

Evaluation of Changes in Insulin Sensitivity in Prepubertal Small for Gestational Age Children Treated with Growth Hormone

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Abstract

Background: Although growth hormone (GH) therapy for children born small for gestational age (SGA) has been approved for many years, there are still concerns about increasing their risk for insulin resistance and diabetes mellitus type 2. Monitoring of glucose homeostasis is therefore generally recommended, but there is no consensus on either the methods or consequences. **Methods and Aims:** The aim of our study was to analyze the oral Glucose Tolerance Tests (oGTTs) which were performed yearly from baseline to 4 years of GH therapy in a collective of 93 SGA children, who were prepubertal during the whole follow-up. We looked for correlations with auxological and laboratory data as well as predictive baseline results for glucose homeostasis during further treatment. **Results:** While glucose levels remained constant, insulin secretion increased from baseline to the first year of GH therapy. Insulin sensitivity index (ISI) showed no significant change afterwards; HOMA1, HOMA2, and QUICKI stabilized after the second year. For all indices mean values never reached pathological levels and no cases of diabetes mellitus were induced. Higher gestational age, lower birth length, and older age at start of GH therapy were associated with lower insulin sensitivity. No predictive factors for later insulin resistance could be found. **Conclusion:** As expected, in GH-treated prepubertal SGA children insulin resistance was induced, but not to pathological levels. No special risk factors for disturbed glucose homeostasis could be identified. Based on our opinion, performing oGTTs in GH-treated SGA children at baseline and in puberty should remain mandatory, but the current study recommendations regarding further surveillance of glucose homeostasis are questionable.

Keywords: Glucose homeostasis, growth hormone treatment, insulin sensitivity, oral glucose tolerance test, small for gestational age children

INTRODUCTION

Small for gestational age (SGA) children are defined as children born with either weight or length below -2.0 SDS (standard deviation score) for their gestational reference data.^[1-3] For those without catch-up growth during the first 2 years of life (about 10–15%),^[1,2,4-8] treatment with recombinant growth hormone (GH) has become a standard procedure. Meanwhile, numerous studies have shown good results, with most children reaching a final height within their genetic target range.^[9-12] GH is however known to have anti-insulinergic effects^[13] and it has often been stated that former SGA children are at higher risk of developing symptoms of the so-called metabolic syndrome in later life, including obesity, arterial hypertonus, coronary heart disease, disorders of lipid metabolism, and in particular insulin resistance and diabetes mellitus type 2.^[1,14-22] In the latter case,

there are concerns that GH therapy might further increase the incidence of diabetes mellitus, perhaps even during childhood and youth.^[4,6,23-25] As a consequence, the monitoring of glucose tolerance in SGA children receiving GH treatment is generally recommended.^[1,26] Nevertheless, there is no consensus about the methods that should be used [e.g., fasting glucose, glucose tolerance tests (GTT), glucose clamp techniques, HbA1c] and the degree of abnormality of glucose homeostasis from which consequences should be drawn concerning GH therapy. Most studies on the one hand show an increase of insulin resistance in

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GH-treated SGA children, but on the other no higher incidence of diabetes mellitus. Nor is it known whether special groups of SGA children are at higher risk for disturbances of glucose metabolism and should be watched more closely.

The aim of our study was to find out which of the methods [oGTT data, HOMA1 and HOMA2 (homeostasis model assessment), QUICKI (quantitative insulin sensitivity check index), ISI (insulin sensitivity index according to Matsuda), and HbA1c] used at our clinic is the most significant to detect insulin resistance in SGA children and its incidence is the most significant. We also looked for potentially associated factors predicting a higher risk for disturbances of glucose metabolism. Especially because of this last aspect and with the aim of excluding other factors influencing glucose tolerance, we decided to focus on children who were prepubertal for the entire duration of the study.

