Comorbidities in patients with non-functioning pituitary adenoma: influence of long-term growth hormone replacement

Casper Hammarstrand1,2, Oskar Ragnarsson1,2, Olivia Bengtsson1,2, Ing-Liss Bryngelsson3, Gudmundur Johannsson1,2,* and Daniel S Olsson1,2,*

1Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden, 2Department of Endocrinology, Sahlgrenska University Hospital, Göteborg, Sweden, and 3Department of Occupational and Environmental Medicine, Örebro University Hospital, Örebro, Sweden

*(G Johannsson and D S Olsson contributed equally to this work)

Abstract

Background: Patients with hypopituitarism have an increased mortality. The aim of this study was to investigate comorbidities including cerebral infarction, type 2 diabetes mellitus (T2DM) and malignant tumors in patients with non-functioning pituitary adenomas (NFPA) with and without growth hormone replacement therapy (GHRT).

Methods: Observational cohort study in patients with NFPA within the western region of Sweden. Subjects were identified through the National Patient Registry and followed between 1987 and 2014. Patient records were reviewed and standardized incidence ratios (SIRs) with 95% CIs for comorbidities were calculated.

Results: In total, 426 patients were included, 206 with GHRT and 219 without. Median (range) follow-up time for patients with and without GHRT was 12.2 (0–24) and 8.2 (0–27) years, respectively. Mean ± s.d. BMI was 28.5 ± 4.5 and 26.5 ± 4.4 for patients with and without GHRT, respectively (P < 0.001). Incidence of cerebral infarction was increased (SIR: 1.39; 95% CI: 1.03–1.84; P = 0.032), with no difference between patients with and without GHRT. SIR for T2DM in patients not receiving GHRT was increased (1.65; 1.06–2.46; P = 0.018), whereas the incidence in patients receiving GHRT was not (0.99; 0.55–1.63; P = 0.99). The incidence of malignant tumors was not increased, either in patients with or without GHRT.

Conclusion: The incidence of cerebral infarction is increased in patients with NFPA irrespective of GHRT. Patients without GHRT had an increased risk of T2DM, whereas patients with GHRT had a normal incidence of T2DM, despite having higher BMI. Incidence of malignant tumors was not increased. Thus, long-term GHRT seems to be safe regarding risk of comorbidities.

Introduction

Hypopituitarism with deficiency of one or more anterior pituitary hormones is associated with excess mortality (1, 2, 3, 4), predominantly attributed to cardiovascular and cerebrovascular diseases (1, 2, 3). The seminal study by Rosén and Bengtsson suggested that untreated growth hormone deficiency (GHD) in patients with hypopituitarism may influence the cardiovascular risk profile in patients with hypopituitarism (2). During the past two decades, several studies have showed that GHD is characterized by decreased lean body
mass with central adiposity, reduced muscle strength, reduced physical activity, dyslipidemia, hypertension, reduced bone mineral density and impaired quality of life (5, 6, 7, 8). In addition, increased intima-media thickness, intimal plaque formation (9) and decreased arterial compliance (10) have been demonstrated, which is associated with increased cardiovascular morbidity.

Although growth hormone replacement therapy (GHRT) is well established and reverses most of the features associated with GHD (11, 12, 13, 14), one of the safety concerns is the reduction in insulin sensitivity and the potential risk of developing type 2 diabetes mellitus (T2DM) (15). Attanasio et al. assessed the incidence of diabetes mellitus in 2922 US and 3709 European patients on GHRT without showing an association between GHRT and an increased incidence of diabetes mellitus (16). In contrast, in a study by Luger et al., 5143 patients with GHRT followed over a mean period of 3.9 years had a six-fold increased incidence of diabetes mellitus, which developed early after commencement of treatment (17). The incidence of diabetes mellitus increased with increasing BMI in both studies. To what extent GHD, and the replacement treatment thereof, independently contributes to the development of diabetes mellitus is however not known. Furthermore, concerns have been raised, suggesting that long-term GHRT may increase the risk of de novo neoplasia (18).

