The Relationship between Adiposity and Height Responses during the First Two Years of Growth Hormone Therapy in Prepubertal Children with Idiopathic Growth Hormone Deficiency

Takeki Hirano, Kazue Takano, Toshiaki Tanaka, Kunihiro Hanew, Yutaka Igarashi,
Yoshikazu Nishi, Kenji Fujieda, Katsuhiko Tachibana and Susumu Yokoya

Executive Committee of the International Cooperative Growth Study in Japan

Department of Pediatrics, Ibaraki Children's Hospital (TH), Ibaraki, Department of Medicine, Institute of Clinical Endocrinology, Tokyo Women's Medical College (KT), Tokyo, Division of Endocrinology & Metabolism, National Children's Medical Research Center (TT), Tokyo, Hanew Clinic (KH), Sendai, Igarashi Children's Clinic (YI), Sendai, Department of Pediatrics, Hiroshima Red Cross Hospital (YN), Hiroshima, Department of Pediatrics, Hokkaido University (KF), Hokkaido, Division of Endocrinology and Metabolism, Kanagawa Children's Medical Center (KT), Yokohama, Department of Pediatrics, Toranomon Hospital (SY), Tokyo, Japan

Abstract Data for a total of 287 prepubertal patients with growth hormone deficiency (GHD) from the International Cooperative Growth Study (ICGS) treated with recombinant growth hormone (GH) for more than two years were analyzed for the relationship between adiposity and growth response. The percent overweight index was used for assessing the degree of adiposity. One hundred eighty-eight patients with GH neurosecretory dysfunction on GH treatment from the same database served as controls. Results: There was a statistically significant decline in % overweight only during the first year. There was no change in adiposity between the first and second year. In a comparison between thin patients with GHD and obese patients, obese patients had better first year growth response (height velocity, its SD score, increase in height SD score) despite older age, and lower GH dosage/kg. Among obese children with GHD, there was a tendency toward better height response in more obese individuals. Simple correlation analysis revealed variables that negatively correlated with % overweight were GH peak levels, GH dosage and height velocity before treatment and variables that positively correlated were the number of injections/week and the first year growth response. Multiple regression analysis in patients with GHD and GH neurosecretory dysfunction revealed that adiposity is an independent factor promoting height response during the first year of GH treatment in prepubertal GHD patients.

Key words: adiposity, obesity, growth hormone deficiency, growth, short children, growth hormone

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Correspondence: Dr. Takeki Hirano, Department of Pediatrics, Ibaraki Children's Hospital, 3-3-1 Futaba-dai, Mito-shi, Ibaraki-ken 311-41, Japan

Introduction

Patients with growth hormone deficiency (GHD) have an increase of adiposity which diminishes during treatment with growth hormone (GH), because GH has lipolytic activity. In the study of adults with GHD on treatment with recombinant GH (1), adiposity was shown to decrease during therapy with GH preparation. Martha *et al.* (2) reported that the first year growth response to GH treatment was significantly correlated with the degree of adiposity in 200 patients with GHD (4). Also Ranke *et al.* (3) showed that the weight/height index was one factor contributing to the first year height response in GHD patients treated with GH. In this study, we tried to determine the effect of GH therapy on adiposity in Japanese prepubertal children with GHD on GH treatment.

Subjects and Methods

Out of 3,508 patients on recombinant GH therapy (as of June, 1993) registered in the largest Japanese data base, International Collaborative Growth Study (ICGS) by Sumitomo Pharmaceutical Company in Japan, we were able to collect 287 prepubertal patients with GHD who had completed two years' treatment by using the criteria of inclusion shown in Table 1. In this group, we analyzed the relationship between growth responses and adiposity. In comparison, we also collected from the same database 188 prepubertal patients by using the same criteria, except stimulated maximal GH levels higher than 10 ng/ml. Patients in this group received GH therapy for one or several of the following reasons: low IGF-I level, low average GH level three hours after going into sleep, low urinary GH level or a history of perinatal abnormalities, including breech delivery. This group of patients was tentatively named GH neurosecretory dysfunction (GHNSD).

As a mean of evaluating adiposity, % over-

Table 1 Criteria of inclusion in this study

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1. Tanner Stage I
 2. idiopathic type as etiological diagnosis
 3. age range male ≥ 3 and < 11 years
 female ≥ 3 and < 9 years
 4. completion of the first two year with treatment with recombinant GH
 5. peak GH values ≤ 10 ng/ml in more than two provocative tests
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weight or the weight-height index was used. The calculation was done with the following formula: Percent overweight = (current weight - ideal weight) $\div$ (ideal weight) $\times 100$. In this formula, ideal weight was obtained from age and gender specific regression quotations developed by Murata (4).

The statistical methods were Student's t-test, one-way analysis of variance, Duncan's multiple comparison, simple regression analysis and stepwise multiple regression analysis.

Variables and their abbreviations in this paper are shown in Table 2.