MATERIALS AND METHODS

The oGTT data and HbA1c values of 93 prepubertal SGA children treated with GH between 2004 and 2016 at our endocrine unit were collected for up to 4 years of treatment. oGTTs were performed before the start of GH therapy and yearly thereafter, alternatively fasting blood samples for glucose and insulin were taken. Children entering puberty, i.e., showing Tanner stage B2 (girls) or testis volume >3 ml (boys) dropped out. Patients with additional GH deficiency and chromosomal or other syndromal disorders as well as those with a family history of diabetes [type 2 or MODY (maturity onset diabetes of the young)] were not included in the study. For GH treatment, biosynthetic GH from Ferring, Ipsen, Lilly, Merck, NovoNordisk, Pfizer, and Sandoz were used. The GH dose was kept constant at 0.034 ± 0.004 mg/kg/day throughout the whole study period.

The oGTTs involved the administration of 1.75 g/kg glucose (maximum 75 g; dilution of 4 g/1 ml water) after an overnight fast and the measurement of glucose and insulin at 0, 30, 60, and 120 min. From the resulting values, in addition to the basal data, we calculated glucose/insulin ratios as well as HOMA1, HOMA2, QUICKI, and ISI in order to estimate insulin sensitivity. The formulas for HOMA1, QUICKI, and ISI were: $HOMA1 = FPG \times FPI / 22.5 \times 18$,^[27] for $QUICKI = 1 / (\log(FPI) + \log(FPG))$,^[28] and for $ISI = 10.000 / \sqrt{FPG \times FPI \times G \times I}$,^[29] respectively, in which FPG is fasting plasma glucose (mg/dl), FPI is fasting plasma insulin (μ U/ml), G and I is the mean of the 60 and 120 min plasma glucose and insulin levels in oGTT, respectively.^[4] HOMA2-index was obtained by the program HOMA Calculator v2.2.2.^[30] Fasting glucose >100 mg/dl, 120-min-glucose >140 mg/dl (impaired glucose tolerance, IGT), fasting insulin >20 μ U/ml, QUICKI <0.33,^[31] HOMA1 >2.5 (reduced fasting insulin sensitivity), and ISI <5.0 (impaired insulin sensitivity) were considered abnormal.^[4] For HOMA2, a generally established cut-off does not exist. Reference values for larger patient cohorts of specific populations have been published,^[32-34] but as HOMA-IR is

considered to be dependent on ethnics,^[35] it would be arbitrary to use any of these values for our study population. Therefore, we decided to exclude HOMA2-IR from analyses concerning cut-off values.

For the analysis of possible correlations with glucose homeostasis and its development we gathered data on gestational age, birth weight and length (both in SDS), mid-parental target height and age at the start of therapy, and for each year of therapy also on age, height, SDS of height (H-SDS), height velocity (HV), standard deviation of height velocity in SDS (HV-SDS), weight, body mass index (BMI), BMI in SDS, GH-dose and insulin-like growth factor-I (IGF-I), the latter expressed in SDS. For HOMA1, ISI, H-SDS, and BMI-SDS delta values were calculated by subtracting baseline values of those of the actual year of therapy. The study protocol was approved by the ethics committee of the Ludwig Maximilian University of Munich, and written informed consent was obtained from patients and their parents.

Statistical analysis

Statistical analyses were carried out by using the SPSS software for Windows version 15.0 (SPSS, Chicago, Illinois). Paired Student's *t*-tests for repeated measures were used to compare variables before and after 1 year of GH treatment in the same patient. Different groups of patients were compared using unpaired *t*-tests. Correlations between variables of the same year as well as between the years before and during GH treatment were determined by the Spearman's method (r_s = Spearman's correlation coefficient). The level of significance for each test was set to 0.05 throughout the study.

RESULTS

Statistical data

Of the 93 children, 46 were male and 47 were female. Thirty-three were born preterm (<37 weeks of gestation). Mean for birth data, auxological, and laboratory parameters at the start of GH therapy are shown in Table 1a. Since at the end of data collection not all the children had been receiving GH for 4 years and others had dropped out because of the start of puberty, the number of included patients decreased between baseline and 4 years. There was a baseline dataset for all 93 children, a first year dataset for 83, second year dataset for 62, and a third year dataset for 49 patients. Thirty nine children could be followed for the whole 4-year period of therapy. These 39 children were analyzed separately in addition to ensure that the higher patient numbers during the first years had no effect on the study results. The age, SDS for auxologic data, BMI, and IGF-I in SDS of the analyzed patient cohort are shown for each year in Table 1b and those for the subgroup of children followed for the whole 4 years in Table 1c.

