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Original

Auxological and Biochemical Continuum of Short Children Born Small for Gestational Age (SGA) during Growth Hormone (GH) Treatment

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Introduction: The role of growth hormone (GH) on body composition in Japanese children born small for gestational age (SGA) has not been fully elucidated.

Methods: Every six months, the total GH dose was adjusted: SGA, 33-66 μg/kg/day, or GHD, 25-30 μg/kg/day. Changes in metabolic parameters (HbA1c, leptin, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol) were recorded. Changes in the body mass index standard deviation score (BMI SDS), BMI percentile, and percent overweight were also evaluated.

Results: Over a 3-year period of GH treatment, significant increases in Δ height SDS and Δ insulin-like growth factor-I (IGF-I) were observed. The HbA1c and leptin levels were generally unaffected. Favorable changes in the lipid profiles were recorded, and these changes were maintained for the study duration. No adverse changes in BMI SDS, BMI percentile, or percent overweight were noted.

Conclusion: GH treatment had a positive impact on height, and any changes observed in safety parameters, such as lipid profiles, HbA1c and BMI SD, were considered to be related to the natural course of growth in children and to be clinically insignificant.

Key Words: small for gestational age (SGA), growth hormone deficiency (GHD), body mass index (BMI)

Introduction

Small for gestational age (SGA) at birth is a relatively common condition, with approximately 5 % of all newborns being below −2 standard deviation scores (SDS) for weight and/or length. While the majority of these children will demonstrate spontaneous catch-up growth in early life, approximately 10 % of children born with SGA will fail to do this by 3 years of age, and this height deficit is likely to continue into adulthood, with a final adult height remaining below −2 SDS of the mean height[1]. Although the mechanism responsible for the stunted postnatal growth in short children born with SGA is poorly understood, studies have shown that continuous or discontinuous treatment with recombinant human growth hormone (GH) at varying dosages accelerates growth significantly in short children born with SGA, resulting in catch-up growth to values within the normal range followed by growth within their target height percentile[2,3].

Restricted fetal growth, which is often studied using SGA at birth as a proxy, has been robustly associated with high blood pressure, type 2 diabetes, and coronary artery disease in later life. Several recent epidemiologic studies have reported that SGA at birth is also associated with greater adiposity (percentage body fat and fat mass), and obesity, particularly truncal obesity, during later childhood and adulthood, suggesting that increased adiposity may be a step on the causal pathway between restricted

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fetal growth and long-term adult chronic disease outcomes[4]. The mechanisms underlying these risks are unknown, although it has been postulated that increased insulin resistance and/or intra-abdominal fat could be responsible[5]. Indeed, insulin resistance and subsequent hyperinsulinemia are common features in children born with SGA who experience a rapid weight gain.

The aim of this study is to examine body composition and growth at the start and during 3 years of GH treatment of short children with SGA and GHD. We hypothesized that the effect of GH on height gain, adiposity and lipid profiles would be similar in both groups.

Patients and Methods

The study population was composed of 16 short children born with SGA and 30 short children with growth hormone deficiency (GHD) aged 3-8 years. The short children born SGA were included after meeting the following criteria: 1) birth weight and birth length <10th percentile for gestational age; 2) birth weight SDS or birth length SDS < −2 SDS for gestational age; 3) chronological age ≧ 3 years; 4) height SDS for chronological age < − 2.5 SDS; 5) peak GH level of >6 ng/mL on at least one GH provocation test conducted within 1 year, and 6) prepubertal children (Tanner stage 1 for both boys and girls). GH-deficiency (GHD) was defined as a peak GH secretion ≦ 6 ng/mL during two GH provocation tests. None of the patients had diabetes insipidus, chromosomal abnormalities, Silver-Russell syndrome, or dysmorphic syndromes, as established by a careful clinical evaluation. All the subjects had normal thyroid function (normal TSH and FT4 circulating levels). Children who had previously received systemic thyroid hormone or anabolic steroid, adrenocortical steroid and analogue of gonadotropin-releasing hormone were not eligible in both groups.

