Prevalence and Incidence of Diabetes Mellitus in GH-Treated Children and Adolescents: Analysis from the GeNeSIS Observational Research Program

Christopher J. Child, Alan G. Zimmermann, Robin S. Scott, Gordon B. Cutler, Jr., Tadej Battelino, and Werner F. Blum on behalf of the GeNeSIS International Advisory Board

Lilly Research Laboratories (C.J.C.), Erl Wood Manor, Windlesham GU20 6PH, United Kingdom; Lilly Research Laboratories (A.G.Z., R.S.S., G.B.C.), Indianapolis, Indiana 46285; Department of Pediatric Endocrinology, Diabetes, and Metabolism (T.B.), University Medical Centre–University Children's Hospital and Faculty of Medicine, Ljubljana, SI-1000, Slovenia; and Lilly Deutschland GmbH (W.F.B.), 61352 Bad Homburg, Germany

Background: GH has an insulin antagonist effect, and GH treatment has therefore been suggested to impair glucose metabolism and increase risk of diabetes mellitus.

Setting: Data from 11,686 GH-treated patients in the Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS), a multinational observational study of children with growth disorders, were analyzed for diabetes incidence. Baseline diabetes prevalence was determined from a GH-naive subgroup.

Methods: Prevalence and incidence (by standardized incidence ratio) were compared with results from patients aged less than 20 yr in the U.S. SEARCH for Diabetes in Youth study.

Results: Baseline type 1 diabetes prevalence per 1000 persons was 4.92 (95% confidence interval = 1.91–12.58) in GeNeSIS and 1.03 (0.97–1.10) in SEARCH for 0- to 9-yr-olds, and 7.33 (4.20–12.77) and 2.99 (2.78–2.98), respectively, for 10- to 19-yr-olds; there were no GeNeSIS cases of type 2 diabetes before GH initiation. During a median 1.8 yr of GH treatment, diabetes standardized incidence ratios for U.S. patients were 1.4 (0.5–3.1) for type 1 and 8.5 (2.8–19.5) for type 2, and for all patients was 1.4 (0.7–2.4) for type 1 and 6.5 (3.3–11.7) for type 2. Among the 11 patients with incident type 2 diabetes, risk factors for diabetes were identified in 10 patients. Glucose concentrations normalized for seven of nine patients for whom glycemic status could be determined (three of whom continued GH therapy and four who discontinued).

Conclusion: The incidence of type 2 diabetes was higher in GH-treated children than the general population. Monitoring of glucose, before and periodically during GH treatment, is recommended for those with preexisting type 2 diabetes risk factors. **(*J Clin Endocrinol Metab* 96: E1025–E1034, 2011)**

Growth hormone is a glucose counterregulatory hormone that can contribute to insulin resistance when administered exogenously (1–5). This GH action has raised concern regarding the effects of GH treatment on glucose homeostasis and risk of type 2 diabetes mellitus. Although the incidence of type 2 diabetes is generally low in childhood and has not been well defined in children with growth disorders, incident cases of type 2 diabetes have been reported in observational studies of GH-treated children (5–7). In 2000, Cutfield and colleagues (5) demonstrated an increased incidence of type 2 diabetes in GH-treated children relative to reference data available at the

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2010-3023 Received December 27, 2010. Accepted March 21, 2011.
First Published Online April 13, 2011

Abbreviations: BMI, Body mass index; CI, confidence interval; GeNeSIS, Genetics and Neuroendocrinology of Short Stature International Study; GHD, GH deficiency; ISS, idiopathic short stature; Q, quartile; SDS, SD score; SGA, small for gestational age; SIR, standardized incidence ratio.

TABLE 1. Baseline demographics (before GH treatment) and GH dose, duration, and person-years of treatment in study populations from GeNeSIS and Cutfield *et al.* (5)

	All countries GeNeSIS[a]	U.S. GeNeSIS	Cutfield *et al.* (5)
n	11,686	5,591	23,333
Age (yr), median (Q1, Q3)	10.2 (6.5, 12.7)	10.9 (7.4, 13.3)	10.3 (7.1, 12.7)
Males/females (%)	60/40	66/34	58/42
Diagnosis [n (%)]			
GHD	7,523 (64.4)	2,909 (52.0)	14,092 (60.4)
ISS	1,600 (13.7)	1,513 (27.1)	3,483 (15)
Turner syndrome	1,135 (9.7)	486 (8.7)	3,800 (13)
SGA	459 (3.9)	155 (2.8)	
Others	969 (8.3)	528 (9.4)	2,835 (12.2)[b]
GH treatment			
Median (Q1, Q3) start dose (mg/kg · wk)	0.27 (0.19, 0.33)	0.31 (0.29, 0.37)	0.19 (0.16, 0.23)
Median (Q1, Q3) GH duration (years)	2.5 (1.3, 4.3)	2.3 (1.2, 3.9)	2.9 (1.5, 4.7)
Person-years	37,562	16,573	52,375

[a] Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, India, Italy, Japan, Kazakhstan, Lithuania, Norway, Pakistan, Russia, Singapore, Slovak Republic, South Africa, Spain, Sweden, Taiwan, Thailand, The Netherlands, United Kingdom, and United States.

