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Different thresholds of tissue-specific dose-responses to growth hormone in short prepubertal children

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Abstract

Background: In addition to stimulating linear growth in children, growth hormone (GH) influences metabolism and body composition. These effects should be considered when individualizing GH treatment as dose-dependent changes in metabolic markers have been reported. *Hypothesis*: There are different dose-dependent thresholds for metabolic effects in response to GH treatment.

Method: A randomized, prospective, multicentre trial TRN 98-0198-003 was performed for a 2-year catch-up growth period, with two treatment regimens (a) individualized GH dose including six different dose groups ranging from 17–100 μg/kg/day (n=87) and (b) fixed GH dose of 43 μg/kg/day (n=41). The individualized GH dose group was used for finding dose–response effects, where the effective GH dose (ED 50%) required to achieve 50% Δ effect was calculated with piecewise linear regressions.

Results: Different thresholds for the GH dose were found for the metabolic effects. The GH dose to achieve half of a given effect (ED 50%, with 90% confidence interval) was calculated as 33(±24.4) μg/kg/day for Δ left ventricular diastolic diameter (cm), 39(±24.5) μg/kg/day for Δ alkaline phosphatase (μkat/L), 47(±43.5) μg/kg/day for Δ lean soft tissue (SDS), 48(±35.7) μg/kg/day for Δ insulin (mU/L), 51(±47.6) μg/kg/day for Δ height (SDS), and 57(±52.7) μg/kg/day for Δ insulin-like growth factor I (IGF-I) SDS. Even though lipolysis was seen in all subjects, there was no dose–response effect for Δ fat mass (SDS) or Δ leptin ng/ml in the dose range studied. None of the metabolic effects presented here were related to the dose selection procedure in the trial.

Conclusions: Dose-dependent thresholds were observed for different GH effects, with cardiac tissue being the most responsive and level of IGF-I the least responsive. The level of insulin was more responsive than that of IGF-I, with the threshold effect for height in the interval between.

Keywords: GH deficiency, GH sensitivity, GH responsiveness, Idiopathic short stature, GH dose-effect, Metabolic effects, Lipolysis

Background

In addition to stimulating linear growth in children, growth hormone (GH) influences metabolism and body composition. For several decades it has been known, based on results of *in vitro* and *in vivo* studies, that GH has effects on amino acid transport, protein synthesis

[1-3], lipolysis [4,5] and glucose metabolism [2,6,7] after targeting receptors at different tissues [8]. In addition, several studies have evaluated metabolic responses to GH treatment [9-16]. GH replacement therapy in children induces favourable changes in metabolic indices and improves body composition, bone density and re-modelling, physical and cardiac performance, as well as overall quality of life [12-17]. If individual responsiveness is taken into account, the metabolic response to GH treatment does not differ markedly between short children with and without classic GH deficiency (GHD)

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[18]. The data at baseline has previously been published [19]. It has been discussed whether any cut-off level of GH secretion chosen to distinguish between children with GHD and idiopathic short stature (ISS) may be arbitrary [19,20].

Dose-dependency with regard to GH has only been studied in a few clinical trials. It has been shown that GH treatment increases adult height in a dose-dependent manner in children with ISS [21]. GH dose-dependency of metabolic variables has not been clearly defined in short children owing to a lack of controlled trials on metabolic outcomes in response to different GH doses.

In a randomized, controlled, clinical trial we have recently shown that the anabolic and lipolytic effects of GH can be dissociated in a GH dose range between 17 and 100 μg/kg/day. Anabolism was found to be dose-dependent while lipolysis was not [18], despite a lipolytic effect being noted in all subjects. It was interpreted that the lipolytic effect of GH was overridden in the dose range used, and that dose-dependency may therefore become apparent at lower doses.

The objective of the present study was to investigate and compare the GH doses required to achieve different metabolic responses. The hypothesis was that there are dose-dependent thresholds for different tissues and metabolic functions. It was expected that the results would provide insight into the effective GH dose required to influence metabolic processes and cardiac tissue in short children with different GH secretion capacities and GH responsiveness. The key question was 'What is the appropriate GH dose in prepubertal children to compensate for deteriorations in body composition and to avoid unfavourable metabolic effects?'

