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CLINICAL STUDY

Prevalence of diabetes mellitus in 6050 hypopituitary patients with adult-onset GH deficiency before GH replacement: a KIMS analysis

Roger Abs, Anders F Mattsson[1], Maria Thunander[2], Johan Verhelst[3], Miklós I Góth[4], Patrick Wilton[1], Maria Kołtowska-Häggström[1] and Anton Luger[5]

Antwerp Centre for Endocrinology, Grotesteenweg 556, B-2600 Berchem, Antwerp, Belgium, [1]Endocrine Care, Pfizer, Inc., SE-191 90 Sollentuna, Sweden, [2]Clinical Sciences, Endocrinology, Central Hospital, Lund University and Internal Medicine, S-351 85 Växjö, Sweden, [3]Department of Endocrinology, ZNA Middelheim, B-2020 Antwerp, Belgium, [4]State Health Centre, Military Hospital, HU-1062 Budapest, Hungary and [5]Clinical Division of Endocrinology and Metabolism, Medical University of Vienna, A-1090 Vienna, Austria

(Correspondence should be addressed to R Abs; Email: roger.abs@skynet.be)

Abstract

Objective: GH deficiency (GHD) in adults is characterized by a tendency toward obesity and an adverse body composition with visceral fat deposit and may thus predispose to the development of type 2 diabetes mellitus. The aim of this study was to assess the observed prevalence proportion (PP) and observed PP over expected PP ratio (standardized prevalence proportion ratio, SPR) of diabetes according to International Diabetes Federation criteria in a large cohort of GH-untreated adult-onset GHD patients.
Design and methods: Associations between baseline variables and diabetes prevalence in 6050 GHD patients from KIMS (Pfizer International Metabolic Database) were studied and robust Poisson-regression analyses were performed. Comparisons between baseline status and HbA1c categories in the nondiabetic patients were done with covariance analysis. P values <0.05 were considered statistically significant.
Results: PP was 9.3% compared with the expected 8.2%. SPR was 1.13 (95% confidence intervals (95% CIs), 1.04–1.23), which was significantly increased in females (1.23; 95% CI, 1.09–1.38%) but not in males (SPR 1.04; 95% CI, 0.92–1.17%). PP increased significantly by age, familial diabetes, country selection, BMI, waist circumference, number of pituitary deficiencies, and GHD etiology. SPR decreased significantly by age and increased significantly by BMI, waist circumference, and IGF1 SDS. Multiple regression model showed that the most important impact on SPR was from age and BMI. HbA1c values of 6.0–6.5% were found in 9.5% of nondiabetic patients and were associated with higher BMI and waist circumference.
Conclusions: GHD is associated with an increased prevalence of diabetes, largely to be explained by the adverse body composition. These data urge toward early initiation of lifestyle modification measures.

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Introduction

GH is an important actor in energy homeostasis and metabolism. An extensive review describing the effects of GH on substrate metabolism has recently been published (1). Overall, GH has diabetogenic effects by reducing the sensitivity of liver, muscle, and fat to insulin action. The reduced insulin sensitivity is probably a consequence of GH-induced lipolysis and release of free fatty acids, which promote liver gluconeogenesis and compete with glucose as an oxidative substrate (2). Insulin resistance is of primary importance to avoid hypoglycemia in periods where glucose usage should be reduced, such as fasting, exercise, and stress; and energy requirements could be overtaken by lipolysis. Although glucagon and catecholamines are of predominant importance, an adequate response to hypoglycemia during treatment of diabetes presumes also a preserved GH secretion (3, 4).

The concept that GH deficiency (GHD) would be accompanied by hypoglycemia due to a decrease in hepatic glucose production was not only regarded self-evident on the basis of the physiological actions of GH but was also recognized in children with isolated GHD (5, 6). In contrast, the clinical presentation of adult GHD, which is characterized by components of the metabolic syndrome, is apparently never accompanied by hypoglycemia (7). Moreover, the first clinical studies pointed toward an impaired carbohydrate metabolism, because an increased prevalence of impaired glucose tolerance was found in 14 out of 40 adult GHD patients (8). Furthermore, using the hyperinsulinemic normoglycemic clamp technique, a significant impairment of insulin sensitivity was observed (9, 10). An increase in

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free fatty acids related to the tendency toward obesity and to the increase in visceral fat has been implicated in the insulin resistance, because reduction of the free fatty acids by the niacin derivative acipimox ameliorates GH secretion in obesity and in GHD (11). Finally, an increase in the prevalence of diabetes mellitus in female GHD patients has been suggested when compared with epidemiological studies (12).