We have previously studied mortality with regard to GHRT in NFPA patients and found that death due to malignancy was not increased (19).

Other studies have shown that the underlying cause of hypopituitarism impacts outcome, with higher risk of death in patients with underlying malignancy or craniopharyngiomas (20). One of the most frequent causes of hypopituitarism is non-functioning pituitary adenomas (NFPAs) (21). When investigating the effects of hormone replacement treatment, NFPA patients are well suited to study, since mortality rates are lower than those for other underlying causes of hypopituitarism (e.g., craniopharyngioma and Cushing’s disease) (22). Also, confounding effects of hormonal hypersecretion does not affect the outcome. The aim of this study was, therefore, to investigate the impact of GHRT on incidence rate of T2DM, cerebral infarction, malignant tumors and other comorbidities (myocardial infarction, sepsis, fractures) in an unselected and well-characterized cohort of patients with GHD due to NFPA.

Subjects and methods

Study design

This was an observational cohort study in patients with NFPA within the western region of Sweden. We used the Swedish National Patient Register (Patient Register) in order to identify all patients treated or followed for NFPA within the western region of Sweden between Jan 1, 1997 and Dec 31, 2011. The registry achieved national coverage in 1987 and contains information from every patient visit including discharge diagnoses and all diagnoses from outpatient clinics within the Swedish hospital system using a unique personal identification number. Malignant tumors were identified through the Swedish Cancer Register (Cancer Register), established in 1958, that contains information on all malignant tumors diagnosed in Sweden, including morphological diagnosis. The Swedish Board of Social Welfare secures high quality and coverage for the Patient Register and the Cancer Register (23, 24).

Inclusion criteria were the diagnosis of a benign pituitary adenoma (ICD-10 code D35.2) at a department of internal medicine, neurology or neurosurgery (19). All patients with hormone-producing adenomas were excluded. The medical charts for all patients were manually reviewed by two physicians to confirm that the NFPA diagnosis was correct and in order to collect information on medical history and clinical characteristics including tumor treatment, hormonal replacement therapy, antihypertensive medication, BMI and duration of GHRT. For patients with T2DM, information regarding HbA1c values, insulin treatment, oral antidiabetic and lipid-lowering medication were collected. GHD was diagnosed according to the recommendations provided by the Growth Hormone Research Society (25) and all patients with confirmed GHD were offered replacement therapy. There were 25 patients in the untreated group with a normal GH provocative test. No formal selection criteria, other than confirmed GHD, were used for offering GH replacement. We were not able to determine the reason for not being put on GH replacement. Before commencement of GHRT, all patients were properly replaced with glucocorticoids, l-thyroxine and sex steroids if needed, with stable replacement doses for at least 3 months. During the first year, clinical and biochemical evaluation was performed every third month to monitor the replacement therapy, glucose metabolism and blood pressure. During the next 5 years, this was performed twice per year and thereafter annually.
For each patient, start of follow-up was defined as either the time point when NFPA was diagnosed or the start of the study, January 1, 1987. The time at risk for patients with GHRT was set to the start of GHRT. All patients were followed until December 31, 2014 or until death. Morbidity data for cerebral infarction, myocardial infarction, T2DM, sepsis, fractures and malignant tumors were collected from the Patient Register and the Cancer Register.

**Patients**

Out of the 570 patients that were identified, 144 were excluded either due to non-verified NFPA diagnosis after review of the patient records \( (n=141) \) or incomplete patient records \( (n=3) \). The majority of the excluded patients had other pituitary-related diseases, for example, hormone-secreting adenomas or pituitary cysts. In total, 426 patients were included and divided into two groups based on whether the patients had received GHRT or not.

**Ethics**

Ethical approval for the study was obtained from the Regional Ethical Review Board, Gothenburg University, Sweden. All patients gave their informed consent.

