Prevalence and Incidence of Diabetes Mellitus in Adult Patients on Growth Hormone Replacement for Growth Hormone Deficiency: A Surveillance Database Analysis

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Context: GH replacement in adult GH-deficient patients may cause insulin resistance, raising concerns of potential increased risk of developing diabetes mellitus (DM).

Objective: Our objective was to assess DM prevalence and incidence in the international Hypopituitary Control and Complications Study (HypoCCS) surveillance database.

Design and Participants: GH-treated patients enrolled into HypoCCS (2922 U.S. and 3709 European patients) were assessed for DM, defined as recorded on the clinical report form, reported as adverse events, fasting glucose at least 7 mmol/liter recorded at least twice, or insulin treatment reported.

Results: DM prevalence was 8.2% [95% confidence interval (CI) = 7.6–8.9] overall, 11.3% in the United States and 5.7% in Europe. Incidence (n/1000 patient-years) was 9.7 (95% CI = 8.4–10.9) overall, 14.1 (11.5–16.7) in the United States, and 7.0 (5.6–8.3) in Europe. Overall incidence was 2.1 (0.9–3.3) for patients with body mass index (BMI) below 25 kg/m^2 increasing to 16.4 (13.7–19.1) for BMI over 30 kg/m^2. Obesity (BMI $>$ 30 kg/m^2) prevalence was higher in the United States than Europe and higher in U.S. patients than a U.S. reference population. After age, gender, and BMI adjustment, U.S. HypoCCS DM incidence was 10.6 (8.1–13.0), compared with 7.1 (6.0–8.1) in the National Health Interview Survey. In Europe, incidence for French and German patients was comparable to reference populations; for Sweden, the point estimate was higher than the reference population, but 95% CI overlapped. GH dose was not correlated with DM incidence.

Conclusions: The present analysis showed no evidence for increased DM incidence in GH-treated adult hypopituitary patients. However, those more prone to develop DM exhibited a higher than normal prevalence of obesity. (***J Clin Endocrinol Metab*** **96: 2255–2261, 2011)**

It has been suggested that GH replacement may increase the risk of developing diabetes mellitus because GH causes insulin resistance (1). Cutfield and colleagues (2) found a 6-fold increase in incidence of type 2 diabetes mellitus in a large series of pediatric patients who were treated with GH and postulated that GH treatment may accelerate the onset of diabetes in predisposed individuals. These findings may be relevant to adult endocrinologists because adult

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Abbreviations: BMI, Body mass index; CI, confidence interval; GHD, GH deficiency; HypoCCS, Hypopituitary Control and Complications Study; KIMS, Kabi International Metabolic Surveillance; NHANES, National Health and Nutrition Examination Survey; NHIS, National Health Interview Survey.

patients with GH deficiency (GHD) are insulin resistant (3, 4) and, as such, may be at higher risk of developing diabetes.

Adult GH-deficient patients suffer from metabolic abnormalities that resemble those of the metabolic syndrome (5), and the prevalence of this condition, which is a strong predictor of type 2 diabetes risk, is increased in adult GH-deficient patients (6). On the other hand, GH replacement reduces the abdominal fat mass accumulated due to GHD, and it has been proposed that this beneficial effect of GH treatment will positively influence insulin resistance and improve glucose homeostasis in adult patients with GHD (7). Such an outcome has been documented in some studies (8) but not in others (9), and data on diabetes prevalence and incidence in adult hypopituitary patients with GHD during GH treatment are scarce. An increased prevalence of diabetes mellitus in GH-treated adult women, but not men, with GHD was reported in a study in Sweden (10). However, an earlier analysis from the Kabi International Metabolic Surveillance (KIMS) study reported no increase in the incidence of diabetes in 5120 patients with normal body mass index (BMI) (11), whereas sporadic new cases of diabetes were reported in single-center study cohorts on long-term GH replacement (12). Recently, an updated analysis of 5143 patients from the KIMS database reported a 6-fold higher incidence of diabetes mellitus compared with a reference population (13), comparable to the observations of Cutfield *et al.* (2) in pediatric patients.

