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CLINICAL STUDY

# Growth hormone deficiency and replacement in hypopituitary patients previously treated for acromegaly or Cushing's disease

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## Abstract

*Objective*: To compare baseline characteristics in adult patients with growth hormone (GH) deficiency (GHD) who had previously been treated for Cushing's disease or acromegaly with data from patients with GHD of other aetiologies. To study the effects of GH therapy in those patients who had completed at least 6 months of GH replacement.

*Design*: Data from a large outcomes research database (KIMS (Pharmacia International Metabolic Database)).

*Methods*: 135 patients were identified with previous Cushing's disease, 40 had had acromegaly, and 1392 had GHD of other aetiologies. The number of additional hormone deficiencies, and the mean age of the patients were similar in the three groups. Similar proportions of patients in each group were treated using surgery, but radiotherapy was used more often in patients with acromegaly than those with other diagnoses.

*Results*: At baseline, the prevalence of diabetes mellitus and hypertension were significantly higher in the group treated for Cushing's disease, and the prevalence of stroke was significantly higher in the group treated for acromegaly. The incidence of coronary heart disease and claudication were similar in all three groups. Patients treated for Cushing's disease had lower bone mineral density and suffered fractures more often than other GHD adults. Body mass index, waist-hip ratio, serum concentrations of lipids and standard deviation scores of serum concentrations of insulin-like-growth factor-I were similar in the three groups. The dose of GH administered was comparable in the three groups and the effects of GH replacement on waist circumference, blood pressure and quality of life were also similar across the groups. The numbers and types of adverse events reported were not different between the groups.

*Conclusions*: These data suggest that the characteristics of patients in these diagnostic groups depend on the primary disease which resulted in GHD, and that the clinical expression of GHD does not differ between the groups. Patients with previous hypercortisolism showed more long-term effects of their disease, such as diabetes mellitus, hypertension and fractures. A benefit from GH replacement was evident in patients previously treated for acromegaly and Cushing's disease particularly in relation to quality of life.

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## Introduction

Although the existence of a specific adult growth hormone (GH) deficiency (GHD) syndrome is now well recognised (1), treatment with GH in adults is still controversial in relation to, for example, old age or some types of hypothalamic/pituitary disease. A number of placebo-controlled clinical trials of GH replacement therapy have demonstrated beneficial effects on quality of life (QoL) and body composition occurring over a few months of therapy (2–7) and in bone mineral density in the longer term (8, 9).

The clinical studies on GH therapy have recruited a mixture of patients with childhood onset GHD (10), adult onset GHD (8, 9) and patients with a variety of hypothalamic/pituitary causes of GHD (11). Rare causes such as treated acromegaly and Cushing's disease have been included but in insufficient numbers to

 

compare either the characteristics of GHD or the response to GH therapy (11, 12). GH therapy of GHD patients previously treated for acromegaly has been much debated not least because of recent studies demonstrating a possible relationship between insulin-like growth factor-I (IGF-I) levels and cancer development in normal populations (13) and the overall increased cancer risk in patients with acromegaly (14). Patients with Cushing's disease have a high risk of muscle atrophy and osteoporosis (15, 16), which are also features of GHD, and GH therapy of GHD in these patients might therefore be of particular benefit on muscle function and bone mineral density (8, 9, 17, 18).

The introduction of large databases for GH therapy has enabled the possibility to evaluate individual responsiveness to the treatment (19–21). Therefore, the aim of the present investigation was to utilise the unique opportunity granted by the KIMS outcomes research database (Pharmacia International Metabolic Database) to compare the medical background, clinical presentation, biochemical findings and response to therapy in adult patients with GHD, who had previously been treated for acromegaly or Cushing's disease, with data from patients with GHD of other aetiologies.

## Patients and methods

### *KIMS outcomes research database*

KIMS (Pharmacia International Metabolic Database) is a pharmaco-epidemiological survey of adult GHD patients receiving recombinant human GH replacement therapy (Genotropin, Pharmacia, Stockholm, Sweden), which has been described previously (19). Quality control systems are in place; the accuracy of entry of data into the database is subject to internal and external audit and has also been scrutinised by the physician members of the KIMS Executive Scientific Committee (J P M, R A, B-Å B, U F-R, C W).

