Prevalence of Metabolic Syndrome in Adult Hypopituitary Growth Hormone (GH)-Deficient Patients Before and After GH Replacement

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Context and Objective: Metabolic and body compositional consequences of GH deficiency (GHD) in adults are associated with a phenotype similar to the metabolic syndrome (MetS).

Patients: We assessed MetS prevalence in adult GHD patients (n = 2531) enrolled in the Hypopituitary Control and Complications Study. Prevalence was assessed at baseline and after 3 yr of GH replacement in a subset of 346 adult-onset patients.

Results: Baseline MetS crude prevalence was 42.3%; age-adjusted prevalence in the United States and Europe was 51.8 and 28.6% ($P < 0.001$), respectively. In the United States, age-adjusted prevalence was significantly higher ($P < 0.001$) than in a general population survey. Increased MetS risk at baseline was observed for age 40 yr or older (adjusted relative risk 1.34, 95% confidence interval 1.17–1.53, $P < 0.001$), females (1.15, 1.05–1.25, $P = 0.002$), and adult onset (1.77, 1.44–2.18, $P < 0.001$). In GH-treated adult-onset patients, MetS prevalence was not changed after 3 yr (42.5–45.7%, $P = 0.172$), but significant changes were seen for waist circumference (62.1–56.9%, $P = 0.008$), fasting glucose (26.0–32.4%, $P < 0.001$), and blood pressure (59.8–69.7%, $P < 0.001$). Significantly increased risk of MetS at yr 3 was associated with baseline MetS (adjusted relative risk 4.09, 95% confidence interval 3.02–5.53, $P < 0.001$) and body mass index 30 kg/m^2 or greater (1.53, 1.17–1.99, $P = 0.002$) and increased risk (with a P value < 0.1) for GH dose 600 μg/d or greater (1.18, 95% confidence interval 0.98–1.44, $P = 0.088$).

Conclusion: MetS prevalence in GHD patients was higher than in the general population in the United States and higher in the United States than Europe. Prevalence was unaffected by GH replacement, but baseline MetS status and obesity were strong predictors of MetS after GH treatment. (***J Clin Endocrinol Metab*** **95: 74–81, 2010)**

Patients with the adult GH deficiency (GHD) syndrome have several metabolic abnormalities (1–3), and it has been postulated that the increased cardiovascular morbidity and mortality reported in hypopituitary GH-deficient patients (4–6) may be related to the missing metabolic effects of GH (7). Johannsson and Bengtsson (8) pointed out that the

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Abbreviations: AO, Adult onset; BMI, body mass index; BP, blood pressure; CI, confidence interval; CO, childhood onset; FG, fasting glucose; GHD, GH deficiency; HypoCCS, Hypopituitary Control and Complications Study; MetS, metabolic syndrome; MPHD, multiple pituitary hormone deficiency; NCEP-ATPIII, National Cholesterol Education Program; NHANES, National Health And Nutritional Examination Survey; RR, relative risk; WC, waist circumference.

adult GHD phenotype shares features such as abdominal obesity, dyslipidemia, and insulin resistance with the metabolic syndrome (MetS), a cluster of risk factors for cardiovascular disease and type 2 diabetes (9, 10).

Accordingly, in overweight or obese adult patients with GHD, the metabolic abnormalities typical of the MetS could be associated with GHD but could also exist independently of GHD. In such a situation, cause and effect may overlap; on the one hand, obesity and metabolic abnormalities may be consequences of GHD (1, 2, 8), whereas on the other, obesity *per se* may cause endocrine perturbations (11). This aspect has been taken into account in the biochemical diagnosis of GHD by standardizing the GH response in stimulation tests for the degree of existing obesity (12, 13). However, obesity *per se* may affect not only GH secretion but also the clinical presentation of the adult GHD syndrome as well as GH treatment effects.