[b] Potentially includes patients born SGA.

time (8). A more recent analysis of the same database (6), which did not separate cases of type 1 and type 2 diabetes, showed diabetes incidence ranging from 11–315 cases per 100,000 treatment-years, depending upon etiology of the growth impairment.

The increased incidence for type 2 diabetes in GH-treated children and adolescents, as reported by Cutfield and colleagues (5), has not been confirmed. Moreover, the rising prevalence of obesity in the general pediatric population during this period (9, 10), and the trend toward higher GH doses, might interact to alter the relative risk of impaired glucose homeostasis during GH treatment. Therefore, we analyzed the incidence of diabetes in GH-treated children from the Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS) observational database, compared with a contemporary population assessment of diabetes incidence in the United States (9). Because reference data matching the age range of our cohort were incomplete for countries other than the United States (11–14), our primary focus for this analysis was the incidence of diabetes in U.S. GeNeSIS patients.

Subjects and Methods

Study population

GeNeSIS is an open-label, multinational, observational, post-authorization safety study sponsored by Eli Lilly and Co. (Indianapolis, IN). The study collects information on clinical management and treatment outcomes of patients with growth disorders as documented by the attending clinician during standard endocrine practice. Pediatric patients who are receiving or who will start therapy with Humatrope (GH, somatropin; Eli Lilly) for treatment of a growth disorder or hypothalamic-pituitary dysfunction may enroll in GeNeSIS; once enrolled, investigators are encouraged to continue patients in the study regardless of changes in brand or discontinuation of GH therapy. Non-GH-treated patients are also followed in GeNeSIS for a subset of growth disorders. Because of the small sample size relative to treated patients, non-GH-treated patients were not included in the analysis for this report.

The GeNeSIS program is conducted in accordance with the guidelines in the Declaration of Helsinki. Institutional review board approval was obtained, and all applicable regulatory requirements in the participating countries (Table 1) were followed. Patients' parents (or guardians) provided written consent for data collection, electronic processing, and publication, in accordance with national requirements. The study protocol requires that investigators report all adverse events in participating patients, irrespective of whether a causal relationship with GH treatment is suspected.

As of September 2007 (the cutoff date for this analysis), 11,686 GH-treated patients (5,591 in the United States) had at least one follow-up visit in the database, contributing over 37,000 person-years of therapy (over 16,000 in the United States). These 11,686 patients were used to calculate diabetes mellitus incidence, taking into account any reported period of GH therapy before enrollment in GeNeSIS. Baseline diabetes prevalence was evaluated from a cohort of 8568 patients (3368 in the United States) who were GH-naive at study entry because reporting of preexisting conditions was expected to be most accurate for this cohort.

Demographic factors at the start of GH therapy and details of GH treatment are provided in Table 1, for U.S. and combined global patients in GeNeSIS, with comparison with patients studied by Cutfield *et al.* (5). GH deficiency (GHD) was the reported cause of growth impairment in 64% of patients, idiopathic short stature (ISS) in 14%, and Turner syndrome in 10%; other conditions, including small for gestational age (SGA), Prader-Willi syndrome and chronic renal insufficiency were reported for the remaining 12% of patients.

Case identification for diabetes and abnormal glucose tolerance

Cases potentially associated with abnormal glucose metabolism from GH-treated patients, with at least one follow-up visit available, were initially identified from the GeNeSIS database using any of the following: 1) preexisting condition or adverse event reports potentially associated with diabetes or abnormal glucose tolerance, 2) medications generally associated with treatment of diabetes or abnormal glucose tolerance, and 3) a specific case report form checkbox indicating the diagnosis of diabetes. For the purposes of this report, abnormal glucose tolerance refers to diagnoses of impaired glucose tolerance and/or impaired fasting glucose. A listing of event terms and concomitant medications that qualified for this initial, potential case identification is presented in Supplemental Table 1 (published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). In addition, reports of serious adverse events received by Lilly's pharmacovigilance department were cross-referenced against the GeNeSIS database to maximize inclusion of potential cases. After this initial identification, a questionnaire was sent to the responsible clinician to gather additional information on glucose metabolism and diabetes, to clarify diagnoses, and to ascertain pre-GH-treatment risk factors. Cases of diabetes and abnormal glucose tolerance were assigned according to questionnaire responses, existing study data, and serious adverse event reports and, when appropriate laboratory data were reported by the investigator, were assessed against standard diagnostic criteria (15).

Analyses and statistical methods

Prevalences of type 1 and type 2 diabetes at initiation of GH therapy were compared with data from a reference population of physician-diagnosed cases of diabetes in patients aged 0–19 yr in the SEARCH for Diabetes in Youth Study (10). Confidence intervals (CI) for GeNeSIS results were calculated in the same manner as in SEARCH, using an inverted score test from the binomial distribution (16).

Diabetes incidence rates for patients in GeNeSIS were compared using standardized incidence ratios (SIR) to the rates reported in the United States from the SEARCH study (9). Although SEARCH is not representative of the entire U.S. population, it provides the best reference population of which we are aware for U.S. patients and provides a finer stratification of ages than reference data on diabetes incidence in pediatric populations in countries outside of the United States (11–14). We also compared rates for the entire database (all countries) to the U.S.-specific rates from SEARCH.