The principal aim of the present analysis was to study the prevalence of diabetes mellitus in a large cohort of patients with adult-onset GHD naïve to GH replacement and to compare their characteristics with the general population. An additional aim was to describe the patients without diabetes and to determine variables known to affect diabetes risk in relation to HbA1c concentrations. The data in these analyses were retrieved from KIMS (Pfizer International Metabolic Database) (13).

Materials and methods

KIMS is a global, multicenter, noninterventional, pharmacoepidemiological study in which data are collected from adults with GHD, receiving recombinant human GH replacement therapy (somatropin, Genotropin; Pfizer, Inc.) and monitored according to routine clinical practice (13). Informed consent was obtained from patients in accordance with local regulations. The studies were performed in accordance with the Declaration of Helsinki (14).

Patients

Patients were included in the diabetes mellitus prevalence study when they presented with severe GHD of adult-onset confirmed by an accepted GH stimulatory test (15), naïve to GH replacement, and without a medical history of acromegaly or Cushing's disease.

Methods

Clinical data Background data, including gender, age (divided into 20-years groups for comparison with the International Diabetes Federation (IDF) references), family history of diabetes, country of origin, etiology of hypopituitarism, estimated duration of GHD (divided into four categories), and extent of hypopituitarism (expressed as the number of pituitary hormone deficits additional to GH), as well as weight, BMI (divided into six groups), and waist circumference (divided into six gender-specific groups), were collected.

Biochemical data Plasma glucose and serum HbA1c were measured locally. Central analysis of serum insulin-like growth factor 1 (IGF1) was available from 2825 patients. Between 1994 and October 1997, measurements of IGF1 were performed at Kabi Pharmacia (Stockholm, Sweden), and thereafter at Sahlgrenska University Hospital (Gothenburg, Sweden), using the following assay methods: until November 2002, RIA after acid/ethanol precipitation of IGF-binding proteins (Nichols Institute Diagnostic, San Juan Capistrano, CA, USA); until September 2006, chemiluminescence immunoassay (Nichols Advantage; Nichols Institute Diagnostics, San Clemente, CA, USA); and after September 2006, Immulite 2500 (Diagnostic Products Corp., Siemens, Deerfield, IL, USA) (16). For each assay, age- and gender-specific reference ranges expressed in microgram per liter were used to calculate IGF1 SDS. Between assay reference ranges and consistency of IGF1 SDS values were validated internally. The algorithm formulas used were as follows: between 1994–1997, $SDS = (\ln(IGF1) - (5.95 - 0.0197 \times age))/0.282$; between 1997–2002, $SDS = (\ln(IGF1) - (5.92 - 0.0146 \times age))/0.272$; and after 2002, as reported by Brabant *et al.* (17). Patients with centralized analysis of serum IGF1 were categorized into six groups according to IGF1 SDS.

Diabetes mellitus prevalence study in GHD patients To ensure an accurate inclusion, two different approaches for the diagnosis of diabetes were used. First, in reference to the patient's medical information, the report of a pre-existing diabetes by the physician or the use of any anti-diabetic medication at baseline; secondly, biochemical data in accordance with the IDF guideline for diagnosis of diabetes, actually the measurement of a fasting plasma glucose ≥ 7 mmol/l (126 mg/dl) or a non-fasting plasma glucose ≥ 11.1 mmol/l (200 mg/dl), or the measurement of a serum HbA1c $\geq 6.5\%$ (18). Diabetic patients were compared with patients excluded by these three criteria (non-diabetic patients).

Non-diabetes mellitus GHD patients study The nondiabetic patients were grouped into five categories depending on the HbA1c concentrations. As the 6.0–6.5% HbA1c category is considered to be at risk for the development of diabetes (18), it was compared with the other four categories (<4.5, 4.5–5.0, 5.0–5.5, 5.5–6.0%) for the following variables: gender, age, duration of GHD, additional hormonal deficiencies, IGF1 SDS, BMI, and waist circumference.

Statistical analysis

Descriptive statistics were presented by mean and SD. Comparison between diabetic and nondiabetic patients regarding baseline characteristics was done with *t*-tests or χ^2-tests, depending on the type of variable.