Thus, available data do not provide a clear picture of the consequences that GH replacement may have on the development of diabetes mellitus in adults with GHD in the setting of clinical practice. Therefore, we carried out a prevalence and incidence assessment of diabetes mellitus in patients in the international surveillance database of the Hypopituitary Control and Complications Study (HypoCCS) (14).

Patients and Methods

Patients

HypoCCS is a surveillance study that collects long-term efficacy and safety data from adult patients with GHD treated with recombinant human GH (Humatrope; Eli Lilly and Co., Indianapolis, IN), in the United States, Canada, and different European countries. Ethical review board approval was obtained, and all patients provided written consent for data collection, electronic processing, and publication, in accordance with national laws and regulations. The study protocol specifies that patients entering HypoCCS should meet the criteria for the adult GHD indication, with either childhood-onset or adult-onset GHD, according to the approved package insert for Humatrope in each participating country.

The study population consisted of the GH-treated patients enrolled into HypoCCS who had not previously received GH as adults and had no missing data on age, gender, or onset type (n = 6672, comprising 2922 from the United States and 3709 from European countries Austria, Belgium, Czech Republic, Denmark, France, Germany, Hungary, Italy, Norway, Spain, Sweden, The Netherlands, and the United Kingdom). In addition, the incidence and risk factors for diabetes (age, gender, BMI, history of Cushing's disease, and GH dose) were assessed in a subset of the study population who were aged 18 to under 80 yr, free of diabetes mellitus at study entry, had at least one follow-up visit, and were followed for a mean of 4.1 yr (incidence population, n = 5839). Patients with a previous diagnosis of Cushing's disease and acromegaly were not excluded, because preliminary analyses had shown that diabetes prevalence and incidence rates in these conditions were not different from the other causes of GHD and hypopituitarism.

Study assessments

A patient from the HypoCCS database was defined as having diabetes mellitus if 1) the checkbox on the clinical report form denoting the presence of diabetes mellitus was ticked, 2) they had a report of diabetes mellitus or related adverse event according to the preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA) coding system (15), 3) a fasting glucose of at least 126 mg/dl (≥7 mmol/liter) was recorded at least two times, or 4) insulin treatment was reported. Patients on oral antidiabetes medication not reporting a diagnosis of diabetes mellitus or a fasting glucose value of at least 126 mg/dl (≥7 mmol/liter) were not considered to have diabetes. No distinction was made between type 1 and type 2 diabetes mellitus because the proportion of patients with type 1 diabetes in the prevalence population was very small, and because the incidence population were all adults, it was assumed that almost all incident cases were type 2. Individual cases were reviewed independently by two of the authors (H.J. and A.F.A.) for consistency of diabetes diagnosis and for assessment of GH dosage during follow-up.

Statistical methods

Mean and SD are presented for continuous variables unless otherwise specified. Counts and percentages are presented to describe categorical variables. Continuous variables were compared between subgroups by ANOVA. Unless otherwise specified, χ^2 tests were applied to compare categorical variables.

A standardization method (16, 17) was used to estimate adjusted prevalence and incidence and their 95% confidence intervals (CI) in the United States, Europe, and the overall HypoCCS populations. For comparisons of diabetes prevalence rates to reference populations, U.S. data were age adjusted to the U.S. 2000 census data (18) and European data were age standardized to the European standard population (National Health Wellness Survey; www.chsinternational.com/nhws.html). For comparison of diabetes incidence rates, U.S. HypoCCS data were age, gender, and BMI adjusted to the U.S. National Health and Nutrition Examination Survey (NHANES) (19) distribution and compared with the incidence rates reported in the National Health Interview Survey (NHIS) (20). Swedish data were age standardized to the world population, and the incidence in Swedish HypoCCS patients was compared with incidence from a recent report, in which type 2 diabetes was assessed by fasting glucose measurements in southeast Sweden (21). The incidence rates of German HypoCCS patients were compared with the MONICA/KORA survey data (22) and those of French patients to the DESIR study (23) in which diabetes was defined by fasting

glucose values and/or diabetes treatment. For these two countries, the age range of patients was chosen to match that of the reference, and no age adjustment was performed because available reference data were also not age adjusted.

No overall standardized incidence rates were calculated because no comparable age-, gender-, and BMI-standardized incidence rates were available for the control populations. However, the difference between adjusted prevalence or incidence rates was considered significant if there was no overlapping of 95% CI in the two samples.