Although the nature of MetS as a disease entity continues to be debated (10), its concept provides a means by which patients at risk can be identified and categorized with routinely available measures (10, 14, 15). In this study, we determined the prevalence of MetS in a cohort of adult GH-deficient patients enrolled in the Hypopituitary Control and Complications Study (HypoCCS), a large international observational study (16). Because patients with GHD are enrolled in HypoCCS in both the United States and Europe, we could compare the MetS prevalence for patients from both regions. We also studied the effects of GH replacement for 3 yr in a subgroup of the total cohort to elucidate the extent to which the metabolic abnormalities seen in adults with GHD are affected by GH replacement.

Patients and Methods

HypoCCS is a surveillance study that collects long-term efficacy and safety data on adult GH-deficient patients treated with recombinant human GH (Humatrope; Eli Lilly & Co., Indianapolis, IN) in the United States, Canada,, and different European countries. Institutional review committee approval and written consent for data collection, electronic processing and publication were obtained from patients in accordance with national laws and regulations. To qualify for the present analysis, patients from the database with documented severe GHD (defined by a peak GH <3.0 μg/liter in a GH stimulation test or <9.0 μg/liter in the GHRH-arginine test) had to have full baseline information on all five criteria defining the MetS. Of 7895 patients enrolled in the observational study from 1996 to 2006, these criteria were fulfilled in 2531 patients from the United States and Europe (Austria, Belgium, Czech Republic, Denmark, France, Germany, Hungary, Italy, Norway, Spain, Sweden, The Netherlands, United Kingdom). To diagnose MetS, we used the definition of the National Cholesterol Education Program (NCEP-ATPIII) (14), as updated in 2004 (17), by which MetS is characterized by three or more of the following: 1) central obesity measured by waist circumference (WC) ($\geq$102 cm for male, $\geq$88 cm for female); 2) fasting glucose (FG) 100 mg/dl or greater ($\geq$5.6 mmol/liter) or diabetes diagnosis or drug treatment for elevated glucose; 3) serum triglyceride concentration 150 mg/dl or greater ($\geq$1.7 mmol/liter); 4) high-density lipoprotein cholesterol less than 40.0 mg/dl ($<$1.03 mmol/liter) for men and less than 50.0 mg/dl ($<$1.29 mmol/liter) for women; and 5) blood pressure (BP) 130/85 mm Hg or greater or on antihypertensive treatment. Of the 2531 evaluable patients, 346 with adult onset (AO) GHD had full information on all five MetS criteria at baseline and at follow-up at yr 3 of GH replacement, allowing calculation of MetS prevalence after GH replacement.

Statistical analysis

Mean and SD are presented for continuous variables unless otherwise specified. Counts and percentages are presented to describe categorical variables. ANOVA was used to compare the continuous variables between subgroups. χ^2 tests were applied to compare categorical variables unless otherwise specified. Age-adjusted MetS prevalence and 95% confidence intervals (CIs) were estimated using a direct standardization method (18). To compare the MetS prevalence between the United States and Europe, age standardization according to the world population structure (19) was performed. For U.S. patients only, the MetS prevalence found in HypoCCS was compared with the data from the National Health And Nutritional Examination Survey (NHANES) 1999–2000 (17) after standardization to the U.S. 2000 census (20). For Europe, a similar comparison was not done because no study population matching the by-country distribution in HypoCCS was available.

Relative risks (RRs) of MetS prevalence were calculated using log-binomial models (21) adjusting for age, gender, onset type, and lipid-regulating medication (yes/no) as well as baseline MetS and duration of GHD if applicable. When nonconvergence occurred, Poisson regression models were used (22). A McNemar test was used to compare the overall MetS prevalence at baseline and yr 3 within the AO patient cohort (n = 346). Average daily GH dose (micrograms per day) was estimated for the first 3 yr from each follow-up visit, excluding the dosing reported during the first 6 months of treatment. The association of GH dose with presence of MetS at yr 3 was investigated using two cutoff levels: 600 and 720 μg/d, which, respectively, correspond to the 75th and 90th percentiles of the GH dose range in HypoCCS.