Standardized prevalence proportion ratio (SPR) was calculated as the observed prevalence proportion (PP)

over the expected PP. The latter was calculated as a sum of age and country stratified products of general population PP and the number of KIMS patients (indirect standardization). The IDF provides regular updates on country-, age-, and gender-specific estimates of diabetes prevalence in the world. Data catch is through literature search using the Medline database and the Internet. Moreover, IDF diabetes researchers were asked to forward country-specific data within their region. Data used for calculation were prioritized based on how recent studies were on the used screening method and on the sample size of studies. The country- and age-specific prevalence estimates, obtained from logistic regression, were applied and adjusted to the level of the corresponding country- and age-specific population for the calendar year the calculations referred to. Population distribution estimates were obtained from the United Nations Population Division. General population prevalence figures were for the calendar year 2007 IDF Atlas, IDF Website May 2009. Data are country-specific and age is divided in three groups: 20–39, 40–59, and 60–79 years. Special considerations were applied for countries without available population data. In that case, estimates from a published study for a 'most similar' country were used. For countries with lower national income, urban/rural-specific estimates were retrieved. IDF publishes even gender-specific prevalence figures, however, not on an age-specific basis. As diabetes prevalence varies more over age than between genders, it was decided for the current study to use the country–age-specific estimates as described above. Owing to the fact that IDF publishes only the number of prevalence cases and not PP, we needed to retrieve population statistics for 2007 to calculate the PP for each country and age group. Such statistics were retrieved from the Eurostat website and for non-European countries from the respective Country Statistics website.

Analyses assessing SPR of diabetes by some selected covariates were conducted using multiple log-linear Poisson working regression models with model-robust standard error estimates and log of expected number of prevalence cases as offset. Studied covariates were gender, age at KIMS entry, country, etiology group, duration of GHD, BMI, waist circumference, and IGF1 SDS. For the reason of comparison, internal reference models were also studied. In these models a number of patients were set as offset. Estimates and 95% confidence intervals (95% CIs) were likelihood based. SAS v8.2 Proc Genmod was used for robust Poisson regression analyses (19).

Covariance analyses for HbA1c categories with adjustment for gender and age were performed with SAS version 8.2 PROC GLM. The statistical analyses for the different outcome variables were performed by covariance analyses for unbalanced designs (SAS version 8.2; PROC GLM, Marlow, UK).

Results

Prevalence of diabetes mellitus and relation to variables

A total of 6050 patients with a mean age ($\pm$S.D.) of 49.0 ± 12.5 years were included in the analysis. Males numbered 2966 (49.0%; mean age, 49.9 ± 12.7 years) and females 3084 (51.0%; mean age, 48.2 ± 12.3 years). Detailed information on prevalence and on standardized prevalence ratio is given in Table 1.

- Whole cohort: the crude PP for diabetes was 9.3% (563/6050) vs the expected PP of 8.2%. The overall SPR was 1.13 (95% CI, 1.04–1.23%).
- Gender: crude PP vs expected PP in males was 8.9% (264/2966) vs 8.6%, and 9.7% (299/3084) vs 7.9% in females. SPR in females was increased (1.23; 95% CI, 1.09–1.38%), while this was not the case in males (1.04; 95% CI, 0.92–1.17%). There was a significant difference in SPR between genders ($P=0.043$).
- Age: mean age ($\pm$S.D.) was 52.2 ± 12.1 years in the diabetes group vs 48.7 ± 12.5 in the nondiabetes group ($P<0.0001$). A gradual and significant increase in diabetes prevalence was observed with increasing age as depicted in 10-year age categories in both males (Fig. 1a) and females (Fig. 1b). The increase was 26% (95% CI, 18–35%) per decade ($P<0.0001$). There was, however, a progressive and significant decrease in SPR ($P<0.0001$). The trend decrease in SPR by age decade was -36% (95% CI, -41 to -31%).
- Family history of diabetes: diabetes prevalence was influenced by the presence of familial diabetes (19.9 vs 5.8%; $P<0.0001$). SPR also showed a significant difference ($P<0.0001$).
- Country of origin: differences in SPR were noted between countries, as shown in Table 1 for the seven countries with at least 400 patients. Heterogeneity test adjusted for gender, age, diagnosis, and BMI showed significance ($P<0.0001$).
- Etiology of GHD: differences in SPR were observed between the most frequent causes of GHD. Heterogeneity test adjusted for gender, age, country, and BMI was marginally nonsignificant ($P=0.057$).
- Duration of GHD: mean duration ($\pm$S.D.) was 6.2 ± 8.2 years in the diabetes group vs 6.1 ± 7.4 in the nondiabetes group ($P=0.79$). Diabetes prevalence was not influenced by the estimated duration of GHD ($P=0.095$). SPR showed no trend ($P=0.53$).
- Number of additional pituitary deficiencies: diabetes prevalence was negatively influenced by the extent of hypopituitarism expressed as the number of additional pituitary deficiencies ($P=0.021$). However, SPR showed a marginally nonsignificant trend ($P=0.060$).
- IGF1 SDS: mean IGF1 ($\pm$S.D.) was -1.7 ± 1.5 SDS in the diabetes group vs -1.6 ± 1.5 in the nondiabetes

group ($P=0.15$). SPR showed a significant 16% (95% CI, 7.3–23.8%) increase per lower IGF1 SDS category ($P=0.0005$).