The characteristics of patients with incident (GH treatment-emergent) cases of type 1 diabetes, type 2 diabetes, or abnormal glucose tolerance and patients without such events were summarized by simple descriptive statistics. Comparisons were conducted between patients without such events and each of the three groups, using Fisher's exact test for gender, and median test for continuous measures. *P* values were considered significant at a two-sided significance level of 0.05.

The observed number of diabetes cases was assumed to follow a Poisson distribution, and exact two-sided 95% CI were calculated (17). SIR for type 1 and type 2 diabetes were calculated as the ratio between cases observed in GeNeSIS and expected number of cases based on incidence reported in the SEARCH reference population, stratified by age, gender, and ethnicity (17). The SEARCH database provides incidence by age group (0–4, 5–9, 10–14, and 15–19 yr), and race/ethnicity (non-Hispanic White, African-American, Hispanic, Asian/Pacific Islander, and American Indian). Race/ethnicity was recorded in GeNeSIS in six categories as Caucasian, African descent, Hispanic, East/Southeast Asian, Western Asian, or other. Person-years in GeNeSIS categories of East/Southeast Asian and Western Asian were combined and compared with Asian/Pacific Islander rates in calculation of expected number of diabetes cases. Similarly, person-years in GeNeSIS category Caucasian were compared with non-Hispanic White in SEARCH, and the GeNeSIS other category was matched to the overall SEARCH rate by age group. Additionally, when race/ethnicity was missing or not recorded, which was the case for many European countries in GeNeSIS, these person-years were compared with SEARCH overall rates. Follow-up time was calculated for each patient from the date of GH therapy initiation (either before enrolling in GeNeSIS for previously treated patients or after starting GeNeSIS participation for GH-naive patients) until the date of last available follow-up visit. All analyses were performed using SAS software (version 9.1; SAS Institute Inc., Cary, NC).

Results

Ascertainment of cases of diabetes and of abnormal glucose tolerance

From the review of cases potentially associated with diabetes or abnormal glucose tolerance, 124 GH-treated patients were identified and questionnaires sent to their attending clinicians. From the GeNeSIS database and questionnaire responses, 58 cases with a potential abnormality of glucose metabolism were determined to be preexisting at initiation of GH therapy, and 66 were incident cases (Fig. 1). Among the 66 incident cases, 27 were diagnosed as diabetes (12 type 1, 11 type 2, and four other). Nine of the 11 type 2 diabetes cases had laboratory confirmation according to standard criteria (15); for example, laboratory confirmation included respective glycosylated hemoglobin levels of 6.7, 6.8 (two patients), 7.3, and 10.7% for five patients and respective 2-h postglucose load oral glucose tolerance test glucose levels of 207 mg/dl (11.5 mmol/liter), 219 mg/dl (12.2 mmol/liter), 272 mg/dl (15.1 mmol/liter), and 406 mg/dl (22.6 mmol/liter) for the remaining four of nine cases. The remaining two of 11 type 2 diabetes cases had a clinical diagnosis and were receiving metformin. Because the GeNeSIS database does not contain data on immunological and human leukocyte antigen evidence of type 1 diabetes, data on risk factors and diagnostic findings for type 1 diabetes cases are not presented in this report.

Among the remaining 39 incident cases were 13 with abnormal glucose tolerance [11 with impaired glucose tolerance (with confirmatory test values for seven patients) (15) and two with impaired fasting glucose (with laboratory confirmation in one patient)], and 13 with insulin

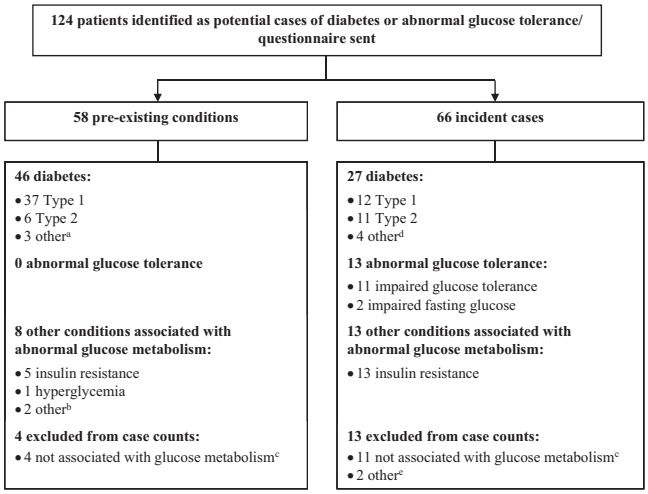

FIG. 1. Potential cases of impaired glucose metabolism identified from 11,686 patients enrolled in GeNeSIS: a, One case of cystic fibrosis-related diabetes and two for whom type of diabetes is unknown; b, impaired fasting insulin (investigator-given diagnosis); c, includes misreported cases of diabetes insipidus and data entry errors; d, cases of diabetes in association with sideroblastic anemia (n = 1; subsequent death due to diabetic ketoacidosis), mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like symptoms (MELAS; n = 2), and cystic fibrosis (n = 1); e, one case of transient pancreatic insufficiency secondary to pancreatic surgery for tumor resection and one case of unknown glucose metabolism status (also excluded from person-years calculation of GH exposure calculation).

resistance; 13 patients were excluded as having diabetes, abnormal glucose tolerance, or insulin resistance (Fig. 1).