oGTT results

Glucose and insulin levels increased to a maximum at 30 min, afterwards falling to the normal range expected for

Table 1: (a) Basal data for the analyzed cohort of patients (GW=gestational week); (b) Yearly auxological data, GH-dose and IGF-I for the entire analyzed patient cohort and (c) for the subgroup followed up for the whole 4 years

		Mean	SDS			
(a)						
Number of patients		93				
Sex						
Male		46				
Female		47				
Term/preterm						
>37 GW		60				
<37 GW		33				
		Mean	SDS			
Gestational age		36.12	4.46			
Birth weight-SDS		-2.04	0.69			
Birth length-SDS		-2.00	0.95			
Age at GH-start (years)		7.13	2.34			
H-SDS at GH-start		-3.12	0.84			
BMI-SDS at GH-start		-1.31	1.21			
IGF-I-SDS at GH-start		-1.14	0.89			
Target height SDS		-0.54	0.73			
(b)						
		Age (years)	Height (SDS)	Height velocity (SDS)	BMI (SDS)	IGF-I (SDS)
All	Mean	7.94	-2.24	2.17	-1.25	0.32
n=93	SDS	2.24	1.04	1.91	1.10	1.42
Baseline	Mean	6.62	-3.13	1.18	-1.33	-1.16
n=93	SDS	2.36	0.83	0.00	1.19	0.86
1 year	Mean	7.64	-2.31	3.20	-1.25	0.83
n=83	SDS	2.09	0.80	2.29	1.13	1.06
2 years	Mean	8.40	-1.81	2.10	-1.17	1.02
n=62	SDS	1.83	0.77	1.32	1.12	1.15
3 years	Mean	9.02	-1.64	1.35	-1.23	0.94
n=49	SDS	1.61	0.87	1.30	0.98	1.10
4 years	Mean	9.67	-1.41	1.18	-1.20	1.02
n=39	SDS	1.33	0.89	1.31	0.94	1.23
(c)						
		Age (years)	Height (SDS)	Height velocity (SDS)	BMI (SDS)	IGF-I (SDS)
All	Mean	8.05	-2.13	1.85	-1.35	0.47
n=39	SDS	2.07	1.05	1.82	0.99	1.40
Baseline	Mean	5.89	-3.21	-	-1.52	-1.35
n=39	SDS	1.40	0.77	-	1.01	0.83
1 year	Mean	7.01	-2.38	3.22	-1.52	0.77
n=39	SDS	1.40	0.80	2.48	0.99	1.04
2 years	Mean	8.15	-1.93	1.68	-1.36	0.95
n=39	SDS	1.48	0.83	1.25	0.96	1.04
3 years	Mean	9.0	-1.67	1.30	-1.25	1.07
n=39	SDS	1.45	0.89	1.15	1.03	1.04
4 years	Mean	10.16	-1.41	1.18	-1.20	1.02
n=39	SDS	1.40	0.90	1.33	0.95	1.23

120 min [Table 2a and b, Figure 1a and b]. Throughout the whole monitored period, there was no significant difference in

the glucose levels. Insulin levels however increased between baseline and the first year of treatment. A further increase between the first and second year was seen at 0 min, whereas the 30-, 60-, and 120-min results of the second year and all of the later years showed no significant differences. We would like to draw attention to the fact that the insulin level at 30 min was highest of all in the second year, but dropped to the lowest (apart from baseline) at 60 min. At 4 years, however, the initial increase of insulin was much lower, but the 60- and 120-min values were higher than all those in the years before. With respect to the means, there was no increase to pathological values for fasting or postprandial glucose or fasting insulin in all prepubertal years.

Looking at the diagram for insulin values, the 0-min values showed the most relevant differences [Figure 1b]. This effect is visualized much better by presenting the glucose/insulin ratios [Figure 1c].

