Efficacy of Growth Hormone Treatment in Children with Type 1 Diabetes Mellitus and Growth Hormone Deficiency—An Analysis of KIGS Data

Walter Bonfig, MD[1,2], Anders Lindberg[3], Martin Carlsson[3], Wayne Cutfield, MD, PhD[4], David Dunger, MD, PhD[5], Cecilia Camacho-Hübner, MD, PhD[6], and Reinhard W. Holl, MD, PhD[7,8]

Objective To analyze first-year treatment growth response and growth hormone (GH) dosage in prepubertal patients with the combination of type 1 diabetes mellitus (T1DM) and growth hormone deficiency (GHD).

Study design A total of 69 patients with T1DM and GHD treated with GH have been enrolled in KIGS (Pfizer International Growth Database). Of these, 24 prepubertal patients had developed T1DM before GHD and were included in this analysis. Of 30 570 patients with GHD without T1DM, 15 024 were prepubertal and served as controls. Values are expressed as mean ± SD.

Results Patients with T1DM and GHD had similar characteristics compared with the GHD-alone group. Neither age (10.2 ± 3.13 vs 8.42 ± 3.46 years, $P = .14$), height SDS corrected for midparental height SDS at start of treatment (–1.62 ± 1.38 vs –1.61 ± 1.51, $P = .80$), nor GH dosage (0.24 ± 0.08 mg/kg/wk vs 0.20 ± 0.04 mg/kg/wk, $P = .09$) were different between those with and without T1DM. First-year catch-up growth was comparable between the 2 patient groups (first treatment year height velocity 7.54 ± 3.11 cm/year compared with 8.35 ± 2.54 cm/year in control patients, $P = .38$). Height SDS of children with T1DM and GHD improved from –2.62 ± 1.04 to –1.88 ± 1.11 over 1 year of GH treatment.

Conclusion Short-term response to GH therapy appeared similar in subjects with T1DM who then developed GHD and in those with GHD alone. Thus, T1DM does not appear to compromise GH response in children with GHD and should not exclude GH treatment in these children. GH treatment was safe in both subgroups of patients. *(J Pediatr 2018;■■:■■-■■).*

With current criteria, the prevalence of growth hormone deficiency (GHD) is between 1:3500 and 1:8700.[1] GHD already may be present in neonates, if caused by genetic disorders, but the average age at diagnosis is 6-8 years.[1] Although rare, it is important to establish early diagnosis of GHD, as a missed or very late diagnosis may result in a poor height outcome. In most cases, GHD represents a relative lack of growth hormone (GH) secretion, leading to decreased growth velocity, retardation of bone maturation, and short stature. GH also plays an important role in glucose, lipid, and protein metabolism.[2]

Both GHD and GH excess are associated with disturbances of carbohydrate metabolism. GH decreases glucose oxidation and glucose uptake by muscle and increases gluconeogenesis, resulting in "insulin antagonist effects."[3] The growth-promoting effects of GH are mediated through the insulin-like growth factors (mainly insulin-like growth factor-I [IGF-I]), which are synthesized and secreted by the liver, as well as in target tissues. Insulin-like growth factors are bound to insulin-like growth factor binding proteins, with insulin-like growth factor-binding protein 3 (IGFBP-3) being the major one. IGF-I, IGFBP-3, and the acid labile subunit form a ternary complex extending the half-life of IGF-I.[3] Adequate insulin secretion and portal insulin concentrations are needed to support normal serum concentrations of IGFs and IGFBPs, because insulin modulates hepatic GH receptor expression. Portal insulin deficiency leads to GH hypersecretion. Despite GH hypersecretion, circulating concentrations of IGF-I and IGFBP-3 are low, and concentrations of insulin-like growth factor-binding protein 1—a major negative regulator of IGF-I bioactivity—is high in the state of insulin deficiency.[3]

The incidence of type 1 diabetes mellitus (T1DM) is increasing, especially in children aged <5 years.[4] Early-diabetes onset and mean hemoglobin A1c >7.0% (>53 mmol/mol) correlate negatively with adult height.[5] Therefore, workup of short

AE	Adverse event
DPV	Diabetes Prospektive Verlaufsdokumentation
GH	Growth hormone
GHD	Growth hormone deficiency
IGFBP-3	Insulin-like growth factor-binding protein 3
IGF-I	Insulin-like growth factor-I
SAE	Serious adverse event
T1DM	Type 1 diabetes mellitus

From the [1]Department of Pediatrics, Klinikum Wels-Grieskirchen, Wels, Austria; [2]Department of Pediatrics, Technical University München, Munich, Germany; [3]Pfizer Health AB, Sollentuna, Sweden; [4]Liggins Institute, University of Auckland, Auckland, New Zealand; [5]Department of Pediatrics and the Wellcome Trust-MRC Institute of Metabolic Science, University of Cambridge, Cambridge, United Kingdom; [6]Pfizer Inc, Endocrine Care, New York, NY; [7]Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm; and [8]German Center for Diabetes Research (DZD), Munich-Neuherberg, Germany

W.C. received consultancy fees from Pfizer and is a member of the KIGS Steering Committee (SC). D.D. was a former member of the KIGS SC. A.L, M.C., and C.C.H. are employees of Pfizer. The other authors declare no conflicts of interest.