Patients who developed type 1 diabetes appeared somewhat younger at initiation of GH, received a somewhat greater initial GH dose, had lower body mass index (BMI), and were not as short as those with type 2 diabetes or abnormal glucose tolerance; however, comparative statistics between groups were not performed because of small sample sizes. Gender distribution, age at start of GH therapy, baseline height SD score (SDS), and the initial dose of GH did not differ significantly for the groups who had type 1 diabetes, type 2 diabetes, or abnormal glucose tolerance *vs.* the group with no recorded diabetes or abnormal glucose tolerance (Table 2). Median [first quartile (Q1), Q3] BMI SDS at start of GH treatment was elevated in patients who developed type 2 diabetes [1.5 (−0.1, 2.4)] compared with patients for whom no abnormality was reported [−0.3 (−1.3, 0.6)]. However, only three of the 11 patients with incident type 2 diabetes were reported as being obese (BMI SDS > +2) by the investigator.

Prevalence of diabetes before GH treatment

U.S. GeNeSIS patients were predominantly (>70%) non-Hispanic White. Prevalence of type 1 and type 2 diabetes according to each race/ethnic group are provided in Supplemental Tables 2 and 3 for the SEARCH and GeNeSIS (8568 GH-naive patients at enrollment) data, using the same 0- to 9-yr and 10- to 19-yr age categories.

Table 3, which provides prevalence data for the non-Hispanic White subset of U.S. patients, demonstrates a higher prevalence of type 1 diabetes in GeNeSIS than in SEARCH. For type 1 diabetes in the 0–9 yr group, estimated prevalence (95% CI) per 1,000 persons was 4.92 (1.91–12.58) in GeNeSIS compared with 1.03 (0.97–1.10) in SEARCH and, in the 10–19 yr age group, was 7.33 (4.20–12.77) compared with 2.88 (2.78–2.98). For type 2 diabetes, there were no U.S. GeNeSIS cases before treatment.

Incidence of diabetes

In the overall incidence population (n = 11,686), the median (Q1, Q3) period of follow-up was 1.8 (0.9, 3.1)

TABLE 2. Comparison of baseline growth data, initial GH dose and treatment duration, and age and pubertal status at onset for GH-treated patients with incident type 1 diabetes mellitus (T1DM), T2DM, abnormal glucose tolerance (AGT), or without reported DM or AGT

	T1DM (n = 12[a])	T2DM (n = 11[a])	AGT (n = 13[a])	No DM or AGT (n = 11,646[a])
Age at GH start (yr), median (Q1, Q3)	8.7 (4.1, 13.0)	12.4 (9.0, 14.7)	10.5 (7.1, 13.4)	10.2 (6.5, 12.7)
Male/female (%)	50/50	55/45	46/54	60/40
BA − CA (yr)	−1.0 (−1.6, −0.4)	−2.4 (−4.2, −1.7)	−1.5 (−2.6, 0.1)	−1.7 (−2.6, −0.8)
Height SDS	−1.3 (−2.4, −1.0)	−2.5 (−3.3, −0.9)	−3.1 (−3.1, −2.4)	−2.5 (−3.0, −2.0)
Max GH Peak (μg/liter)[b]	2.9 (1.0, 6.9)	3.2 (0.2, 3.7)	7.3 (1.2, 12.7)	6.3 (3.2, 9.3)
BMI SDS at GH start	−1.0 (−2.0, −0.3)	1.5 (−0.1, 2.4)[c]	1.2 (−1.3, 2.4)	−0.3 (−1.3, 0.6)
Age at event onset (yr)	13.6 (9.8, 15.4)	15.3 (12.3, 17.4)	13.5 (13.2, 14.7)	
Pubertal at event onset	5 yes, 3 no, 4 Unk	7 yes, 3 no, 1 Unk	9 yes, 2 no, 2 Unk	
Initial GH dose (mg/kg · wk)	0.30 (0.18, 0.36)	0.22 (0.16, 0.32)	0.23 (0.18, 0.28)	0.27 (0.19, 0.33)
Duration of GH at onset (yr)	1.9 (0.6, 5.9)	2.5 (1.1, 2.9)	3.6 (1.5, 4.3)	

BA, Bone age (Greulich-Pyle); CA, chronological age; Unk, unknown.

[a] Fewer for some measures.

[b] Patients with GHD diagnosis.

[c] $P < 0.05$ for comparison with no DM or AGT.

