

Short-term effects of growth hormone on body composition as a predictor of growth

Citation for published version (APA):

Hoos, M. B., Westerterp, K. R., & Gerver, W. J. M. (2003). Short-term effects of growth hormone on body composition as a predictor of growth. *Journal of Clinical Endocrinology & Metabolism*, 88(6), 2569-2572. <https://doi.org/10.1210/jc.2002-021633>

Document status and date:

Published: 01/01/2003

DOI:

[10.1210/jc.2002-021633](https://doi.org/10.1210/jc.2002-021633)

Document Version:

Publisher's PDF, also known as Version of record

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Short-Term Effects of Growth Hormone on Body Composition as a Predictor of Growth

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The objective of this study was to investigate whether short-term changes in metabolism, as a result of GH therapy, could be used to predict its growth effect after 1 yr.

Twenty-eight children (8.7 ± 2.8 yr) were selected, based on anthropometric criteria characterizing GH-deficient patients. In addition, 21 healthy, age- and sex-matched controls (8.9 ± 3.1 yr) were included. Total body water (TBW) and height were measured before and at 6 wk and 1 yr after the start of treatment. After 1 yr of treatment, patients were divided into good and poor responders, based on a change in height of at least 0.7 SD.

Because individuals of different heights were compared,

changes in TBW after 6 wk were corrected for height², in accordance with the body mass index. Eighty percent of the children who showed a good response to GH therapy had a change in TBW divided by height² exceeding the 2 SD reference line of the controls. In contrast, poor responders did not differ from controls. Maximum GH concentrations found during endocrine tests were not significantly different between good and poor responders.

Changes in body composition data, after 6 wk, proved valuable in identifying good responders to GH therapy. (*J Clin Endocrinol Metab* 88: 2569–2572, 2003)

GH THERAPY IS prescribed to correct height deficits in children whose own GH secretion is insufficient. Although the diagnosis and prediction of the effect of GH therapy on growth cause few problems in severely GH-deficient patients, difficulties arise with children suffering from partial GH deficiency. The outcome of endocrine tests in these patients is not discriminative and does not adequately predict the effect of therapy on growth. In addition, height measurement over a period of 1 yr is required for a reliable evaluation of the growth response. The drawbacks of daily injections and high therapy costs are further reasons to try and find other ways to improve diagnosis and prediction in the short term.

Besides its growth-promoting effect, GH also influences metabolism in adults (1–3) as well as in children (4–8), producing changes that have been found to be related to changes in height (9, 10).

In view of this, the present study investigated whether short-term changes in metabolism, as a result of GH therapy, could be used to predict its growth effect after 1 yr. Body composition changes were measured 6 wk after the start of GH therapy in 28 children and in 21 age-matched controls without therapy. The patients were included purely on anthropometrical indications, the outcome of the endocrine tests not being decisive to start therapy. Growth was evaluated through the first year of therapy, after which children were classified as good or poor responders to GH therapy. Our hypothesis was that changes in body composition exceeding those found in the control group would occur only in patients with a good response to GH therapy.

Subjects and Methods

Subjects

Eligibility for therapy was based solely on one or more of the anthropometric criteria characterizing GH-deficient patients: height, at the

start of treatment, less than -2.5 SD score (SDS); deviation from target height more than 1.3 SDS; and deviation of growth, in the year before treatment, more than -0.25 SDS. Children were excluded if reasons other than those related to GH for growth retardation were present. Because it is known that girls with Turner syndrome show a growth response to GH therapy, they were included in the analysis. To minimize the influence of environmental factors, age- and sex-matched healthy controls were selected from friends or relatives of the patients living in the same neighborhood. They were assumed to be healthy, normally growing children, based on anamnestic information from the parents. The controls were measured simultaneously with the patients but did not receive GH therapy. Parents and children were informed about the nature of the study, and written consent was obtained. The study was approved by the Ethical Committee of the University Hospital Maastricht.

Of the 30 children who started treatment, 2 were not included in the analysis. One child (and the corresponding control) was excluded because of recurrence of a pituitary tumor. Another child was excluded because of missing data. As a result, 28 children, with a mean age of $8.7 (\pm 2.8)$ yr, suspected of being GH-deficient and 21 healthy age-matched controls (8.9 ± 3.1 yr of age) were included in the study. Height SDS at the start of study was $-3.12 (\pm 0.9)$ for the patient group and $-0.91 (\pm 1.2)$ for the control group.

Of the 28 children suspected of being GH-deficient, 21 had a height below -2.5 SDS, 25 deviated by more than 1.3 SDS from their target height, and 10 children showed a deviating growth chart. All patients, including one late-presenting Turner patient (16 yr old), were prepubertal by physical examination. Two control patients were already pubertal.