### *Patients*

In 1998 a total of 2084 GHD patients from 16 countries were recruited in KIMS; 1567 patients had adult onset GHD and were included in the analysis of baseline characteristics, 135 of the patients had been treated for Cushing's disease and 40 had been treated for acromegaly. The 1392 patients enrolled into KIMS with other aetiologies (157 craniopharyngiomas, 1079 pituitary tumours) were used for comparison purposes (Table 1). Sixty-six percent of patients with Cushing's disease, 60% of patients with acromegaly and 50% of patients with GHD of other aetiologies had previously received GH therapy at the time of enrollment into KIMS (not significant). There was a significantly higher proportion of females in the groups with Cushing's disease (78%) and acromegaly (65%) compared with patients with GHD of other aetiologies (44%) ($P < 0.001$). Among the whole group of 1567 patients, males were slightly younger (47.5 years) compared with females (49.9 years) ($P < 0.01$). The estimated duration of GHD did not differ between the three groups. Diagnosis of GHD was based on a peak serum GH less than 9 mU/l (<3 mcg/l) on dynamic testing, in the majority of the cases by insulin tolerance test (22), followed in frequency by arginine, growth hormone-releasing hormone (GHRH), glucagon, and others. In general, more than 95% of the patients in the database follow the strict diagnostic criteria published by the Growth Hormone Research Society (1).

Most of the patients with Cushing's disease and acromegaly were recruited from 6 of 16 participating countries (The Netherlands, Sweden, Germany, UK, Belgium, Australia). The median proportion of GHD patients with Cushing's disease in these countries was 8.3% (range: 5.5–16.2), whereas 7 of the countries did not enroll any patient with Cushing's disease. The percentage of inclusion for acromegaly was 3.1% (range: 1.5–4.0) with 7 countries without enrollment.

Similar proportions in each group were treated previously using surgery, but radiotherapy was used more often in patients with acromegaly (76%) than in other diagnoses, including Cushing's disease (46%) (Table 1).

**Table 1** Characteristics of GHD in patients previously treated for Cushing's disease, acromegaly or other causes of GHD. Data are given as means±S.D.

| | Cushing's disease | Acromegaly | Other aetiologies |
|---|---|---|---|
| Number of patients | 135 | 40 | 1392 |
| Age (years) | 48.5±11.6 | 49.3±9.1 | 48.8±11.9 |
| Number >65 years | 12 (8.9%) | 2 (5%) | 137 (9.8%) |
| Females % | 78** | 65** | 44 |
| Surgery % | 84.9 | 82.9 | 79.1 |
| Radiotherapy % | 45.7 | 75.6* | 42.7 |
| Duration (years) | 10.8±7.5 | 15.0±7.2 | 8.9±7.8 |
| Number of additional deficiencies | 2.3±1.2 | 2.3±1.0 | 2.5±1.3 |

*$P < 0.05$, **$P < 0.001$: acromegaly/Cushing's disease compared with other aetiologies.

GH replacement was initiated at a maximum dose of 0.125 IU/kg/week (0.042 mg/kg/week) with a subsequent increment to a maximum of 0.25 IU/kg/week (0.083 mg/kg/week) based on individual requirement and responsiveness. These guidelines for therapy did not preclude the use of dose titration independent of body weight but based on clinical response and serum IGF-I measurements. Maintenance GH replacement doses are achieved well within 6 months of commencement of therapy (23) and we have therefore used this time point to examine the effect of GH on quality of life, body composition and blood pressure. In all, 122 patients with Cushing's disease, 33 with acromegaly and 1258 with other aetiologies had data at 6 months. However, numbers were smaller for analyses of individual variables.