TABLE 3. Type 1 and type 2 diabetes prevalence (per 1000 persons) in comparison with SEARCH (10), overall and by primary diagnostic category, in the non-Hispanic White (Caucasian) subset of U.S. GeNeSIS patients who were naive to GH at study entry

	SEARCH		GeNeSIS				
	Prevalence	CI	Diagnosis	n	Cases	Prevalence	CI
T1DM							
Age 0–9 yr	1.03	0.97–1.10	All	813	4	4.92	1.91–12.58
			GHD	371	1	2.70	0.48–15.11
			ISS	229	3	13.10	4.47–37.80
			TS	80	0	0.00	0.00–45.82
Age 10–19 yr	2.88	2.78–2.98	All	1637	12[a]	7.33	4.20–12.77
			GHD	764	6	7.85	3.60–17.03
			ISS	633	4	6.32	2.46–16.13
			TS	77	0	0.00	0.00–47.52
T2DM							
Age 0–9 yr	0	0.00–0.01	All	813	0	0.00	0.00–4.70
			GHD	371	0	0.00	0.00–10.25
			ISS	229	0	0.00	0.00–16.50
			TS	80	0	0.00	0.00–45.82
Age 10–19 yr	0.19	0.16–0.21	All	1637	0	0.00	0.00–2.34
			GHD	764	0	0.00	0.00–5.00
			ISS	633	0	0.00	0.00–6.03
			TS	77	0	0.00	0.00–47.52

T1DM, Type 1 diabetes mellitus; TS, Turner syndrome.

[a] Includes cases from diagnostic categories not listed in the table.

years; median age at onset of GH treatment was 10.2 (6.5, 12.7) years, and the proportion of males was 60%. The median initial dose of GH was 0.27 (0.19, 0.33) mg/kg · wk, and the median duration of GH treatment was 2.5 (1.3, 4.3) years (Table 1).

The SIR (95% CI) for type 1 diabetes in U.S. GeNeSIS patients relative to the U.S. SEARCH study rates was 1.4 (0.5–3.1), and for type 2 diabetes was 8.5 (2.8–19.9) (Table 4). For GeNeSIS overall (U.S. and other countries), the SIR relative to the U.S. SEARCH study rates was 1.4 (0.7–2.4) for type 1 diabetes and 6.5 (3.3–11.7) for type 2 diabetes (Table 4). Among the U.S. patients with GHD, the organic GHD group appeared to have the higher incidence of type 2 diabetes [SIR 32.1 (6.6–93.8)] compared with the idiopathic GHD group [4.2 (0.1–23.1)], although the person-years of exposure were small and the confidence intervals wide (Table 4). Notably, each of the five patients with organic GHD who developed type 2 diabetes had one or more risk factors in addition to GH therapy (pretreatment obesity, pretreatment insulin resistance, previous cranial irradiation, and the combination of obesity, positive family history of type 2 diabetes, total body irradiation, and pharmacological glucocorticoid treatment).

Overall rates divided by major etiologies of growth disorder, but not standardized by age or race/ethnicity, are also summarized in Table 4. Overall U.S. rates as cases per 100,000 treatment-years (95% CI) for type 1 diabetes ranged from 0 (0–222) in Turner syndrome to 97.2 (20.1–284) in ISS, and for type 2 diabetes from 0 (0–120) for ISS to 94.0 (19.4–275) for organic GHD.

Risk factors and outcomes for type 2 diabetes

The median (Q1, Q3) age at diagnosis of type 2 diabetes was 15.3 (12.3, 17.4) years, and the median duration of GH treatment at type 2 diabetes onset was 2.5 (1.1, 2.9) years (Table 2). Duration of GH at onset for each individual patient is shown in Table 5, and a Kaplan-Meier plot of type 2 diabetes-free survival *vs.* patient GH exposure is presented in Supplemental Fig. 1. Three patients were prepubertal, seven patients had entered puberty, which is a period of physiological insulin resistance (18–21), and one patient, age 12 at diagnosis of diabetes, was of unknown pubertal status (Table 5).

Of the 11 patients who developed type 2 diabetes, one had preexisting insulin resistance (a patient with hypopituitarism due to *PROP1* gene defect), and one had preexisting impaired glucose tolerance (a patient with Turner syndrome). Five other patients had baseline diagnoses that are associated with increased risk of insulin resistance: Turner syndrome (22–24), Prader-Willi syndrome and obesity, obesity and organic GHD due to glioma, and SGA birth in two patients (25–28). Three patients were childhood cancer survivors with GHD due to leukemia and irradiation, which are also considered risk factors for diabetes (29). The first patient had received cranial irradiation for acute lymphocytic leukemia; the second had received total body irradiation for acute lymphocytic

TABLE 4. Incidence of diabetes mellitus (DM), with SIR and 95% CI, and incidence of DM or abnormal glucose tolerance (AGT)