Subjects and methods
Ethical consideration
The study protocol (TRN 98-0198-003) was approved by the Ethics Committees of the Universities of Göteborg (for Göteborg and Halmstad), Umeå, Uppsala and Malmö and the Medical Product Agency of Sweden. Written informed consent was obtained from all parents and from children if possible. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice.

Subjects and study protocol
The study was a 2-year prospective, randomized, open-label, multicentre trial in short prepubertal children with isolated GHD or ISS [22] naïve to GH treatment. Individual GH responsiveness was estimated by our growth response prediction model for children with GHD and ISS [23], and the patients were randomized in 1:2 proportions to receive either a standard or an individualized GH dose during 2 years of catch-up growth to a preset

growth target, mid-parental height SDS (MPH_{SDS}). Randomization variables included gender, $weight_{SDS}$ at birth, $height_{SDS}$ at age 1 year, $GH_{max}AITT$ (during an arginine–insulin tolerance test), $GH_{max}24h$ profile (during 24h spontaneous GH sampling), age and $height_{SDS}$ at start, the child's $height_{SDS}$ difference to its MPH_{SDS} (diff MPH_{SDS}) at start, and predicted 1st year Δ $height_{SDS}$ [23]. No patients with syndromes, chronic diseases or complete GH insensitivity were included in the study population.

Upon inclusion, all patients had a $height_{SDS}$ below −2.0 [24] and a growth velocity below −1.0 SDS. 128 children (38 girls, 90 boys) followed the protocol [22]. Both the results from the $GH_{max}AITT$ and the $GH_{max}24h$ profile were used to separate children with GHD from those with ISS. Classic GHD was defined based on a GH_{max} below 32 mU/L (using polyclonal assay, WHO IRP 80–505) corresponding to 24 mU/L (using monoclonal assay) and equivalent to the 'old cut-off of 10 μg/L' [18]. According to this definition, 39 children had isolated GHD and 89 had ISS. However, when using GH_{max} results exclusively from the AITT, 90 children were assigned the diagnosis of GHD and 38 the diagnosis of ISS. Additionally, all of our patients fulfilled the criteria for GHD according to a growth velocity lesser than −1.0 SDS, IGF-I below −1 SD of sex and age specific references, bone age retardation of more than 1,5 years [18,22].

To address the question concerning GH thresholds and to study the possible dose-dependency, the analysis focused on the individualized treatment group (n=87). We used data from prepubertal children included in a trial, randomized to individual GH doses in the range of 17–100 μg/kg/d according to their growth-related GH responsiveness; with dose-adjustment for the estimated difference to the preset height target (i.e. MPH_{SDS}) at 2 years on GH in order to make it possible for each child to reach its MPH_{SDS} within a 2 year period. [22]. Children with a higher predicted growth response, calculated before start of treatment, received a lower individual GH dose, and those with a lower predicted growth response received a higher GH dose. The GH doses used in the individualized-dose group were 17 μg/kg/day (n=3), 33 μg/kg/day (n=27), 40 μg/kg/day (n=10), 50 μg/kg/day (n=26), 66 μg/kg/day (n=14), and 100 μg/kg/day (n=7): the mean GH dose in this group was 49 μg/kg/day [22].

The fixed GH dose group was used as a control group for estimating a metabolic effect of the dose selection procedure in the trial by regressing the metabolic variables on the intended dose of the fixed GH dose group. The intended dose is the GH dose that the patients would have been given if they had been randomized to the group treated with individualized dose. Since this group was randomised to receive the fixed GH dose, any

metabolic effect of the intended dose implicates an effect of the dose selection procedure independent of the dose given. None of the six metabolic effects appeared to be related to the dose selection procedure in the trial. Δ ALP, Δ LST$_{SDS}$, Δ insulin and Δ IGF-I$_{SDS}$ showed no significant effect, whereas Δ LVDd and to a lesser extend Δ height$_{SDS}$ were even somewhat negative correlated to the intended dose of the fixed GH dose group (data not shown).

Laboratory analyses and growth evaluation

GH and insulin-like growth factor I (IGF-I) assays were performed at the Göteborg Pediatric Growth Research Center (GP-GRC) laboratory (accredited number 1899). For analyses of serum IGF-I, leptin, insulin, alkaline phosphatase (ALP) and plasma GH, see our previous publication [18]. IGF-I was converted to SDS [25].