### *Methods*

Serum IGF-I was measured by an HCl-extraction radioimmunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). Intra-assay, interassay and total coefficients of variation were <9% in the concentration range 125–1046 μg/l. The assay detection limit was 13.5 μg/l (24). Standard deviation score (SDS) was calculated as Z-score in relation to age-specific values (19):

$$\frac{\text{patient value} - \text{mean of control group}}{\text{standard deviation of control group}}$$

Serum total cholesterol was measured according to the method of Lie *et al.* (25); high density lipoprotein (HDL)-cholesterol as described by Lopez-Virella *et al.* (26) ; and triglycerides by a colorimetric method based on generation of hydrogen peroxide (27). Serum low density lipoprotein (LDL)-cholesterol was calculated according to the Friedewald formula (28). All measurements were conducted centrally.

Waist and hip measurements were conducted according to KIMS Guidelines circulated to all participating physicians, and body mass index (BMI) was calculated as kg body weight/m height$^2$. Blood pressure was measured supine after 5 min rest.

Quality of life (QoL) was measured using the Assessment of Quality of Life in GHD Adults (QoL-AGHDA). This cross-cultural, disease specific, unidimensional, needs-based quality of life instrument has been developed specifically for the detection of deficits in needs achievement in areas which had previously been demonstrated to be most commonly implicated in GHD adults (29). The questionnaire has been shown to have excellent reliability, reproducibility and construct validity across a range of languages (29–31). Higher numerical scores (to a maximum of 25) denote poorer quality of life.

Bone mineral density (BMD) was measured by dual energy X-ray absorptiometry (DXA) of the spine and hip and Z-scores were calculated in accordance with the manufacturer's reference curves (32). Frequency of previous serious fractures was determined by specific enquiry on the case record form.

Presence of diabetes mellitus was defined as a history of diabetes mellitus or a fasting blood glucose above 120 mg/dl or a non-fasting blood glucose above 140 mg/dl. Presence of hypertension was defined as history of hypertension or resting blood pressure above 140/90.

### *Statistics*

Analyses were performed using SAS (Statistical Analysis System, version 6.12, SAS Institute, Cary, NC, USA). Treatment effects were analysed using paired *t*-tests and between group comparisons using unpaired *t*-tests. QoL data were analysed using corresponding non-parametric statistics. Correlations were calculated according to Pearson. Comparison of proportions were performed using Fischer exact test (two proportions) or Chi-square test (more than two proportions). *P* values of $<0.05$ were considered significant.

## Results

### *Baseline characteristics*

The number of additional hormone deficiencies did not differ between the three groups (Table 1). Seventy-three percent of patients treated for Cushing's disease were adrenocorticotrophic hormone (ACTH) deficient and were receiving substitution, and 27% were without substitution therapy and without evidence of hypercortisolism based on either 24-h urinary free cortisol or dexamethasone suppresibility according to each participating centre (in 4 patients information on actual adrenal status could not be obtained).

The prevalence of diabetes mellitus and hypertension were significantly higher in the female patients treated for Cushing's disease ($P < 0.002$) (Fig. 1). Both systolic and diastolic blood pressure correlated with BMI, age and presence of Cushing's disease, while diastolic blood pressure also correlated with female gender and duration of GHD. The prevalence of stroke was significantly higher in the group treated for acromegaly compared with the group with GHD of other causes ($P = 0.003$) and there was no relationship to radiotherapy, duration of GHD, presence of additional deficiencies or gender. Stroke was related to higher age in all groups (Fig. 2). There was a small but significant relationship between stroke and hypertension in the patients treated for acromegaly ($P = 0.03$) (Fig. 3). The incidence of coronary heart disease and claudication was similar in the three groups.

QoL scores by AGHDA demonstrated a poorer quality of life in females treated for Cushing's disease or acromegaly compared with GHD of other causes ($P < 0.05$), but no significant differences in males (Table 2).

