Muscle Function Improves during Growth Hormone Therapy in Short Children Born Small for Gestational Age: Results of a Peripheral Quantitative Computed Tomography Study on Body Composition

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Background: Short small for gestational age (SGA) children can be affected by a lack of muscle mass rather than fat mass. They also face a high risk of the metabolic syndrome developing after childhood. It is not known whether low muscle mass influences muscle function.

Aim: Our aim was to investigate muscle-fat distribution and muscle function before and during GH treatment in short SGA children.

Patients: A total of 34 prepubertal short SGA children (11 females, seven with Silver-Russell syndrome) were included in the study. Mean values were: age at GH start 7.3 yr; height SD score (SDS) −3.3; and birth weight SDS −2.7.

Methods: Investigations over 24 months on GH treatment (57 μg/kg·d) were performed. Body composition, including fat area and muscle area (MA), was assessed through peripheral quantitative computed tomography (XCT 2000; Stratec, Inc., Pforzheim, Germany). Maximal isometric grip force was performed with a Jamar dynamometer (Preston, Jackson, MI). Comparison with height-dependent reference values (SDS_{Height}) was calculated.

Results: MA SDS_{Height} at GH start was −1.8 and increased to −0.8 ($P < 0.001$) and −0.8, and fat area SDS_{Height} decreased from −0.6 to −2.0 ($P < 0.001$) and −1.5 after 12 and 24 months on GH. Maximal isometric grip force SDS_{Height} increased from −0.9 to 0.3 ($P < 0.001$) and 0.5. MA at start correlated negatively with height velocity ($R = -0.54$; $P < 0.001$) and MA SDS at start and Δ-height SDS during the first year of GH treatment ($R = -0.40$; $P < 0.001$).

Conclusions: Short stature in SGA children is associated with low muscle mass and function. Supraphysiological GH doses led to a concomitant increment in height, muscle mass, and function, whereas fat mass decreased. Furthermore, body composition at GH start gives insight into GH responsiveness and the individual risk of metabolic syndrome. (***J Clin Endocrinol Metab*** **93: 2978–2983, 2008)**

In 8–10% of children born small for gestational age (SGA), short stature persists after the third year of life (1), thus leading to an adult height that is 11–15 cm lower than target height (2). In these children low weight development can be expected, and some present with severe dystrophy. Several studies suggest that they are more affected by a lack of muscle mass rather than fat mass (3–5). GH was approved for the treatment of short stature in SGA patients in 2003 after studies showed an effective increase in short-term and long-term height development. Because motor ability is considered a major factor in the developmental process of young children, our study focused on the development of muscle mass, fat mass, and muscle function during

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Abbreviations: BMI, Body mass index; FA, fat area; GHD, GH deficiency; MA, muscle area; MIGF, maximal isometric grip force; N, newton; pQCT, peripheral quantitative computed tomography; SDS, SD score; SDS_{CA}, chronological age reference values; SDS_{Height}, height-dependent reference values; SGA, small for gestational age; SRS, Silver-Russell syndrome; TBA, total bone area; TCSA, total cross-sectional area.

TABLE 1. Basal characteristics of patients

	Treated with GH for 24 months (n = 34)
Age start GH (yr)	7.31 (2.65)
Height start GH SDS	−3.30 (0.68)
Target height SDS	−0.35 (0.80)
Gestational age (wk)	36.09 (3.91)
Birth weight SDS	−2.66 (1.05)
Birth length SDS	−2.96 (1.33)
GH peak in test (μg/liter)	13.44 (4.80)
GH dose (μg/kg·d)	57.17 (7.62)

Values are expressed as mean (SD).

GH treatment in SGA children. The monitoring of changes in body composition is also relevant in light of the risk of the metabolic syndrome developing in these individuals in adulthood.