Growth evaluation

Height was measured [22] and converted to SDS [24], as previously described, with use of the childhood component of the total reference [26].

Body composition

Body composition was measured by dual-energy X-ray absorptiometry (DXA), using only one DPX-L scanner (Lunar Co., Madison, WI) at each study centre. Regular harmonization between the centres was performed following GCP/GMP. DXA assessment results in a three-compartment model of the body consisting of fat mass, lean soft tissue (LST) mass and bone mineral content (BMC). All analyses were conducted using the extended analysis program for total body analysis including bone mineral density (BMD).

Echocardiography

Echocardiography was performed by four pediatric cardiologists and one experienced sonographer. Each child was examined longitudinally throughout the study by the same cardiologist/ sonographer. Interventricular septum thickness (IVSd), left ventricular diameter (LVDd) and left ventricular posterior wall (LVPWd) thickness were measured in diastole using M-mode. Left ventricular mass (LVM) was calculated using Devereux's anatomically corrected formula [27].

Statistics

For all analyses, the assumptions of normality were assessed by analysis of skewness, kurtosis and frequency histograms. A p-value of < 0.05 was considered to be statistically significant.

Delta values (Δ-values) for the metabolic variables were calculated in order to quantify changes at 2 year of treatment compared with baseline. S-shaped piecewise linear regression models were fitted with GH dose as the predictor variable and the Δ-value of the metabolic variables as response variables. It consists of 3 pieces: a horizontal head and tail and a linear piece in the middle and was plotted based on the GH-dose effect on the dependent metabolic variables. Fitting this regression comes down to fitting a bounded linear model with four parameters; the usual slope and intercept of a linear regression and an upper and lower bound for the fitted model values. The GH dose effect was given by the maximum range of the fitted piecewise function, which is equal to the difference between the fitted upper and lower bound. Half of the GH dose effect on the respective variables was calculated based on the value halfway between the lowest and highest level of the piecewise function (50% Δ effect). The number of cases within each dose group was taken into account by weighting. Corresponding 90% confidence bands were calculated.

The fitted upper and lower bounds minus the fitted intercept, divided by the fitted slope provide the two breakpoints of the predictor variable separating the middle linear part from the horizontal head and tail. The ED 50% required to achieve (50% Δ effect) is located halfway the two breakpoints of the predictor variable and a corresponding 90% confidence interval is computed. We considered the ED 50% values of pairs of metabolic variables as significantly different if their ED50% values were mutually outside each other's 90% confidence interval, each providing a 5% significance level one-sided. This ED 50% is halfway the two breakpoints of the predictor variable separating the middle linear part from the horizontal head and tail.

A one-way analysis of variance (ANOVA) with GH dose as a bounded continuous predictor was performed to test the piecewise linear GH effect. A non-parametric comparison of group means (robust test of equality of means – Welch test and Brown–Forsythe test) was conducted when variances of dependent variables were not equal across groups. To examine the influence from the 17 µg/kg/day dose group consisting of only three children, analysis were repeated with these children excluded. No significant differences resulted compared to the the complete study population. Only data consistently significant were reported.