Results

MetS prevalence in the total adult GHD cohort at baseline

In Table 1, the demographic and clinical characteristics, as well as the crude and age-adjusted prevalence of MetS at baseline, are presented for the total cohort of 2531 patients and for U.S. and European cohorts separately. The U.S. cohort was statistically significantly older than the European cohort. Gender distributions were comparable, and there were significantly more patients with childhood-onset (CO) GHD in Europe than the United States; CO patients were significantly younger than AO patients. For the total cohort, the overall crude MetS prevalence was 42.3% and for the U.S. and European cohorts,

TABLE 1. Baseline demographics, clinical characteristics, and prevalence of MetS in the total HypoCCS cohort and in the United States *vs.* European patients

	Total cohort (n = 2531)	United States (n = 1111)	Europe (n = 1420)	*P* value (United States *vs.* European Union)
Age (yr, mean ± SD)				
All patients	47.7 ± 15.3	50.5 ± 15.0	45.6 ± 15.3	<0.001
AO	51.4 ± 13.4	52.8 ± 13.4	50.1 ± 13.3	<0.001
CO	30.2 ± 11.6	32.0 ± 13.3	29.5 ± 10.7	0.037
Female/male (%)	46.2/53.8	44.7/55.3	47.3/52.7	0.195
AO/CO (%)	82.9/17.1	88.6/11.4	78.5/21.5	<0.001
BMI (kg/m^2)				
Mean ± SD	29.9 ± 6.8	31.8 ± 7.2	28.4 ± 6.1	<0.001
Median		30.6	27.5	
Q1:Q3 interquartile range		26.7:35.5	24.3:31.2	
MetS prevalence (%)				
Total cohort crude	42.3	56.6	31.1	<0.001
Age adjusted[a]		51.8	28.6	<0.001
AO (n = 2095) crude	46.8	59.4	35.6	<0.001
Age adjusted[a]		54.6	30.7	<0.001
CO (n = 431) crude	20.6	35.4	14.5	<0.001
Age adjusted[a]		28.1	15.5	0.012

[a] Prevalence standardized to the world population age structure.

56.6 and 31.1% ($P < 0.001$), respectively. The age-adjusted prevalence was 51.8% (95% CI 48.1–55.4%) in the U.S. cohort and 28.6% (95% CI 26.2–31.0%) in the European cohort ($P < 0.001$). By onset, the overall crude prevalence was 46.8% in AO and 20.6% in CO patients, and in both onset groups, MetS prevalence was higher in the United States than Europe (AO: 59.4 *vs.* 35.6%, $P < 0.001$; CO: 35.4 *vs.* 14.5%, $P < 0.001$). For the U.S. cohort, the age-adjusted MetS prevalence, standardized to the U.S. 2000 census population, was 53.2% (95% CI 49.9–56.6%), significantly ($P < 0.001$) higher than the reported prevalence of 32.3% in the NHANES survey (17).

Because of the difference in the proportion of AO and CO patients between the United States and Europe, prevalence of individual MetS criteria was assessed in AO patients only. As shown in Fig. 1, the most prevalent MetS criteria in the combined cohort were WC (total cohort: 54.9%; United States: 64.2%, Europe: 54.0%) and BP (total cohort: 55.7%; United States: 57.6%; Europe: 52.5%). For each MetS criterion, the prevalence was significantly ($P < 0.001$) higher in the United States than the European cohort. The most pronounced difference was seen in the FG criterion, with a prevalence of 44.3% in the United States and 12.5% in Europe.

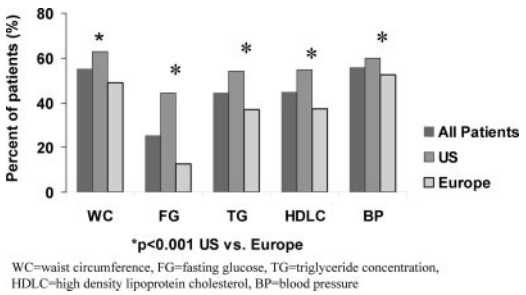

FIG. 1. Prevalence of individual MetS criteria at baseline in patients in HypoCCS with AO GHD.

