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Clinical Research Article

Children born SGA receiving growth hormone have similarly impaired glucose-insulin metabolism as children with obesity

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Abstract

Context: Being born small for gestational age (SGA) and growth hormone (GH) treatment are linked to disturbed glucose-insulin metabolism.

Objective: We investigated how GH treatment affects glucose-insulin metabolism in children born SGA compared to children with isolated growth hormone deficiency (iGHD), obesity and lean controls.

Methods: We analyzed glucose-insulin metabolism indices derived from oral glucose tolerance tests (Matsuda index, AUC insulin) and fasting parameters (fasting glucose, HOMA-IR) in 134 SGA patients without catch-up growth (CUG) receiving GH therapy (SGA-GHT), 27 untreated SGA patients with catch-up growth (SGA-CUG), 308 iGHD patients under GH treatment, 427 children with obesity, and 356 lean controls. We adjusted for sex, age, and BMI through matching and multivariable regression.

Results: Treatment-naïve SGA-GHT patients were more insulin-resistant than iGHD patients (higher insulin AUC [$P = .002$] and HOMA-IR [$P < .001$], lower Matsuda index [$P < .001$]) with levels approaching those of the obesity cohort. Under GH therapy, HbA1c was higher in SGA-GHT and iGHD patients ($5.26\% \pm 0.35$ vs $5.25\% \pm 0.25$) than in lean controls ($5.09\% \pm 0.27$). Insulin resistance in SGA-GHT patients approached levels seen in obesity. Prediabetes prevalence was highest in SGA-GHT children (11.11%) compared to those with iGHD (1.59%) or obesity (3.13%). After stopping GH therapy, SGA-GHT patients retained elevated markers of prediabetes (4.65%) and insulin resistance compared to controls and iGHD patients, similar to children with obesity (6.38%). No overt type 2 diabetes was observed.

Conclusion: SGA patients have an impaired glucose-insulin metabolism similar to that of children with obesity, which worsens under GH therapy. Close metabolic monitoring of GH-treated SGA patients is recommended.

Key Words: small for gestational age, insulin resistance, growth hormone deficiency, obesity, growth hormone therapy, diabetes

The variability of body height is due to multiple factors, including genetic and epigenetic background, prenatal development (1) and extrinsic factors like nutrition, social situation (2) and socioeconomic influences (3). Children born small for gestational age (SGA) are defined as having either a birth length and/or birth weight below −2 SD scores (SDS) based on their reference population (4) considering gestational age and sex. Approximately 13% have persistent short stature without sufficient catch-up growth later in life (CUG) (4, 5). Therefore, in 2003 the European Medicines Agency approved treatment with recombinant human growth hormone (GH) for children born SGA lacking catch-up growth until the age of 4 years (6). Furthermore, children born SGA have a higher risk for insulin resistance, type 2 diabetes, cardiovascular diseases, and impaired lipid metabolism later in life (7-11).

GH therapy itself can also cause impairment of glucose-insulin metabolism (12). GH has metabolic effects as it counteracts insulin effects in peripheral tissues, increases gluconeogenesis and glycogenolysis in liver and kidneys, and decreases glucose uptake by the adipose tissue (13). Furthermore, GH negatively affects insulin sensitivity, leading to insulin resistance and increased insulin secretion (14), which predisposes to type 2 diabetes (15). In line with those findings, children with (isolated) growth hormone deficiency (iGHD) tend to have higher insulin sensitivity, but may develop insulin resistance in adulthood, which had been

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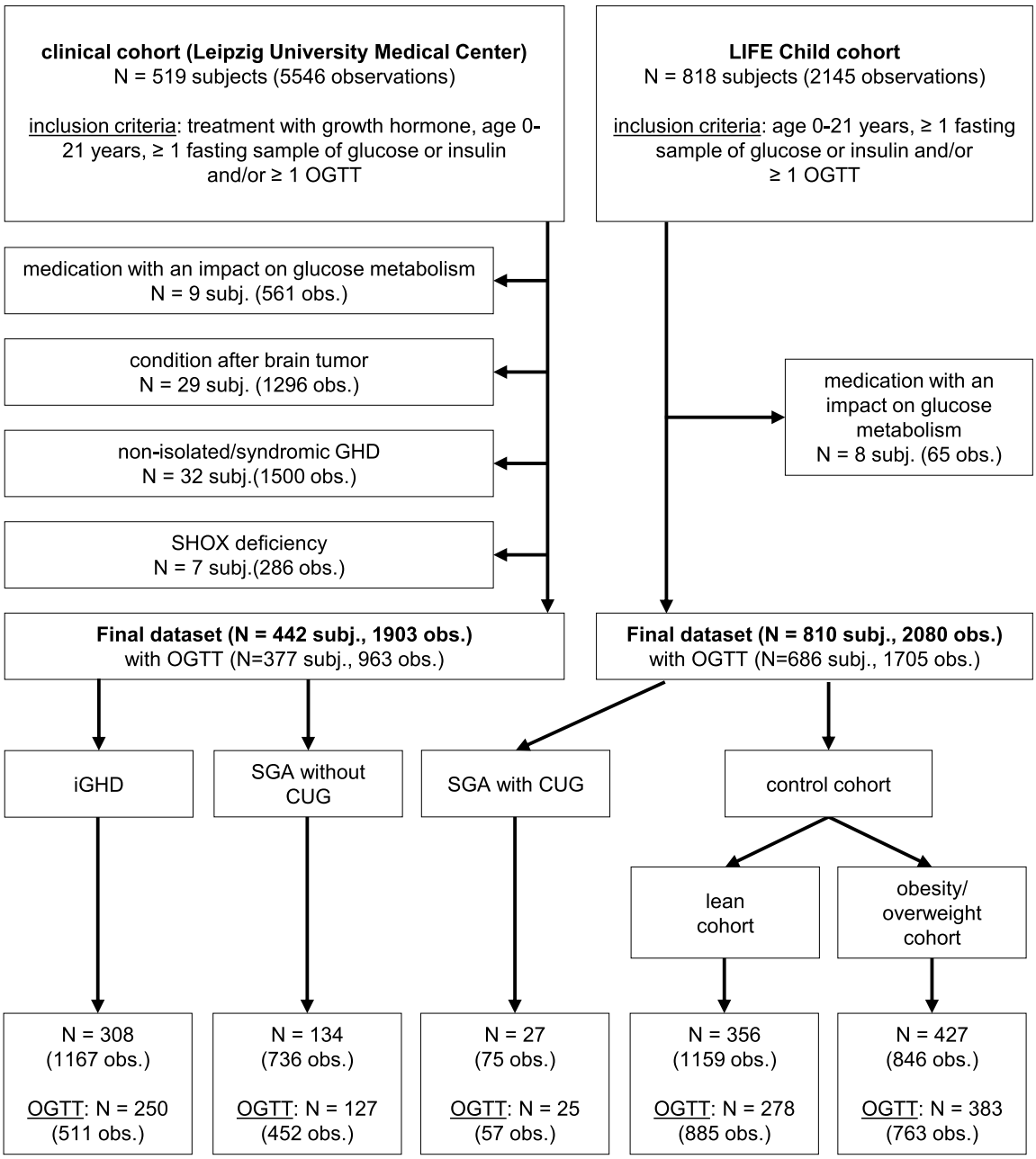

Figure 1. Selection of study population. Medications with an impact on glucose metabolism were excluded (beta blockers, infliximab, MTX, systemic glucocorticoids, digoxin, metformin, antipsychotic medication), diseases with an impact on glucose metabolism were excluded (syndromic diseases such as Silver-Russell syndrome, Bloom syndrome, condition after brain tumor). The control cohort was divided into lean controls (BMI-SDS < 1.28) and controls with overweight/obesity (BMI-SDS ≥ 1.28).

hypothesized to be related to GH replacement therapy (16-18). Hence, GH treatment might pose a higher risk for an impaired glucose-insulin metabolism in both SGA- and in iGHD patients.