- BMI: mean BMI ($\pm$S.D.) was 33.4 ± 7.4 kg/m^2 in the diabetes group vs 29.3 ± 6.4 in the nondiabetes group ($P<0.0001$). Escalating BMI categories were associated with a progressive increase of diabetes prevalence in both genders ($P<0.0001$), reaching 25% in the highest BMI category (Fig. 1c). SPR increased gradually and significantly by BMI

Table 1 Background data of GHD patients before GH replacement. Crude prevalence and standardized prevalence ratio (SPR) for diabetes mellitus is presented for different variables.

	Prevalence (%)	**SPR**	**95% Confidence interval for SPR**	***P* for SPR**
Gender				
All	9.3	1.13	1.04–1.23	0.043
Males	8.9	1.04	0.92–1.17	
Females	9.7	1.23	1.09–1.38	
Age categories (years)				
20–39	6.3	5.18	4.18–6.34	*P* trend <0.0001
40–59	9.1	1.29	1.15–1.45	
60–79	13.5	0.67	0.57–0.78	
Familial diabetes mellitus				
No	5.8	0.72	0.62–0.82	<0.0001
Yes	19.9	2.39	2.09–2.72	
Country of origin				
Germany	8.1	0.71	0.57–0.88	*P* heterogeneity <0.0001
Belgium	6.7	0.84	0.58–1.16	
Sweden	9.0	1.09	0.82–1.41	
Spain	6.9	1.11	0.76–1.56	
The Netherlands	9.1	1.18	0.84–1.62	
USA	14.3	1.35	1.15–1.58	
UK	9.8	2.39	1.95–2.90	
Etiology of GHD				
Pituitary adenoma	8.0	0.88	0.77–1.00	*P* heterogeneity 0.057
Other pituitary tumors	6.7	0.98	0.62–1.49	
Extrasellar tumors	4.8	1.18	0.43–2.58	
Craniopharyngioma	8.2	1.41	1.01–1.90	
Idiopathic/congenital GHD	14.1	1.49	1.25–1.78	
GHD duration (years)				
<1	10.7	1.18	0.97–1.43	*P* trend 0.53
1–2	9.7	1.18	0.95–1.46	
2–5	7.7	1.01	0.82–1.23	
>5	9.0	1.13	0.98–1.29	
Additional deficiencies				
+0 (isolated GHD)	11.2	1.29	1.07–1.55	*P* trend 0.060
+1	10.2	1.23	1.01–1.48	
+2	10.1	1.27	1.04–1.55	
+3	7.9	0.89	0.76–1.04	
+4	8.5	1.25	0.98–1.57	
IGF1 SDS				
+2 to +1	6.1	0.74	0.20–1.89	*P* trend 0.0005
+1 to 0	7.5	0.86	0.54–1.31	
0 to −1	7.0	0.91	0.66–1.21	
−1 to −2	8.1	1.04	0.81–1.32	
−2 to −3	10.3	1.54	1.16–2.01	
<−3	9.8	1.53	1.12–2.05	
BMI categories (kg/m^2)				
<20	1.8	0.29	0.03–1.03	*P* trend <0.0001
20–25	4.5	0.59	0.44–0.78	
25–30	6.2	0.70	0.58–0.83	
30–35	11.0	1.30	1.10–1.52	
35–40	15.9	2.09	1.67–2.57	
>40	24.8	3.47	2.80–4.27	
Waist circumference (cm)				
Males <94 to females <80	3.4	0.50	0.34–0.74	*P* trend <0.0001
Males 94–98 to females 80–84	3.5	0.45	0.26–0.73	
Males 98–102 to females 84–88	7.5	0.94	0.67–1.28	
Males 102–106 to females 88–92	6.7	0.78	0.54–1.08	
Males 106–110 to females 92–96	8.1	1.00	0.70–1.38	
Males >110 to females >96	15.0	1.83	1.59–2.08	