Study design

All measurements were done by the same investigator (M.B.H.). Before treatment was started, three endocrine tests were performed in the patient group, to measure maximum serum GH values. The patients received 0.7 mg Humatrope/m²·d. Four girls with Turner syndrome received 1.3 mg Humatrope/m²·d, in accordance with Dutch treatment criteria.

Height and weight were measured at the start of therapy, at 6 wk, and then every 3 months, up to a total of 1 yr. Height was expressed as SDS. The difference in SDS over 1 yr ($SDS_{t1\text{ yr}} - SDS_{t0}$) was used to divide the patient group into good and poor responders. A change in SDS more than 0.7 was considered to be a good response, based on the mean response to GH therapy found in the study by Ranke *et al.* (11).

Abbreviations: SDS, SD score; TBW, total body water.

As a metabolic effect parameter, total body water (TBW) was measured, with the deuterium dilution technique, before and at 6 wk and 1 yr after the start of therapy. TBW was used instead of fat-free mass because the hydration level of the fat-free mass (which, in adults, is assumed to be 73%) is age-dependent in children (12).

To interpret TBW in individuals who differed in height, the results were corrected for height (13–15) as $TBW/height^2$.

Height

Height was measured using a stadiometer. After shoes and socks had been removed, body height was measured, exerting a gentle upward pressure on the mastoid processes, so that the child was fully extended (16). A weight of 0.5 kg was placed on the headboard to flatten the child's hair and enable the physician to keep the child in the correct upright position.

Deuterium dilution method

TBW was measured with the stable isotope of hydrogen, according to the Maastricht protocol (17). The water was labeled at the hydrogen atom. Before the dose was administered, a background sample was taken to determine the natural abundance of deuterium in the urine. The children drank the water in the evening before they went to bed. The next morning, a urine sample was taken after the first voiding. TBW was calculated as follows: $C_1 \cdot V_1 = C_2 \cdot V_2$, where C_1 = concentration of the label in the ingested fluid, V_1 = volume of the dose, C_2 = concentration of the tracer in the sample, and V_2 = distribution volume in the body.

Because of the exchange of the tracer with nonaqueous substances in the body, V_2 had to be divided by 1.04 to determine TBW (17).

Endocrine tests

Arginine test. The arginine test was performed in the morning, after an overnight fast. Arginine hydrochloride (0.5 g/kg) was infused for 30 min. Blood samples were taken to measure GH levels at -15, 0, 30, 45, 60, 75, 90, and 120 min after the start of the infusion (18).

Clonidine test. The clonidine test was performed in the morning, after an overnight fast. After an oral dose of clonidine (0.15 mg/m²; maximum, 0.15 mg), blood samples were taken every 30 min for the next 2 h, to measure GH levels (18).

Sleeping test. Because natural peaks of GH secretion occur during the first hours of sleep, blood samples were taken every 10 min during the first 2 h of sleep, to measure GH levels.

GH analysis. The AutoDELFIaGH assay (Wallac, Inc., Turku, Finland) was used to establish GH concentrations in serum (coefficient of variation = 3.5%, lower detection limit = 0.03 mU/liter).

Calculations

TBW data of the control group were plotted against $height^2$ at the start of the study, at 6 wk and at 1 yr, to evaluate the relation between $height^2$ and body composition. A reference line was constructed from the baseline data.

The intraindividual difference in body composition of the controls, at the start of the study and at 6 wk thereafter, was used to estimate the limits of normality.

The difference in TBW between t_0 on t_{6wk} divided by $height^2$, was plotted against the change in height SDS after 1 yr of GH therapy (see Fig. 2). This graph was then used to calculate the sensitivity and specificity of the body composition measurement, for the prediction of the effect of GH therapy on growth.

Results

Patient characteristics are given in Table 4. Figure 1 shows the correlation between TBW and $height^2$ for the control group at the start of the study [$TBW = 3.5 \cdot (height^2)^2 - 0.95 \cdot height^2 + 6.83$ ($R^2 = 0.97$)]. The plotted data of the measurements taken at 6 wk and 1 yr were not significantly

different from the data expected according to the reference line based on baseline data. A two-sample *t* test found no significant difference in $TBW/height^2$ at the start of treatment, between controls and poor responders, whereas good responders showed a significantly lower $TBW/height^2$ at the start of treatment ($P < 0.05$).

In the control group, the mean difference in TBW between t_0 on t_{6wk} divided by $height^2$ was 0.39, with an SD of 0.27. The use of 2 SD resulted in an upper limit of 0.93 liter/m².