Diagnosis group	n	Person-years	Condition	Cases	Incidence rate per 100,000 person-years (95% CI)	Expected cases	SIR (95% CI)
U.S. patients							
All	5,591	16,573	Type 1 DM	6	36.2 (13.3–78.8)	4.18	1.4 (0.5–3.1)
			Type 2 DM	5	30.2 (9.8–70.4)	0.59	8.5 (2.8–19.9)
			All DM	12[a]	72.4 (37.4–127)	4.77	2.5 (1.3–4.4)
			DM or AGT	14	84.5 (46.2–142)		
ISS	1,513	3,085	Type 1 DM	3	97.2 (20.1–284)	0.79	3.8 (0.8–11.1)
			Type 2 DM	0	0 (0–120)	0.13	0.00 (0–29.1)
			All DM	3	97.2 (20.1–284)	0.92	3.3 (0.7–9.5)
			DM or AGT	3	97.2 (20.1–284)		
Turner syndrome	486	1,665	Type 1 DM	0	0 (0–222)	0.42	0.00 (0–8.8)
			Type 2 DM	0	0 (0–222)	0.06	0.00 (0–62.6)
			All DM	0	0 (0–222)	0.48	0.00 (0–7.7)
			DM or AGT	0	0 (0–222)		
GHD	2,909[b]	9,874	Type 1 DM	3	30.4 (6.3–88.8)	2.48	1.2 (0.3–3.5)
			Type 2 DM	4	40.5 (11.0–104)	0.34	11.9 (3.2–30.4)
			All DM	7	70.9 (28.5–146)	2.82	2.5 (1.0–5.1)
			DM or AGT	8	81.0 (35.0–160)		
Idiopathic GHD	2,241	6,605	Type 1 DM	2	30.3 (3.7–109)	1.70	1.2 (0.1–4.3)
			Type 2 DM	1	15.1 (0.4–84.4)	0.24	4.2 (0.1–23.1)
			All DM	3	45.4 (9.4–133)	1.94	1.6 (0.3–4.5)
			DM or AGT	3	45.4 (9.4–133)		
Organic GHD	645	3,192	Type 1 DM	1	31.3 (0.8–175)	0.77	1.3 (0.0–7.2)
			Type 2 DM	3	94 (19.4–275)	0.09	32.1 (6.6–93.8)
			All DM	4	125 (34.2–321)	0.86	4.6 (1.3–11.9)
			DM or AGT	5	157 (50.9–366)		
All countries patients							
All	11,686	37,562	Type 1 DM	12	32 (16.5–55.8)	8.92	1.4 (0.7–2.4)
			Type 2 DM	11	29.3 (14.6–52.4)	1.69	6.5 (3.3–11.7)
			All DM	27[a]	71.9 (47.4–105)	10.61	2.6 (1.7–3.7)
			DM or AGT	40	106 (76.1–145)		
ISS	1,600	3,386	Type 1 DM	3	88.6 (18.3–259)	0.86	3.5 (0.7–10.2)
			Type 2 DM	0	0 (0–109)	0.15	0 (0–25.4)
			All DM	3	88.6 (18.3–259)	1.01	3.0 (0.6–8.7)
			DM or AGT	3	88.6 (18.3–259)		
Turner syndrome	1,135	4,052	Type 1 DM	2	49.4 (6.0–178)	0.98	2.1 (0.3–7.4)
			Type 2 DM	2	49.4 (6.0–178)	0.19	10.8 (1.3–38.8)
			All DM	4	98.7 (26.9–253)	1.16	3.4 (0.9–8.8)
			DM or AGT	8	197 (85.3–389)		
GHD	7,523[b]	25,992	Type 1 DM	7	26.9 (10.8–55.5)	6.11	1.2 (0.5–2.4)
			Type 2 DM	7	26.9 (10.8–55.5)	1.17	6.0 (2.4–12.3)
			All DM	15[a]	57.7 (32.3–95.2)	7.28	2.1 (1.1–3.4)
			DM or AGT	23	88.5 (56.1–133)		
Idiopathic GHD	5,725	17,814	Type 1 DM	3	16.9 (3.5–4.92)	4.23	0.7 (0.1–2.1)
			Type 2 DM	1	5.6 (0.1–31.2)	0.86	1.2 (0.0–6.5)
			All DM	5[a]	28.1 (9.1–65.5)	5.10	1.0 (0.3–2.3)
			DM or AGT	11	61.8 (30.8–110)		
Organic GHD	1,771	8,091	Type 1 DM	4	49.4 (13.5–127)	1.86	2.2 (0.6–5.5)
			Type 2 DM	6	74.2 (27.2–161)	0.31	19.5 (7.2–42.5)
			All DM	10	124 (59.3–227)	2.17	4.6 (−2.2–8.5)
			DM or AGT	12	148 (76.6–259)		

[a] Includes patients where type of diabetes is not defined as type 1 or 2 (see Fig. 1).

[b] Includes patients where type of GHD has not been specified.

leukemia; and the third had received total body irradiation for acute myeloid leukemia and had additional diabetes risk factors of obesity, glucocorticoid use, and family history (obesity and type 2 diabetes in both maternal grandparents and obesity in both parents).

Among the 11 patients who developed type 2 diabetes, hyperglycemia resolved in seven patients (four of whom were treated with metformin or insulin and three for whom no diabetes medications were recorded) (Table 5). In 4 of these 7 patients, normalization of glucose concen-

TABLE 5. Risk factors, outcomes, and other characteristics for patients with incident cases of type 2 diabetes