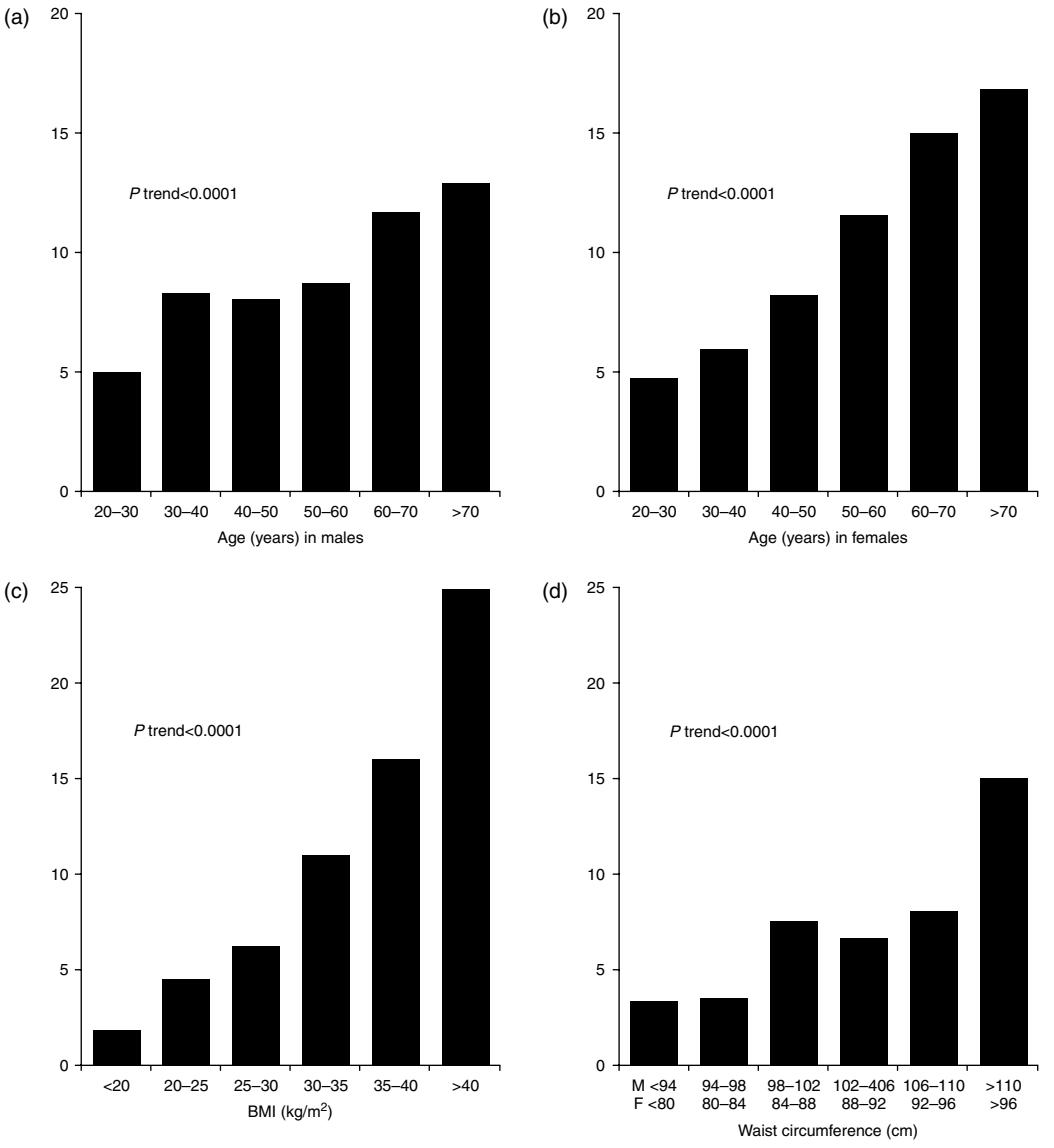

Figure 1 Prevalence of diabetes mellitus in hypopituitary patients with GH deficiency according to the KIMS database and presented per decade in males (a), per decade in females (b), per BMI group (c), and per waist circumference group (d).

category ($P<0.0001$). The trend increase in SPR by BMI category was 63% (95% CI, 52–75%). However, an elevated SPR was only found in patients with BMI >30 kg/m^2.

- Waist circumference: mean waist ($\pm$S.D.) was 106.8 ± 15.6 cm in the diabetes group vs 97.4 ± 14.2 in the nondiabetes group ($P<0.0001$). Escalating waist circumference categories were associated with a nonlinear increase of diabetes prevalence in both genders ($P<0.0001$), reaching 15% in the highest waist category (Fig. 1d). SPR increased by higher waist category ($P=0.0001$), but an increased SPR was observed only in the highest waist category.