Still, data on direct comparison of SGA and iGHD children, as well as comparison with an appropriately matched control group, are sparse and have heterogenous outcomes (19, 20). Moreover, in this context, insulin resistance is often measured by fasting parameters only, like homeostasis model assessment of insulin resistance (HOMA-IR), and not by more comprehensive oral glucose tolerance testing (OGTT) (21). Furthermore, and to our best knowledge, there is no study directly comparing glucose-insulin metabolism between the 2 high-risk populations: SGA children under GH treatment and children with obesity. Herein, we aimed to place the risk for an impaired glucose-insulin metabolism of SGA children under GH treatment in context by direct comparison to iGHD patients, to children with obesity, and to an appropriately matched control group.

Methods

Study population

For this retrospective cohort analysis, we included 1337 subjects (7691 observations) between 0 and 21 years of age with at least one measurement of fasting glucose or insulin and/or one valid

OGTT who were either treated at Leipzig University Medical center between 1994 and 2022 (SGA-GHD cohort, iGHD cohort) or had participated in the LIFE Child study (lean controls, SGA-CUG cohort, Fig. 1). The selection of the clinical cohort was facilitated by the CrescNet registry (NCT0307253). The population-based LIFE Child study (NCT02550236) has been described elsewhere (22). SGA was defined as birth weight and/or length below −2 SDS of the age- and sex-matched populational norm (23). This group was further stratified into children with CUG (SGA-CUG), defined as a height of greater than −2.5 SDS at 4 years of age (or older) and children without CUG who therefore received GH treatment (SGA-GHT). Children were diagnosed with iGHD if they displayed a GH peak of less than 8 µg/L in at least 2 subsequent stimulation tests and no other signs of pituitary dysfunction. Overweight was defined as a body mass index (BMI)-SDS ≥ 1.28 and obesity as a BMI-SDS ≥ 1.88 according to German reference standards (23). After exclusion of children under medications with an impact on glucose metabolism or growth (eg, β-blockers, methotrexate, infliximab, systemic glucocorticoids, digoxin, metformin), as well as exclusion of children with chronic diseases or syndromes (SHOX deficiency, brain tumor, non-isolated or syndromic GH deficiency), we included 161 children born SGA, 308 iGHD patients, 427 children with obesity, and 356 lean controls for further analyses. All study procedures and analyses were approved by the local institutional review board (registration numbers: 203/22-ek, 477/19-ek).

Procedures

Weight and height were measured by trained staff members to the nearest tenth of 1 kilogram or to the nearest millimeter, respectively, following standardized procedures. Glucose and insulin indices were either derived from OGTT (Matsuda index (24)), area under the curve insulin (AUC insulin (25)), 1-hour glucose (26), 2-hour glucose) or from fasting measures (fasting glucose, HOMA-IR (27), C-peptide-based HOMA-IR [HOMA-CIR] (28), C-peptide/glucose ratio (29)). For OGTT, subjects ingested 1.75 g dextrose per kg body weight (maximum 75 g) after a 10-hour overnight fast, with subsequent venous blood samples taken every 30 minutes for 2 hours. Glucose concentrations were either analyzed in serum samples using the automated laboratory analyzer Cobas 8000 (Roche Diagnostics, Mannheim, Germany) or in hemolysates using the automated analyzer Super GL speedy (Dr. Müller Gerätebau GmbH, Dresden, Germany). Insulin serum concentrations were determined on 2 different laboratory analyzers: Cobas 8000 (Roche Diagnostics, Mannheim, Germany) or LIAISON (DiaSorin, Saluggia, Italy). We had compared the respective methods for both analytes previously with no relevant inter-assay differences that would require further correction (30).

The insulin sensitivity index proposed by Matsuda was calculated as $10,000/\sqrt{\text{Fasting glucose}_{\left(\frac{\text{mmol}}{\text{l}}\right)} \times \text{Fasting insulin}_{\left(\frac{\text{mIU}}{\text{l}}\right)} \times \text{mean glucose}_{\left(\frac{\text{mmol}}{\text{l}}\right)} \times \text{mean insulin}_{(\text{mIU/l})}}$. Ins_{mean} and $\text{Gluc}_{\text{mean}}$ represent the mean insulin and glucose concentrations, respectively, during the OGTT. AUC insulin was calculated using the trapezoid method (25). Oral disposition index (ODI) reflects insulin secretion in relation to insulin sensitivity (31) and was calculated as: $ODI = \frac{Insulin_{30min} - Insulin_{0min}}{Glucose_{30min} - Glucose_{0min}} \times Matsuda\ index$.

HOMA-IR as a fasting proxy for insulin resistance was calculated as follows:

$$HOMA - IR = \frac{Fasting\ glucose_{(mmol/l)} \times Fasting\ insulin_{(mIU/l)}}{22.5}$$

HOMA-CIR (C-peptide-based HOMA-IR) was calculated as follows:

$$HOMA - CIR = \frac{Fasting\ glucose_{(mmol/l)} \times\ C - Peptide_{(nmol/l)}}{22.5}$$

C-peptide/glucose ratio was calculated as follows:

$$C - Peptide/\ Glucose\ ratio = \frac{C - Peptide_{(\,pmol/l)}}{Fasting\ glucose_{(mmol/l)}}$$

Insulin-like growth factor 1 (IGF1) and insulin-like growth factor binding protein 3 (IGFBP3) measures were performed by a chemiluminescence immunoassay (CLIA) by iSIS. Glycated hemoglobin (HbA1c) values were measured by immuno-turbidimetry using Cobas 8000 (Roche Diagnostics, Mannheim, Germany). According to American Diabetes Association guidelines (32), fasting glucose levels were considered prediabetic if they were in the range of 5.6 to 6.9 mmol/L, and diabetic if they reached 7.0 mmol/L. A glucose tolerance at 2 hours of OGTT between 7.8 and 11 mmol/L was classified as prediabetic, and above 11.1 mmol/L as diabetic. Elevated HbA1c levels were either considered prediabetic (5.7%-6.4%) or diabetic (≥6.5%).