**Statistics**

Person-years at risk were calculated from study inclusion to death, or end of study, and stratified according to gender, 5-year age groups and 1-year calendar periods. The expected number of cases for each stratum was calculated assuming a Poisson distribution of the background population and standardized incidence ratios (SIRs) calculated. Ninety-five percent CIs were calculated depending on whether the patients had other pituitary-related diseases, for example, hormone-secreting adenomas or pituitary cysts. In total, 426 patients were included and divided into two groups based on whether the patients had received GHRT or not.

For comparison between groups, we used independent \( t \)-test for normally distributed data and Mann–Whitney \( U \) test for non-normally distributed data. Chi-square test was performed for comparison between groups with dichotomous variables. The level of significance was set to \( P<0.05 \). IBM SPSS (version 24) and STATA SE (version 14) software were used to perform the statistical analyses.

**Results**

**Patient characteristics**

Out of 426 patients, 207 had received GHRT (145 men; 70%) and 219 had not (129; 59%; Table 1). The median (range) duration of GHRT was 11.7 (0–24) years. The mean \( (\pm S.D.) \) age at NFPA diagnosis was 56.3 \( \pm \) 11.5 years for treated patients and 65.2 \( \pm \) 15.0 years for untreated patients \( (P<0.001) \), and the median follow-up time was 12.2 and 8.2 years \( (P<0.001) \), respectively. GH-treated patients had higher BMI, were more likely to have received radiotherapy and had a more extensive hypopituitarism than patients without GHRT (Table 1).

**Cardiovascular morbidity**

In the whole cohort, the incidence of cerebral infarction was increased (SIR 1.39; 95% CI: 1.03–1.84; \( P=0.032 \); Fig. 1 and Table 2). This was most evident in patients who had received radiotherapy \( (n=97) \), where 19 cerebral infarctions occurred compared with the expected number of 9.8 \( (P=0.011) \). SIR was similar for patients with and without GHRT. The incidence of myocardial infarction was not increased (SIR: 1.21; 95% CI: 0.89–1.60; \( P=0.21) \), neither for patients receiving GHRT (SIR: 1.18; 95% CI: 0.73–1.80; \( P=0.51) \) nor for those without (SIR: 1.23; 95% CI: 0.82–1.78; \( P=0.31) \). One hundred seventeen patients with GHRT (57%) and 114 patients without GHRT (52%) \( (P=0.44) \) received medical treatment for hypertension (Table 1).

**Diabetes mellitus**

During the study period, we identified 39 patients with T2DM, of whom 15 had GHRT and 24 had not. The debut of T2DM occurred before GH was introduced in eight patients and after in seven patients, one diagnosed within a year after commencement of GHRT and six more than 1 year after start of GH. At the start of the study, 25 patients had T2DM, of whom 8 received GHRT and 17 did not (Supplementary Table 1, see section on Supplementary data given at the end of this article). SIR for T2DM was
increased (1.65; 95% CI: 1.06–2.46; \( P = 0.027 \)) among patients without GHRT, while the incidence was similar to that in the general population for patients receiving GHRT (0.99; 95% CI: 0.55–1.63; \( P = 0.99 \)) (Table 2). Patients with GHRT and T2DM had higher BMI than patients with T2DM in the non-treated group (\( P = 0.010 \)) (Table 3). The intensity of diabetes therapy, measured as frequency of oral medications, insulin treatment and daily insulin doses, was similar among the two groups as was the glycemic control at the first and last follow-up.

**Sepsis and fractures**

The incidence of sepsis (requiring hospitalization) was close to doubled compared to the general population, with no difference between patients with and without GHRT (Table 2). Patients with GC replacement had an increased incidence of sepsis (SIR 2.39; 95% CI: 1.54–3.52, \( P < 0.001 \)), while patients without had not (Fig. 2). The incidence of fracture was not increased and did not differ between patients receiving GHRT and untreated patients. Patients receiving GC replacement did not have an increased incidence of fracture (Fig. 2).