Hazard ratio of risk of developing diabetes mellitus was estimated by the Cox proportional hazards model, with independent variables of age, BMI, gender, average GH dose, and Cushing's disease history, fitted for both U.S. and European patients. In preliminary analyses, other factors examined included number of pituitary hormone deficiencies, IGF-I SD score, and glucocorticoid replacement (yes/no) and were found not to be significant; these were therefore not included in the proportional hazard model. No two-way or three-way interaction terms for these variables were significant in the model, and statistical results were consistent, irrespective of use of categorical variables or continuous variables for age, BMI, and GH dose; presented results were from the model using continuous variables. Statistical analyses used SAS (version 9.1).

Results

Diabetes mellitus prevalence and incidence data are presented in Table 1 for all patients and for the United States and the European countries separately. Overall mean age was not different for the prevalence and incidence populations. Compared with European patients, U.S. patients were slightly older, with a smaller proportion of males, and had a higher mean BMI. As shown for the incidence population, this difference in BMI reflected the higher prevalence of overall obesity (BMI $>$ 30 kg/m^2), with higher rates of both obesity grade 1 (BMI 30 to $<$35 kg/m^2) and grade 2/3 (BMI $\geq$ 35 kg/m^2) in the United States compared with the European population.

Overall standardized diabetes mellitus prevalence (Table 1) was 8.2% (95% CI = 7.6–8.9), and crude, as well as age-standardized, prevalence was doubled in the United States compared with Europe (age-standardized: United States 11.3% *vs.* Europe 5.7%).

The incidence population accounted for 22,493 patient-years, with a mean follow-up time of 4.1 $\pm$ 3.2 yr. Overall crude and age-standardized diabetes incidence (n/1000 patient-years) were both 9.7 (95% CI = 8.4–10.9). Consistent with prevalence, incidence was also doubled in the United States compared with Europe: United States 14.1 (95% CI = 11.5–16.7) and Europe 7.0 (95% CI = 5.6–8.3). This difference in diabetes mellitus incidence between United States and Europe appeared to be due to the different distribution of obesity among the two patient populations; at enrollment, 24.6% of U.S. patients had a BMI of at least 35 kg/m^2, whereas only 11.3% of Europeans were in that category (Table 1). When incidence was assessed by BMI category (Table 2), rates were very consistent and comparable in United States and Europe for

TABLE 1. Prevalence and incidence of diabetes mellitus in U.S. and European HypoCCS patients with GHD

	All patients	U.S.	EU
Prevalence population			
n	6672	2922	3709
Age (yr)	45.4 $\pm$ 15.1	46.8 $\pm$ 14.7	44.2 $\pm$ 15.3
Male (%)	52.3	50.6	53.7
Diabetes prevalence [% (95% CI)]			
Crude	8.2 (7.6–8.9)	11.8 (10.6–12.9)	5.5 (4.7–6.2)
Age-standardized	8.2 (7.6–8.9)	11.3 (10.2–12.4)	5.7 (4.9–6.4)
Incidence population			
n	5839	2458	3349
Age (yr)	44.7 $\pm$ 14.8	45.8 $\pm$ 14.1	43.8 $\pm$ 15.2
Male (%)	52.1	50.3	53.4
Follow-up time (yr)	4.1 $\pm$ 3.2	3.4 $\pm$ 2.8	4.6 $\pm$ 3.4
BMI (kg/m^2)	29.5 $\pm$ 6.7	31.3 $\pm$ 7.1	28.2 $\pm$ 6.1
$<$25 kg/m^2 (%)	25.2	17.0	31.2
25–30 kg/m^2 (%)	34.0	30.5	36.6
$>$30 kg/m^2 (%)	40.8	52.6	32.2
Obesity degree 1: 30 to $<$35 kg/m^2 (%)	23.9	27.9	20.9
Obesity degree 2/3: $\geq$35 kg/m^2 (%)	16.9	24.6	11.3
Diabetes incidence			
n/patient-yr	217/22493	113/7797	104/14599
Crude, n/1000 patient-yr (95% CI)	9.7 (8.4–10.9)	14.5 (11.8–17.2)	7.1 (5.8–8.5)
Age-standardized, n/1000 patient-yr (95% CI)	9.7 (8.4–10.9)	14.1 (11.5–16.7)	7.0 (5.6–8.3)