Puberty stages were assessed according to Tanner stages and testicular volume as outlined previously (30).

Statistical analysis

All analyses were conducted with R version 4.2.0. Due to differences in age, sex, and BMI between our cohorts, we matched all groups at each time point using the R package *MatchIt* (33). Therefore, we considered children born SGA as the reference group and applied nearest neighbor matching in a 1:1 ratio to select children with obesity, lean controls, and iGHD children with a similar distribution of covariates age and sex, and for lean controls and iGHD children, also for BMI-SDS. Furthermore, we log-transformed data for insulin secretion, HOMA-IR, Matsuda index, and Oral Disposition Index (ODI) to achieve a near-symmetric distribution. To assess differences between matched groups, we used a *t* test for continuous variables and χ^2-tests for categorical variables. We performed an analysis of variance (ANOVA) followed by Tukey's post hoc test for group comparisons in matched cohorts.

For comparison between unmatched groups, linear mixed model analyses were applied to adjust for multiple visits of the same participant and also adjusted for age, sex, and BMI-SDS because of their potential impact on insulin sensitivity.

Results

Height and effect of growth hormone on growth parameters

We analyzed data from 161 SGA and 308 iGHD patients, 427 children with obesity, and 356 lean controls at 3 different timepoints: treatment-naïve children, children during GH treatment, and children after cessation of GH therapy. Due to significant differences in age, sex, and BMI-SDS between the 4 groups (Table S1 (34), which may affect glucose-insulin metabolism, we matched the distribution of those 3 covariates

Table 1. Clinical characteristics of matched cohorts at different time points

	SGA	iGHD	lean	obesity	*P* value SGA vs lean	*P* value SGA vs obesity	*P* value iGHD vs lean	*P* value iGHD vs obesity	*P* value SGA vs iGHD	*P* value lean vs obesity
Treatment-naïve										
n subj.	61	61	61	61	—	—	—	—	—	—
n male (%)	28 (45.9)	36 (59.01)	32 (52.54)	36 (59.01)	n.s.	n.s.	n.s.	.046	n.s.	n.s.
age in years, mean (SD)	10.04 (±4.89)	9.22 (±3.67)	9.74 (±2.95)	9.69 (±3)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
gestational age, mean (days)	268.3 (±25.4)	269.02 (±0.9)	270.86 (±15.2)	272.25 (±15.2)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
preterm birth, %	16.39	16.39	4.91	4.91	<.001	<.001	<.001	<.001	n.s.	n.s.
birth length, mean (SD)	−2.55 (±0.94)	−0.9 (±0.98)	−0.64 (±1.08)	−0.38 (±1.03)	<.001	<.001	n.s.	.015	<.001	n.s.
birth weight, mean (SD)	−1.76 (±1.01)	−0.56 (±1.01)	0.07 (±1.02)	0.61 (±1.42)	<.001	<.001	.003	<.001	<.001	.04
BMI-SDS, mean (SD)	−0.09 (±1.69)	−0.37 (±1.04)	−0.37 (±1.29)	2.38 (±0.48)	n.s.	<.001	n.s.	<.001	n.s.	<.001
height-SDS, mean (SD)	−1.81 (±1.5)	−2.47 (±0.7)	0.13 (±1)	0.94 (±0.97)	<.001	<.001	<.001	<.001	.002	<.001
weight-SDS, mean (SD)	−1.19 (±2.29)	−1.82 (±1.14)	−0.1 (±1.28)	2.4 (±0.57)	<.001	<.001	<.001	<.001	n.s.	<.001
IGF1-SDS, mean (SD)	−0.71 (±1.11)	−1.8 (±1.42)	−0.58 (±0.98)	−0.28 (±0.85)	n.s.	n.s.	<.001	<.001	.0011	n.s.
n pubertal stage 1 (%)	24 (50)	30 (71.43)	29 (49.15)	35 (57.38)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
n pubertal stage 2-4 (%)	14 (29.17)	12 (30.95)	26 (44.07)	22 (36.07)	n.s.	n.s.	.02	n.s.	n.s.	n.s.
n pubertal stage 5 (%)	10 (20.83)	0	4 (8.16)	4 (6.56)	n.s.	n.s.	.04	.04	.002	n.s.
Under GH treatment										
n subj.	132	132	132	132	—	—	—	—	—	—
n male (%)	68 (51.52)	64 (48.48)	64 (48.48)	66 (50.0)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
age in years, mean (SD)	12.34 (±3.23)	12.28 (±3.36)	12.32 (±3.32)	12.31 (±3.23)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
gestational age, mean (days)	264.2 (±25.01)	271.09 (±17.3)	274.08 (±15.6)	276.75 (±13)	.004	<.001	n.s.	.04	.009	n.s.
preterm birth, %	25.37	10.45	3.79	3.03	<.001	<.001	<.001	<.001	<.001	n.s.
birth length, mean (SD)	−2.68 (±1.05)	−1.01 (±1.03)	−0.52 (±0.91)	−0.47 (±1.17)	<.001	<.001	<.001	<.001	<.001	n.s.
birth weight, mean (SD)	−2.09 (±0.81)	−0.69 (±0.85)	0.13 (±1.14)	0.34 (±1.23)	<.001	<.001	<.001	<.001	<.001	n.s.
BMI-SDS, mean (SD)	−0.58 (±1.24)	−0.5 (±1.14)	−0.12 (±0.85)	2.35 (±0.58)	n.s.	<.001	n.s.	<.001	n.s.	<.001
height-SDS, mean (SD)	−1.8 (±0.97)	−1.54 (±0.83)	0.12 (±0.88)	0.7 (±1.1)	<.001	<.001	<.001	<.001	.021	<.001
weight-SDS, mean (SD)	−1.53 (±1.46)	−1.27 (±1.15)	−0.08 (±0.90)	2.36 (±0.79)	<.001	<.001	<.001	<.001	n.s.	<.001
IGF1-SDS, mean (SD)	0.4 (±1.78)	0.15 (±1.43)	−0.27 (±0.94)	0.02 (±1.01)	.0012	n.s.	.007	n.s.	n.s.	.0016
GH dose µg/kg, mean (SD)	34.34 (±5.23)	29.97 (±6.26)	—	—	—	—	—	—	<.001	—
n pubertal stage 1 (%)	25 (23.81)	33 (31.13)	41 (33.88)	45 (34.09)	.04	.02*	n.s.	n.s.	n.s.	n.s.
n pubertal stage 2-4 (%)	55 (52.38)	53 (50.00)	64 (52.89)	58 (43.94)	n.s.	n.s.	.03	n.s.	n.s.	n.s.
n pubertal stage 5 (%)	25 (23.81)	20 (18.87)	19 (15.70)	29 (21.97)	n.s.	n.s.	.001	n.s.	.02	n.s.
After GH treatment										
n subj.	47	47	47	47	—	—	—	—	—	—
n male (%)	20 (42.55)	17 (36.17)	20 (42.55)	19 (40.43)	n.s.	n.s.	.039	.023	.039	n.s.
age in years, mean (SD)	15.85 (±1.6)	15.68 (±1.89)	15.70 (±1.65)	15.74 (±1.71)	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