Table 2 summarizes the risk factors associated with MetS at baseline. Patients aged 40 yr or older had a significantly higher risk of MetS than patients younger than 40 yr (RR 1.34) after adjusting for gender, onset, and use of lipid-regulating medication. Similarly, females had a significantly higher risk than males (adjusted RR 1.15) and AO patients higher than CO patients (adjusted RR 1.77). Crude RR for MetS was significantly elevated in patients with GH deficiency after pituitary adenoma (RR 1.18, $P < 0.001$), but the significance disappeared after adjustment for confounders. We did not find increased prevalence of MetS among patients with craniopharyngioma, previous Cushing disease, or multiple pituitary hormone deficiencies.

MetS prevalence after 3 yr of GH replacement in patients with AO GHD

Because of significant baseline differences between AO and CO patients and the limited number of CO patients with follow-up data, MetS prevalence after 3 yr of GH treatment was assessed in AO patients (n = 346) only. This GH-treated AO GHD group, when compared with the remaining AO patients (n = 1749) of the baseline cohort (n = 2531), was slightly older (52.7 ± 13.2 *vs.* 51.1 ± 13.5 yr, $P = 0.043$) but had comparable gender distributions (53.5% male), body mass index (BMI) values (30.2 ± 6.0 kg/m^2; median: 29.5; Q1-Q3 range: 25.7–33.5) and MetS prevalence (42.5% *vs.* 47.6%, $P = 0.079$). Also, there was no statistically significant difference between U.S. and European patients for age, distributions of gender, and

TABLE 2. Relative risk of baseline MetS in the total cohort (n = 2531)

	Patients with MetS (%)	Crude RR (95% CI)	Crude *P* value	Adjusted RR (95% CI)[a]	Adjusted *P* value[a]
Age					
≥40 yr	48.8	1.75 (1.55–1.98)	<0.001	1.34 (1.17–1.53)	<0.001
<40 yr	27.9				
Gender					
Female	45.8	1.17 (1.06–1.28)	0.001	1.15 (1.05–1.25)	0.002
Male	39.3				
Onset					
AO	46.8	2.27 (1.87–2.74)	<0.001	1.77 (1.44–2.18)	<0.001
CO	20.7				
GHD type					
IGHD	43.9	1.05 (0.92–1.19)	0.507	1.09 (0.96–1.23)	0.181
MPHD	42.0				
GHD cause					
Adenoma	45.5	1.18 (1.07–1.31)	<0.001	0.95 (0.87–1.05)	0.315
Craniopharyngioma	42.4	1.10 (0.94–1.29)	0.217	1.12 (0.97–1.29)	0.119
Any other cause	38.4				
Previous Cushing[b]					
Yes	46.2	0.99 (0.81–1.21)	0.900	1.02(0.84–1.23)	0.846
No	46.8				

IGHD, Isolated GHD; MPHD, multiple pituitary hormone deficiency.

[a] After adjustment for age, gender, onset, and use of lipid-regulating medication.

[b] AO patients only.

type of GHD [isolated IGHD *vs.* multiple pituitary hormone deficiency (MPHD)].

Baseline and yr 3 prevalence of MetS and individual criteria in the GH-treated group overall and for U.S. and European groups are presented in Fig. 2. Overall MetS prevalence did not change significantly from baseline to yr 3 (42.5 *vs.* 45.7%, $P = 0.172$). Corresponding values for the United States were 65.6 and 68.8% ($P = 0.467$), and for Europe 33.6 and 36.8% ($P = 0.248$), respectively. For individual MetS criteria, significant differences between baseline and yr 3 were seen for WC (from 62.1 to 56.9%, $P = 0.008$), FG (from 26.0 to 32.4%, $P < 0.001$), and BP (from 59.8 to 69.7%, $P < 0.001$), with no significant change in lipids. For U.S. and European GH-treated groups, the trends were parallel and consistent with those of the entire group.