Biosynthetic GH was given subcutaneously once daily at bedtime using a pen injection system. Every six months, the total GH dose was adjusted: SGA, 33-66 µg/kg/day or GHD, 25-30 µg/kg/day. All the children were seen at our hospital for a physical examination, including measurements of standing height and weight at baseline and every 3 months thereafter, by trained observers. Height was expressed as SDS. Body mass index (BMI: weight [in kilograms]/height squared [in meters]) was expressed as the SD-score and percentile for sex and chronological age. Percent overweight was calculated as follows: (actual weight) − (ideal weight)/(ideal weight)[6][7]. The pubertal stages were assessed by the same two investigators according to the Tanner stage using an orchidometer in boys. Changes in height, IGF-I, BMI SDS, BMI percentile, and percent overweight were reported at 1, 3, and 6 months and at 1, 2, and 3 years. This report also presents data on the effect of long-term GH therapy on the following metabolic parameters: glucose, HbA1c (glycosylated hemoglobin A1c, NGSP), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and leptin in Japanese children born with SGA and GHD.

All the analyses were performed using the full analysis set consisting of all the randomized patients. The summary statistics (mean with SD) were calculated for treatment differences (SGA vs GHD, baseline vs 3 years) in Ht-SDS, IGF-1, leptin, BMI-SDS, BMI percentile, percent overweight, lipid parameters and HbA1c for patients who had baseline and 3-year data (last observation carried forward). Data were analyzed using 2-sided, 2-sample t-tests performed at a significance level of p<0.05.

This study was approved by the institutional ethics review board of the Tokyo Women's Medical University (No. 3859).

Results

Clinical data

Table 1 lists the baseline clinical data of the 45 children. Both the SGA and the GHD groups had similar initial characteristics. No significant differences in baseline data between the SGA and the GHD groups were found. After three years of GH treatment, all the children were still getting height gain and receiving GH treatment.

Height, IGF-I, and leptin

During 3 years of GH treatment, catch-up growth was accompanied by changes in height SDS (SGA:

−2.92 to −1.60, p<0.01; GHD: −2.66 to −1.93, p< 0.01; SGA vs GHD at 3 years, p=0.21) and IGF-I level (SGA: 121.5 to 359.9, p<0.01; GHD: 118.6 to 280.8, p< 0.01; SGA vs GHD at 3 years, p=0.12). No significant differences in the changes in height SDS or IGF-I measurements after three years of GH treatment were seen between the two groups. During the first 6 months, the leptin levels decreased by 25 % in

Table 1 Patient demographics

	SGA	GHD
N, gender (male/female)	14 (7/7)	31 (18/13)
CA, years	7.61 (3.23)	8.62 (3.62)
Height SDS	−2.92 (0.41)	−2.66 (0.46)
IGF-I, ng/mL	121.5 (50.1)	118.6 (52.2)
Leptin, ng/mL	2.7 (1.5)	3.3 (2.3)
HbA1c, %	4.9 (0.3)	4.9 (0.3)
TC, mg/dl	180 (33)	172 (41)
LDL-C, mg/dl	108 (33)	100 (39)
HDL-C, mg/dl	69 (17)	63 (17)
TSH, μIU/ml	2.27 (1.01)	2.58 (0.96)
f T4, ng/dl	1.39 (0.18)	1.32 (0.16)
BMI SDS	−0.87 (1.08)	−0.31 (1.13)
BMI percentile	28.8 (26.0)	42.8 (31.6)
percent overweight	0.3 (9.2)	7.4 (15.4)

Results are expressed as means with standard deviations in parentheses.

SGA children, indicating a body fat reduction. Thereafter, these levels increased to a value that was not significantly different from the pretreatment values (Fig. 1).

BMI SD, BMI percentile, and percent overweight

At the start of GH treatment, the mean SD for BMI was −0.87, which was lower than zero, indicating that untreated children born with SGA had a lean and fragile body mass and reflecting a suboptimal nutritional status. After 3 years of GH treatment, it had increased, but not significantly, compared to the baseline value, with values that were closer to zero. The increment in the BMI SD-score was not significantly different between these two groups during GH treatment. The changes in BMI percentile and percent overweight were not significantly different between the GHD group and the SGA group during the 3-year study period (Fig. 2).