(*continued*)

Table 1. Continued

	SGA	iGHD	lean	obesity	*P* value SGA vs lean	*P* value SGA vs obesity	*P* value iGHD vs lean	*P* value iGHD vs obesity	*P* value SGA vs iGHD	*P* value lean vs obesity
gestational age, mean (days)	270.98 (±20.9)	268.78 (±18.9)	270.93 (±18.3)	282.9 (±6.84)	n.s.	.002	n.s.	<.001	n.s.	.03
preterm birth, %	17.02	19.15	4.26	0	<.001	<.001	<.001	<.001	<.001	<.001
birth length, mean (SD)	−2.68 (±0.88)	−1.15 (±0.94)	−0.62 (±1.05)	0.21 (±1.12)	<.001	<.001	.03	<.001	<.001	.004
birth weight, mean (SD)	−2.04 (±0.71)	−0.66 (±0.98)	0.04 (±1.38)	1.08 (±1.19)	<.001	<.001	.015	<.001	<.001	.002
BMI-SDS, mean (SD)	0.04 (±1.38)	−0.05 (±1.15)	−0.10 (±0.74)	2.34 (±0.7)	n.s.	<.001	n.s.	<.001	n.s.	<.001
height-SDS, mean (SD)	−1.94 (±0.66)	−1.23 (±0.8)	−0.07 (±0.97)	0.38 (±1.03)	<.001	<.001	<.001	<.001	<.001	n.s.
weight-SDS, mean (SD)	−1.03 (±1.29)	−0.71 (±1.2)	−0.18 (±0.79)	2.48 (±0.94)	<.001	<.001	.011	<.001	n.s.	<.001
IGF1-SDS, mean (SD)	0.68 (±0.86)	−0.28 (±0.79)	−0.05 (±0.81)	−0.03 (±0.76)	.026	.017	n.s.	n.s.	.0039	n.s.
n pubertal stage 1 (%)	0	1 (2.86)	2 (4.55)	0	n.s.	.01	n.s.	n.s.	n.s.	n.s.
n pubertal stage 2–4 (%)	7 (21.88)	16 (45.71)	17 (38.64)	6 (15)	.04	n.s.	n.s.	.03	n.s.	.02
n pubertal stage 5 (%)	25 (78.13)	18 (56.25)	25 (56.82)	34 (75)	n.s.	n.s.	n.s.	.02	n.s.	n.s.

The control cohort and iGHD cohort were matched to SGA cohort for age, sex, and BMI-SDS, children with overweight/obesity were matched to SGA cohort for sex and age. Differences between groups were assessed by a *t* test for continuous variables and χ^2-test for categorical variables.
Abbreviations: BMI, body mass index; GH, growth hormone; IGF1, insulin-like growth factor 1; iGHD, isolated growth hormone deficiency; lean, lean controls; n.s., not significant; obesity, children with obesity; SDS, standard deviation score; SGA, children born SGA.

from each cohort according to the distribution within the SGA cohort (only the obesity cohort was not matched in regard to BMI-SDS). Subsequently, the matched cohorts had a similar distribution of age, sex, pubertal stage and BMI-SDS, respectively (Table 1).

As expected, the mean height-SDS in treatment-naïve children was lower for iGHD subjects and SGA subjects than for lean controls and children with obesity. Children with iGHD had reduced IGF1-SDS in comparison to lean controls and children with obesity. The majority of treatment-naïve children in all 4 groups were in pubertal stage 1.

During treatment, IGF1-SD scores normalized in both the iGHD and the SGA cohort (Table 1). Still, mean height-SDS was lower in SGA children and iGHD children and higher in children with obesity when compared to lean controls. On average, the duration of GH treatment was 1.7 years longer for children born SGA than for iGHD patients (SGA 7.5 years, iGHD 5.8 years). Moreover, SGA patients received higher dosages of GH relative to body weight (SGA: 34.34 µg/kg, iGHD: 29.97 µg/kg, $P < .001$).

The first visit after treatment cessation occurred at a mean age of 15 years, which was an average of 8 months after the end of GH treatment. Height-SDS was still reduced in SGA and iGHD children when compared to lean controls and children with obesity but was remarkably higher than for treatment-naïve iGHD patients (Table 1). IGF1-SDS values after treatment were within the normal range for all 4 groups, varying between −0.3 and +0.7 SDS. At the end of therapy, most children in all groups had completed puberty, although 25% of iGHD patients had not reached pubertal stage 5 yet.

Taken together, iGHD patients had the most pronounced short stature before treatment and benefited better from GH treatment in comparison to children born SGA. Of note, young children with obesity were taller than lean controls, but had no significant difference in height after puberty.

Glucose-insulin metabolism in treatment-naïve children

Children born SGA had comparable fasting glucose levels, HbA1c levels and 2-hour (2h)-glucose levels in the OGTT in comparison to matched lean controls and iGHD patients (Fig. 2). As expected, children with obesity had significantly higher fasting glucose levels (5.18 mmol/L, $P < .001$) compared to the lean cohort (4.92 mmol/L), SGA-GHT patients (4.91 mmol/L), and iGHD patients (4.77 mmol/L). The 1-hour glucose levels as an early predictor of future dysglycemia were comparable between all groups (Fig. S1 (34)). Treatment-naïve SGA-GHT patients were more insulin-resistant than iGHD patients, as indicated by a higher insulin AUC (1721.44 pmol/L × h vs 406 pmol/L × h, $P = .002$), higher HOMA-IR (2.76 vs 0.79, $P < .001$), and lower Matsuda index (6.67 vs 18.73, $P < .001$). Moreover, their HOMA-IR and Matsuda index were comparable to those in the obesity cohort and also indicated higher insulin resistance than in the lean controls (HOMA-IR: 2.76 vs 1.34; Matsuda: 6.67 vs 7.54). Based on age-dependent reference values, already 25.7% of children born SGA had pathological HOMA-IR values (Fig. 3). The HOMA-CIR and C-peptide/glucose ratio were comparable to that of children with obesity and significantly higher when compared to lean children (Fig. S2 (34)).