Figure 2 shows the change in TBW, over 6 wk, divided by $height^2$, plotted against the change in height during 1 yr (SDS) for all children. Two reference lines are shown. The reference line on the x-axis represents a change in SDS_{t+1} of 0.7, which is the cut-off value chosen between good ($n = 10$) and poor responders ($n = 18$). The reference line on the y-axis indicates the mean change in TBW divided by $height^2$ of the

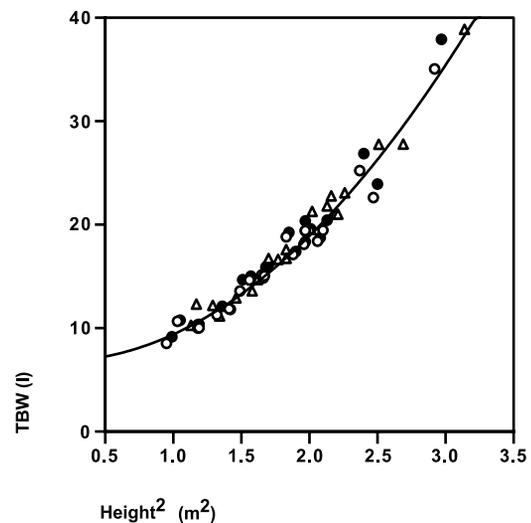


FIG. 1. Relation between total TBW and $height^2$ for healthy children at the start of study (\circ), after 6 wk (\bullet), and 1 yr (Δ). The reference line is based on baseline data.

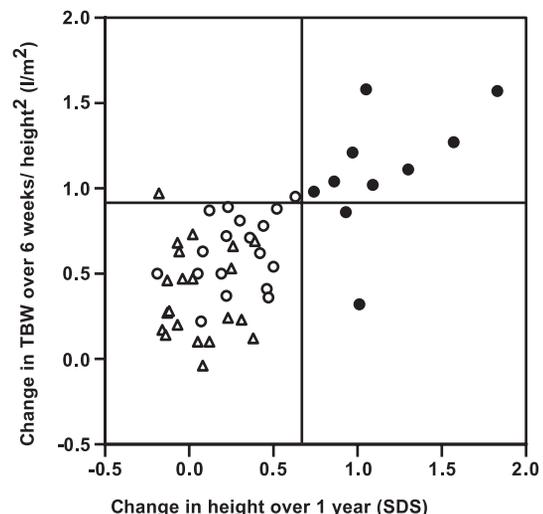


FIG. 2. Change in TBW over 6 wk, divided by $height^2$, plotted against change in SDS after 1 yr for healthy controls (Δ), good responders (\bullet), and poor responders (\circ).

control group plus two times the SD of this value (0.93 liter/m²).

Eighty percent of the children who showed a good response to GH therapy had a change in TBW/height² exceeding the 2 SD reference line of the control group. In contrast, the poor responders did not differ from the control group. The good responders showed a significantly higher TBW change/height² than the poor responders, as tested by an unpaired *t* test ($P < 0.01$). Based on the chosen cut-off values, the specificity of TBW change/height² was 88%, and the sensitivity was 89%. The Turner patients were all in the nonresponding quadrant and did not deviate from controls and poor responders.

Good responders were indistinguishable from poor responders, with regard to the outcome of the endocrine tests (Fig. 3). Figure 3 shows the maximum GH concentrations found during the three endocrine tests before the start of therapy. The reference line on the x-axis indicates the difference between good and poor responders. A second reference line, on the y-axis, indicates a GH concentration of 20 mU/liter. This value is usually taken as the maximum value found in GHD children.

The good responders had the following mean maximum values on the three endocrine tests: 20.8 (± 7.4) mU/liter for the arginine test, 36.3 (± 27.9) mU/liter for the clonidine test, and 14.8 (± 11.1) mU/liter for the sleep test. Mean values for the poor responders were 21.7 (± 10.9), 35.5 (± 29.8), and 19.8 (± 9.9) mU/liter, respectively. These values were not statistically different, according to an unpaired *t* test.

The percentage of patients whose response was correctly predicted by their height at the start of treatment was 57%. This means that the patients who were smaller than -2.5 SDS and responded well to GH therapy, together with the patients who were taller than 2.5 SDS and did not respond to GH, constituted 57% of all patients. The percentage of patients whose response was correctly predicted by their deviation from the target height was 50%. The corresponding value for the change in height, in the year before therapy, was