Multiple regression model

Variables included in the multiple regression model performed on the total cohort of 6050 patients were gender, age, country, etiology, and BMI. Results for the external reference model are presented in Table 2. When the above-listed variables were incorporated into the model, age explained 41% of total χ^2 and BMI 38%. The SPR increased by 56% per BMI category (95% CI, 45–68%), whereas SPR decreased by age, indicating that, with increasing age, PP in the GHD cohort became more similar to the PP in the general population.

In the model with internal reference, BMI demonstrated the greatest relative impact in terms of total χ^2

Table 2 Multiple regression model with external reference.

Covariate	Relative SPR	95% Confidence limits	Explanatory value for covariate	χ^2	Pr$>\chi^2$	Percentage of total χ^2
Females vs males (reference)	1.00	0.83–1.19	Gender	0.00	0.9749	0
Age group 40–59 vs 20–39 (reference)	0.24	0.19–0.31	Age group	147.96	<0.0001	41
Age group 60–79 vs 20–39	0.14	0.11–0.19				
Country			Country	64.79	<0.0001	18
Etiology			Etiology	12.25	0.0566	3
BMI <25 (reference)	1.00	–				
BMI 25–30 vs <25	1.35	0.98–1.86				
BMI 30–35 vs <25	2.43	1.77–3.33				
BMI 35–40 vs <25	3.57	2.53–5.03	BMI group	140.71	<0.0001	38
BMI >40 vs <25	5.44	3.84–7.71				
Trend per BMI unit	1.56	1.45–1.68				

Relative standardized prevalence ratio (SPR) and percentage total χ^2 are presented per variable.

with 71% followed by age with 21%. The relative PP (RPP) increased by 58% per BMI category (95% CI, 47–70%), similar to the external reference model. The RPP increased by 59% (95% CI, 38–82%) per 20-year age category or 26% (95% CI, 17–35%) per decade. Estimates for genders were, as in the external reference model, similar.

In the subgroup of 2825 patients with centralized IGF1 analysis, the external reference multiple regression model also included the IGF1 SDS categories as variable. Results were similar to results in Table 2 and SPR decreased by 14.7% per IGF1 SDS category (95% CI, −23.1 to −5.4%; $P=0.003$). Results for the internal reference model were similar.

Characteristics of nondiabetic patients

Patients without the diagnosis of diabetes and with data on HbA1c numbered 2790 (mean age, 48.8 ± 12.7 years) and consisted of 1431 males (51.3%; mean age, 50.2 ± 12.5 years) and 1359 females (48.7%; mean age, 47.4 ± 12.6 years). Detailed information is given in Table 3.

- Gender: about 9.5% (264/2790) of this cohort, 9.7% males and 9.2% females, presented with an HbA1c concentration between 6.0 and 6.5%.
- Age: increased by HbA1c group, also for both genders.
- Duration of GHD: covariance analysis with adjustment for gender and age showed no statistically significant correlation between HbA1c groups and GHD duration ($P=0.058$).
- Additional hormonal deficiencies: ACTH deficiency was present in about 65% of patients without a significant difference between the HbA1c groups ($P=0.64$).
- IGF1 SDS: the highest percentage of patients with an IGF1 SDS <−2 was found in the <4.5 HbA1c group, while the lowest percentage was found in the 6.0–6.5 HbA1c group. There was a statistically significant trend in increasing IGF1 SDS by increasing HbA1c category, also after adjustment for gender and age ($P=0.0016$). Covariance analysis with adjustment for gender and age showed that the only significant difference for the 6.0–6.5 HbA1c group was with the <4.5 HbA1c group, which presented with the lowest IGF1 SDS ($P=0.028$).
- BMI: covariance analysis with adjustment for gender and age showed a progressive and significant increase in BMI by escalating HbA1c group ($P<0.0001$ for each successive group).
- Waist circumference: covariance analysis with adjustment for gender and age showed a progressive and significant increase in waist circumference by HbA1c group ($P<0.0001$ for each successive group).

Discussion

This study from the KIMS database demonstrated that the prevalence of diabetes mellitus in the GHD patients included was significantly increased compared with the general population, reaching a SPR of 1.13 (95% CI, 1.04–1.23%). This prevalence can be considered a conservative estimation as the database was not intended to collect stringent data on glucose metabolism by performing tolerance testing in patients. The diagnosis of diabetes was therefore only retained in those patients presenting with one of the following three conditions, namely the report by the treating physician of the presence or treatment of diabetes, an increased fasting or non-fasting plasma glucose concentration, or an elevated HbA1c. This information can be compared with data made recently available from the HypoCCS Database, where the crude and the age-standardized prevalence of diabetes mellitus in 6672 GHD patients was estimated at 8.2% (95% CI, 7.6–8.9%), while in KIMS the prevalence amounted to 9.3% (20). Differences in the KIMS approach might explain this variance, such as country recruitment, restriction to adult-onset GHD, older age group, and higher mean BMI.