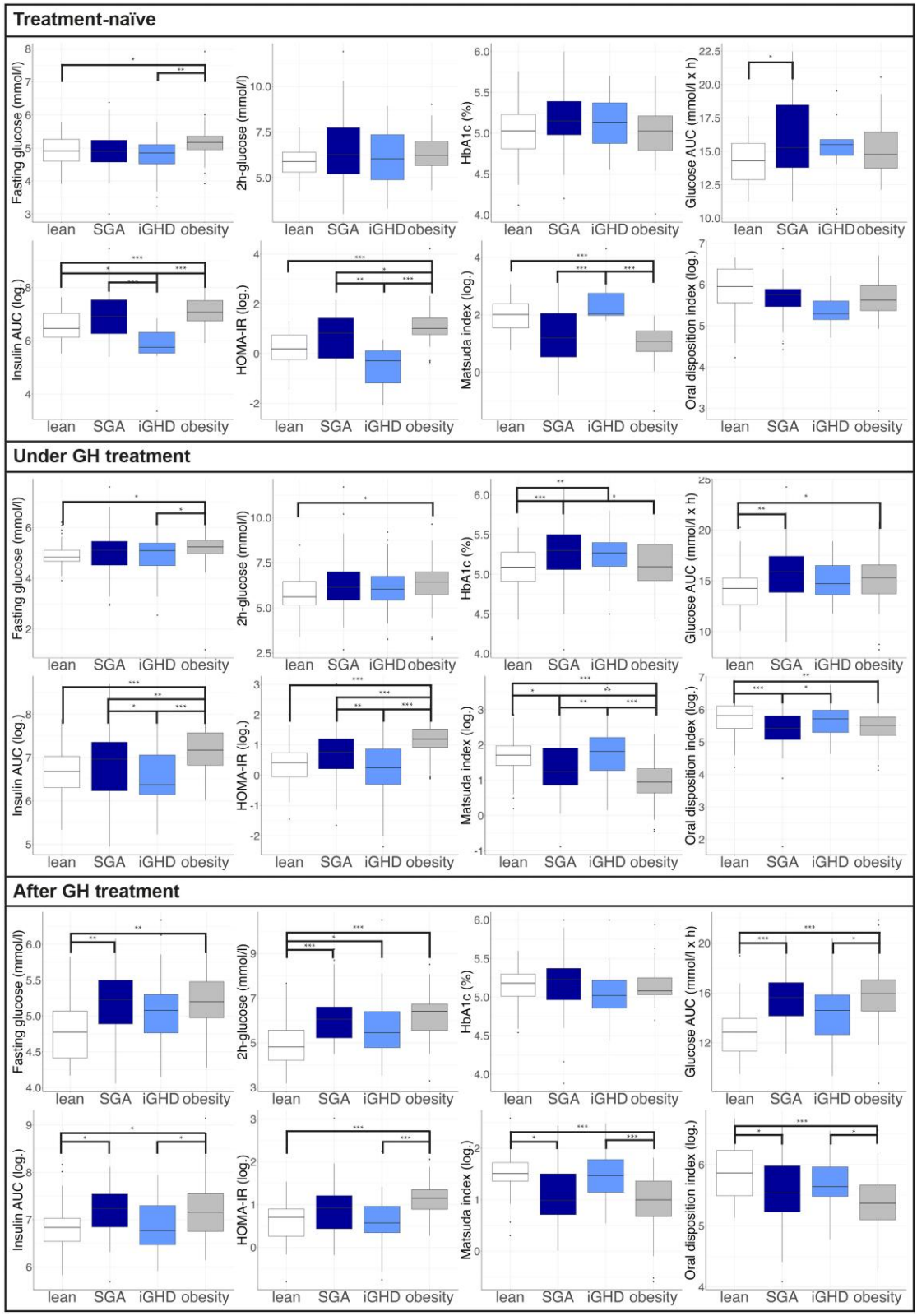

Figure 2. Glucose-insulin metabolism at different time points. The iGHD cohort and lean controls were matched to SGA children according to their age, sex, and BMI-SDS distribution, children with overweight/obesity were matched to SGA children according to age and sex. Statistical differences were determined by ANOVA with Tukey post hoc test. Abbreviations: iGHD, children with isolated growth hormone deficiency; SGA, children born small for gestational age. $*P < .05$, $**P < .01$, $***P < .001$.

We validated those results in the unmatched data set through linear mixed model analysis, adjusting for age, sex, pubertal stage, BMI-SDS and multiple visits (Table S2 (34)). The results supported those of the matched-cohort analyses. Additionally, there was a significantly higher 2h-glucose level in children born SGA compared to lean children and a