Statistical analyses were performed with SPSS 17.0 (SPSS Inc., Chicago, USA) and with Matlab version 7.13.0 (R2011b, The Mathworks, Natick, MA, USA).
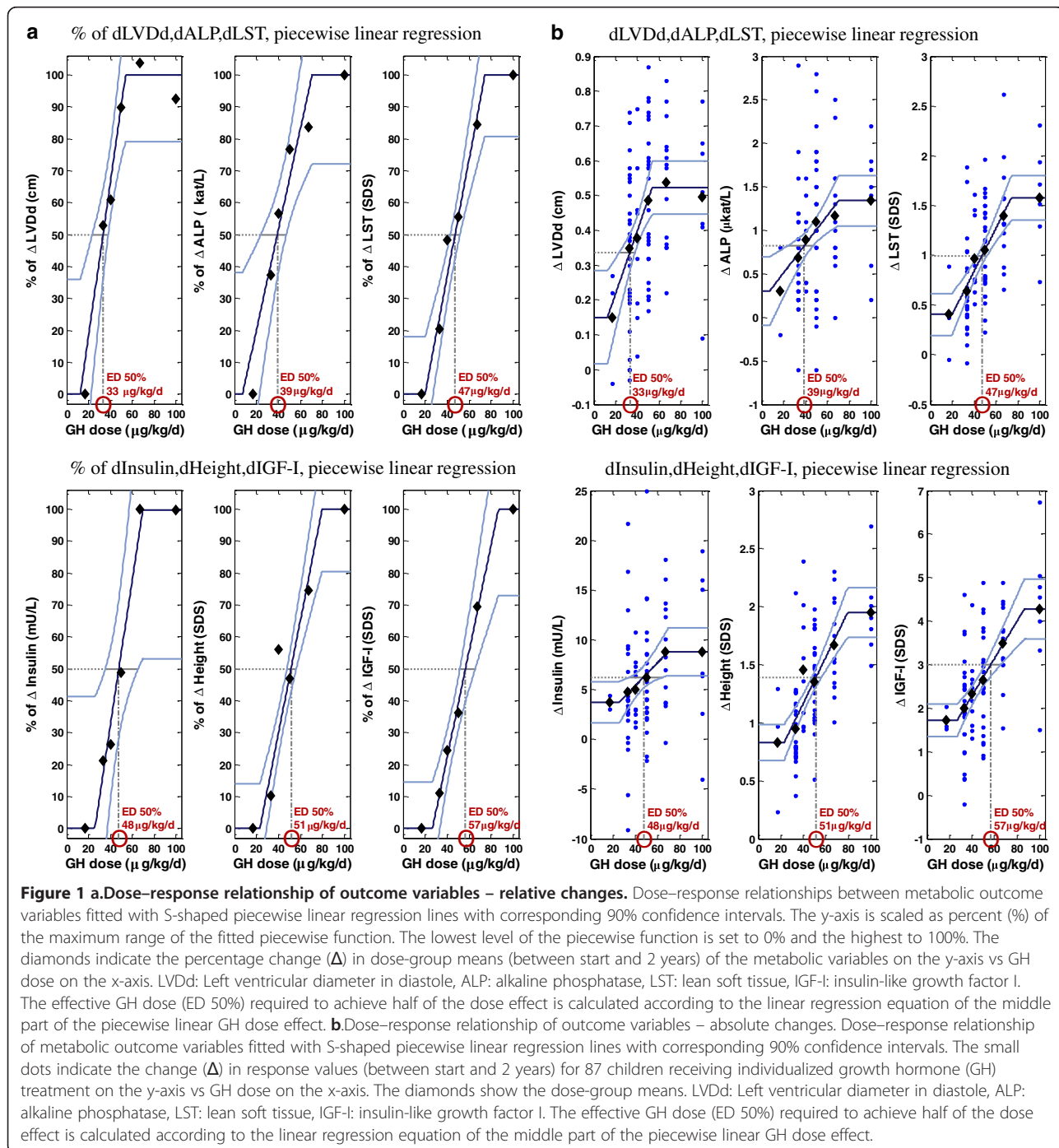
Results

Dose-dependency

The variables were analyzed as Δ values between the start and 2 years of GH treatment. For each of the six dose groups, the mean Δ was calculated (Δ dose-group mean), and is shown for the 87 children receiving

individualized GH treatment, Additional file 1. The dose–response relationships are shown in Figure 1. When performing ANOVA and linear regression, substantial lipolytic effects were seen in all groups as demonstrated by changes in the variables fat mass and leptin from baseline to 2 yrs of treatment; however, no dose–response differences were observed between the GH dose groups for Δ fat mass$_{SDS}$, Δ leptin, Δ bone age, Δ BMD, Δ IVSd or Δ LVPWd (data not shown). The Δ

LVM was found to be significant at the initial analysis (ANOVA p-value = 0.013) and ED 50% of 36 µg/kg/day. Excluding the small 17 µg/kg/day group, significance was lost and the data is not included in Additional file 1.