Regarding the three indices for fasting glucose and insulin pairs, as expected, a very good correlation between HOMA1, HOMA2, and QUICKI was found (HOMA1 vs HOMA2: $r_s + 0.977$, HOMA1 vs QUICKI: $r_s - 0.988$, HOMA2 vs QUICKI: $r_s - 0.983$). However, due to low insulin levels which are not unusual in healthy children, 50 fasting insulin levels in our study population were below the accepted minimal limit of $2.9 \mu\text{U/ml}$ ^[30,36] and in consequence, HOMA2 could not be calculated for them. This would have meant to exclude quite a large number of datasets for which the other parameters exist and even more to exclude especially the children with the best insulin sensitivity. In our opinion, this would not have been correct, so in spite of the well-known advantages of the HOMA2 model,^[30,34,36] we decided to focus on HOMA1 as index representing fasting insulin sensitivity for further analyses. QUICKI showed the same results as HOMA1 in all analyses. Therefore, only those for HOMA1 will be presented in the following.

The HOMA1-index slightly increased between the start and the second year (0.83–1.59, statistically significant) and was lower again in the third and fourth year, thus remaining below the cut-off for pathological values. ISI fell continuously, with the largest (and statistically significant) decrease between baseline and the first year of treatment (16.0–9.56). The mean ISI at 4 years was not below the cut-off of 5.0 either. HbA1c levels remained unchanged during all 4 years [Figure 1d].

These 39 children followed for the whole 4 years (see “statistical data”) were also analyzed separately for their oGTT data. The results are shown in Table 2b and Figure 1c-h.

Unexpectedly, HOMA1 had improved in 18 children and ISI in 11 children after the first year of treatment before deteriorating afterwards. 15 children followed for 4 years had a better final HOMA1-index than individual maximum. There was also no continuous decrease of ISI in most children. However, these deviations were not very high, so they were not analyzed further and are not shown.