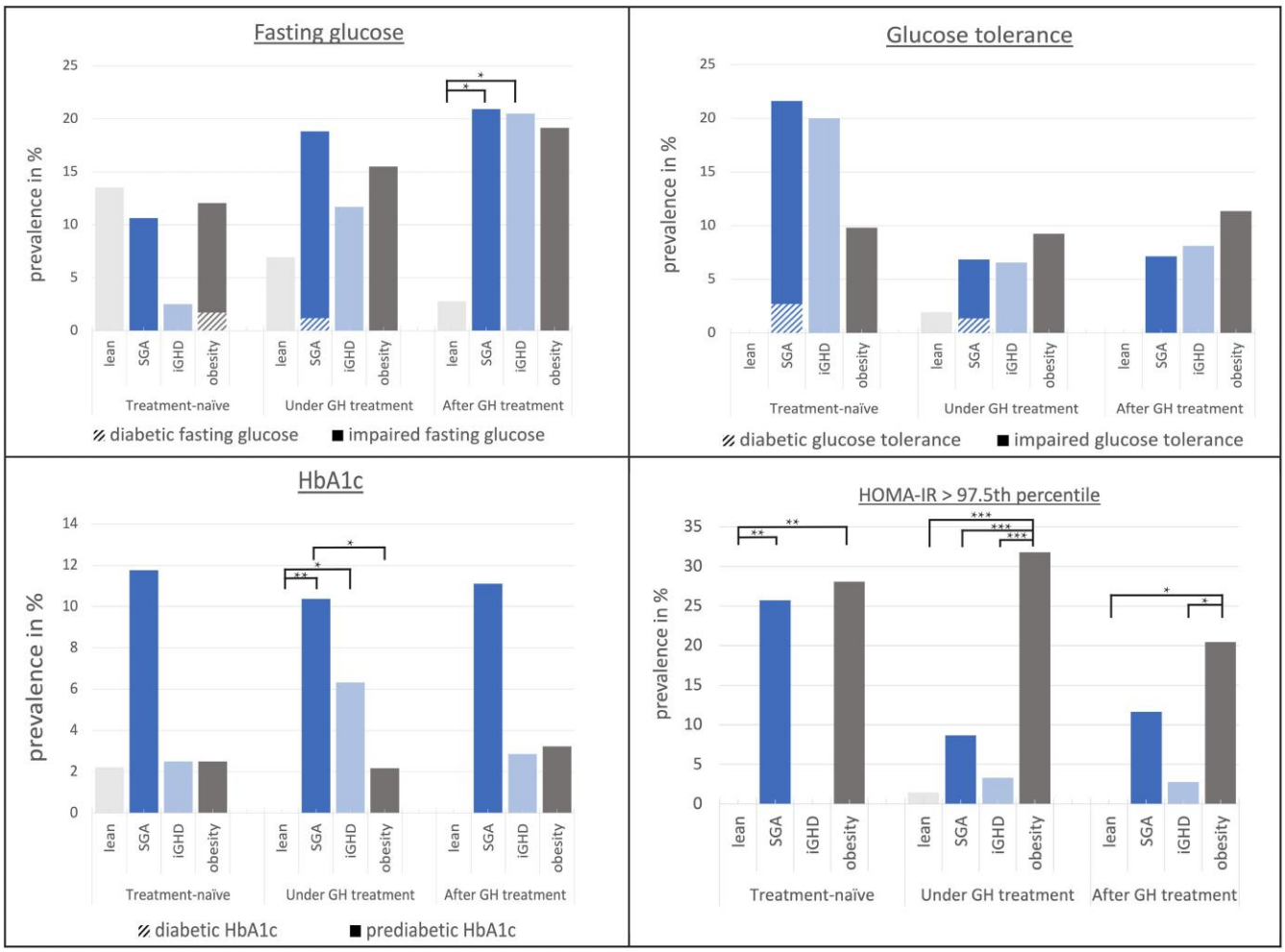

Figure 3. Prevalence of (pre-)diabetic measures in matched cohorts. Pathological HOMA-IR was calculated according to age-specific references (30). Of note, there was no occurrence of overt diabetes more (more than one diabetic measure at the same time) in any subject; Statistical differences were determined by χ^2-test. $^*P < .05$, $^{**}P < .01$, $^{***}P < .001$.

significantly higher ODI of children born SGA in comparison to children with obesity. Overall, glucose-insulin metabolism was diminished in treatment-naïve children born SGA compared to lean controls, whereas iGHD patients had a comparable glucose-insulin metabolism to lean controls.

Glucose-insulin metabolism during growth hormone treatment

Both cohorts under GH treatment (SGA-GHT and iGHD patients) showed a shift toward an impaired glucose metabolism in comparison to lean controls (Fig. 2). SGA-GHT children had higher levels of glucose AUC (15.6 mmol/L × h) than lean controls (14.4 mmol/L × h, $P < .001$). 1-hour glucose levels were significantly higher for SGA patients compared to lean children (7.4 mmol/L vs 5.7 mmol/L, $P < .001$) (Fig. S1 (34)). Also, HbA1c levels were significantly higher in children born SGA compared to lean controls and children with obesity (SGA-GHT 5.3% vs lean controls 5.1%, $P < .001$, vs children with obesity 5.1%, $P < .05$). Likewise, SGA-GHT children showed higher insulin AUC than iGHD patients and lean controls (1252.1 pmol/L × h vs 870.7 pmol/L × h vs 956.6 pmol/L × h), as well as higher insulin resistance and less insulin sensitivity than the iGHD cohort (HOMA-IR: 2.6 vs 1.8, $P < .001$, Matsuda index: 5.4 vs 8.2, $P < .001$) (Fig. 2). Levels of insulin sensitivity and secretion in the SGA-GHT group approached those of children with obesity. Children born SGA also had less pathological age-adjusted HOMA-IR values (8.7%) in comparison to children with obesity (31.8%) (Fig. 3). The insulin response adjusted for the degree of insulin sensitivity (ODI) was diminished in children born SGA (252.6) and children with obesity (270.9) compared with lean controls (348.0).

In line with those findings, results from adjusted linear modeling of unmatched cohorts (Table S2 (34)) indicated significantly higher fasting glucose levels for children born SGA in comparison to lean controls and iGHD patients (5.0 mmol/L vs 4.9 mmol/L, vs 4.9 mmol/L, $P < .001$). Children born SGA and iGHD patients also had higher 2h-glucose levels in comparison to lean controls (6.2 mmol/L vs 6.1 mmol/L vs 5.84 mmol/L, $P < .001$). Overall, glucose-insulin metabolism deteriorated under GH treatment, particularly in children born SGA.

Glucose-insulin metabolism after cessation of GH treatment

To address the question of whether potentially GH treatment-induced metabolic changes are reversible, we

compared glucose-insulin metabolism in SGA-GHT and iGHD children after cessation of treatment (on average 8 months later) with age, sex, and BMI-matched lean controls and children with obesity (Fig. 2). Of note, we only had metabolic data (OGTTs) after treatment from 30% of iGHD patients and children born SGA, either due to treatment continuation in adulthood or due to incomplete medical records. Children born SGA still had significantly higher fasting glucose levels (5.2 mmol/L vs 4.9 mmol/L, $P < .001$), 1h-glucose levels (7.52 mmol/L vs 5.92 mmol/L, $P < .001$) (Fig. S1 (34)), and 2h-glucose levels (6.2 mmol/L vs 5.6 mmol/L, $P < .001$) compared to lean controls that were similar to children with obesity. On the contrary, no differences in HbA1c levels could be detected (SGA: 5.2%, lean controls: 5.1%, obesity cohort: 5.2%). Moreover, children born SGA displayed significantly higher insulin AUC and lower Matsuda index compared to lean controls, indicating diminished insulin sensitivity even after GH treatment. Likewise, the prevalence of pathological HOMA-IR was higher in children born SGA (11.6%) and children with obesity (21%) as compared to lean controls (0.9%) (Fig. 3). The ODI of children born SGA was comparable to that of children with obesity. The HOMA-CIR and C-peptide/glucose ratio were comparable to that of children with obesity (Fig. S2 (34)).

Additionally, results from adjusted linear model analysis showed higher fasting glucose levels of SGA and iGHD patients in comparison to lean children (5.2 mmol/L vs 5.1 mmol/L vs 4.9 mmol/L, $P < .001$, Table S2 (34)). Insulin secretion of children born SGA was significantly higher than that of iGHD patients (1477 pmol/L × h vs 1087 pmol/L × h, $P = .005$). Furthermore, they had significantly higher HOMA-IR levels (3.0 vs 2.2, $P = .002$) than iGHD patients.

In summary, impaired insulin sensitivity and elevated insulin resistance persisted in children born SGA following GH cessation, whereas glucose metabolism in iGHD patients returned to normal.

Prevalence of (pre-)diabetic values

For comparison of the prevalence of (pre-)diabetic measures, we matched cohorts for age and sex and where appropriate (lean controls and iGHD children) also for BMI-SDS (Fig. 3; Fig. S3 (34) and additionally analyzed the whole dataset (Fig. S4 (34)).

In the matched cohorts analyses, treatment-naïve children born SGA had a similar prevalence of impaired fasting glucose in comparison to lean controls and children with obesity and a higher prevalence compared to iGHD children (SGA 10.64%, lean controls 13.51%, obesity 10.34%, iGHD 2.5%). Children born SGA showed a higher prevalence of pathological glucose tolerance in comparison to all other groups (SGA 21.62%, iGHD 20%, obesity 9.8%, controls 0%) and comparable levels of insulin resistance as children with obesity (Fig. 3). Furthermore, the share of prediabetic HbA1c levels was highest in the group of children born SGA compared with all other groups (SGA 11.76% vs iGHD 2.5%).