Patients and Methods

Patients

Before and during treatment with GH of various brands, children followed at our Pediatric Endocrinology Section are subjected to a structured examination that includes clinical investigations and anthropometrical measurements. The present study was approved by the independent ethics committee of the medical faculty of the University of Tuebingen, and informed, written consent was given by the parents. Inclusion criteria for SGA children were a birth weight and/or length lower than −2 SD (6), with height at GH start being −2 SD score (SDS) or lower (7). GH deficiency (GHD) was excluded as follows: height velocity less than the 50th centile, and GH peak more than 8 μg/liter in an arginine test or overnight GH secretion profile. An in-house RIA was used to measure GH levels (8). Patients with malformation syndromes, except Silver-Russell syndrome (SRS), and those with major organic and neurological defects were excluded from the study. The total group of short children born SGA, who received GH treatment between June 1999 and June 2005 at our center, comprised 60 patients (28 female, 14 with SRS). Nine short SGA children were excluded from the analysis because GH stimulation tests revealed impaired GH secretion, and four others due to pubertal signs during the study period. There were 13 children excluded because they could be followed for only 12 months. Thus, this study is based on 34 children (11 female, seven with SRS).

Methods

Measurements of height, weight, and body composition were done for all 34 children at GH start, and at intervals of 6, 12, and 24 months of therapy. SDSs for height and weight were estimated according to the standards of Prader *et al.* (7). The body mass index (BMI) was calculated as weight (kg) divided by height^2 (m). BMI SDS calculations were based on the British reference data of Freeman *et al.* (9). Birth weight and birth length SDS calculations were done according to the standards devised by Niklasson *et al.* (6). Target height was calculated according to the method of Tanner (10), and bone age was assessed according to the method of Greulich and Pyle (11). Table 1 shows the basal characteristics of the patient group. Body composition was measured using a peripheral quantitative computed tomography (pQCT) device (XCT 2000; Stratec, Inc., Pforzheim, Germany). The scanner was equipped with a low-energy (38 keV) x-ray tube. The radiation dose for a single scan was 0.3 μSv, with an effective dose for the forearm of 0.1 μSv. The radiation source was 45 kV at 150 μA. The device was calibrated once a week with a standard phantom and once a month with a cone phantom provided by the manufacturer. The proximal radius of the nondominant arm was chosen, and cross-sectional measurements were taken at exactly 65% of the ulna length, distant from the radius growth plate. For this, the radius growth plate was precisely located using a scout-view scan. This position of measurement was chosen because it is the site comprising the biggest muscle area (MA) cross-section for which Neu (12) and Schoenau (13) *et al.* established age-dependent reference values for healthy German children, using the same pQCT device. A relative (65%) distance was chosen because the arm is constantly growing during childhood. This