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stature and diagnosis of GH deficiency in children with diabetes might become more frequent in the future. Very few data regarding GH treatment in children who are GH deficient with T1DM have been published.[6,7] In a previous study, we showed that GH treatment is safe if the insulin dosage is adjusted accordingly.[6] In that study, decreased efficacy of GH treatment was observed; no data on GH dosage and IGF-I concentrations were available. Therefore, our aim was to analyze first-year treatment growth response and GH dosage in prepubertal patients with T1DM and GHD and to compare these data with a large control cohort within the KIGS database (Pfizer International Growth Database).

Methods

Patient data were retrieved from KIGS (Pfizer International Growth Database). KIGS is a worldwide observational registry established in 1987 to monitor the outcome and safety of treatment with GH (Genotropin; Pfizer Inc, New York, New York). It is conducted in accordance with the Declaration of Helsinki. Patients enrolled in KIGS are classified according to the primary cause of short stature.[8] Data collection and entry were performed by KIGS investigators. In this study, children with T1DM who then developed idiopathic GHD were compared with those with GHD alone during the first year of treatment. GHD was defined as a peak stimulated GH level <10 μg/L. All subjects were prepubertal with Tanner breast stage B1 in girls and testes volume ≤3 mL in boys during the first year of GH therapy.

In total, 69 patients with T1DM and idiopathic GH deficiency treated with GH are documented in KIGS. Of these 24, developed T1DM before GHD and were prepubertal during the first year of GH treatment and were included for analysis. Of 30 570 control patients with the diagnosis of GHD, 15 934 were prepubertal and served as controls. Of these, 13 010 control patients (80.5%) had isolated GHD and 2924 control patients (19.5%) had multiple pituitary hormone deficiency. Because treatment and control groups significantly differed in birth weight SDS, height, and weight SDS at start of treatment (**Table I**), we also performed a matched-pairs analysis. A propensity score–matched cohort of patients with T1DM and GHD and GHD alone was created by using 5 variables collected at start of GH therapy (height SDS, weight SDS, age, body mass index SDS, and start of GH therapy) to achieve matching balance between the 2 cohorts. Then, 1:2 matching was applied (2 controls per case) to minimize the selection bias and to increase the number of subjects in the control group from 24 to 48.

To include as many patients with T1DM and GHD in the analysis, a second matched-pairs analysis was performed also including pubertal patients. Therefore, matching for pubertal status, GH peak, and midparental height SDS became necessary to achieve balanced matched populations. Complete matching confounder covariates were available in 45 patients with T1DM and GHD. Of these 45 matched patients, 1-year data were available in 33 subjects. Quality of diabetes control was not assessed in this analysis because of insufficient longitudinal data on hemoglobin A1c in both groups.

Standing height was measured approximately 6 monthly with a wall-mounted stadiometer. Height SDS was calculated by using reference data from Prader et al.[9] GH dosage was calculated as milligram per kilogram of body weight per week (mg/kg/wk).

Statistical analyses (descriptive data analysis, calculation of SDS, and Wilcoxon rank-sum test) were carried out with SAS software (SAS, Version 9.2; SAS Institute, Cary, North Carolina). A 2-sided significance level of 5% was applied to all statistical tests. Growth velocity data were adjusted for age and sex. Values are expressed as mean with SDs unless otherwise stated.

Table I. Clinical characteristics and response to the first year of GH treatment in treatment and control group.

	T1DM and GHD			GHD only			
Variables	**n**	**Median**	**Mean ± SD**	**n**	**Median**	**Mean ± SD**	***P***
Background							
Birth weight SDS	19	0.06	−0.02 ± 1.15	13 582	−0.80	−0.81 ± 1.23	.003
MPH SDS	19	−0.23	−0.96 ± 1.32	14 127	−1.40	−1.36 ± 1.24	.111
Max GH peak, μg/L	22	6.93	6.80 ± 3.22	15 024	6.10	5.75 ± 2.75	.208
Start of GH therapy							
Chronological age, y	24	10.20	9.39 ± 3.13	15 024	8.42	8.40 ± 3.46	.144
Height SDS	24	−2.62	−2.58 ± 1.04	15 024	−3.01	−3.13 ± 1.15	.032
Height—MPH SDS	19	−1.62	−1.59 ± 1.38	14 127	−1.61	−1.76 ± 1.51	.802
Weight SDS	24	−1.55	−1.45 ± 1.22	15 024	−2.18	−2.25 ± 1.47	.006
BMI SDS	24	0.04	0.13 ± 1.09	15 024	−0.32	−0.32 ± 1.27	.084
GH dose, mg/kg/wk	24	0.24	0.23 ± 0.08	15 024	0.20	0.22 ± 0.07	.089
1 y on GH therapy							
Height velocity, cm/y	24	7.54	8.16 ± 3.11	15 024	8.35	8.67 ± 2.54	.375
Height SDS	24	−1.88	−1.90 ± 1.11	15 024	−2.30	−2.36 ± 1.10	.058
Delta height SDS	24	0.57	0.70 ± 0.55	15 024	0.69	0.78 ± 0.51	.381
Weight SDS	24	−1.06	−1.01 ± 1.27	14 935	−1.69	−1.73 ± 1.35	.017
BMI SDS	24	−0.05	0.11 ± 1.14	14 935	−0.40	−0.39 ± 1.21	.077
GH dose, mg/kg/wk	24	0.23	0.24 ± 0.08	15 024	0.20	0.21 ± 0.07	.041

BMI, body mass index; *MPH*, midparental height.

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