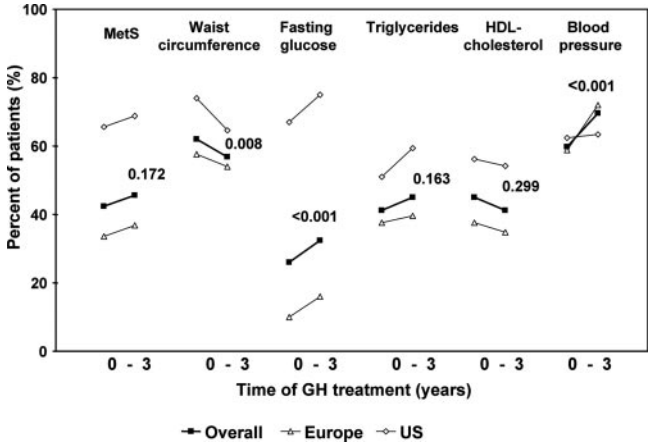

FIG. 2. Prevalence of MetS and individual MetS components at baseline and yr 3, overall (n = 346) and for U.S. (n = 96) and European (n = 250) patients with AO GHD; *P* values are for changes in overall prevalence between baseline and yr 3.

Table 3 presents the RR of having MetS at yr 3 of GH treatment for baseline variables and the GH dose. After adjustment for age, gender, onset, and use of lipid-regulating medication, significantly increased risk of MetS at yr 3 was found in patients who had MetS (RR 4.09, 95% CI 3.02–5.53, $P < 0.001$) and who were obese to overtly obese (BMI ≥ 30, RR 1.53, 95% CI 1.17–1.99, $P = 0.002$) at baseline. Adjusted relative risk was not significant for females *vs.* males (RR 1.16, $P = 0.054$) and for daily GH dose. However, for GH dose the RR increased from 1.18 ($P = 0.088$) for patients taking 600 μg/d or greater to 1.23 ($P = 0.058$) for patients taking 720 μg/d or greater.

Discussion

We assessed the MetS prevalence in 2531 adult GHD patients in a large international surveillance database (16). The crude MetS prevalence for the total cohort was high, at 42.3%, and the U.S. cohort had a significantly higher MetS prevalence than the European cohort. No general population prevalence for MetS for the United States and Europe combined was available for an overall comparison. In the U.S. NHANES survey (17, 20), however, the age-adjusted prevalence rate for MetS using the same NCEP definition was 32.3%, which was 20 percentage points less than the standardized 51.8% seen in the U.S. HypoCCS cohort at base-

TABLE 3. Relative risk of MetS at yr 3 of GH replacement in 346 AO GHD patients

	Patients with MetS (%)	Crude RR (95% CI)	Crude *P* value	Adjusted RR (95% CI)[a]	Adjusted *P* value[a]
Age (yr)					
≥40	48.3	1.50 (1.01–2.24)	0.046	1.09 (0.82–1.44)	0.550
<40	32.1				
Gender					
Female	52.2	1.30 (1.04–1.64)	0.024	1.16 (1.00–1.35)	0.054
Male	40.0				
BMI					
≥30 kg/m^2	70.4	2.90 (2.20–3.81)	<0.001	1.53 (1.17–1.99)	0.002
<30 kg/m^2	24.3				
Baseline MetS					
Yes	81.6	4.27 (3.18–5.75)	<0.001	4.09 (3.02–5.53)	<0.001
No	19.1				
GH dose					
≥600 μg/d	59.0	1.39 (1.08–1.78)	0.010	1.18 (0.98–1.44)	0.088
<600 μg/d	42.6				
≥720 μg/d	62.9	1.44 (1.09–1.92)	0.012	1.23 (0.99–1.52)	0.058
<720 μg/d					

[a] After adjustment for age, gender, duration of GHD, use of lipid-regulating medication, and baseline MetS.

line. This difference was even higher for AO patients alone, in whom the standardized prevalence was 54.6%.

Although we could not find suitable MetS prevalence from a European general population matching the HypoCCS European patients for a direct comparison, recent epidemiological studies using the NCEP-ATPIII definition have reported prevalence in European cohorts ranging from 17% in Spain (23) to 27% in Germany (24) and 25.9% in the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe study, which assessed nine different European population-based cohorts aged 30–88 yr (25). Also, a recent study using the NCEP-ATPIII definition in a Dutch cohort of adult AO GHD patients found a MetS prevalence of 38.0%, more than doubled compared with age-matched controls (26); this was relatively similar to the prevalence of 35.8% in the European AO GHD cohort in HypoCCS. Thus, MetS prevalence is possibly also increased in the European HypoCCS cohort, at least in AO patients.