During treatment, children born SGA showed the highest prevalence of prediabetic fasting glucose levels (17.65%) and prediabetic HbA1c (10.37%) among all cohorts. The degree of impaired glucose tolerance was comparable to those of children with obesity.

After terminating GH therapy, the prevalence of prediabetic fasting glucose in children born SGA was comparable to that in children with obesity (20.93% vs 19.15%), and significantly higher than in lean children (2.78%). By the end of therapy, the prevalence of impaired glucose tolerance was elevated across all groups in comparison to lean controls. On the contrary, the prevalence of prediabetic HbA1c levels was higher for SGA children (11.1%) than for all other cohorts. Both SGA children and children with obesity showed elevated levels of insulin resistance (11.63% and 20.45% respectively).

According to American Diabetes Association guidelines, the diagnosis of diabetes requires at least 2 pathological values out of the 3 above-mentioned. Hence, we compared the simultaneous occurrence of 2 or more (pre)diabetic values and observed the highest prevalence of prediabetes in children born SGA during GH treatment (11.1%), whereas prediabetes occurred in only 3.1% of age- and sex-matched children with obesity (Fig. S3 (34)). However, after GH treatment, the prevalence of prediabetes was lower for children born SGA in comparison to children with obesity (4.7% vs 6.4%). Of note, none of the patients developed overt diabetes, defined as 2 or more simultaneous measures within the diabetic range.

Longitudinal dynamics of BMI, growth factors, and glucose-insulin metabolism

In order to assess whether alterations in glucose-insulin metabolism were related to changes in body composition or growth factor levels, we compared the longitudinal course of these parameters between different timepoints: before initiating GH therapy, at the beginning and the end of GH treatment, and after cessation of GH therapy (Table S3 (34)).

Insulin resistance/insulin secretion rose upon initiation of GH treatment, increased further during treatment and decreased again after cessation of treatment in both SGA and iGHD children. As expected, this was accompanied by an increase of IGF1 levels upon initiation of GH treatment and a drop in IGF1 levels upon cessation of therapy in both groups. SGA children showed a significant rise in BMI-SDS during GH treatment (0.53 SDS, $P < .001$) and still thereafter (0.2 SDS, $P = .008$), while iGHD children revealed no significant changes in BMI-SDS during the entire time course but a tendency of increasing BMI during GH therapy (0.3 SDS, n.s.).

When correlating changes in insulin resistance with change in BMI or change of growth factors, we observed a positive association of increasing insulin resistance with increasing BMI-SDS during GH therapy in SGA children (insulin AUC $P = .02$, HOMA-IR $P = .04$). However, this association did not remain significant after adjusting for age and sex. Likewise, changes in IGF1 levels were positively correlated with changes in insulin resistance only in children born SGA during GH therapy (HOMA-IR $P = .001$, Matsuda index $P = .013$) with no significant association after correction for sex and age.

Comparison of SGA with CUG and without CUG

We stratified children born SGA into patients without catch-up growth within the first 4 years of life who therefore received GH therapy (SGA-GHT) and, on the other hand, into SGA children with sufficient catch-up growth who did not receive GH treatment (SGA-CUG) (Table 2).

Treatment-naïve SGA-GHT children showed slightly lower 2-hour glucose levels, lower insulin resistance (HOMA-IR), lower insulin secretion (AUC insulin), and a higher Matsuda

Table 2. Differences of glucose-insulin metabolism of children born SGA without CUG vs SGA with CUG

	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Treatment-naïve, SGA-GHT (n = 34) vs SGA-CUG (n = 22)						
	fasting glucose level		HbA1c		Matsuda index	
beta slope	−0.317	0.083	−0.089	0.127	1.733	0.289
P value	.109	.997	.509	.829	<.001	.741
	2h-glucose level		HOMA-IR		Oral disposition index	
beta slope	−0.997	0.607	−1.864	−0.485	0.301	−0.395
P value	.095	.887	<.001	.247	.302	.626
	glucose AUC		insulin AUC			
beta slope	−0.918	1.802	−1.211	−0.125		
P value	.55	.645	<.001	.973		
During GH treatment, SGA-GHT (n = 132) vs SGA-CUG (n = 26)						
	fasting glucose level		HbA1c		Matsuda index	
beta slope	−0.005	1.802	0.036	0.067	0.662	−0.11
P value	.998	.645	.71	.866	<.001	.846
	2h-glucose level		HOMA-IR		Oral disposition index	
beta slope	−0.333	1.802	−0.572	0.168	−0.159	−0.333
P value	.193	.645	<.001	.642	.241	.075
	glucose AUC		insulin AUC			
beta slope	−0.334	0.282	−0.564	0.104		
P value	.588	.978	<.001	.821		
After GH treatment, SGA-GHT (n = 47) vs SGA-CUG (n = 20)						
	fasting glucose level		HbA1c		Matsuda index	
beta slope	0.132	0.228	−0.054	−0.036	0.083	−0.143
P value	.456	.446	.739	.995	.77	.832
	2h-glucose level		HOMA-IR		Oral disposition index	
beta slope	−0.035	0.65	−0.151	0.135	−0.168	−0.383
P value	.99	.195	.465	.832	.384	.082
	glucose AUC		insulin AUC			
beta slope	0.233	1.293	−0.013	0.119		
P value	.881	.207	.992	.914		

Coefficients estimate fixed effects of a linear mixed model with the respective glucose-insulin index as dependent variable and either the treatment group alone (unadjusted) or the treatment, as well as age, sex and BMI-SDS (adjusted) as independent variables. A mixed model with the subject ID as random effect was applied to take repeated measurements of the same participant into account. The SGA-CUG was matched to the SGA-GHT cohort by age range at different time points. Positive values indicate higher values in SGA-GHT, while they were lower with negative values.
Abbreviations: AUC, area under the curve; BMI, body mass index; GH, growth hormone; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; SGA-CUG, children with catch-up growth; SGA-GHT, children without catch-up growth who received GH treatment.

index, indicating better insulin sensitivity. However, these tendencies did not reach statistical significance in linear mixed model analyses after adjusting for age, sex, BMI-SDS, and multiple measurements of the same participant, likely due to small sample sizes. During treatment, SGA-GHT still had slightly lower 2-hour glucose levels, lower insulin secretion, lower HOMA-IR, and higher Matsuda index. Once again, these differences did not reach statistical significance after adjustment.

After treatment, levels of insulin sensitivity and secretion were comparable between SGA-GHT and SGA-CUG patients, with a tendency to lower insulin resistance in SGA children without CUG.

Of note, the main weight- and height gain of SGA-CUG children was accomplished during the first year of life (Fig. S5 (34)) and insulin resistance (HOMA-IR) in treatment-naïve SGA patients did not correlate with the extent of this early weight gain (Fig. S6 (34)).