In the crude analysis, females were presented with a significant higher diabetes prevalence than males, but

Table 3 Background data of GHD patients without reported diabetes mellitus and with available HbA1c before GH replacement.

HbA1c group	<4.5%	4.5–5.0%	5.0–5.5%	5.5–6.0%	6.0–6.5%
n (%)	396 (14.2)	604 (21.7)	817 (29.2)	709 (25.4)	264 (9.5)
Gender					
Males (%)	13.6	21.9	28.2	26.6	9.7
Females (%)	14.9	21.3	30.4	24.2	9.2
Age (years±S.D.)					
All	45.6±12.2	48.4±13.1	48.5±12.6	49.9±12.5	53.1±11.2
Males	48.3±12.5	49.2±13.1	49.6±12.7	50.9±12.1	55.3±10.5
Females	43.0±11.4	47.5±13.1	47.3±12.5	48.8±12.9	50.5±11.4
GHD duration (years±S.D.)	7.0±7.2	7.3±8.1	6.4±7.1	6.8±7.8	6.4±6.7
IGF1 SDS±S.D.	−2.0±1.7	−1.7±1.5	−1.5±1.4	−1.4±1.5	−1.4±1.4
<−2 (%)	43.9	36.4	33.6	28.1	26.4
−2 to 0 (%)	47.7	53.2	53.1	55.0	58.1
BMI (kg/m^2±S.D.)	27.9±5.1	28.7±5.4	29.0±5.6	29.4±5.5	31.1±6.1
<25 (%)	30.0	24.8	24.7	21.8	13.6
>30 (%)	27.6	34.3	37.2	39.7	52.1
Waist circumference (cm±S.D.)	94.5±12.8	96.6±13.9	97.5±14.8	98.6±13.6	102.7±12.9
Males <102, females <88 (%)	56.1	48.7	44.0	41.4	24.7
Males >110, females >96 (%)	24.0	27.5	32.7	35.6	44.4

the significance was no longer observed when gender was entered as an independent variable in the regression analysis. The female preponderance has also been observed in a Swedish study reporting on 685 GHD patients (21). The prevalence odds ratio was reported to be 2.53 (95% CI, 1.54–4.13%) in females and 1.07 (95% CI, 0.68–1.68%) in males. However, after excluding acromegaly and Cushing's disease and after confounder adjustment for BMI, this prevalence odds ratio was no longer statistically significant (1.57; 95% CI, 0.87–2.84%).

In GHD patients, as in the general population (18, 22), age was an important variable influencing the prevalence of diabetes in GHD as the increase paralleled age progression. This was apparent in both genders, but crude analysis and regression analysis showed that it occurred at a slower pace compared with the increase in the reference population. This latter observation could be due to the fact that in the general reference population diabetes prevalence is relatively low in young adults, resulting in an elevated SPR, and to the increased prevalence of risk factors for diabetes in GHD patients, as reported previously (23). Other factors related to a younger age, such as a profound clinical impact of obesity inducing a more rapid insulin resistance, have been proposed (24). The multiple regression models, the external as well as the internal, emphasized the importance of age as a determinant for the development of diabetes, as the impact amounted to 41% of SPR and 21% of PP respectively. The difference between the reference models may be explained by the difference in prevalence related to the distributions of age and countries between the KIMS cohort and the general population.

A feature even more profoundly associated with the prevalence of diabetes than age is obesity. This has been clearly demonstrated in the general population using BMI, waist circumference, and waist–hip ratio as markers for weight (25, 26). Also in this study, diabetic patients showed a significantly higher BMI and waist circumference than the nondiabetic patients. Both SPR and PP estimates were elevated in overweight patients and became significantly increased in the case of obesity with a strong relationship to increasing BMI categories. Escalating waist categories were also associated with a progressively increasing SPR. The major influence of BMI on the development of diabetes was demonstrated in the multiple regression analysis as BMI accounted for an impact of 38% on SPR in the external reference model and for 71% on PP in the internal reference model.