TABLE 2. Height, BMI, and parameters of MA, FA, and MIGF during GH treatment

	Time with GH								
	Start	6 months	To start (*P* value)	12 months	To start (*P* value)	To 6 months (*P* value)	24 months	To 12 months (*P* value)	To start (*P* value)
Age (yr)	7.31 (2.65)	7.75 (2.60)	[a]	8.35 (2.68)	[a]	[a]	9.45 (2.65)	[a]	[a]
Height (cm)	107.36 (13.97)	112.30 (13.54)	[a]	116.96 (13.39)	[a]	[a]	125.19 (12.65)	[a]	[a]
Height SDS	−3.30 (0.68)	−2.73 (0.71)	[a]	−2.39 (0.74)	[a]	[a]	−1.90 (0.82)	[a]	[a]
Weight (kg)	16.61 (5.44)	18.12 (5.68)	[a]	20.05 (6.39)	[a]	[a]	23.78 (7.25)	[a]	[a]
Weight SDS	−2.61 (0.80)	−2.34 (0.76)	[a]	−2.06 (0.85)	[a]	[a]	−1.63 (0.88)	[a]	[a]
BMI (kg/m^2)	14.04 (1.84)	14.02 (1.73)	ns	14.28 (2.05)	[b]	[b]	14.82 (2.34)	[c]	[a]
BMI SDS	−1.15 (0.98)	−1.16 (0.84)	ns	−1.07 (0.95)	ns	[b]	−0.88 (0.98)	[c]	[a]
FA (cm^2)	682.42 (288.06)	443.80 (258.22)	[a]	477.68 (238.09)	[a]	ns	507.48 (351.70)	ns	[a]
FA % of TCSA	35.31 (11.09)	24.30 (10.41)	[a]	21.10 (9.32)	[a]	[b]	21.51 (11.80)	ns	[a]
FA SDS_{CA}	−0.66 (1.00)	−1.44 (0.70)	[a]	−1.58 (0.80)	[a]	ns	−1.29 (0.86)	[c]	[a]
FA SDS_{Height}	−0.62 (1.85)	−1.93 (1.46)	[a]	−2.07 (1.55)	[a]	ns	−1.51 (1.54)	[a]	[a]
MA (cm^2)	1070.36 (307.27)	1300.19 (342.58)	[a]	1409.03 (365.57)	[a]	[a]	1565.69 (417.99)	[a]	[a]
MA % of TCSA	55.80 (9.67)	66.22 (9.34)	[a]	69.12 (9.56)	[a]	[b]	69.25 (11.66)	ns	[a]
MA SDS_{CA}	−2.87 (0.88)	−1.99 (0.93)	[a]	−1.72 (0.87)	[a]	[c]	−1.54 (1.05)	ns	[a]
MA SDS_{Height}	−1.79 (1.01)	−0.80 (1.24)	[a]	−0.75 (1.28)	[a]	ns	−0.78 (1.37)	ns	[a]
MIGF (N)	49.48 (34.23)	67.06 (40.82)	[c]	88.00 (52.37)	[a]	[a]	108.34 (51.22)	[a]	[a]
MIGF SDS_{CA}	−3.50 (2.58)	−2.42 (2.30)	[b]	−1.71 (1.96)	[a]	[c]	−1.23 (1.03)	ns	[a]
MIGF SDS_{Height}	−0.92 (2.58)	−0.20 (2.25)	ns	0.33 (1.93)	[c]	[b]	0.49 (1.15)	ns	[c]
MIGF/MA (N/cm^2)	4.35 (2.19)	4.87 (2.13)	ns	5.84 (2.54)	[a]	[c]	6.73 (2.14)	[c]	[a]

Values are expressed as mean (SD). ns, Not significant.

[a] $P < 0.001$.

[b] $P < 0.05$.

[c] $P < 0.01$.

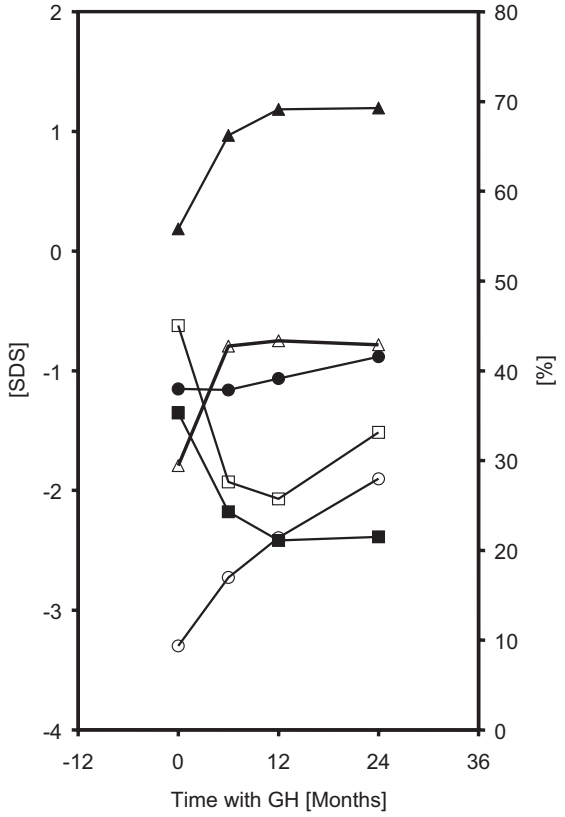

FIG. 1. Development (mean SDS) of height, BMI, and parameters of body composition during GH therapy. ○, Height SDS. ●, BMI SDS. □, FA SDS_{Height}. △, MA SDS_{Height}. ■, FA percentage. ▲, MA percentage.