Discussion

Herein, we report a detailed characterization of glucose and insulin parameters to assess the metabolic risk in children born SGA under GH treatment by direct comparison to iGHD patients, healthy lean controls, and children with obesity of appropriate age, sex, and BMI-matched distribution. We were thereby able to show that already treatment-naïve children born SGA have an elevated risk for dysglycemia that is aggravated during GH therapy to an extent comparable to the diabetes risk of children with obesity, whereas iGHD patients showed better insulin sensitivity compared to lean controls and children born SGA. In line with previously published research, children born SGA have higher insulin secretion and insulin resistance (35), as well as higher fasting glucose levels and twice as many metabolic abnormalities like type 2 diabetes or metabolic syndrome than lean controls (10, 36).

According to newly published age-dependent reference values (30), 25.7% of children born SGA before GH treatment in our matched cohort had a pathological HOMA-IR, compared to 28% of the overweight group, while none of the lean cohort or IGHD individuals were affected. Also, better insulin sensitivity in iGHD children had been demonstrated before (37-39). However, the underlying molecular mechanisms are still unclear, with both GH and IGF1 being potential candidates for interfering with glucose-insulin metabolism (40). In mouse models, it was shown that mice with decreased IGF1 levels and increased GH levels exhibited impaired glucose tolerance and more insulin resistance (41). After blocking GH secretion, a reduction in blood glucose and insulin levels and an increase in insulin sensitivity could be measured (42), which indicates a better sensitivity to insulin due to the absence of GH. Furthermore, GH did not have a direct influence on insulin receptor levels. However, GH deficiency results in an upregulation of insulin receptor levels without a direct interaction between GH and the insulin receptor. The authors speculated that post-receptor events and similar signaling molecules might explain the anti-insulin effect of GH (41).

During treatment, we illustrated that children born SGA tend to have an increased insulin secretion, worse insulin sensitivity and higher insulin resistance compared to iGHD patients and lean controls, which is supported by previous research (20). Furthermore, SGA and iGHD patients both had higher HbA1c levels during treatment, which was also shown by other studies (10-12, 37). In this study, we were able to demonstrate that insulin resistance of children born SGA is only slightly better than that of children with obesity and that children born SGA have a higher prevalence of prediabetes during GH treatment than children with obesity (11.1% vs 3.1%), whereas less than 2% of iGHD patients had prediabetes during GH therapy. Still, GH treatment has been found to aggravate insulin resistance in both children born SGA and in children with iGHD (43). It is well-established that GH modulates tissue responses to insulin, with excess GH causing insulin resistance and growth deficiency leading to insulin sensitivity (44). In this study, after cessation of GH therapy, SGA and iGHD patients still had significantly higher fasting glucose levels and 2-hour glucose levels than lean controls but comparable levels to patients with obesity. Furthermore, children born SGA tended to carry on insulin resistance even after stopping GH treatment. In contrast, other studies showed the reversibility of these effects after cessation of GH treatment (45-47). However, the above-mentioned studies analyzed data after several years, whereas in this study the mean time between cessation of treatment and first post-cessation measurement was 8.42 months for children born SGA and 7.69 months for iGHD patients. It is conceivable that insulin resistance and insulin sensitivity could recover fully in the subsequent years (13, 15, 20, 35). Previously published results on diabetes risk during GH therapy are contradictory: most studies did not identify an increased risk of type 2 diabetes for GH-treated children (19, 46, 48, 49). On the contrary, other studies assessed an up to 6-times higher diabetes risk for GH-treated children (11, 50). These differences might be due to the inclusion of patients with different underlying conditions, such as Prader-Willi or Turner syndrome. As a result, a higher incidence is found in genetically predisposed individuals. In our matched study cohort without any (known) syndromic patients, we found a higher prevalence of prediabetes for children born SGA in comparison to children with obesity during GH treatment, without a single case of overt type 2 diabetes.

It is of ongoing debate whether SGA children with CUG differ from those without CUG regarding their metabolic risk. Few studies indicated that SGA-CUG children are more at risk of developing insulin resistance; however, these studies only analyzed small case numbers and fasting indices (7, 51). Our analysis showed no significant differences between those 2 groups, but in line with published results indicated a tendency toward a worse glucose-insulin metabolism in SGA-CUG children.

As strengths of our study, this is the first time—to our best knowledge—that metabolic risk (including insulin response) in children born SGA under GH treatment is directly compared to children with obesity. Furthermore, we used OGTTs at several time points, whereas most studies so far were based on fasting indices only which are less meaningful (21). Moreover, we provide larger case numbers than earlier studies with well-matched control cohorts.

As a limitation, data at different time points (treatment-naïve, and during and after GH therapy) were not necessarily retrieved from the same subjects, as most patients did not meet every appointment or switched doctors during their treatment. Still, we were able to investigate longitudinal dynamics of insulin resistance, BMI, and growth factors by pairwise comparison of 2 of these time points. Our results were further limited by a small case number for SGA-CUG children because glucose-insulin metabolism is not routinely assessed in children without GH treatment. Additionally, we did solely rely on proxies for insulin sensitivity rather than using a gold standard method like the euglycemic hyperinsulinemic clamp. Furthermore, we used BMI as the only measurement for adiposity and not more accurate measures for body composition, such as waist-to-hip ratio or dual-energy x-ray absorptiometry (DXA) scans, as SGA individuals with a normal BMI can have a higher degree of abdominal obesity. Future research should comprise prospective longitudinal monitoring of SGA patients throughout the entire course of GH therapy with a predefined assessment schedule, ideally incorporating gold standard techniques such as the euglycemic hyperinsulinemic clamp to evaluate glucose-insulin metabolism and more precise measures of body composition such as waist-to-hip ratio or DXA assessments.

In conclusion, children born SGA have an impaired glucose-insulin-metabolism in comparison to iGHD and lean children, with levels comparable to those of children with obesity and further deterioration during GH therapy. We recommend that children born SGA treated with GH should receive similar metabolic monitoring as children with obesity, which may comprise annual measures of HbA1c, fasting glucose, fasting insulin, and lipid status. In cases with elevated fasting indices or additional risk factors (such as overweight or obesity, family history of diabetes, ethnicity at risk for diabetes, acanthosis nigricans) we recommend using OGTT. Likewise, the management of insulin resistance in children with obesity primarily relies on lifestyle interventions, including dietary modification and physical activity, and in some cases on pharmacological treatment with insulin-sensitizing agents such as metformin. We recommend similar treatment approaches for SGA patients who develop insulin resistance or prediabetes during GH therapy. Additionally, lowering the dose of GH should be considered first before initiating further pharmacotherapy.

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Author contributions

L.P. designed the study, compiled the data, performed the statistical analysis, interpreted the results, and drafted the manuscript. R.S. was involved in study design, statistical analysis, interpretation of results, and drafted the manuscript. C.B., R.G., M.V., E.W., and A.S. contributed to data acquisition, interpreted the results, and revised the manuscript. W.K. and R.P. acquired funding, helped with study conception and revised the manuscript. A.K. was involved in study conception, funding acquisition, interpreted the results, and revised the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Disclosures

The authors have no conflicts of interest to declare.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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