Country	Underlying diagnosis	Origin	Age at onset (yr)[a]	Duration of GH at onset (yr)[a]	Pubertal[a,b]	Additional risk factors	BMI SDS[c]	Initial GH dose (mg/kg · wk)	GH status[d]	Metformin/ insulin	Hyperglycemia resolved?[e]
Belgium	Org GHD (*PROP1 defect*)	Unk	17.6	0.4	No	Insulin resistance[f]	−0.3	0.16	Discontinued[g]	Yes	Yes
Germany	PWS	Cauc	9.1	1.3	No	Obesity	4.0	0.12	Continued	NR	Yes
Hungary	TS	Cauc	19.0	1.1	Yes	NR	0.7	0.33	Discontinued[g]	NR	Yes
Japan	TS	Asian	17.4	5.0	Yes	Impaired glucose tolerance[f]	1.6	0.34	Continued	NR	Unk
Japan	SGA	Asian	10.1	2.9	Yes	NR	−0.1	0.29	Discontinued	Yes	Yes
Japan	Org GHD (TBI for ALL)	Asian	15.3	2.6	Yes	NR	0.1	0.18	Discontinued	NR	Yes
U.S.	SGA	Cauc	13.0	2.5	Yes	Prednisone	−2.0	0.15	Continued	Yes	No
U.S.	IGHD	Cauc	14.7	2.7	Yes	NR	2.9	0.23	Continued	Yes	Unk
U.S.	Org GHD (Glioma)	Cauc	15.9	1.9	Yes	Obesity	2.4	0.32	Continued	Yes	Yes
U.S.	Org GHD (TBI for AML)	Cauc	15.8	1.0	No	Family history, obesity, prednisolone	1.5	0.21	Continued	Yes	Yes, then relapsed
U.S.	Org GHD (Cr Irr for ALL)	Cauc	12.3	3.3	Unk	NR	1.6	0.22	Continued	Yes	No

ALL, Acute lymphocytic leukemia; AML, acute myeloid leukemia; Cauc, Caucasian; Cr Irr, cranial irradiation; EPP, ectopic posterior pituitary; IGHD, idiopathic GHD; NR, none reported; Org GHD, organic GHD; PWS, Prader-Willi syndrome; TBI, total body irradiation; TS, Turner syndrome; Unk, unknown.

[a] At onset of diabetes.

[b] Entered or completed puberty.

[c] At start of GH treatment.

[d] GH therapy status after onset of diabetes.

[e] Patient no longer met diagnostic criteria for diabetes as interpreted by the investigator/standard diagnostic criteria.

[f] Present before initiation of GH-treatment.

[g] GH was discontinued but restarted after normalization of glucose metabolism.

trations followed discontinuation of GH treatment (two of whom restarted treatment 3 and 6 months later and continued treatment for 0.5 and 2.7 yr without reported diabetes recurrence). In the remaining three of the seven patients, GH treatment was continued through the period of diabetes for 1.8–7.4 yr until later discontinuation at adult height, patient/parent decision, or for reasons not available. In two of the 11 patients who developed type 2 diabetes, the condition was considered still present for 1.4 yr (point of last patient contact) and 2.8 yr (point of last record of type 2 diabetes), respectively, after onset; in both cases, GH treatment continued through the period of reported type 2 diabetes. Outcome of diabetes status was unknown for the remaining two of 11 patients, one of whom continued GH treatment for 0.1 yr after diagnosis of diabetes until attainment of adult height, and one of whom discontinued GH treatment and study participation immediately.

Discussion

In this study with over 36,000 person-years of GH treatment in 11,686 patients, 11 cases of type 2 diabetes were identified, representing an incidence of 29.3 cases per 100,000 person-years. This incidence is similar to the 34.4 cases per 100,000 person-years of GH treatment observed a decade ago by Cutfield and colleagues (5). Moreover, the incidence was also similarly increased in relation to that of the general population, by 6.5-fold in the current study for patients from all countries compared with 6.4-fold in the earlier study (5). Thus, despite concern that the increasing prevalence of childhood obesity will increase type 2 diabetes in the pediatric age group (8, 9, 30–33), the incidence of type 2 diabetes among GH-treated children does not appear to be increasing at a rapid rate. Median initial GH dose in our more recent cohort was higher than that reported earlier by Cutfield *et al.* (5), 42% higher for the entire GeNeSIS cohort, and 63% higher for the U.S. patients (Table 1). The trend toward higher initial GH dose as the earlier study does not appear to have an effect on incidence of type 2 diabetes, because doses were similar in those from our cohort who developed type 2 diabetes and those who did not develop diabetes or abnormal glucose tolerance (Table 2). Additionally, as in the earlier study (5), we did not observe an increased incidence of type 1 diabetes in relation to the general population.

Despite the presence of risk factors (in addition to GH) for type 2 diabetes in 10 of 11 patients who developed type 2 diabetes, there was no increase in the prevalence of type 2 diabetes before initiation of GH therapy in the study cohort that was naive to treatment at study entry. During GH treatment, however, 13 cases of incident abnormal glucose tolerance were reported, with the incidence in girls with Turner syndrome almost twice that of the overall GH-treated cohort (Table 4). The less severe impairment of glucose metabolism in these 13 patients compared with those who developed overt type 2 diabetes was consistent with the current understanding of the spectrum of insulin sensitivity in the general population, as determined by both environmental and genetic factors (34). We hypothesize that patients who develop insulin resistance or impairments of glucose metabolism during GH treatment, in addition to those with overt diabetes, represent a population at risk for later type 2 diabetes, analogous to patients with gestational impaired glucose tolerance or diabetes. We recommend enhanced surveillance of such patients, both during and after GH treatment, to assess glucose metabolism periodically and, where appropriate, to encourage those lifestyle measures that have been shown to be effective for prevention of diabetes (35).