Effective GH dose at ED 50%

Dose-dependent increases of the dose-group means of Δ LVDd, Δ ALP, Δ LST$_{SDS}$, Δ insulin, Δ height$_{SDS}$ and Δ IGF-I$_{SDS}$ at 2 years of individualized GH treatment

Figure 1 a. Dose–response relationship of outcome variables – relative changes. Dose–response relationships between metabolic outcome variables fitted with S-shaped piecewise linear regression lines with corresponding 90% confidence intervals. The y-axis is scaled as percent (%) of the maximum range of the fitted piecewise function. The lowest level of the piecewise function is set to 0% and the highest to 100%. The diamonds indicate the percentage change (Δ) in dose-group means (between start and 2 years) of the metabolic variables on the y-axis vs GH dose on the x-axis. LVDd: Left ventricular diameter in diastole, ALP: alkaline phosphatase, LST: lean soft tissue, IGF-I: insulin-like growth factor I. The effective GH dose (ED 50%) required to achieve half of the dose effect is calculated according to the linear regression equation of the middle part of the piecewise linear GH dose effect. **b.** Dose–response relationship of outcome variables – absolute changes. Dose–response relationship of metabolic outcome variables fitted with S-shaped piecewise linear regression lines with corresponding 90% confidence intervals. The small dots indicate the change (Δ) in response values (between start and 2 years) for 87 children receiving individualized growth hormone (GH) treatment on the y-axis vs GH dose on the x-axis. The diamonds show the dose-group means. LVDd: Left ventricular diameter in diastole, ALP: alkaline phosphatase, LST: lean soft tissue, IGF-I: insulin-like growth factor I. The effective GH dose (ED 50%) required to achieve half of the dose effect is calculated according to the linear regression equation of the middle part of the piecewise linear GH dose effect.

are plotted in Figure 1. All values in Figure 1a are given as percentages of the maximum range, while Figure 1b shows the same data, but now with the original scale. The lower the ED 50%, the higher is the responsiveness of a given variable. The ED 50% was lowest for Δ LVDd and highest for Δ IGF-I$_{SDS}$ (). The ED 50% for Δ ALP, Δ LST, Δ insulin, and Δ height$_{SDS}$ lay in the interval between these two extremes in ascending order. Differences between the Δ dose-group means for the metabolic variables were tested for a piecewise linear GH dose effect by one-way ANOVA with GH dose as a bounded continuous predictor, Additional file 1.

Dose-responses to GH treatment

Classic dose–response curves are depicted for the six different GH doses in the 87 children receiving individualized GH treatment, Figure 2.

Absolute dose-group means of LST$_{SDS}$, insulin (mU/L), and IGF-I$_{SDS}$ at start of treatment were set to 0% and compared with values from 1 and 2 years of treatment. IGF-I$_{SDS}$ at start of treatment was also compared with values at 3 months of treatment.

Low GH doses were associated with the smallest responses. High GH doses resulted in marked responses, with an increase in LST$_{SDS}$ by more than 60% relative to baseline and an increase of more than 250% for levels of insulin and IGF-I$_{SDS}$ during the 2-year treatment period, Figure 2.

Thresholds of GH dose effects

An overview of the principal relationships between GH dose effects is shown in Figure 3. GH dose thresholds, correspond to the ED 50%,. are depicted as a staircase with increasing GH doses needed to achieve a certain metabolic effect. Variables are given as Δ between start and at 2 years of GH treatment.

Discussion

In the present study, different thresholds for tissue and metabolic responses to GH treatment were found in short children who had varying GH secretion capacities, as well as varying responsiveness to GH.