Lipids & HbA1c

The mean pretreatment lipid profiles and HbA1c levels were normal in both groups. Four children had a TC level of more than 200 mg/dL, one child had an LDL cholesterol level of more than 140 mg/
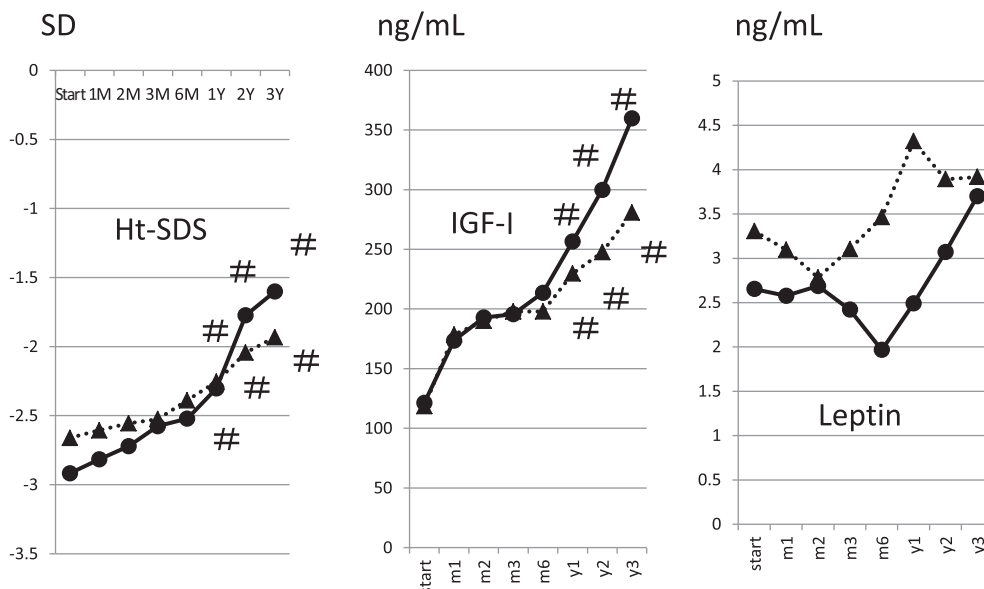

Fig. 1 Time sequence of changes in height (Ht) SDS, IGF-I, and leptin before the start of GH treatment and for the first 3 years of treatment in the SGA (circle symbol) and GHD (triangle symbol) groups. Note the significant increase in Ht SDS and IGF-I during the first year of treatment, with ongoing (although more gradual) increases thereafter in both groups. Significant changes from baseline to each year of GH treatment (#p<0.05) are indicated.