ensured measurement of the site that corresponds exactly, regardless of changing arm lengths. A 2-mm thick, single tomographic slice was taken at a voxel size of 0.4 mm. Image processing and calculation of numerical values were performed by the software package supplied by the manufacturer (Version 5.4; Stratec). The following parameters were measured: total cross-sectional area (TCSA) (mm^2), total bone area (TBA) (mm^2), and MA (mm^2). The following calculations were done: fat area (FA) (mm^2) = TCSA (mm^2) − MA and − TBA (mm^2); MA percentage of TCSA = MA (mm^2)/TCSA (mm^2); and FA percentage of TCSA = FA (mm^2)/TCSA (mm^2).

The TCSA was determined by detecting the outer contours at a threshold of 0 mg/cm^3. MA was measured at a threshold of 30–70 mg/cm^3, which is the standard threshold for muscle tissue in pQCT, and TBA at a threshold of 280 mg/cm^3. The measurements were transformed into SDSs, based on references that were both dependent on chronological age as well as height (12–14). We used unpublished references for FA, which were measured by pQCT and based on the same investigations by Schoenau *et al.* (13). In addition, we chose to express FA as a percentage of TCSA and MA as a percentage of the TCSA. The coefficients of variation for TCSA, MA, and FA were 1.2, 0.9, and 3.9%, respectively.

To measure muscle strength, we used the maximal isometric grip force (MIGF) of the nondominant hand [newton (N)], determined with a standard adjustable-handle Jamar dynamometer (Preston, Jackson, MI). We used the same procedure as described by Rauch *et al.* (14). To calculate the age- and height-dependent SDS, we applied the formula described by Rauch *et al.* (14). In addition, we calculated the MIGF per cm^2 MA (N/cm^2) as a parameter of muscle function before and during GH treatment. Because there is a close relationship between muscle and bone (15), we calculated the strength strain index according to the method described by Schoenau *et al.* (16), and, in the present study, we applied it as a parameter for bone strength.

Statistical analyses

Statistical analysis was done using the computed statistics program JMP (SAS Institute, Cary, NC). Results are expressed in means and SD, unless otherwise specified. Significance of changes was tested using a paired *t* test. Regression analyses were done using Pearson's coefficient of correlation. SDSs were calculated as patient value minus mean of age- (or height-) and sex-matched reference divided by SD of age- (or height) and sex-matched reference. Δ Values (Δ = change in) are expressed as the difference between a value at time point "t2" minus a value at time point "t1." Unless otherwise specified, Δ mean represents the mean of the individual Δ values.

Results

At the start of GH treatment, the total group of patients (n = 34) had a mean age of 7.3 yr (range 3.5–12.4). Mean height was −3.30 SDS, and the mean GH dose was 57 μg/kg·d (range 41–70), with target height being −0.35 SDS, birth weight −2.66 SDS, birth length −2.96 SDS, and the maximum GH peak during testing being 13.4 μg/liter (range 8.1–23.9). Table 1 shows the characteristics before and at the start of GH treatment.

Table 2 and Fig. 1 depict the changes in height and BMI, as well as parameters of body composition and MIGF before GH start, and at 6, 12, and 24 months of treatment. The effect of GH treatment as seen in terms of changes in parameters over time (Δ) is shown in Table 3.