The prevalence population were patients with GHD who were GH treated in HypoCCS, with no previous GH therapy as adults and no missing information on age, gender, and onset type (adult or childhood onset); age-standardized prevalences were adjusted to HypoCCS prevalence population. The incidence population was a subgroup of the prevalence population aged 18 to $<$80 yr, free of diabetes at baseline, and with at least 1 post-baseline visit; age-standardized incidences were adjusted to the HypoCCS incidence population. EU, European Union.

TABLE 2. Age-standardized incidence of diabetes mellitus by BMI category

	BMI category		
	<25 kg/m²	25–30 kg/m²	>30 kg/m²
All patients			
n/patient-yr	12/5831	58/8003	147/8659
Incidence	2.1	6.8	16.4
95% CI	0.9–3.3	5.0–8.6	13.7–19.1
U.S. HypoCCS			
n/patient-yr	3/1290	21/2456	89/4051
Incidence	2.1	7.2	21.7
95% CI	0–4.5	4.1–10.2	17.2–26.3
EU HypoCCS			
n/patient-yr	9/4522	37/5520	58/4557
Incidence	2.2	6.5	11.8
95% CI	0.8–3.8	4.4–8.7	8.7–14.9

Incidence was adjusted to the age structure of HypoCCS population aged 18 to <80 yr who were GH treated, GH naive as adults, free of diabetes at baseline, and had at least one post-baseline visit; incidence data are n/1000 patient-years. EU, European Union.

BMI below 25 kg/m² and 25–30 kg/m² but almost doubled in United States *vs.* Europe for the BMI higher than 30 kg/m² category.

As shown in Fig. 1, the high prevalence of obesity in U.S. HypoCCS patients was also evident when compared with normative U.S. reference data from the NHANES survey (20). Compared with the NHANES obesity trend report for 1998–2008, the U.S. HypoCCS patients had more than 20% higher prevalence of obesity, with a significant shift to higher degrees of obesity (obesity degree 1, BMI 30–35 kg/m²: U.S. HypoCCS 27.9%, NHANES 15.5%; obesity degree 2/3, BMI > 35 kg/m²: U.S. HypoCCS 24.6%, NHANES 13.0%). Therefore, the U.S. HypoCCS incidence rates were adjusted not only for age and gender but also for BMI, taking the NHANES obesity distribution as reference. In the upper row of Table 3, this BMI-standardized U.S. HypoCCS diabetes incidence rate (10.6,

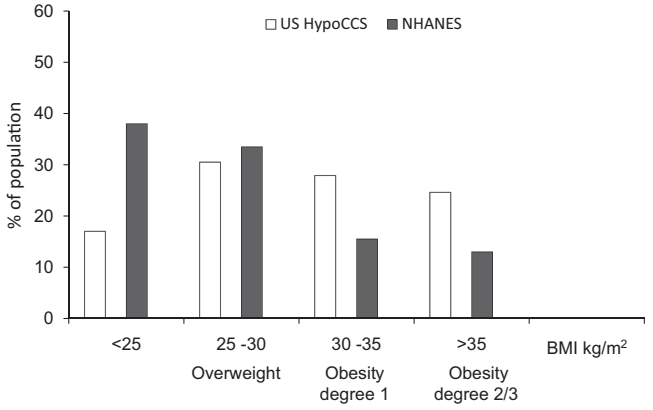

FIG. 1. Distribution of BMI in U.S. GH-deficient patients at entry to HypoCCS and in a normal U.S. reference population. The proportion of patients in HypoCCS and proportion of the reference population are shown according to degree of obesity by BMI category. The reference population is taken from the NHANES (19).