Cardiac response to GH

Cardiac tissue, estimated by LVDd, was found to be the most GH-sensitive of the variables evaluated (effects seen from a dose of 33 µg/kg/d). This is in line with the findings of Capalbo *et al.* [28] who found that LVDd increased during treatment with a dose of 30 µg/kg/d. From the available data, it is difficult to draw conclusions concerning the mechanism responsible for GH effects on heart size. We have, however, previously shown the presence of GH receptors in cardiac tissue in children, indicating that a direct effect of GH on the heart is likely [29]. Even though GH responsiveness was high, there were no adverse effects seen on any measurement of cardiac function or on blood pressure during the study [30].
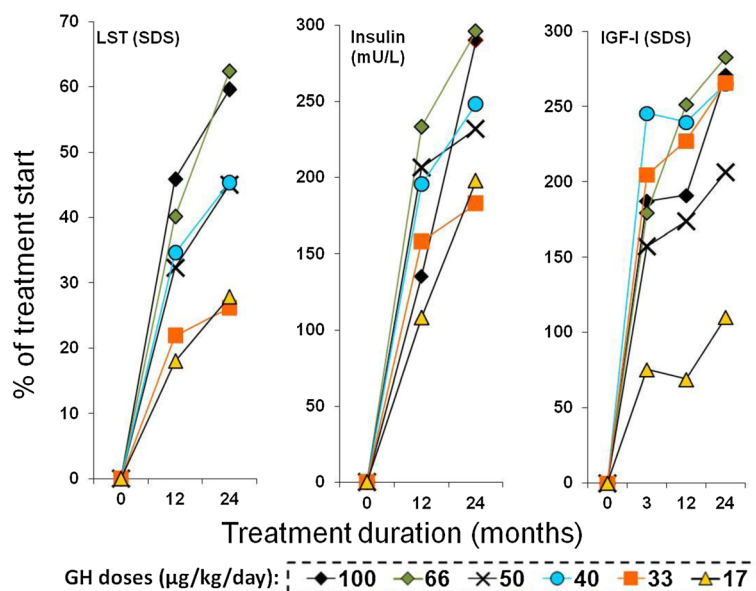
Figure 2 Examples of Dose–response relationship. Dose–response relationship for the six different growth hormone (GH) doses in 87 children receiving individualized GH treatment. The dose-group means at start of treatment are set to 0% increase from baseline values, and compared with dose group mean values at 3 months, and after 1 and 2 years of treatment. LST: Lean soft tissue, IGF-I: Insulin-like growth factor I, SDS: standard deviation score. (The absolute **Δ** values are presented in ref 18).
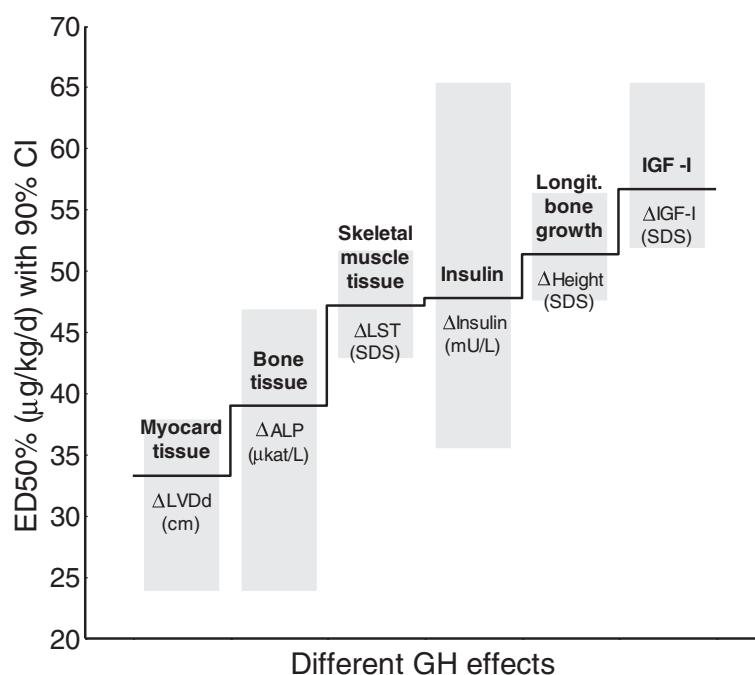
Figure 3 The threshold staircase hypothesis. The "threshold hypothesis" is presented in accordance with results from the present study as a staircase of growth hormone (GH) dose needed for an effect (no scaling). Dose–response thresholds for metabolic markers represent different metabolically active tissues or metabolic functions compared with the longitudinal growth response. LVDd: Left ventricular diameter in diastole, ALP: alkaline phosphatase, LST: lean soft tissue, IGF-I: insulin-like growth factor I. Variables are given as change (Δ) between start and at 2 years of GH treatment. The light-grey boxes mark the 90% confidence interval (CI).

GH dose-effect on body composition

It has been shown that GH treatment at a dose of 57 µg/kg/d given to children born small for gestational age (SGA) can lead to an increase in muscle mass, and a concomitant decrease in fat mass [31]. However, data showing a dose-dependency increase in LST are lacking. We found that LST mass increased in a dose-dependent manner for the six GH doses administered. This effect was most marked at GH doses above 33 µg/kg/d, and the ED 50% for gain in LST mass was in the mid-range (47 µg/kg/d). This dose is in the same range as that found to promote longitudinal bone growth (51 µg/kg/d), confirming our previous findings of anabolic GH effects.