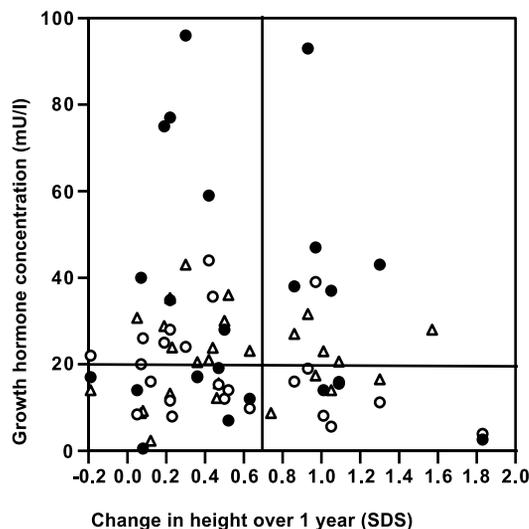


FIG. 3. GH concentrations found by the clonidine test (●), sleep test (○), and arginine test (Δ), plotted against change in height SDS after 1 yr.

79%. The change in TBW, over 6 wk, divided by height² correctly predicted the response of 89% of the patients.

Discussion

The present study evaluated the use of changes in body composition for the prediction of the effect of GH therapy. Most children who responded well to GH therapy showed an evident increase in TBW/height², whereas the poor responders were indistinguishable from controls. TBW was measured as a function of height, in accordance with the body mass index (weight/height²), because children of different heights were compared. This correction was justified by the strong correlation between TBW and height² found in the control group.

Two limits of normality were assumed. The upper limit for the change in TBW, over 6 wk, divided by height² was established by taking the mean change in the control group plus two times the SD (0.93 liter/m²).

Because we applied age and sex matching, the two eldest prepubertal patients were matched with already-pubertal controls. However, we assumed that puberty has no detectable effect on body composition within a period of 6 wk.

Based on their response to GH therapy after 1 yr, patients were divided into good and poor responders (change in height above or below 0.7 SDS). Applying these 2 limits of normality (0.7 SDS on the x-axis and 0.93 liter/m² on the y-axis) leads to 4 quadrants, when the change in SDS over 1 yr is plotted against the change in TBW divided by height². As expected, all controls are situated in the lower left quadrant. The poor responders are also found in this quadrant, meaning that no distinction can be made between controls and poor responders. By contrast, 8 of the 10 good responders are in the upper right quadrant. This graph thus shows sensitivity and specificity to be high (88% and 89%, respectively), indicating that the use of changes in body composition is a reliable tool for the diagnosis of GHD.

Patient selection, in the present study, was based only on anthropometric arguments and not on endocrine testing, to prevent any bias from false positive or false negative biochemical results. The present study could be performed only by including children with idiopathic short stature, because of the need to include the whole range of expected responses to GH therapy, poor as well as good. Parents were fully informed, in advance, of the possibility that the therapy could have a disappointing effect. If, after 1 yr, the therapy did not prove to be successful, the treatment was stopped. The endocrine tests that were nevertheless performed showed that most children had two endocrine test results less than 20 mU/liter (Fig. 3), but a third test above 20 mU/liter.

TABLE 1. Subject characteristics

	Controls (n = 21)	Patients (n = 28)
Age (yr)	8.9 \pm 3.1	8.7 \pm 2.8
Sex (M/F)	10/11	14/14
Height before therapy (SDS)	-0.91 \pm 1.2	-3.12 \pm 0.9
Height after 1 yr of therapy (SDS)	-0.86 \pm 1.2	-2.53 \pm 0.8
Weight before therapy (kg)	27.9 \pm 10.0	21.7 \pm 9.4
Weight after 1 yr of therapy (kg)	31.3 \pm 11.2	25.0 \pm 9.9

Values are means \pm SD. M, Male; F, female.

Plotted against the change in height after 1 yr, the results of the endocrine tests were randomly distributed. If the start of GH treatment had been dependent on these endocrine tests, meaning that all measured GH values had to be less than 20 mU/liter, one good and one poor responder would have been treated.

In our group of patients, therefore, the use of endocrine tests did not lead to an accurate prediction of the response to GH therapy, corroborating the conclusions of other reports in the literature, which have questioned the reliability of endocrine tests (19–24). By contrast, the change in height in the year before therapy was found to predict the response of 79% of the patients correctly, which comes close to the percentage of children whose response was predicted correctly on the basis of the change in TBW, over 6 wk, divided by height², *i.e.* 89%.

In conclusion, changes in body composition data proved to be valuable for the distinction between good and poor responders to GH therapy. However, it should be realized that the cut-off values used for growth response, as well as change in body composition, are more or less arbitrary.

Acknowledgments

We thank Drs. J. M. J. Sijstermans and P. M. V. M. Theunissen of the Atrium Hospital Heerlen for contributions to this study.

Received October 22, 2002. Accepted February 27, 2003.

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This work was supported by Eli Lilly & Co. (Houten, The Netherlands).

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