Height SDS increased gradually and significantly from −3.30 at start to −2.73, −2.39, and −1.90 after 6, 12, and 24 months, respectively. The most pronounced increase in height was ob-

TABLE 3. Changes of (Δ, mean) height, BMI, parameters of body composition (MA, FA), and MIGF during GH therapy

	0–6 months	6–12 months	0–12 months	12–24 months	0–24 months
Height velocity (cm/yr)	9.59 (1.92)	8.92 (1.94)	9.27 (1.66)	7.51 (1.23)	8.37 (1.27)
ΔHeight SDS	0.55 (0.24)	0.36 (0.20)	0.90 (0.39)	0.49 (0.30)	1.40 (0.55)
ΔBMI SDS	−0.04 (0.31)	0.13 (0.29)	0.09 (0.29)	0.18 (0.38)	0.27 (0.39)
Δ Muscle area SDS_{CA}	0.85 (0.62)	0.33 (0.57)	1.15 (0.61)	0.15 (0.70)	1.30 (0.88)
Δ Muscle area SDS_{Height}	0.91 (0.95)	0.00 (0.95)	0.99 (0.98)	−0.07 (0.97)	0.92 (1.01)
Δ FA SDS_{CA}	−0.79 (0.78)	−0.15 (0.59)	−0.92 (0.86)	0.29 (0.51)	−0.63 (0.81)
Δ FA SDS_{Height}	−1.32 (1.33)	−0.14 (1.13)	−1.45 (1.38)	0.39 (0.72)	−0.90 (1.09)
Δ MIGF SDS_{CA}	0.94 (2.46)	0.93 (1.80)	1.79 (2.37)	0.52 (1.63)	2.31 (2.30)
Δ MIGF SDS_{Height}	0.62 (2.70)	0.73 (1.95)	1.25 (2.65)	0.22 (1.71)	1.47 (2.55)
Δ MIGF/MA (N/cm^2)	0.55 (2.27)	0.95 (1.53)	1.49 (2.29)	0.89 (1.65)	2.38 (2.08)

Values are expressed as mean (SD).