The increased MetS prevalence in the HypoCCS patients compared with the general population may be associated with the metabolic abnormalities caused by GHD (8). However, the patients in HypoCCS suffer from pituitary disease, in which obesity and metabolic abnormalities may also be caused by other hormonal deficiencies and/or different mechanisms such as hypothalamic involvement. Consistent with van der Klaauw *et al.* (26), we did not find within the HypoCCS database that patients with MPHD, or specifically with craniopharyngioma or Cushing disease, had a higher risk of having MetS, as suggested by other studies (27, 28). This might be explained by the fact that the current study used a composite measure of MetS as the major outcome, whereas other studies used individual metabolic and cardiovascular risk factors, which, taken alone, may have different weight for prospective risk calculation than combined in the MetS algorithm.

Our data, however, suggest that the patients analyzed suffered not only from the metabolic abnormalities caused by GHD and possibly inadequate replacement therapy with L-thyroxine, glucocorticoids, and sex steroids but also from preexisting, GHD-independent conditions, notably obesity and its consequences, and it would be difficult to establish to what extent MetS in an individual patient in HypoCCS is due to GHD alone or preexisting obesity or both. Although the difference in MetS prevalence between the United States and Europe seen in HypoCCS may be partly explained by the older age and the lower proportion of CO patients in the U.S. cohort, the main cause seems to be primarily the difference in the background obesity prevalence. As a consequence, the obesity phenotype of adult GHD patients is different in the United States compared with Europe, which may also imply different prospective cardiovascular and metabolic risk. In the US HypoCCS cohort, the distribution of BMI values indicated that almost 75% of U.S. patients were overweight to obese, and in the NHANES survey, the prevalence of MetS steeply increased with increasing BMI, even after adjustment for age and gender (17). Therefore, it was not surprising that 41.3% of U.S. HypoCCS patients fulfilled the FG criterion because 51.3% of subjects with a BMI 25.0 kg/m^2 or greater were reported to have impaired fasting glucose in the NHANES survey (29).

However, it should be noted that differences in obesity and MetS epidemiology also exist between individual European countries, and, accordingly, the prevalence of MetS in adult patients with GHD may vary throughout Europe. Therefore, country- or population-specific prevalence may significantly contribute to the prospective risk

of adult GHD patients and are likely to influence GH treatment outcomes.

As in the general population, RR for MetS increased significantly with age. In contrast to the general population, in which gender differences have been inconsistent across cohorts (10), the females in the present GHD cohort had a higher RR for MetS. Such higher risk in females has been reported in adult hypopituitary GHD patients (30, 31), and a recent study in 750 adult Swedish GHD patients found an increased prevalence of type 2 diabetes mellitus in women compared with men (32), suggesting that aspects specifically related to GHD or hypopituitarism may contribute to this difference.

In our analysis, the RR for MetS was much higher in AO than CO GHD patients. One major reason for this may be the difference in age range of patients in the two onset groups; the majority of CO patients on adult follow-up in HypoCCS are not older than 40 yr and thus have not reached an age at which risk factors can be reliably evaluated (33). On the other hand, due to the developmental nature of their condition (34), CO patients have been exposed to the consequences of GHD and/or pituitary disease since childhood and may have accumulated metabolic risk that is not identified by the thresholds for the individual MetS components established in otherwise normal adult populations. In this respect, it is noteworthy that available data on adult morbidity and mortality of patients with CO GHD are presently limited and inconsistent (33, 35, 36).