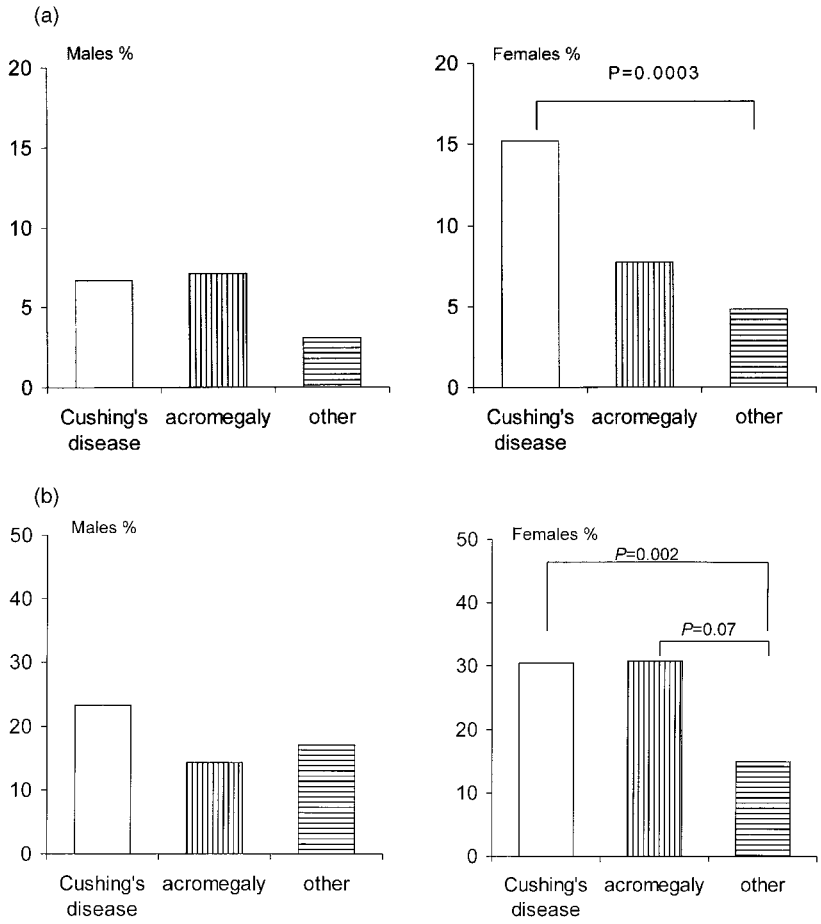


**Figure 1** Prevalence of diabetes mellitus (a) and hypertension (b) in male and female patients with GHD and previously treated Cushing's disease (open bars) ($n = 135$), acromegaly (vertical line bars) ($n = 40$) or other aetiologies of GHD (horizontal line bars) ($n = 1392$).

Waist-hip ratio correlated with age and gender ($P = 0.0001$) but not with aetiology of GHD. No differences were noted between the groups with respect to body mass index, waist-hip ratio, serum lipid concentrations (total, HDL and LDL cholesterol and triglyceride) or IGF-I SDS (Table 2).

BMD both at the lumbar spine and femoral neck was significantly lower in patients treated for Cushing's disease ($P < 0.02$), while that in patients with treated acromegaly did not differ from patients with GHD of other causes (Fig. 4). Female patients treated for Cushing's disease had a significantly higher fracture rate

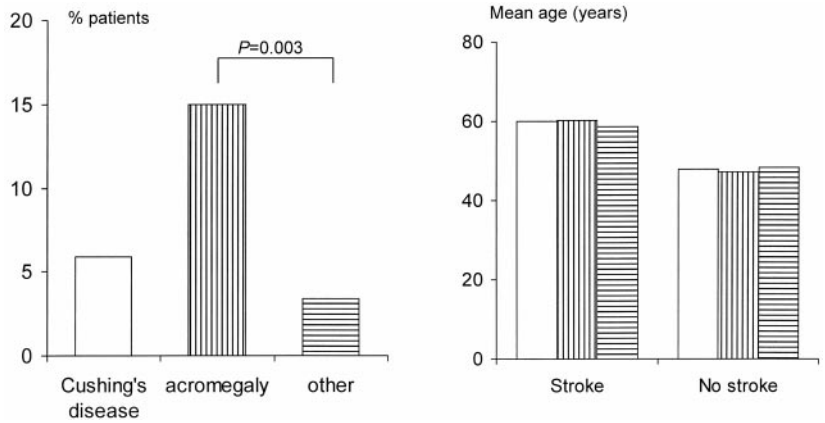


**Figure 2** Prevalence of stroke in patients with GHD and previously treated Cushing's disease, acromegaly or other aetiologies for GHD (left), and relationship with age (right). There was a significant difference between the age of the patients with stroke and the age of the patients without a stroke in Cushing's disease (open bars, $P = 0.004$), acromegaly (vertical line bars, $P = 0.001$) and GHD of other aetiologies (horizontal line bars, $P < 0.001$).