As demonstrated previously using principal component analysis [18], a strong lipolytic effect was found for all GH doses, seen by changes in fat mass and fat mass index, but no GH dose–response effect was seen. A possible explanation is that in the dose range studied the lipolytic effect had already reached its maximum, making lipolytic variables the most sensitive to GH. Early leptin reduction after the start of GH treatment was found previously to be positively correlated with first year growth response in a group of short children treated with 33 µg/kg/day; however, there was a wide range in Δ leptin levels as for growth response; at that time no

individual responsiveness was possible to estimate [11]. It is well known that fat mass decreases in GH-deficient adults when they are treated with GH [32]. Further studies are needed to determine the dose response for the lipolytic effects at lower doses in children.

GH effect on alkaline phosphatase

Increased serum bone-specific ALP is known to be a reliable and early sign of increased bone metabolism and correlates to first year growth response in GH-deficient children [33]. In the present study, ALP activity was found to be more responsive than longitudinal bone growth to a given GH dose.

GH dose-effect on insulin and insulin-sensitivity

GH doses above the common dose range of 25–35 µg/kg/d used for GH-deficient children [34], resulted in greater insulin increases than lower doses, although insulin levels did not exceed the normal range. This confirms previous studies that insulin levels are lower than normal at baseline in GH-deficient individuals [35]. In short children born SGA, no impaired GH dose–response effect on insulin has been reported in a dose range between 33 and 66 µg/kg/d [36].

GH exerts both insulin-like and insulin-antagonistic effects *in vitro* [4]. An insulin-like effect has been

reported in some *in vivo* studies [37], but not in all [38]. In the present study the ED 50% for the insulin enhancement was 48 µg/kg/d, which is very close to the ED 50% of 51 µg/kg/d for height gain found in the present study. Thus, the insulin antagonist effect of GH seems to be equally or more responsive to GH than the effect on IGF-I. An explanation for this may be that we used SDS for IGF-I, but not for fasting insulin, where mU/L was used. Insulin may be required as a growth factor during the catch-up growth phase, so the observation of a dose-dependent increase should be viewed as more than just compensation for GH-induced insulin resistance.

GH dose-effect on IGF
We demonstrated a marked dose–response effect on IGF-I_{SDS}. Thus, as for LST mass, the prediction of growth response is not valid for IGF-I_{SDS} levels. This is in line with findings in groups where individual responsiveness was not addressed, and GH therapy resulted in increasing IGF-I_{SDS} in a dose-dependent manner in prepubertal children, with more dramatic changes being observed at higher doses (50 and 100 µg/kg/day vs 25 µg/kg/d) [39], and 100 µg/kg/d compared to 43 µg/kg/d in pubertal GH-deficient patients [40].

In the present study, the ED 50% for IGF-I_{SDS} was 57 µg/kg/d, which was the highest dose observed for any metabolic variable. Therefore, liver response to IGF-I secretion was found to have a higher threshold than both height gain and muscle growth in the present study.

GH dose-effect on catch-up growth
In order to be able to compare metabolism and growth, height gain was studied in the present study and not the height target of the study, i.e. the diff MPH_{SDS}. The growth effect associated with individualized GH doses was quantified and presented in Figure 1. Thus, a GH dose of 51 (47, 56) µg/kg/d was necessary in order to achieve half of the height gain. In previously performed studies in children with ISS, GH had a dose-related effect on longitudinal bone growth in the dose ranges of 33–67 µg/kg/d [21] and 31–47 µg/kg/d [41]. In GH-deficient children, an increase in GH dose from 25 to 50 µg/kg/d resulted in a sustained increase in growth velocity, whereas in this study no additional effect was observed with a further increase in dose to 100 µg/kg/d, the highest GH dose in the trial given only to the most non-responsive children [39]. However, in a randomized GH dose study during puberty in GH-deficient children, a dose dependent effect (33 µg/kg/d vs. 67 µg/kg/d) was found [42]. This is in line with prior evidence for a dose-dependent effect of higher doses on adult height in children with ISS [43]. To summarize, the adult height achieved in GH-deficient children treated with GH replacement therapy has been found to be dose-dependent [34,42], as has adult height in children with ISS [21,41,43].