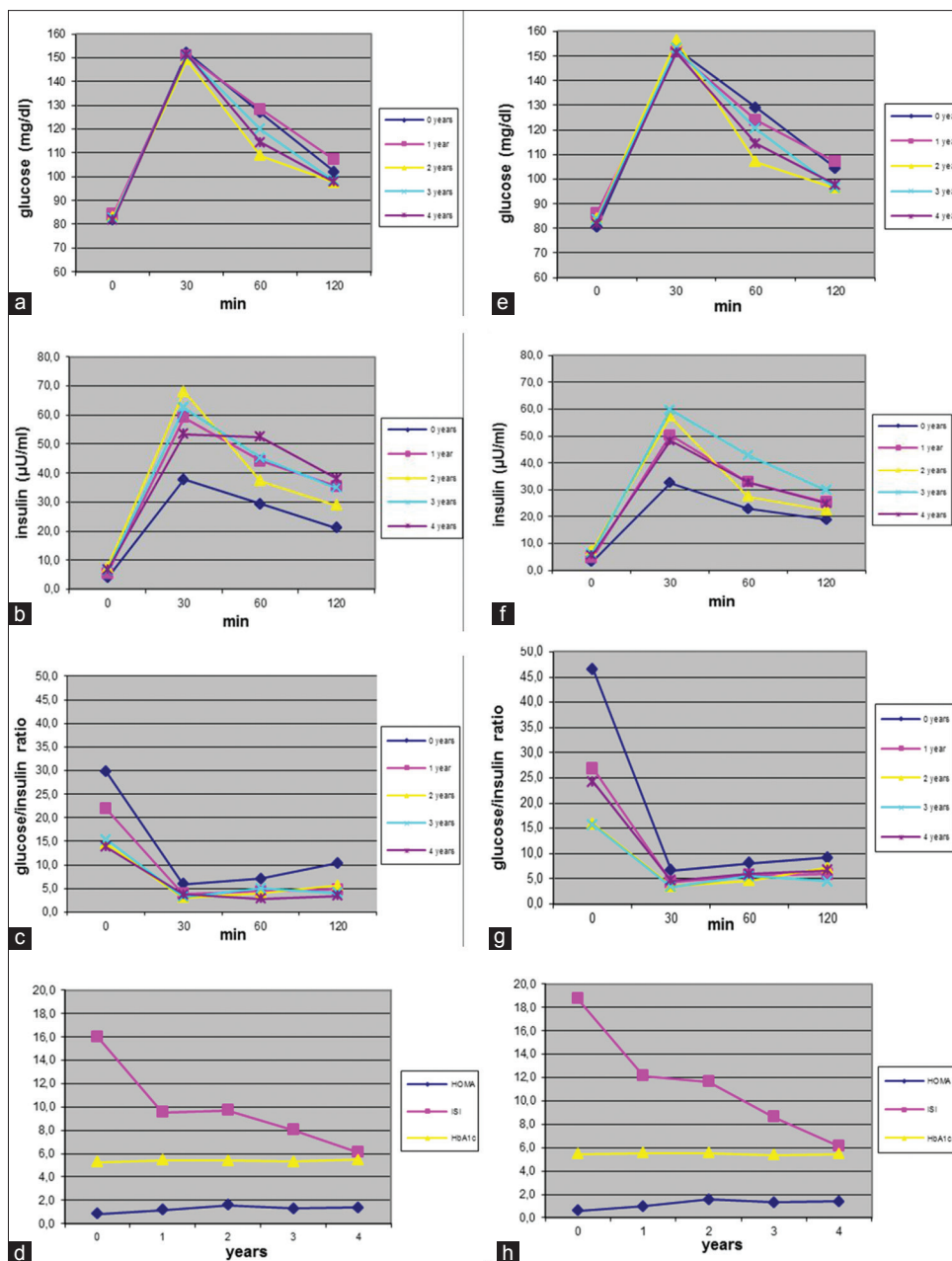


Figure 1: Mean values for (a) and (e) glucose, (b) and (f) insulin, (c) and (g) glucose/insulin-ratio and (d) and (h) HOMA, ISI and HbA1c from baseline to the 4th year of GH-treatment for the whole group of patients (a-d) and the cohort followed for the entire 4 years (e-h)

Pathological oGTT values

In spite of this, in every year there were individual cases with elevated FPG, FPI, IGT, or abnormal indices [Table 3]. There was at least one abnormal parameter during the whole follow up in 41 children. Abnormal values were seen more often in the last prepubertal year (16 of the 34 children whose last prepubertal year was included in the study). Every child in this group had a low ISI, several, but not all of them had an elevated HOMA1- (or QUICKI) index as well.

Correlations with birth, auxologic, and laboratory data

One of our aims was to find out whether the levels of the oGTT parameters were associated with other demographic

(gender, gestational age, age at start of treatment), auxological (including genetic target height), or laboratory data.

Significant correlations were found between gestational age, HOMA1, and ISI at baseline ($r_s + 0.313$ and $- 0.355$) and after 2 years of treatment ($r_s + 0.346$ and $- 0.443$). The same correlations were found for birth length apart from those for HOMA1 after 2 years (r_s for HOMA1 at 0 years $- 0.316$, for ISI at 0 years $+ 0.302$, for ISI at 2 years $+ 0.470$). In addition better ISI and HOMA1 results at baseline were associated with a younger age at the start of treatment at baseline ($r_s + 0.398$ and $- 0.274$) and after the first year ($r_s + 0.447$ and $- 0.431$). After the first year of treatment, ISI also showed slight negative

Table 2: Mean data and SDS for oGTT-results for glucose and insulin, glucose/insulin ratio, HOMA1, HOMA2, QUICKI, ISI and HbA1c for baseline and the individual years of GH-treatment (a) for the entire patient cohort and, (b) for the subgroup followed for the whole 4 years