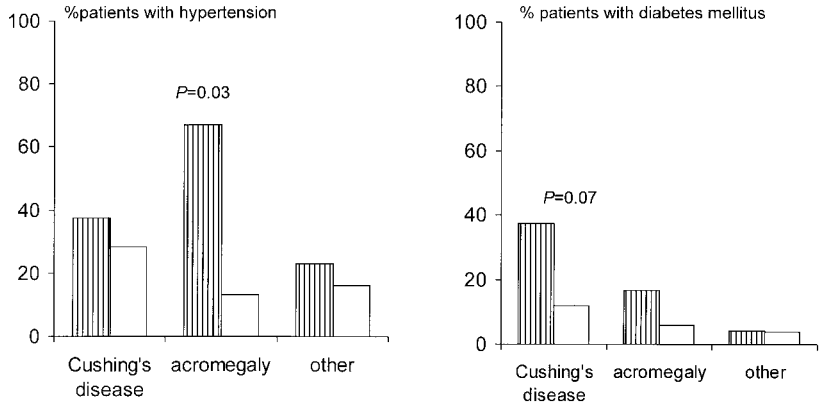


**Figure 3** Influence of the presence of hypertension (left) and diabetes mellitus (right) on stroke in patients with GHD and previously treated Cushing's disease, acromegaly or other aetiologies (other). Vertical line bars indicate percentage of patients with stroke, open bars those without stroke.

after the age of 20 years compared with patients treated for acromegaly ($P = 0.04$) (Fig. 5).

### *Response to GH replacement*

Mean GH replacement doses (1.1 units/day) were similar among the groups without any age or gender difference. Serum IGF-I SDS (mean (S.D.)) on maintenance GH therapy for patients with treated Cushing's disease was +0.8 (±1.9), for acromegaly it was +1.1 (±2.3) and for other aetiologies it was +0.7 (±1.8) (not significant (NS)); there was a similar percentage of patients with serum IGF-I above the age-related reference range in the three groups (2 patients with Cushing's, 1 with acromegaly and 141 of other aetiologies had IGF-I values above 2 S.D.).

In patients with GHD of other aetiologies there were significant improvements in waist circumference and diastolic blood pressure (Table 3). A similar trend was noted in patients with Cushing's disease and acromegaly, but this did not reach statistical significance.

The AGHDA score improved (numerical reduction) in patients with GHD of other aetiologies and quantitatively similar, but statistically non-significant improvements were noted in patients with treated Cushing's disease or acromegaly (Table 3). There was a tendency towards a more substantial improvement in females compared with males, but numbers were too small to obtain statistical significance (data not shown).

The number of non-serious adverse events were similar across the three groups (1.18/treatment year in Cushing's disease, 1.61 in acromegaly and 1.31 in other aetiologies) The figures for serious adverse events were 0.13, 0.07 and 0.10/treatment years for the three groups respectively (NS).

## Discussion

An outcomes research database such as KIMS provides the opportunity to investigate the baseline characteristics and response to therapy in subgroups of patients which are numerically very small in individual clinics.

This analysis shows clearly that hypopituitary, GHD adults previously treated for acromegaly demonstrated mostly similar clinical characteristics to patients with GHD of other causes, whereas GHD patients previously treated for Cushing's disease had significantly increased prevalences of diabetes mellitus, hypertension, more

**Table 2** Baseline clinical characteristics in GHD patients perviously treated for Cushing's disease or acromegaly compared with GHD of other aetiologies. Data are shown as means (S.D.).