**Malignancy**

The incidence of malignant tumors in the whole cohort was not increased compared to the general population (Table 4). SIR for colorectal cancer was not increased (1.07; 95% CI: 0.54–1.92; \( P = 0.89 \)) and was not influenced by GHRT (SIR: 0.98; 95% CI: 0.32–2.28; \( P = 0.99 \)). The overall incidence of prostate cancer was not increased (SIR: 1.28; 95% CI: 0.81–1.92; \( P = 0.29 \)), nor was it increased for the subgroup of patients receiving GHRT (SIR: 1.33; 95% CI: 0.71–2.28; \( P = 0.37 \)). Also, SIRs for malignant melanoma of the skin (0.66; 95% CI: 0.14–1.93; \( P = 0.67 \)), other malignant neoplasms of skin (0.87; 95% CI: 0.48–1.47; \( P = 0.73 \)), malignant neoplasm of bladder (0.95; 95% CI: 0.29–4.11; \( P = 0.18 \)) and malignant neoplasm of bronchus and lung (0.39; 95% CI: 0.05–1.42; \( P = 0.24 \)) were not increased.
Discussion

We investigated the incidence of several comorbidities in patients with NFPA in relation to long-term GHRT in a large and an unselected cohort of patients with NFPA. The study showed an increased overall incidence of cerebral infarction in patients with NFPA compared to the general population that was related to previous radiotherapy, but not to GHRT. Patients without GHRT had an increased incidence of T2DM, whereas the incidence for patients with GHRT did not differ from that in the general population. The incidence of sepsis was more than doubled and strongly related to presence of adrenal insufficiency.

Incidence of malignancies, including colorectal and prostate cancer, was not increased in patients with NFPA and was not influenced by GHRT.

We have previously shown that patients with NFPA on long-term treatment with GHRT have a reduced mortality rate in comparison with the background population (19). Findings from other studies in patients with hypopituitarism treated with GHRT are not consistent, with some reporting an excess mortality (20, 26, 27) but others not (28). This difference may be affected by the underlying cause of GHD (e.g., craniopharyngioma, malignant causes of hypopituitarism and Cushing’s disease), which is an important predictor for mortality (20, 27), as well as for the reference population. The previously shown association between

Table 2  Standardized incidence ratios (SIR) for patients with non-functioning pituitary adenoma with and without growth hormone replacement therapy.

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>No. expected</th>
<th>No. diagnosed</th>
<th>SIR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral infarction (n=426)</td>
<td>35.2</td>
<td>49</td>
<td>1.39 (1.03–1.84)</td>
<td>0.032</td>
</tr>
<tr>
<td>GHRT (n=219)</td>
<td>14.8</td>
<td>22</td>
<td>1.49 (0.93–2.25)</td>
<td>0.093</td>
</tr>
<tr>
<td>Non-GHRT (n=207)</td>
<td>20.5</td>
<td>27</td>
<td>1.32 (0.87–1.92)</td>
<td>0.19</td>
</tr>
<tr>
<td>Treated with RT (n=97)</td>
<td>9.8</td>
<td>19</td>
<td>1.95 (1.17–3.04)</td>
<td>0.011</td>
</tr>
<tr>
<td>Treated without RT (n=329)</td>
<td>25.6</td>
<td>30</td>
<td>1.17 (0.79–1.67)</td>
<td>0.44</td>
</tr>
<tr>
<td>Myocardial infarction (n=426)</td>
<td>40.5</td>
<td>49</td>
<td>1.21 (0.89–1.60)</td>
<td>0.21</td>
</tr>
<tr>
<td>GHRT (n=219)</td>
<td>17.8</td>
<td>21</td>
<td>1.18 (0.73–1.80)</td>
<td>0.51</td>
</tr>
<tr>
<td>Non-GHRT (n=207)</td>
<td>22.7</td>
<td>28</td>
<td>1.23 (0.82–1.78)</td>
<td>0.31</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus (n=426)</td>
<td>29.7</td>
<td>39</td>
<td>1.32 (0.93–1.80)</td>
<td>0.11</td>
</tr>
<tr>
<td>GHRT (n=219)</td>
<td>15.2</td>
<td>15</td>
<td>0.99 (0.55–1.63)</td>
<td>0.99</td>
</tr>
<tr>
<td>Non-GHRT (n=207)</td>
<td>14.5</td>
<td>24</td>
<td>1.65 (1.06–2.46)</td>
<td>0.027</td>
</tr>
<tr>
<td>Sepsis (n=426)</td>
<td>16.5</td>
<td>32</td>
<td>1.94 (1.33–2.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GHRT (n=219)</td>
<td>7.5</td>
<td>15</td>
<td>1.99 (1.11–3.28)</td>
<td>0.021</td>
</tr>
<tr>
<td>Non-GHRT (n=207)</td>
<td>8.9</td>
<td>17</td>
<td>1.90 (1.11–3.05)</td>
<td>0.021</td>
</tr>
<tr>
<td>Fracture (n=426)</td>
<td>53.6</td>
<td>55</td>
<td>1.03 (0.77–1.34)</td>
<td>0.89</td>
</tr>
<tr>
<td>GHRT (n=219)</td>
<td>22.6</td>
<td>18</td>
<td>0.79 (0.47–1.26)</td>
<td>0.39</td>
</tr>
<tr>
<td>Non-GHRT (n=207)</td>
<td>31.0</td>
<td>37</td>
<td>1.19 (0.84–1.64)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