Other covariates with a clear influence on the prevalence of diabetes were a familial history of diabetes, as expected from the genetic background of the disease, the country of origin, and the IGF1 SDS. Across countries, different approaches in the recruitment of GHD patients, excluding diabetic patients from GH replacement and thus from KIMS enrollment, may reflect the significant differences in SPR in the crude analysis and in the regression model. Lower IGF1 SDS categories were associated with a significant increase in diabetes prevalence, which was obvious in the case of an IGF1 SDS <-2. This finding is in line with the observation that IGF1 may have a protective role against the development of glucose intolerance (27).

Covariates with a less pronounced or absent effect on the prevalence of diabetes were the etiology of GHD, the number of pituitary deficiencies, and the duration of GHD. Two etiologies associated with an increased diabetes prevalence were craniopharyngioma and idiopathic GHD, as reflected in the significant impact in the PP analysis, although marginally nonsignificant in the SPR analysis. The number of additional deficiencies apart from GH showed some impact, as indicated by the highest prevalence of diabetes in isolated GHD, but without a trend in SPR by increasing number of deficiencies. The fact that isolated GHD and

GHD in combination with multiple pituitary deficiencies are both equally associated with the development of diabetes adds an indirect argument to the concept that GHD in adult-onset hypopituitarism by itself plays a not unimportant role in the development of the characteristic adverse metabolic profile, and therefore GH replacement may be regarded essential (28). The duration of GHD had no influence on the presence of diabetes, despite this determinant having previously been demonstrated to be the single most important predictor of insulin resistance in a study using the hyperinsulinemic normoglycemic clamp technique in a small group of patients (10).

The advantages and drawbacks of large pharmacoepidemiological databases are now well recognized (13). The KIMS database was not conceived to permit an accurate analysis of glucose metabolism in GHD patients as no preliminary requirements for the measurement of glycemia and insulin had been defined. The presented information therefore suffers from individual preferences of the treating physician, biased selection of patients, and incomplete data, but this imperfection is in a way compensated for by the large number of patients with documented severe GHD. Moreover, the criteria for diabetes used here may potentially not be strictly identical to the ones from the general population assessment. Nevertheless, the present criteria used to define diabetes in this study are strict and restrictive as they relate to an elevated glycemia, an elevated HbA1c, and an anti-diabetic treatment, and are thus in accordance with the latest IDF requirements (18). The SPR and PP for diabetes in GHD reported here can therefore be considered a conservative assessment.

Recently, serum HbA1c has been proposed as a screening tool for the early detection of diabetes (18). A systematic review of primary cross-sectional studies of HbA1c using the glucose tolerance test as the reference standard and fasting plasma glucose as a comparison has indicated that HbA1c is an effective screening tool and that a cutoff point of equal to or more than 6.1% was recommended to detect diabetes (29). For the whole cohort of GHD patients, a HbA1c more than 6.5% was considered to be the diagnostic marker of diabetes and these patients were included in the global analysis. As a consequence, this choice left in the HbA1c study a subset of 9.5% potentially diabetic patients with a value between 6.0 and 6.5%. This hitherto unreported finding might be the cause for the recently published observation that GHD patients have a significantly increased risk for developing diabetes especially during the first years of GH replacement that decreases with duration of this treatment (30). In the comparative analysis to lower HbA1c categories, these patients were characterized by older age, higher BMI, and larger waist circumference, while GHD duration and additional deficiencies, including ACTH deficiency, did not show major differences. The data regarding IGF1 SDS were intriguing since higher values are related to a higher HbA1c concentration, leading to a significant difference between the lowest and highest HbA1c groups. A more liberal assessment of the prevalence of diabetes would thus include the 563 patients from the diabetes mellitus prevalence study and the 264 patients from the HbA1c study, resulting in a crude PP for diabetes of 13.7%.

In conclusion, we have demonstrated an increased prevalence of diabetes mellitus in a large cohort of GHD patients before GH replacement. We consider the figures presented as a conservative estimate, because especially in the first years of the database patients with known diabetes might have been excluded from GH replacement due to the expectation that this treatment might negatively affect carbohydrate metabolism. Despite the well-defined GH effects on carbohydrate metabolism suggesting a decreased diabetes prevalence in GHD patients, the observed increased prevalence might be due to GHD-associated changes in body composition and associated risk factors. Moreover, we identified an additional group of GHD patients associated with elevated HbA1c at risk to develop diabetes and characterized by the highest BMI and waist circumference values. In view of the increased incidence of diabetes during the first year of GH replacement, it may be imperative to initiate simultaneously a lifestyle modification program with intensified weight management and increased physical activity.

Declaration of interest

P Wilton has nothing to disclose and was an employee of Pfizer, Inc. at the time this manuscript was written but is no longer employed by Pfizer, Inc. M Thunander has nothing to disclose.

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Author contribution statement

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