short statured subjects to increase over time. Arch dimension means might have "increased" simply because of the exclusion of those children with severe crowding (smaller arch dimensions), complicating the interpretation of the rhGH treatment response of the short statured subjects. Furthermore, arch dimensional changes observed following rhGH treatment may have been limited due to the occlusion and the intercuspidation of the teeth. Dental compensation could conceivably have masked any alveolar growth.

Based on the current evidence, recombinant human growth hormone treatment of children with idiopathic short stature significantly influences statural growth rate but does not appear to have a major effect on dental arch development.

Conclusions

Within the recognized limits of this study:

1. Pretreatment arch dimensions of children with idiopathic short stature were reduced compared to a normative reference population and to age- and gender-matched controls.

2. Arch dimensions of an rhGH immediate treatment group did not differ significantly from the arch dimensions of an rhGH delayed treatment group after one year of recombinant human growth hormone administration. Although there was a statistically significant trend for the relative arch dimensions of the treated short statured children to increase over time, the arch dimensions of the control group also increased. Thus, the influence of rhGH treatment on arch dimensions over time remains equivocal based on the evidence from this investigation.

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