Results

A mean pretreatment % overweight of 5.8% indicated increased adiposity in GHD patients as a whole, though standard deviation was large. There was a statistically significant decline in % overweight only during the first year ($p < 0.0001$), as shown in Table 3. There was no change in adiposity between the first and second year.

According to the % overweight, we classified the subjects into thin (less than -10%) group and obese (more than +20%) group. In the obese group there were better height responses in HVI, HVSDSI and Δ HSDSI despite older age, and lower GH dosage/kg in the obese group than in the thin group (Table 4). There was no difference in growth response in the second year of therapy.

To know the effect of the severity of obesity on growth response, we divided the obese group

Table 2 Classifications of variables

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1. Age when GH started : Chronological Age (CA), Bone age (BA), Height (H)
 2. Degree of short stature
 - Pretreatment height standard deviation score (Pre HSDS)
 - Height standard deviation score in the first year (HSDS1)
 - Height standard deviation score in the second year (HSDS2)
 3. Adiposity: Pretreatment % overweight, % overweight 1, % overweight 2 (calculated by Murata's method)
 4. Pre Growth Parameter
 - Pretreatment height velocity (Pre HV),
 - Pretreatment height velocity SDS (Pre HVSDS)
 5. GH secretory capacity
 - Maximal GH concentrations during provocative stimulation tests (Peak GH)
 - Insulin-like growth factor I (IGH-I)
 - Growth hormone releasing factor (GRF)
 6. GH dose related
 - Number of injections/wk during the first year (Inj1),
 - Dose of GH by U/kg/wk during the first year (Dose1)
 - Number of injections/wk during the second year (Inj2),
 - Dose of GH by U/kg/wk during the second year (Dose2)
 7. Growth responses after 1 yr
 - HV1, HVSDS1, HVSDSBA1
 - Increment from the pretreatment year to the first year
 - Δ HV1, Δ HSDS1, Δ HVSDS1
 8. Growth responses after 2 yr
 - HV2, HVSDS2, HVSDSBA2, %HV2/HV1
 - Increment from the pretreatment year and the second year
 - Δ HV2, Δ HVSDS2
 - Increment from the first year to the second year
 - Δ HSDS2
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The numbers after the variables denotes the first and the second years of GH treatment. For example, HV1 means height velocity during the first year of GH therapy.

Table 3 Changes in percent overweight during the first two years of GH therapy

	Mean $\pm$ SD	Range	N
1. Pre % overweight	5.8 $\pm$ 13.0	– 21.9 ~ 75.2	287
2. % overweight 1	1.7 $\pm$ 11.3	– 22.8 ~ 73.2	286
3. % overweight 2	2.4 $\pm$ 11.9	– 21.9 ~ 73.4	285

Analysis of variance $F=14.2$ ($p=0.0000$). Comparison: 1 & 2 $p<0.0001$, 1 & 3 $p<0.01$.

Table 4 Comparison of thin and obese group variables during GH therapy in GHD patients

	Age	Peak GH	Inj 1	Dose1	Dose2	HV1	Δ HSDS1	HVSDS1	HV2	Δ HSDS2	HVSDS2	%HV2/HV1
Thin*	5.4	6.5	4.0	0.62	0.48	7.4	0.65	1.7	6.4	0.35	0.6	88.1
Obese**	6.9	4.8	4.9	0.50	0.57	8.3	0.84	3.5	6.3	0.32	0.7	77.7
p value	0.005	0.01	0.01	0.001	0.002	0.064	0.07	0.001	0.66	0.51	0.85	0.064

*Thin: % overweight < - 10.0% (N=21), **Obese: % overweight >20.0% (N=29).

Table 5 Adiposity and Growth response to the degree of obesity among obese patients

	N	AGE	GH peak* ¹	Inj 1	Pre- HV	HV1	HV2	%HV2 /HV1	Δ HSDS1	Δ HSDS2* ²	HVSDS1	HVSDS2	Δ HVSDS2
Group 1	26	8.4	6.8	5.2	3.2	7.3	5.6	79.6	0.55	0.19	2.8	0.13	4.93
Group 2	18	6.6	5.4	4.8	4.3	8.5	6.5	79.4	0.87	0.38	3.6	1.05	6.23
Group 3	6	7.7	3.5	4.5	3.3	7.9	5.7	74.0	0.67	0.20	3.0	0.17	4.19
Group 4	5	7.2	4.3	5.8	4.9	8.4	6.1	75.5	0.90	0.22	3.7	0.28	6.90
p value		0.16	0.014	0.33	0.49	0.677	0.18	0.904	0.079	0.03	0.77	0.31	0.59

Group 1 15 to 19.99%, Group 2 20 to 29.99%, group 3 30 to 39.99%, Group 4 more than 40%. p value by one way analysis of variance and multiple comparison by Duncan.