Due to the differences between AO and CO patients, we assessed MetS prevalence after GH treatment in patients with AO GHD only. In view of the established effects of GH action and the favorable changes on metabolic abnormalities seen in many controlled studies in patients with GHD (3), and their postulated effect on prospective risk, the unchanged MetS prevalence after 3 yr of GH replacement was an unexpected finding. However, no effect of GH replacement on MetS prevalence was also seen by van der Klaauw *et al.* (26), and baseline MetS prevalence was the strongest predictor of prevalence at yr 3 of GH therapy. Despite the baseline differences in MetS prevalence between the United States and Europe, the trends over time with GH treatment in prevalence of MetS and of its individual components were almost identical in the overall cohort and in the United States and Europe separately. In longitudinal population-based cohorts, persistence of MetS has been found to be variable and influenced by different factors such as aging, new treatment interventions (*e.g.* lipid regulating), or intraindividual variability of laboratory measurements (37).

In our HypoCCS treatment cohort after 3 yr of GH replacement no change in the lipid criteria was seen, but there was a significant reduction in central obesity, paralleled by a significant increase in patients fulfilling the FG and BP criteria. The limited but significant reduction in the prevalence of the WC component may indeed reflect a GH treatment effect, whereas the increased prevalence of the FG and BP components could primarily be related to ageing of the treated patients (2). On the other hand, the long-term effect of GH substitution on glucose homeostasis in GH-deficient adults has been a matter of debate and published data report improvement as well as deterioration of insulin sensitivity with prolonged GH treatment (3, 38–40). Besides aging, the increasing prevalence of the FG MetS component with GH treatment may be related to several factors, particularly the preexisting obesity because a BMI of 30 kg/m^2 or greater was a strong predictor of MetS prevalence at yr 3. The GH-induced effects may not have been sufficient to affect MetS risk thresholds or, alternatively, beneficial treatment effects on some MetS criteria were canceled out by opposing directional changes in others. Finally, the higher GH dose was weakly associated with MetS prevalence at yr 3; although HypoCCS patients are treated according to current clinical standards and centralized IGF measurements are performed to achieve optimal dose (16, 41, 42), the borderline significance for the 90th percentile GH dose indicate that some patients may have been on a dose higher than optimal. It has been shown that GH overdosing, even if not excessive, may affect FG in the presence of preexisting obesity (43, 44). Improvements in insulin sensitivity in adult GHD patient with GH replacement have been predominantly reported in patients who were not overtly obese and on a strictly low-dose regimen (45).

Our analysis has several limitations. MetS prevalence was not assessed directly in a representative sample of all adult patients with GHD but in an observational study cohort of patients selected for GH treatment. Data sets in observational study cohorts are often incomplete and in fact for baseline prevalence assessment only about one third, and for GH treatment effects only one seventh, of patients from the HypoCCS database had sufficient data for analysis. Therefore, although the number of patients assessed was comparable with other published studies on prospective risk from adult GHD surveillance databases (46), we cannot rule out the possibility that subsets of patients with different MetS risk have been excluded from the prevalence calculations. Possibly they may have carried higher MetS risk because patients with certain preexisting abnormalities, such as glucose intolerance, tend to be excluded from GH treatment. However, for prevalence assessment after GH treatment, this selection bias was likely to be limited because differences between the treatment group and the remaining patients in the baseline analysis were relatively small.

Despite these limitations, the present analysis showed that in adult patients with GHD enrolled into HypoCCS, a database that reflects patients treated with GH, the prevalence of MetS and its individual components is high and is higher in the United States compared with Europe and that the metabolic phenotype of adult patients with GHD differs between the two regions. With GH treatment, nonuniform changes in component indices of the MetS were seen; there were both beneficial and detrimental changes, which collectively resulted in no net change in the overall prevalence of MetS as defined by the criteria used. The data, from a relatively large cohort of patients with AO GHD, raise the question of what impact GHD and its treatment may have on preexisting abnormal metabolic status or obesity. The prospective metabolic and cardiovascular risk associated with the diagnosis of MetS has been established in populations without GHD or pituitary disease, and we can only speculate to what extent its predictive value is applicable to adult patients with GHD. Despite GH replacement, the prevalence of MetS remained unchanged in the treated cohort, suggesting that GH intervention alone cannot affect MetS-associated risk if other non-GHD factors contribute to it. The data confirm that aggressive treatment of these non-GHD-related aspects may be required for measurable metabolic benefits of GH replacement to be achieved.

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