SD

BMI-SDS

percentile

BMI-percentile
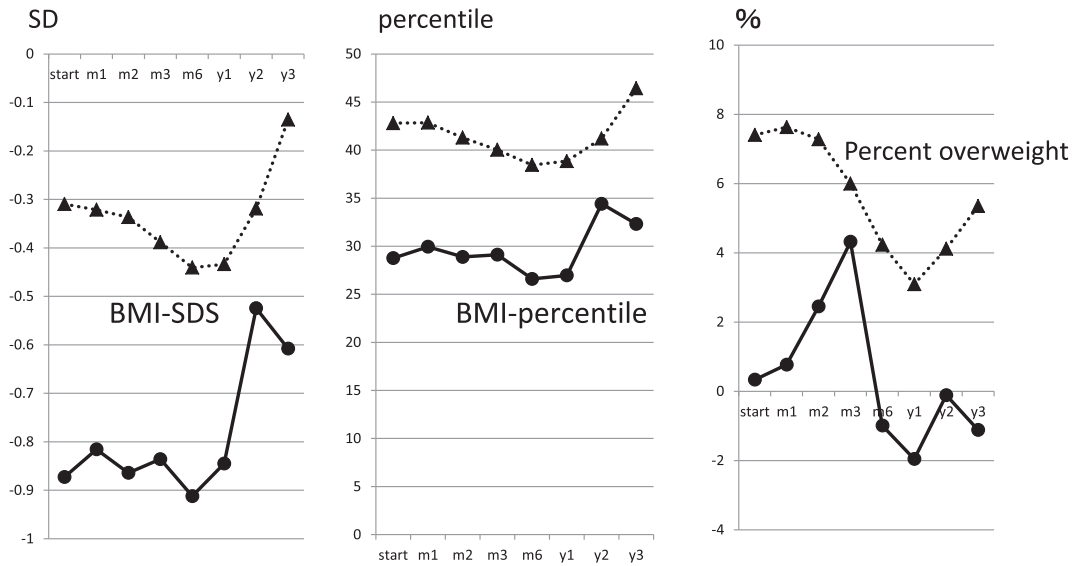
%

Percent overweight

Fig. 2 Body mass index (BMI) SD-score, BMI percentile and percent overweight using reference values for healthy Japanese children according to sex, chronological age, height and weight at baseline and during 3 years of GH treatment in the SGA (circle symbol) and GHD (triangle symbol) groups.
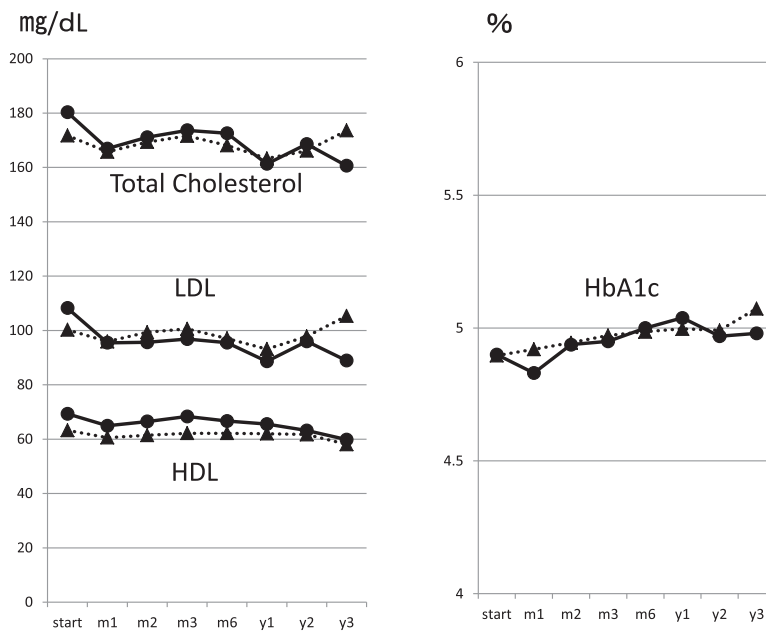
mg/dL

Total Cholesterol

LDL

HDL

%

HbA1c

Fig. 3 Time sequence for changes in total cholesterol, LDL cholesterol, HDL cholesterol and HbA1c at baseline and during 3 years of GH treatment in the SGA (circle symbol) and GHD (triangle symbol) groups.

dL, and none of the children had an HDL cholesterol level of less than 40 mg/dL in the SGA group. Despite the observed decreases during the 3-year GH treatment period in the SGA group, the mean TC, LDL, and HDL measurements did not exceed the normal limits for healthy children, and the subjects in this study were considered normotensive. After 3 years of GH treatment for SGA, one of the children had an abnormal TC, whereas none of the children had an LDL cholesterol level of more than 140 mg/dL and one child had an HDL cholesterol level of less than 40 mg/dL. The mean HbA1c values had marginally increased in both groups after 3 years of GH treatment (0.08 % and 0.17 % in the SGA and

GHD groups, respectively), although none of the subjects exceeded the upper limit of the HbA1c reference range (4.3 %-5.8 %) (Fig. 3).

Discussion

We decided to compare SGA children with already well-described GHD children. It would have been useful to have two measurements at different times after the start of GH treatment so as to quantify the effect of GH more precisely in each group[8]. A lack of treatment might provide a psychological advantage (no injection stress) or a disadvantage (thoughts that "no one is doing anything about my short stature"), while the use of placebo injections is not acceptable to many parents whose SGA children have often had varying degrees of traumatic hospital experiences in the past. Both the SGA and the GHD children showed similar increases in height SDS after three years of GH treatment. An indicator of GH sensitivity, the IGF-I level, was measured throughout this study; these levels were low at the start of treatment but increased in a similar manner in both groups. GH is a crucial regulator of substrate metabolism during fasting, and its anabolic actions are tightly coupled with energy balance. A low adiposity in SGA children may reflect a suboptimal energy balance and may alter their sensitivity to GH.

BMI expressed as the SDS for age, which is a better parameter for assessing the degree of overweightness since it takes into account age as well as height, has not been studied extensively in SGA children. Correction for age is important because the BMI changes substantially with age, decreasing during preschool years and then increasing into adulthood[9][10]. Unfortunately, no reference values are available for the BMI SD score in untreated short children born with SGA. Therefore, the natural development of the BMI SD score in these children remains unknown; consequently, we cannot prove whether the changes in the BMI SD score during treatment are caused by GH. In the present study, however, during the 3 years of treatment, the height SD score and the IGF-I improved significantly, while the BMI SD score, BMI percentile, and percent overweight did not change. Therefore, it is likely that the changes in the BMI SD score during the GH treatment are more a result of the natural childhood growth of subjects with a short stature who were born with SGA or that the changes in the BMI SD score reflect catch-up growth in these children, rather than a direct effect of the GH treatment. GH causes the body to utilize fat mass stores for energy to aid in the production of muscle, which is proportionally increased in patients receiving GH. It is possible that GH may have affected body composition, as GH promotes the development of muscle over fat, but specific tests such as dual-energy X-ray absorptiometry would be needed to show such a change[11].