| | Cushing's disease | Acromegaly | Other aetiologies |
|---|---|---|---|
| BMI (kg/m$^2$) | 27.2 (5.7) | 29.1 (5.5) | 28.2 (5.3) |
| Waist/hip ratio, males | 0.96 (0.07) | 0.94 (0.05) | 0.95 (0.07) |
| Waist/hip ratio, females | 0.87 (0.07) | 0.85 (0.06) | 0.87 (0.08) |
| QoL-AGHDA score, males | 8.5 | 6.0 | 7.7 |
| QoL-AGHDA score, females | 13.4** | 14.7* | 10.0 |
| Total cholesterol (mmol/l) | 6.2 (1.2) | 6.5 (1.4) | 6.2 (1.3) |
| Triglycerides (mmol/l) | 2.1 (2.3) | 2.0 (0.8) | 2.1 (1.6) |
| HDL-cholesterol (mmol/l) | 1.4 (0.5) | 1.4 (0.4) | 1.3 (0.4) |
| LDL-cholesterol (mmol/l) | 3.8 (1.2) | 4.1 (1.5) | 3.9 (1.4) |
| IFG-I SDS | −2.4 (2.2) | −2.4 (2.2) | −2.5 (2.2) |

*$P < 0.05$, **$P < 0.02$: acromegaly/Cushing's disease versus other aetiologies.

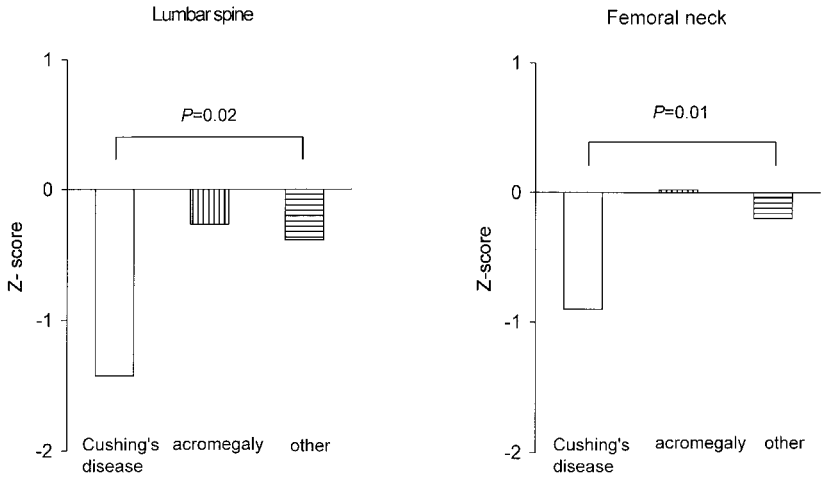


**Figure 4** Bone mineral density (Z-score) measured by DXA at lumbar spine and femoral neck in patients with GHD and previously treated Cushing's disease, acromegaly or other aetiologies (other).

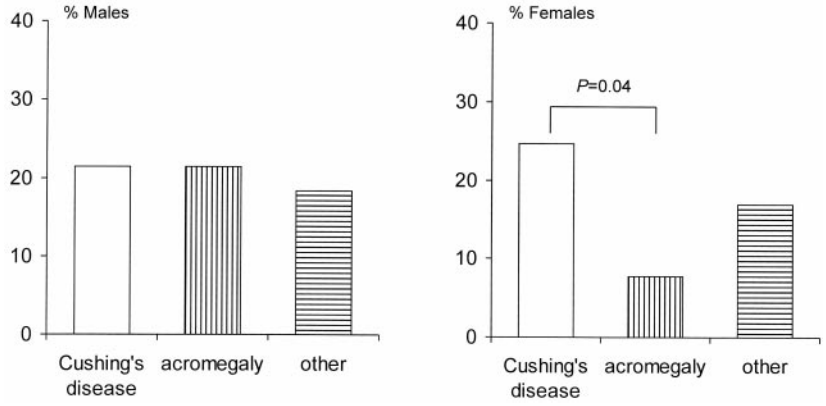


**Figure 5** Prevalence of fractures after 20 years of age in males (left) and females (right) with GHD and previously treated Cushing's disease, acromegaly or other aetiologies (other).