TABLE 3. By-country incidence of diabetes mellitus in GH-treated patients in HypoCCS compared with reference data

	HypoCCS	Reference data
United States		
n/patient-yr	113/7797	
Incidence (95% CI)[a]	10.6 (8.1–13.0)	7.1 (6.0–8.1)
France		
n/patient-yr	2/490	
Incidence (95% CI)[b]		
Female	0.0 (0.0–16.8)	3.1 (2.2–4.2)
Male	7.4 (0.9–26.7)	7.8 (6.3–9.5)
Germany		
n/patient-yr	10/1329	
Incidence (95% CI)[b]	7.5 (3.6–13.8)	7.3
Sweden		
n/patient-yr	17/2112	
Incidence (95% CI)[c]	5.6 (2.6–8.7)	2.6 (2.6–2.7)

Reference data are from Geiss *et al.* (20) for the United States, Balkau *et al.* (23) for France, Meisinger *et al.* (22) for Germany, and Thunander *et al.* (21) for Sweden.

[a] HypoCCS incidence standardized to age, gender, and BMI structure of NHANES (19).

[b] HypoCCS data subset to match age range of reference, but HypoCCS incidence rate is crude rate (no standardization).

[c] HypoCCS incidence rate is standardized to world population age structure.

95% CI = 8.1–13.0) was greater than the incidence rate of self-reported diabetes from the U.S. NHIS 2002–2003; the NHIS rate was 7.1 per 1000 patient-years, with the upper 95% CI of 8.1 corresponding to the lower 95% CI of the HypoCCS assessment.

Table 3 also presents incidence rates in three European countries participating in HypoCCS where national reference data were available. The national HypoCCS cohorts of France, Germany, and Sweden were taken as representative of the variance of diabetes incidence in HypoCCS patients in Europe and were compared with specific country reference populations standardized for age, gender, and where feasible, BMI distribution depending on the specific reference population. This approach showed that, despite the limited number of patient-years and the wide confidence limits in the individual countries, incidence estimates for French and German HypoCCS patients were comparable to French and German reference populations (21, 22). For Sweden, on the other hand, the point estimate in HypoCCS was doubled compared with the reference population (23), but the lower 95% CI was below the reference estimate.

The proportional hazard model used on the incidence population to explore factors that could predict the risk of diabetes showed that, for both United States and Europe regions, only BMI and age were significant predictors of diabetes mellitus incidence; gender, GH dose, and history

of Cushing's disease were not significant in the model, and there was no significant interaction between any of the variables examined. For age, the hazard ratio was 1.021 (95% CI = 1.006–1.037) for U.S. patients and 1.032 (1.016–1.047) for European patients. For BMI, hazard ratios were 1.073 (1.052–1.095) and 1.080 (1.051–1.109), respectively, for each unit increase; *i.e.* the likelihood of developing diabetes was increased by 7.3% for each kilogram per square meter gain in the United States and by 8.0% in Europe, irrespective of the levels of other factors.

Discussion

The possible relationship between GH treatment and the development of diabetes mellitus is an important safety aspect of hormone replacement therapy, in pediatric as well as in adult patients (1). A previous HypoCCS analysis showed that the baseline prevalence of the metabolic syndrome in the HypoCCS population was higher than in the normal reference populations and was about 20% higher in the United States than in Europe (6). Because the metabolic syndrome increases the risk of developing diabetes by up to 6-fold (24), we hypothesized that diabetes prevalence and incidence could be increased in an adult population of hypopituitary patients with GHD replaced with GH, whatever the factors or conditions predisposing to, or directly causing, diabetes mellitus.

Prevalence rates in both the United States and Europe were comparable to population reference data. In the United States, the prevalence of 11.8% (95% CI = 10.6–12.9) among GHD patients compares favorably with the 2005–2006 NHANES survey (25), where total (diagnosed + undiagnosed) prevalence of diabetes in subjects aged over 20 yr was 12.9% (95% CI = 10.8–14.9). On the other hand, overall prevalence in European HypoCCS patients was 5.5% (95% CI = 4.7–6.2), which was lower than the 8.6% reported by the European Union Public Health Information System (EUPHIX) (26) for the EU-27 adult population aged 20–79 yr. The lower prevalence may result from the different quantitative by-country enrollment of patients into HypoCCS in Europe. This assumption is supported by the EUPHIX data, according to which diabetes mellitus prevalence in Europe is not uniform, with country estimates ranging from 4.0% in the United Kingdom to 11.8% in Germany. Also, although the difference between the United States and Europe primarily reflected the background epidemiology (27), patients are enrolled into HypoCCS with the decision to treat with GH, and the lower diabetes prevalence found in Europe could possibly result from a more conservative approach to GH replacement in Europe compared with the United States.