*¹ significant between Group 1 and Group 3, *² significant between Group 1 and Group 2.

into four subgroups according to the degree of obesity, as shown in Table 5. A statistically significant difference in peak GH values was found. There was a tendency toward better height responses in more obese individuals, but no statistical significance was found.

Simple correlation analysis (Table 6) revealed that variables negatively correlated with % overweight were GH peak levels, GH dosage and pretreatment HV, and variables positively correlated were the number of injections/week and the first year growth responses.

There was a negative correlation between GH secretory capacity and the degree of obesity before treatment (Fig. 1), whereas there was a positive relationship between HVSDSI and % overweight.

Multiple correlation analysis (Table 7) revealed that both the adiposity and GH secretory capacity were selected as factors contributing to the first year height response by similar stan-

Table 6 Simple correlation coefficients between adiposity and variables in GHD

	% overweight
Age at start	0.266**
GH maximal levels	- 0.233**
Pre HSDS	- 0.167**
Pre HV	- 0.201**
Number 1 inj/wk	0.199**
Number 2 inj/wk	0.180**
Dose 1 U/kg/wk	- 0.302**
Dose 2 U/kg/wk	- 0.303**
HV1	0.130*
Δ HV1(pre & 1)	0.208**
HVSDS1	0.244**
Δ HVSDS1(pre & 1)	0.182**
Δ HSDS1(pre & 1)	0.127*
HV2	- 0.031
Δ HV2(pre & 2)	0.123
HVSDS2	0.002
Δ HSDS(pre & 2)	0.014

*p<0.05, **p<0.01.

Fig. 1 Simple regression in patients with GHD

standardized partial regression coefficients.

Table 8 shows that in the GHNSD patients % overweight contributed largely to the first year height response, though GH secretory capacity did not. But in the two multiple regression analyses, R square, or the coefficient of determination, was only 34% or 38%, respectively. This suggests that unknown factors may be present to explain growth response during GH therapy.

Discussion

This study was characterized by a relatively large number of prepubertal patients, not comparable to other study. There are several shortcomings in a study involving multiple centers, such as a lack of uniformity to judge bone age, different staging of puberty or different methods of measuring hormones.

Another problem is assessing the degree of adiposity. Percent overweight is an indirect means of judging the severity of obesity. In children the

Table 7 Standardized partial regression coefficient in stepwise multiple regression analysis during the first year in GHD

Δ HSDS1	Dependent variables
N=178	
Age	-0.31
GH peak	-0.16
Pre HVSDS	-0.17
Injection 1	0.22
THSDS	0.24
Pre HSDS	-0.22
Pre % overweight	0.14
R square*	0.38

*coefficient of determination.

Table 8 Standardized partial regression coefficient in stepwise multiple regression analysis during the first year in GHNSD

Δ HSDS1	Dependent variables
N=130	
Age	-0.37
% overweight	0.25
Pre HSDS	-0.23
GH Peak	-0.25
Dose 1	0.16
R square	0.34

body weight and height index may not exactly show the amount of adipose tissue. Standard weight for height in particular tends to be overestimated in short children. In this study, however, % overweight is only one parameter used.

Our data showed blunted GH secretion during GH provocative tests in obese subjects that has already been reported in the literature (7). Adiposity was positively related with the first year height response to GH. Even if obese patients received a smaller dosage of GH on a weight basis and were in an older age group than thin patients, they grew better. Growth response in GH

treated GHD patients is known to be negatively correlated with GH secretory capacity as shown by Tanaka (8). It is therefore possible that a better growth response in patients with increased adiposity was mediated through poor GH secretory capacity. From multiple regression with dependent variation in height response during the first year, obesity and poor GH secretion contributed to growth response to the same extent, but in patients with GHNSD on GH treatment, adiposity is a positive factor for growth response, whereas no significant relationship between adiposity and GH secretory capacity was detected. This fact supports the theory that adiposity may affect growth response in patients on GH therapy. Martha *et al.* (2) reported adiposity as a factor contributing to growth response and showed that the role of adiposity in GH therapy is closely associated with GH binding protein (GHBP), which was not measured in this study. A recent study showed that concentrations of GHBP increased in obese children (9). The GHBP/receptor level is nutritionally regulated, with levels low in undernutrition and high in overnutrition (10). Because GHBP is an extramembrane domain of GH receptor, increased levels may reflect increased growth response. In the second year of treatment, however, fat mobilizing effect of GH disappear. Simultaneously HV will drop to 70-80% of the first year HV. This phenomenon is called a waning effect of growth response to GH treatment. We speculate that the waning effect may have some relationship to adiposity, although there is no evidence of this.

Better growth response in patients with increased adiposity suggests that proper nutrition is necessary for better growth response.

The current study shows that GH administration is not effective for the treatment of obesity because the lipolytic action lasts only for one year. In conclusion, adiposity appears to be an independent factor in promoting height response during the first year of GH treatment in prepubertal GHD patients. Proper nutrition during

GH therapy should be stressed.

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