**Table 3** Effect of GH replacement (6 months) on body composition, blood pressure and quality of life in patients with GHD and previously treated for Cushing's disease or acromegaly or with GHD of other aetiologies. Data are shown as means (S.D.).

| | Cushing's disease | Acromegaly | Other aetiologies |
|---|---|---|---|
| BMI (kg/m$^2$) | −0.5 (1.4) | −0.3 (1.0) | 0.1 (1.7) |
| Waist (cm) | −3.2 (5.5) | −1.1 (3.0) | −1.7 (5.0)*** |
| Systolic blood pressure (mmHg) | 0.4 (11.9) | −2.9 (16.9) | −0.3 (16.0) |
| Diastolic blood pressure (mmHg) | −1.2 (9.7) | −2.3 (10.5) | −1.7 (10.2)** |
| HbA1c (% change) | 4.5 (13.7) | −0.9 (9.1) | 5.2 (13.5)*** |
| QoL-AGHDA (improvement in score) | 4.7 (5.9) | 2.3 (9.4) | 2.8 (5.3)*** |

HbA1c, glycated haemoglobin A1c.
**$P = 0.002$; ***$P = 0.0001$, compared with baseline before GH treatment.

fractures in adult age, and decreased BMD. Baseline QoL was more impaired in females with treated acromegaly and Cushing's disease compared with GHD from other aetiologies, and patients with treated acromegaly had a higher prevalence of stroke. Although Cushing's disease is associated with increased central adiposity, our patient groups (including patients with treated acromegaly) were similar in terms of IGF-I SDS, BMI and waist-hip ratio. This and the fact that the number of additional hormone deficiencies did not differ among the groups indicate that we were comparing three populations with equivalent degrees of GHD. The present study does not include comparison with age-matched normal individuals but the distribution of patients was similar in the groups with respect to age. However, there was a slight age difference between male and female patients. There was a slight over representation of female patients with Cushing's disease and acromegaly compared with patients with GHD of other causes. This may have

affected the differences in statistical significance in, for example, hypertension and QoL-AGHDA, due to small numbers in the male groups and consequently a higher risk of a type 2 error.

The enrollment of GHD patients with Cushing's disease was what might be expected from the prevalence of the disease, whereas enrollment of patients with acromegaly was much lower, probably reflecting the overall difficulty in diagnosing GHD in treated acromegaly on the one hand and overall awareness of GHD in this condition on the other.

Baseline quality of life, as measured by QoL-AGHDA, appeared to be similarly impaired in male patients treated for acromegaly, Cushing's disease or other aetiologies and to an extent that we have previously shown to be distinct from values in a Swedish general population sample (33). Female patients with Cushing's disease or acromegaly had an even poorer quality of life, which is presumably attributable to their original disease and not only to GHD. Most studies have demonstrated a poor QoL in patients with GHD (11) and improvement after GH therapy (11). One of the exceptions is a randomised cross-over trial which failed to demonstrate improved psychological well-being during GH replacement of adult GHD patients (12). However, this latter study also included patients with treated Cushing's disease among the total study population and may, by virtue of exclusion criteria have failed to include patients most likely to benefit in terms of quality of life.

The increased prevalence of diabetes mellitus, hypertension, low BMD and high fracture rate in patients with Cushing's disease compared with GHD patients of other aetiologies is likely to be due to an additional long-term effect of previous hypercortisolism. This might indicate a particular case for treating GHD patients with previous Cushing's disease with GH at an early stage in order to alleviate the consequences of a combined deleterious effect of hypercortisolism and GHD on glucose metabolism, cardiovascular risk factors and bone mineral density. In this context, it is important to note that insulin resistance may improve in adult GHD during long-term GH replacement (34).

Our data indicate clearly that some consequences of GHD are broadly similar in patients treated previously for acromegaly and Cushing's disease compared with other GHD patients, particularly body composition and lipids. In addition, patients treated for Cushing's disease had an increased prevalence of diabetes mellitus, hypertension, low BMD, more fractures and a poorer quality of life, features attributed to a combination of GHD and Cushing's disease. Patients treated for acromegaly also had a poorer quality of life, but no worsening of the other features. Quality of life improved significantly during GH replacement. On the basis of these data GHD patients previously treated for acromegaly or Cushing's disease should be considered for GH replacement similarly to other GHD patients.

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Sadly, Professor Tauber died before completion of the manuscript.

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