Similar to prevalence, incidence rates in U.S. HypoCCS patients were doubled compared with European patients. However, U.S. HypoCCS patients had a very significant shift to higher obesity degrees, not only compared with European patients but also compared with the U.S. obesity reference data from the NHANES survey (19), and were, therefore, at much higher risk of developing diabetes. Adjustment of the U.S. incidence for this additional risk, *i.e.* for the BMI distribution of the U.S. population according to the NHANES survey, reduced the initial rate of 14.1 (11.5–16.7) to 10.6 (8.1–13.0). This was still higher than the 7.1 (6.0–8.1) point estimate reported in the NHIS survey (20), although the respective lower and upper confidence limits were equivalent. In European country cohorts, incidence rates in France and Germany were comparable to population references, but the results for Sweden were similar to those obtained in the United States, with a higher point estimate in the HypoCCS cohort and overlapping confidence limits. Thus, even if the trends among countries are not consistent, the results obtained in the United States and Sweden indicate that, if at all, diabetes incidence may be only slightly increased in adult patients with GHD who are receiving hormone replacement including GH. Our analysis would indicate that this possible increased risk of developing diabetes is primarily related to the degree of preexisting obesity. This is confirmed by the results of the proportional hazard modeling, which also show that GH dose was not a predictor of diabetes incidence, at least in our cohort of patients. Our initial hypothesis, based on the higher than normal prevalence of the metabolic syndrome found in HypoCCS patients, in fact predicted that the preexisting degree of obesity could be a major predisposing variable. This would not contradict previous reports of improvement of glucose control in relation to a loss of abdominal fat mass with GH treatment in some patients (8, 28), because different obesity phenotypes would also carry a different prospective risk.

Patients with a history of Cushing's disease did not have an increased incidence of diabetes. This was consistent with a previous analysis carried out on the HypoCCS database, comparing incidence of diabetes in patients with history of Cushing's disease and nonfunctioning pituitary adenoma, in which no difference in diabetes incidence was found between the two entities (29). Information on glucocorticoid treatment was not available for all patients, and therefore, we did not specifically investigate the possible impact of glucocorticoid replacement regimens on diabetes incidence. However, in a previous analysis from the KIMS database, frequency of diabetes mellitus

was found to be independent of glucocorticoid type and dose (30).

The present analysis has some limitations but also some strengths. First, the prevalence and incidence assessments were derived from an observational study cohort of patients selected for GH replacement therapy, and diabetes cases, and/or diabetic presentations, were reported at the discretion of the investigator. Second, our criteria for defining diabetes were not necessarily the same as those used for diabetes assessment in the reference populations. These two limitations of reporting and definition bias are, however, common to the assessments in the reference populations because a consistent proportion of diabetes cases remain undiagnosed (25, 31). Third, our analysis was adjusted for age, gender, BMI, and history of Cushing syndrome, but not for other confounders (*e.g.* lifestyle patterns, alcohol consumption, and socioeconomic status); however, this was also the case for the comparator analyses. Fourth, there have been potential changes over time in population rates of diabetes and obesity; although a precise temporal match for reference data were not possible, the time of collection of HypoCCS data overlapped the time period of the reference data. On the other hand, despite such limitations we believe that our present analyses using country/region-specific comparisons provide a more reliable diabetes mellitus assessment than that presented by Cutfield *et al.* (2) or in the recent analysis of the KIMS database (13), wherein incidence rates in GH-treated patients from a variety of countries were compared with incidence rates from a single reference population. By the present approach, it becomes evident that diabetes incidence varies among GH-treated HypoCCS patients from different countries, depending on distribution of risk factors (obesity) and background epidemiology.

In summary, adult patients with GHD may be prone to developing diabetes mellitus due to a higher prevalence of obesity and the metabolic syndrome than reference populations. Our analysis suggests that increased incidence of diabetes mellitus during GH replacement therapy is associated with the continuing presence of obesity and metabolic syndrome rather than GH therapy *per se*.

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