(a)														
Year	Min	Glucose				Insulin				HOMA1	HOMA2	QUICKI	ISI	HbA1c
		0	30	60	120	0	30	60	120					
0	Mean	81.9	152.1	127	102	4	37.7	29.4	21.1	0.83	0.64	0.43	16.00	5.28
n=93	SDS	9.79	33.2	33.1	25.7	3.8	22.7	21.6	19.2	0.81	0.48	0.08	10.28	0.84
1	Mean	84.1	150.8	128	107.1	5.5	59.2	44.2	35.4	1.18	0.80	0.39	9.56	5.43
n=83	SDS	11.5	33.3	41.2	24.9	3.2	40.9	30.7	28.4	0.75	0.38	0.06	7.71	0.72
2	Mean	83.1	149.1	109	97.4	7.5	68.1	37.3	28.8	1.59	1.03	0.37	9.72	5.38
n=62	SDS	9.0	28.7	30.3	14.3	4.7	39.6	24.6	21.3	1.03	0.58	0.04	6.61	0.77
3	Mean	82.5	150.8	120	98.1	6.2	62.5	45.2	34.8	1.30	0.83	0.38	8.04	5.32
n=49	SDS	8.5	32.8	33.2	20.7	2.6	30.8	32.3	23.9	0.58	0.32	0.03	4.95	0.71
4	Mean	81.8	151.3	114	97.7	6.7	53.5	52.4	38.1	1.38	0.92	0.37	6.10	5.46
n=39	SDS	9.1	32.4	29.1	18	2.5	21.1	27.3	24.5	0.57	0.26	0.04	1.31	0.25
Total	Mean	82.8	151.1	123	102.1	5.7	52.5	37.9	28.8	1.20	0.83	0.39	11.81	5.36
n=93	SDS	9.8	32.2	35.4	23.3	3.8	34.5	27.3	24	0.83	0.45	0.06	8.98	0.73

(b)														
Year	Min	Glucose				Insulin				HOMA	HOMA2	QUICKI	ISI	HbA1c
		0	30	60	120	0	30	60	120					
0	mean	80.8	152.9	129	104.5	3	32.6	22.9	18.8	0.59	0.49	0.45	18.76	5.46
n=39	SDS	10.4	35.1	31.5	24.5	1.5	21.8	15.5	14.9	0.32	0.14	0.09	11.79	0.93
1	mean	86	151.7	124	107.1	4.5	50.3	32.8	25.4	0.98	0.69	0.41	12.14	5.54
n=39	SDS	13.1	31	35.1	24.3	2.4	29.1	21.8	15.9	0.63	0.27	0.06	9.34	0.23
2	mean	83.9	156.2	107	96.2	7.4	57.2	27.5	22.3	1.55	1.00	0.37	11.64	5.54
n=39	SDS	9.8	29.2	31.8	14.8	4.7	32.5	13.7	17.4	1.00	0.56	0.04	7.39	0.96
3	mean	93.6	153.2	121	96.4	6.2	59.8	42.8	29.9	1.32	0.81	0.38	8.63	5.37
n=39	SDS	7.7	33.5	34.9	19.6	2.6	31.7	34	16.8	0.60	0.32	0.03	5.15	0.82
4	mean	81.8	151.3	114	97.7	6.7	53.5	52.4	38.1	1.38	0.92	0.37	6.10	5.46
n=39	SDS	9.1	32.4	29.1	18	2.5	21.1	27.3	24.5	0.57	0.26	0.04	1.31	0.25
Total	mean	83.1	153.1	121	101.8	5.5	48.3	32.6	24.9	1.15	0.50	0.45	12.97	5.47
n=39	SDS	10.3	32	33.2	21.9	3.3	29.1	23.8	17.8	0.72	0.14	0.09	9.86	0.71

Table 3: Number of patients with pathological results for fasting glucose, postprandial glucose, fasting insulin, HOMA1, and insulin at baseline and after every year of treatment

Pathological value	Cut-off	0 years n=93	1 year n=83	2 years n=62	3 years n=49	4 years n=39
Glucose 0 min	>100 mg/dl	4	7	5	4	0
Glucose 120 min	>140 mg/dl	7	3	1	0	0
Insulin 0 min	>10 µU/ml	1	0	2	0	0
HOMA1	>2.5	1	5	8	2	1
ISI	<5.0	3	9	8	5	3

correlations with HV-SDS ($r_s = -0.357$), BMI-SDS ($r_s = -0.322$), and IGF-I-SDS ($r_s = -0.387$), but there were no correlations with any parameters at baseline.

No statistically significant correlations were found for gender, birth weight, genetic target height, H-SDS, HV-SDS, BMI-SDS, and IGF-I-SDS at other times as mentioned.