*Analyzer on first diagnosis in the registry; †all patients had medical treatment for type 2 diabetes mellitus; ‡requiring hospitalization.
GHRT, growth hormone replacement therapy; RT, radiotherapy.

Table 3  Characteristics of the 39 patients with type 2 diabetes mellitus and non-functioning pituitary adenoma enrolled in the study.

<table>
<thead>
<tr>
<th></th>
<th>Patients with GHRT (N=15)</th>
<th>Patients without GHRT (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (s.d.) age at start of study (years)</td>
<td>59.1 (8.6)</td>
<td>69.6 (8.9)</td>
</tr>
<tr>
<td>Mean (s.d.) BMI (kg/m²)†</td>
<td>32.2 (6.1)</td>
<td>27.6 (4.2)</td>
</tr>
<tr>
<td>Insulin treatment, no. (%)</td>
<td>7 (47)</td>
<td>14 (58)</td>
</tr>
<tr>
<td>Median daily dose of insulin (range) (E)</td>
<td>40 (20–144)</td>
<td>87 (8–250)</td>
</tr>
<tr>
<td>Oral antidiabetes medication, no. (%)</td>
<td>14 (93)</td>
<td>19 (79)</td>
</tr>
<tr>
<td>Mean HbA1c – first value (mmol/mol)‡</td>
<td>54.2</td>
<td>57.9</td>
</tr>
<tr>
<td>Mean HbA1c – last value (mmol/mol)§</td>
<td>60.8</td>
<td>64.4</td>
</tr>
<tr>
<td>Lipid-lowering medication, no. (%)</td>
<td>9 (60)</td>
<td>14 (58)</td>
</tr>
<tr>
<td>Antihypertensive medication, no. (%)</td>
<td>14 (93)</td>
<td>19 (79)</td>
</tr>
</tbody>
</table>