The observation of reversibility of type 2 diabetes in some of our cases differs from that of Cutfield and colleagues (5), in which all 18 cases of type 2 diabetes still had overt diabetes after discontinuation of GH therapy. Because insulin resistance associated with GH administration is considered to be reversible (36, 37), the persistence of overt diabetes in all cases reported by Cutfield *et al.* (5) suggests that diabetes risk factors other than GH may have had an etiological role. Additionally, the median GH dose in our study was higher than that in the earlier study, and thus the potential improvement in insulin sensitivity from discontinuation of GH may have been correspondingly greater for our patients. Other potential explanations for the difference in diabetes outcome include the severity of hyperglycemia at time of diagnosis (and the resulting severity of pancreatic β-cell glucotoxicity) and the timing of observations after discontinuing GH.

The incidence of type 2 diabetes in our study (29.3 per 100,000 person-years overall; 30.2 per 100,000 person-years in the United States; Table 4), although similar to that of Cutfield and colleagues (5), was higher than the incidence of 14 per 100,000 person-years calculated for the period 1985–2006 in the U.S.-based National Cooperative Growth Study (7). Potential explanations for this difference include the different time period for the observations, during which the incidence of type 2 diabetes in youth has been increasing (8–10), as well as differences in study populations, ascertainment, and reporting.

In our study, patients with GHD, and more specifically organic GHD, had type 2 diabetes risk that was significantly greater than that of the general population. This may in part be explained by the fact that among our five cases of type 2 diabetes in patients with organic GHD, three had a history of leukemia and total body or cranial irradiation (29).

Our study has a number of limitations. First, as an observational study, it has limited value in assessing causality. Second, our determination of SIR was in comparison with the general U.S. population, not to an untreated group of patients with growth disorders. Thus, the increased diabetes incidence compared with the general population may reflect, in part, the known increased risk of insulin resistance and/or diabetes in some of the patient groups for whom GH treatment is currently indicated. Third, because our patients were under care of a pediatric endocrinologist, a surveillance bias toward higher observed type 2 diabetes rates might be hypothesized in GeNeSIS compared with SEARCH, which was a survey of diagnosed diabetes. Limited screening studies, however, suggest that undiagnosed type 2 diabetes is relatively uncommon in youth (38). Fourth, and potentially in opposition to the hypothesized surveillance bias toward higher observation rates in GeNeSIS, is the dependency of our analysis on complete reporting of all events of, and risk factors for, abnormal glucose metabolism by participating physicians. Fifth, the potentially changing population rates of obesity and type 2 diabetes make it difficult to ensure appropriate temporal matching of study and reference populations; GeNeSIS data collection spanned the period 1999–2007, whereas the SEARCH data were obtained in 2002–2003 (9), roughly midway through our period of observation.

We conclude that the incidence of type 2 diabetes during GH treatment remains low, with approximately one case for every 3000 person-years of treatment. Although GH product labeling recommends periodic monitoring of glucose metabolism of all patients receiving GH treatment, this study indicates that most patients who develop type 2 diabetes during GH treatment have preexisting risk factors for impairment of glucose homeostasis. Therefore, particular attention to glucose metabolism, both before initiation of and during GH treatment, appears warranted in such patients, including advice regarding preventive lifestyle measures. Although type 2 diabetes that presents during GH treatment may be reversible, with or without discontinuation of GH, the long-term type 2 diabetes risk of such patients and of those with incident abnormal glucose tolerance requires further study.

Acknowledgments

Membership of the GeNeSIS Advisory Board as of November 2010 was T. Battelino (Ljubljana, Slovenia), W. F. Blum (Bad Homburg, Germany), J. Brämswig (Münster, Germany), C. Deal (Montreal, Canada), S. L. S. Drop (Rotterdam, The Netherlands), T. Hasegawa (Tokyo, Japan), J. Lebl (Prague, Czech Republic), J. Léger (Paris, France), M. Maghnie (Genova, Italy), J. Parks (Atlanta, GA), R. W. Pfäffle (Leipzig, Germany), C. A. Quigley (Indianapolis, IN), L. L. Robison, (Memphis, TN), R. Rosenfeld, (Palo Alto, CA), J. Ross (Philadelphia, PA), E. Schönau (Cologne, Germany), and A. G. Zimmermann (Indianapolis, IN).

We offer grateful thanks to all participating investigators, patients, and their families. Additionally, we thank Dr. Peter Bates (Cambridge Medical Writing Services, Cambridge, UK) for his editorial review of the manuscript and Catherine Sampson (i3 Statprobe, Cary, NC) and Gina Garding (i3 Statprobe, Eden Prairie, MN) for their assistance in statistical programming.

Address all correspondence and requests for reprints to: Dr. Chris J. Child, Lilly Research Centre, Erl Wood Manor, Windlesham, Surrey GU20 6PH, United Kingdom. E-mail: cjc@lilly.com.

GeNeSIS is registered with www.ClinicalTrials.gov, number NCT 01088412.

Disclosure Summary: C.J.C., A.G.Z., R.S.S., and W.F.B. are employees of Eli Lilly and Co. G.B.C. is a former employee of and consultant to Eli Lilly and Co. (current address Deltaville, VA). T.B. is a member of the GeNeSIS International Advisory Board. The study was sponsored by Eli Lilly and Co.

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