Leptin, the first adipocyte hormone identified, influences food intake through a direct effect on the hypothalamus. In humans and rodents, plasma leptin concentrations are strongly correlated with the BMI[12]. Far from hormonally inert, adipose tissue has, in recent years, been recognized as a major endocrine organ, as it produces hormones such as leptin, PAI-1, resistin, and the cytokine TNFα. Moreover, adipose tissue can affect other organ systems of the body and may lead to disease. Our leptin data in SGA is comparable with the results of fat and muscle measurements made using magnetic resonance imaging and described by Leger et al.[13]. They reported an increase in the cross-sectional area of muscle tissue in 14 prepubertal short children born with SGA but without GH deficiency during 3 years of GH treatment with 0.2 IU/kg per day (≈ 6 IU/m^2 per day). In addition, the adipose tissue cross-sectional area showed an initial decrease during the first year of treatment, followed by an increase during the second and third years to values similar to those in a control group of GHD children. GH increases basal lipolysis and increases the activity of hormone-sensitive lipase, resulting in a rapid decrease in the adipose area and an increase in muscle tissue. It seems likely that the reduction in leptin levels is attributable to the reduction in adipose tissue mass that occurs during GH treatment.

GH deficiency is associated with dyslipidemia. Barker et al demonstrated a negative correlation between birth weight and syndrome X (hyperten-

sion, diabetes mellitus type 2, and hyperlipidemia) in adult men[14]. Being born with SGA has been associated with the onset of hyperlipidemia at a relatively young age later in life[15] hence, we were interested in the effect of GH therapy on the lipid profiles in these patients. The pretreatment levels of TC and LDL-C in the SGA group were normal, compared with those in the GHD group which were slightly low. An analysis of the change from the baseline TC and LDL-C values in a model that included the baseline values as covariates showed treatment differences for TC and LDL, and a clear trend towards a reduction in both lipid parameters was evident in the SGA group. In a previous study, no change in the HDL-C levels was seen during GH treatment[16]. Further investigations are warranted to evaluate the impact of GH treatment on lipid parameters in children born with SGA in greater detail. Long-term monitoring is needed to assess whether the effects of GH on the lipid profiles of children with SGA or GHD has long-term benefits (or risks) for their metabolic health.

GH therapy is known to affect glucose homeostasis and insulin action. Despite slight increases in HbA1c during the initial 3 years of this study, no clinically relevant HbA1c changes were observed, and none of the patients were classified as "diabetic type". SGA children with spontaneous catch-up growth are at an increased risk of developing type 2 diabetes[17], in addition to other chronic conditions that are risk factors for cardiovascular disease. Therefore, it is encouraging that these data suggest that in Japanese children born with SGA, prolonged GH treatment is not associated with the development of diabetes. These data are in accordance with recent studies demonstrating that long-term GH treatment did not increase the risk of type 2 diabetes and metabolic syndrome in young adults born with SGA[18]. Nevertheless, our data is limited to the first 3 years of GH therapy, and further studies with an extended follow-up period lasting until the final stature has been reached are needed to confirm that the "non-diabetic type" persists after 3 years of GH treatment and that the treatment affects the final height of children with SGA or GHD.

Conclusion

GH treatment had a positive impact on height, and any changes observed in safety parameters, such as lipid profiles, HbA1c and BMI SD, were considered to be correlated with the natural course of childhood growth and to be clinically insignificant.

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SGA 性低身長症における成長ホルモンの体格および脂質代謝に及ぼす影響

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〔緒言〕SGA 性低身長症小児の体組成に及ぼす成長ホルモン（GH）の影響については，本邦での報告がない．成長ホルモン分泌不全性低身長（GHD）小児との GH 治療期間中の体格の経時的な比較をすることで検討した．

〔対象と方法〕SGA 群 16 名，GHD 群 30 名を対象として，GH 治療期間中に 6 月ごとに外来受診時に身体計測と成長関連および糖脂質代謝パラメーターの血液検査を施行して，治療開始前後および両群間で比較検討した．

〔結果〕3 年間にわたる GH 治療期間中，SGA 群では GHD 群と同様に身長 SD スコアおよび IGF-1 は両群ともに治療開始後，有意に増加したが，糖脂質代謝および血中レプチン値に変化はなかった．BMI SD スコア，BMI パーセンタイル，肥満度の各体格指数は治療前後および両群間で有意な変化を認めなかった．

〔結論〕SGA 性低身長症における GH 治療は有意な身長増加をもたらすが，体格に及ぼす影響はなく自然な成長パターンでの身長増加効果がある．この間，糖尿病や脂質異常などの副作用出現はみられなかった．