Effects on metabolism
There are, however, only a few studies on the metabolic consequences of GH therapy in children. Ciresi *et al.* [12] studied metabolic parameters in GH-deficient children, but the question of dose-dependency was not investigated. Mauras *et al.* [40] compared IGF-I levels in two different GH dose groups in adolescents with GHD. Cohen *et al.* [39] analyzed the response of IGF-I, IGFBP-3, fasting glucose, fasting insulin, HbA1c and height to three different GH doses (25, 50, and 100 µg/kg/day) in prepubertal GH-deficient children. However, the question of whether there were different metabolic thresholds was neither addressed nor individual responsiveness.

In a recent report on our study group, we found dose-dependent effects on height gain, body composition and metabolism [18]. There are no comparable prospective randomized studies. Nevertheless, our data can be compared with reported qualitative effects in response to different GH doses, which suggest that dose–response effects exist [21,39].

Our study included children classified as both GHD and ISS as our study also includes aspects on tissue responsiveness, ranging from high to low within both diagnostic groups. Without a wide range, it would not have been possible to perform our study on the hypothesis of varying thresholds for different tissues and metabolic markers [19,20].

A fact that influences the interpretation of the results is, that the individual GH dose in the trial was selected based on GH responsiveness according to estimated/expected growth response and adapted so that the child would reach MPH_{SDS} within 2 years, although limited by the set maximal GH dose of 100 µg/kg/d. None of the metabolic effects presented here was found to be related to the dose selection procedure in the trial.

The strengths of the present study are that we were able to compare many different effects within the same individual, as well as assessing inter-individual variations. When monitoring GH treatment in the clinical setting, it is essential to know which processes will be affected and which marker will be the first to react to treatment based on responsiveness. The aim with estimating individual responsiveness is to set a target for treatment effect – it may be growth response for which we now have prediction models. In the future, prediction models may also be constructed for the metabolic markers studied in this paper.

Conclusions
GH dose-dependent thresholds for different metabolic effect were found in the current study, Figure 3. Cardiac

tissue was found to be the most responsive to GH treatment, followed by muscle tissue and height gain. Insulin levels incresed, reflecting GH-induced resistance and insulin was found to be more sensitive to GH than IGF-I, suggesting that insulin is as a growth factor during the catch-up growth phase in prepubertal short children.

Additional file

Additional file 1: Table S1. Increase in studied variables in the different dose groups.

Abbreviations

ALP: Alkaline phosphatase; ANOVA: Analysis of variance; Apo A-II: Apolipoprotein A-II; BMC: Bone mineral content; BMD: Bone mineral density; Δ: Delta; ED 50%: Effective dose 50%; DBP: Diastolic blood pressure; DXA: Dual-energy X-ray absorptiometry; DPX-L: Proper name of the Lunar pencil beam scanner; GH: Growth hormone; GHD: Growth hormone deficiency; GP-GRC: Göteborg Pediatric Growth Research Center; HbA1c: Glycosylated haemoglobin; HDL: High-density lipoprotein; HOMA: Homeostasis model assessment of insulin resistance calculated as ((fasting serum insulin* fasting plasma glucose)/22.5); IGF-I: Insulin-like growth factor I; ISS: Idiopathic short stature; IVSd: Interventricular septal thickness in diastole; LDL: Low-density lipoprotein; Lp(a): Lipoprotein (a); LST: Lean soft tissue; LVDd: Left ventricular diameter in diastole; LVM: Left ventricular mass; LVPWd: Left ventricular posterior wall in diastole; SBP: Systolic blood pressure; SDS: Standard deviation score.

Authors' contributions

All authors contributed intellectually to analyses and interpretation of the data; to the writing and revising of the manuscript; and have all given approval of the final version to be published. Moreover, RD took the lead of the writing and the preliminary analyses; AN contributed with the cardiac variables and further analyses; BK, as study coordinator and investigator both in Gothenburg and in Umeå; AFMN contributed with the final statistical analyses; JG as the Uppsala investigator; KAW as the initiator of the study and principle investigator and JD as a Gothenburg investigator and planned the statistical analyses.

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