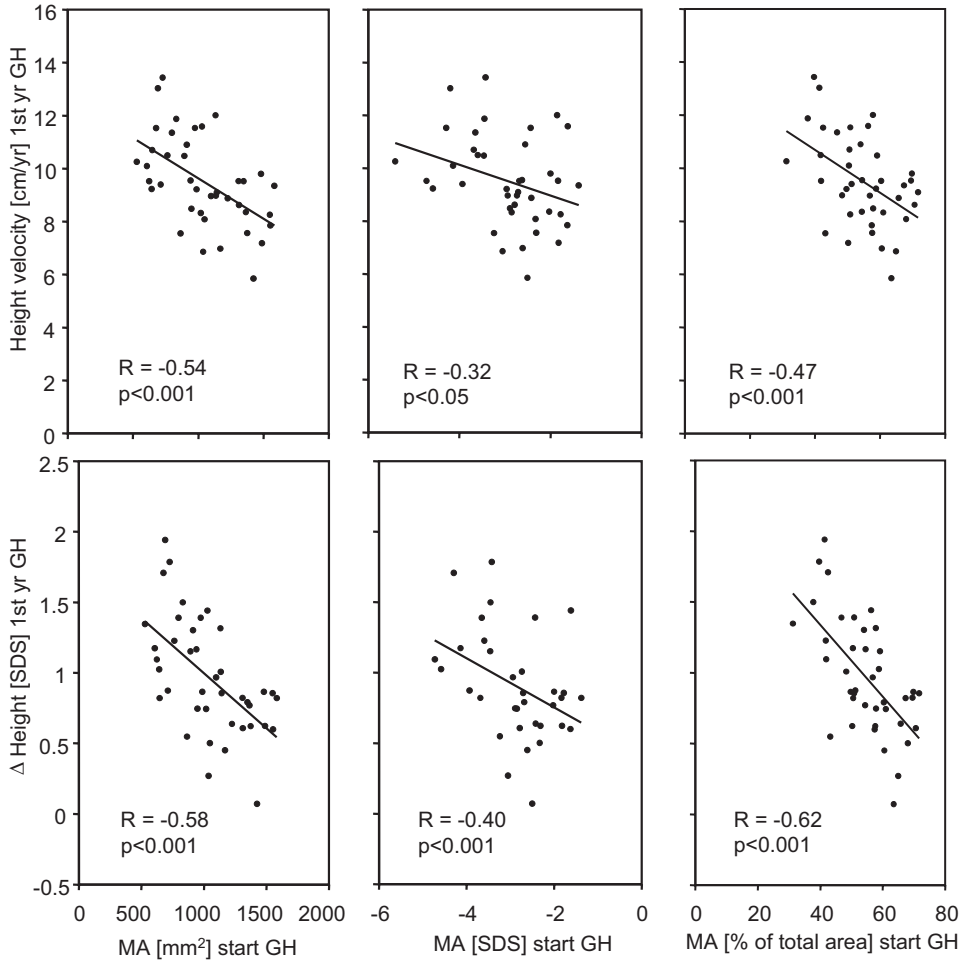

FIG. 2. Correlation of height SDS and height velocity (cm/yr) during the first year on GH with parameters of MA.

served during the first 6 months of treatment (Δ Height SDS = 0.55). Height gain (Δ height SDS) during the first year of GH treatment correlated negatively with the MA SDS for chronological age-dependent reference values (SDS_{CA}) at GH start (R = −0.40; $P < 0.001$). Similarly, height velocity during the first year correlated negatively with MA (mm^2) at GH start (R = −0.54; $P < 0.001$) (Fig. 2).

BMI in relationship to chronological age was diminished at the start of GH treatment (−1.15 SDS) and did not change during the first 12 months. Small increments in BMI were observed after 24 months. Our findings showed a highly positive correlation, at GH start, between BMI and TCSA (mm^2) (R = 0.72), and a much weaker correlation between BMI and FA (mm^2) (R = 0.62) and MA (mm^2) (R = 0.44; all $P < 0.001$).

At GH start, MA SDS was low in comparison to the normal population, both in relationship to chronological age and height: MA SDS_{CA} = −2.87 ($P < 0.01$), and MA SDS_{Height} = −1.79 ($P < 0.01$). MA accounted for 56% of TCSA. MA increased significantly during GH treatment, with respect to age as well as height (mean Δ MA SDS_{Height} = 0.91, from start to 6 months); however, only a slight increase followed thereafter, and MA did not completely normalize. The MA percentage increased significantly during the first 12 months (from 56–69%), with the most striking increase during the first 6 months (to 66%). MA percentage correlated negatively with height velocity (R = −0.47; $P < 0.001$) and Δ height SDS in the first year of GH (R = −0.62; $P < 0.001$) (Fig. 2).

MIGF was diminished when compared with age (MIGF SDS_{CA} = −3.50) ($P < 0.01$) and when compared with height-dependent reference values (SDS_{Height}) (MIGF SDS_{Height} = −0.92; $P < 0.01$) (Fig. 1). A significant increase to MIGF SDS_{Height} = 0.33 occurred during the first year of GH treatment. During the subsequent period of treatment, there was no significant change in MIGF. The ratio of MIGF to MA increased during GH treatment in the first [MIGF/MA = 4.35 to 5.84 (N/cm^2)] and second year [to 6.73 (N/cm^2)]. Figure 1 shows the development of the parameters (mean) during 24 months of GH treatment. There was a highly positive correlation between MA and MIGF (R = 0.72; $P < 0.001$) and between MIGF and the strength strain index (as a parameter of bone strength) (R = 0.78; $P < 0.001$).

FA was low when compared with age-dependent references (SDS_{CA} = −0.66; $P < 0.05$) and also when compared with SDS_{Height} (−0.62; $P < 0.05$). FA accounted for 35% of the TCSA (Fig. 1). FA SDS decreased significantly with respect to CA (Δ FA SDS_{CA} = −0.79; $P < 0.01$) as well as to height (Δ FA SDS_{Height} = −1.32; $P < 0.01$) during the first 6 months of treatment, followed by a further decrease up to 12 months. A small but

significant increase occurred during the second year. The FA percentage decreased continuously (Fig. 1.)