Analyses to detect predictive parameters

It would be particularly interesting to find out whether any data at the start or after the first year could predict the

development of glucose homeostasis during the later years of treatment. In our collective, we found significant correlations between HOMA1, ISI, and BMI-SDS at baseline and HOMA1 ($r_s + 0.533$, -0.519 , and $+0.436$) and ISI ($r_s - 0.423$, $+0.557$, and -0.592) after 2 years of GH therapy. Gestational age was positively associated with HOMA1 ($r_s + 0.346$) and negatively with ISI ($r_s - 0.443$) after 2 years, birth length positively with ISI after 2 years ($r_s + 0.470$). There were no correlations between baseline or first year data and any of the third and fourth year results.

DISCUSSION

Numerous articles on glucose homeostasis in SGA children treated with GH have been published in recent years, but our study adds several interesting aspects. First of all, although many of the reports in the literature with longer follow-up time started with only prepubertal children, we found almost none that differentiated between patients who remained prepubertal and patients who started puberty during the study period.^[9] However, in our collective we can clearly exclude any influence of the physiological changes in hormone balance in puberty.

Results for oGTT data, HOMA1, and ISI

In line with the findings in all other studies,^[6,9,17,23,37] in our group none of the children developed diabetes. The significant rise of insulin levels in oGTT has also been reported before, but the results differ in detail: some studies find changes in insulin levels only after 6 months^[38] or the first year,^[39,40] others see a continuous rise throughout their follow-up period.^[6,8,41] In our cohort of prepubertal children, apart from fasting values, we could demonstrate a stabilization of insulin levels after the first year of treatment. It is quite probable that onset of puberty is at least one reason for the further deterioration of insulin sensitivity in the studies mentioned above, but a dependence on dose, e.g., must of course also be taken in account.^[8] In line with this, we suspect that the most probable explanation for the better results of the subgroup of children followed up for the whole 4 years is that they were younger at the beginning (5.9 ± 1.4 vs 8.0 ± 2.5 years).

On the other hand, we found an increase of insulin in the fasting state until the second year, but afterwards there was no further change. These findings are quite surprising as this would mean that basal insulin sensitivity worsens for a longer time than that of the postprandial state.

For further analysis of glucose homeostasis it is common to calculate indices of basal and/or postprandial glucose and insulin levels. HOMA1, HOMA2, QUICKI, and ISI are generally accepted parameters for the estimation and surveillance of insulin sensitivity and sufficiently good correlations with the results of hyperinsulinemic clamp techniques, the gold standard, but not a useful method for clinical practice, have been shown.^[28,36,42-44] In our cohort, ISI showed a continuous decrease until the fourth year, but – consistent with the insulin values – only the difference between baseline and the first year was statistically significant. Correlating with the findings for fasting insulin, the indices for fasting insulin sensitivity (HOMA1, HOMA2, and QUICKI) increased significantly until the second year of treatment and remained stable thereafter. On the other hand, according to our results and as has also been stated before,^[41,45] ISI seems to be more sensitive than the above mentioned indices for fasting insulin sensitivity as it detects impaired insulin sensitivity in more patients. But the use of ISI as a single parameter to detect impaired insulin sensitivity could also be questioned: the 30-min-values for glucose and insulin (not part of ISI) are the highest in every year. The relevance of this increase has

never been studied. Taking all together, it can be stated that in our study the means for the three indices for fasting insulin sensitivity and ISI never reached pathological levels.

Individual pathologic oGTT results

As a consequence we decided, for the first time, to take a closer look at the single individuals with values for FPG, IGT, FPI, HOMA1, and ISI considered abnormal according to study criteria. The finding of abnormal results for at least one of the analyzed criteria in almost half of our children seems to be in contrast with the normal mean values. This can be explained by the fact that most patients showed just one abnormal parameter and only in 1 year, which means that they returned to normal at the following control. Only 12 children (12.9%) showed abnormal results in 2 years and a single one in 3 years. It is therefore questionable if these temporary changes are relevant. Like others,^[38,39,40] we are also unable to detect a tendency to deterioration with a longer period of GH treatment. However, puberty might have an influence, as a relatively large number of abnormal values were found in the individual last prepubertal year of these children. It was also interesting that relatively more of the children with abnormal results were born at term, while even for the children with more than one abnormal parameter no differences for gender or any other of the analyzed auxological or laboratory parameters (see “Materials and Methods”) were found.