Discussion

There are only a few studies focusing on fat and muscle in SGA children (3–5, 17). Even fewer studies deal with the development of these parameters during GH treatment (4, 5, 17). In addition, diverse techniques were used for the measurement of body composition, *e.g.* skinfold, arm circumference, magnetic resonance imaging measurements, and dual-energy x-ray absorptiometry. However, in comparing fat and muscle mass, the aforementioned studies by Hediger (3), Leger (4), Hokken-Koelega (5), and Willemsen (17) *et al.* did not consider height-dependent normative reference data. This led to an underestimation of muscle and fat mass.

We used pQCT to study the lower arm. This is a technique that allows the measurement of regional fat and muscle mass, as well as provides data on size and geometry of the regional bone structures (18). This "pars pro toto" method depicts the overall content of body muscle and fat (19), and the availability of references for this method allowed the standardization of our data on chronological age as well as height (13, 14).

Thus, ours is the first study based on a reliable method for differentiating between fat and muscle mass. Using this method we established that short children born SGA have normal to low fat mass and an even lower muscle mass when compared with healthy age- and height-matched children. However, when viewed against the reference data of Van der Sluis *et al.* (20), who applied dual-energy x-ray absorptiometry, the percentage of fat (FA percentage) in our cohort was found to be high for age. The same is true if FA in SGA patients is compared with SDS_{Height}. As a rule, BMI in healthy children is an indicator of fat mass. Our study showed that the lower BMI in SGA children is the result of low muscle mass, not low fat mass. This suggests that there is an impairment in protein metabolism that leads to changes in body composition in SGA (21).

In our cohort of short SGA children, we documented for the first time that MIGFs were lower than those for age- and height-matched controls. This suggests that low muscle function is a consequence of low muscle mass. The high correlation between MA and MIGF supports this finding. MA is possibly a more accurate parameter than MIGF; it is dependent not only on muscle mass but also on the patient's cooperation and motivation.

In this group of short SGA children in whom GHD was excluded, and whose GH doses were twice the usual replacement dose, we observed a gain in height similar to that seen in treated GHD children. We observed that fat and muscle mass development showed a characteristic pattern over time. Fat mass decreased during the first 6 months, and muscle mass increased concurrently. A further increase in MA occurred up to 12 months on GH, whereas the FA remained stable during this time, and increased slightly up to the 24th month of treatment. These findings confirm our published report relating to a group of GH-treated GHD patients (18). Thus, in analogy to treated GHD children, a sustained increase in muscle mass was observed, whereas the decrease in fat mass was only of transient nature. It could be speculated that an increase in muscle mass would prevent a decrease in insulin sensitivity; however, a decrease in insulin sensitivity has only been reported after the start of GH treatment (22), *i.e.* due to the diabetogenic effect of GH.

To date, there are no published reports describing investigations of muscle function or strength in GH-treated SGA children. Our present data reveal an MIGF pattern that is similar to that of the aforementioned group of GHD patients (18). Our observations with regard to MIGF are similar to those for MA. An increase occurs during GH treatment; however, the increase in MA takes place at an earlier time point (first 6 months). One explanation could be that, during the first phase of GH treatment, muscle becomes hypertrophic, and water is retained in muscle tissue, and thereafter muscle function increases. This is reflected in our findings that show that, during GH treatment, an increase occurred not only in muscle mass, but also in the ratio between MIGF and MA. This increase is more pronounced in the second half of the first year on GH.

The success of GH therapy in short SGA children not only depends on the normalization of height but also on the improvement of protein metabolism through the anabolic effects of IGF-I and GH. Evidently, patients with the greatest impairment in protein metabolism, reflected by low muscle mass, benefit the most from GH treatment for height promotion. Our findings showed a high negative correlation between height gain and muscle mass at GH start. To counteract the possible effects of impaired sensitivity to GH and/or IGF-I in SGA children (21), the GH dosage should be higher than standard replacement doses. An increase in muscle mass and function and a concomitant decrease in fat mass during GH treatment may partly compensate for the negative effects of GH on insulin sensitivity in SGA children. Therefore, we conclude that, in addition to the main benefit of augmented stature, GH therapy in SGA children indirectly leads to improvements in the general development, such as motor ability, via the changes we observed in body composition and function.

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