Correlations with birth, auxologic, and laboratory data

Birth data seem in fact to be the parameters with at least some influence on glucose homeostasis. According to the correlations, we found it was not the small and low-weight early-preterm children but those born at or near term with smaller birth length who showed a higher frequency of abnormal values and higher levels of insulin resistance calculated by HOMA1 as well as ISI at baseline as well as after stabilization of glucose homeostasis after the start of GH treatment. So, if there is actually a group that should be monitored more closely it is those who might have a risk of more severe deterioration possibly with at least single individuals who really reach pathological glucose tolerance, perhaps during further GH therapy in puberty. It was interesting that there were correlations between glucose homeostasis and birth length, but not birth weight. It might therefore be asked whether prenatal growth factors like IGF-II and others have an influence on insulin secretion in later life. In their study on SGA children with and without spontaneous catch-up growth, Soto *et al.*^[22] reported an association between fasting insulin sensitivity and rapid weight gain and between postprandial insulin secretion and rapid increase in length. Although we did not see the former development in the GH-treated SGA children, this might suggest to a similar etiology, possibly involving prenatal influences on other growth factors, e.g., IGF-II. Our findings from our collective that glucose homeostasis parameters were not associated with birth weight, but with age at the start of therapy, as we could see in our collective, was also described e.g., by Gies *et al.*^[39] and Martin *et al.*^[46] On the other hand, we could not detect relevant correlations, e.g., IGF-I-SDS, height gain, or

BMI-SDS as described by others^[39,40,41,47] and it has to be said that all the associations we found were, although significant, rather weak. Despite the general higher frequency for elevated androgens seen in SGA children, there were no correlations between these laboratory and birth data in our collective either. It is also worth noting that all the children in our collective were lean at the start and showed a rise in BMI-SDS during treatment, but not one of them developed obesity apart from one boy who was already obese at the start due to a strong family disposition.

Analyses to detect predictive parameters

As we identified no group of children with clearly pathological insulin sensitivity, we additionally tried to find factors that could predict insulin sensitivity in subsequent years of GH therapy. As already mentioned, there was an association between gestational age and birth length and insulin tolerance not only at baseline, but also after 2 years of treatment. Moreover, the children with lower insulin sensitivity before the start of treatment also had a higher insulin resistance after 2 years. However, predictions for subsequent years of GH treatment from baseline parameters were not possible and the deteriorated parameters for insulin sensitivity after the first year of GH therapy also provided no information on their further development.

CONCLUSION

In conclusion, in our collective of exclusively prepubertal children we could demonstrate an increase in insulin resistance after the start of GH therapy, but throughout the surveillance period the values for insulin and the calculated indices did not reach pathological levels. Although there were abnormal results in many children, they usually normalized in the following year and, as reported in all former studies, no case of diabetes mellitus developed. Apart from a possible higher risk for disturbed glucose homeostasis in SGA children with higher gestational age and lower birth length, we could not detect significant correlations with any of the other analyzed parameters or any other predictive factors. In all the studies we found no reports on consequences on GH treatment (e.g., withdrawal, lowering of dose) because of insulin resistance.

Thus, regarding our results, a baseline-oGTT before starting GH therapy in SGA children is of course indicated in order to exclude pre-existing glucose tolerance abnormalities. From a scientific point of view it could be worth performing an oGTT with calculation of ISI after the first year as well as HOMA or QUICKI after the second year of treatment for follow-up in the individual child. Of further interest could be to evaluate the 30-min insulin levels, i.e., the maxima of insulin secretion. At the onset of puberty, however, further monitoring should be mandatory because of the increase of insulin resistance already seen physiologically in all children and it will be interesting to follow up our collective of patients during this period. A comparison of data from the last

prepubertal year with those of puberty should be included. But our results demonstrate that in the prepubertal age group the monitoring of glucose homeostasis in the now recommended frequency of once a year does not show any clinically relevant changes. Therefore, the current recommendations regarding surveillance of glucose homeostasis in GH-treated SGA children are questionable.

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Conflicts of interest

There are no conflicts of interest.

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