*Missing data in two cases in the group without GHRT; †12 patients received Metformin and two patients received Gilbenclamide; ‡12 patients treated with Metformin, three with Gilbenclamide, two with Repaglinide, one with Glipizide and one with Sitagliptin; §missing data in eight cases in the group without GHRT; ‡missing data in five cases in the group without GHRT.
GHRT, growth hormone replacement therapy; E, enheter (units).
The increased insulin resistance seen in patients with GHD is partly explained by central adiposity, on which GHRT has a beneficial effect (34, 35). During the first year of GHRT, a transient decline in insulin sensitivity occurs, due to GH per se and an increased release of free fatty acids (34). In a large surveillance study, it was shown that patients receiving GHRT had an increased incidence of DM, in particular during the first and second year after initiation of therapy (17). Of note is that many of the earlier studies assessing the effects of GHRT on glucose metabolism and insulin sensitivity used weight-based GH dosing, whereas current practice is to use an individualized dosing with lower starting doses, resulting in much less frequent side effects (36). Furthermore, it has been demonstrated that lower starting doses of GH may improve insulin sensitivity in healthy subjects, notably in males, in contrast to the earlier standards using higher doses which induced insulin resistance (37). In our cohort, the incidence of T2DM was not increased in patients receiving long-term GHRT but was increased for patients without such treatment. This was true despite the fact that patients with GHRT had higher BMI and more severe hypopituitarism at baseline compared to patients without GHRT. For patients with T2DM and GHRT, the debut of T2DM occurred before introduction of GHRT in half of the patients and only in one patient during the first year of replacement arguing against a causative role of GHRT on the development of T2DM. However, our results must be interpreted with caution since patients with T2DM, as well as older patients, may be less likely to be selected for GHRT. Also, intensity of diabetes treatment and glycemic control was similar among those with and without long-term GH replacement, suggesting a neutral effect of long-term GH replacement on glucose metabolism in patients.

Table 4 Standardized incidence ratios (SIR) of malignant tumors for patients with non-functioning pituitary adenoma with and without growth hormone replacement therapy.

<table>
<thead>
<tr>
<th>Malignant tumors (ICD-10)</th>
<th>No. expected</th>
<th>No. diagnosed</th>
<th>SIR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant neoplasm of colon and rectum (C18–20)</td>
<td>10.24</td>
<td>11</td>
<td>1.07 (0.54–1.92)</td>
<td>0.89</td>
</tr>
<tr>
<td>GHRT (n=219)</td>
<td>5.12</td>
<td>5</td>
<td>0.98 (0.32–2.28)</td>
<td>0.99</td>
</tr>
<tr>
<td>Non-GHRT (n=207)</td>
<td>5.72</td>
<td>6</td>
<td>1.17 (0.43–2.55)</td>
<td>0.99</td>
</tr>
<tr>
<td>Malignant neoplasm of breast (C50)</td>
<td>5.71</td>
<td>3</td>
<td>0.53 (0.11–1.53)</td>
<td>0.36</td>
</tr>
<tr>
<td>GHRT (n=219)</td>
<td>2.87</td>
<td>1</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>Non-GHRT (n=207)</td>
<td>2.84</td>
<td>2</td>
<td>0.70 (0.09–5.54)</td>
<td>0.92</td>
</tr>
<tr>
<td>Malignant neoplasm of prostate (C61)</td>
<td>17.98</td>
<td>23</td>
<td>1.28 (0.81–1.92)</td>
<td>0.29</td>
</tr>
<tr>
<td>GHRT (n=219)</td>
<td>9.75</td>
<td>13</td>
<td>1.33 (0.71–2.28)</td>
<td>0.37</td>
</tr>
<tr>
<td>Non-GHRT (n=207)</td>
<td>8.23</td>
<td>10</td>
<td>1.22 (0.58–2.23)</td>
<td>0.62</td>
</tr>
<tr>
<td>Malignant neoplasm of brain (C71)</td>
<td>1.06</td>
<td>2</td>
<td>1.88 (0.23–6.79)</td>
<td>0.57</td>
</tr>
<tr>
<td>GHRT (n=219)</td>
<td>0.062</td>
<td>0</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>Non-GHRT (n=207)</td>
<td>0.44</td>
<td>2</td>
<td>4.55 (0.55–16.42)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

GHRT, growth hormone replacement therapy.

www.eje-online.org
with T2DM. Nevertheless, glucose metabolism should be carefully monitored in patients receiving GHRT, in particular those with high BMI and family history of T2DM.

An increased risk of malignancies in hypopituitary patients has previously been observed in some studies (38), but not others (39). A prospective study of 289 hypopituitary patients in Sweden showed a near four-fold increase in overall mortality risk due to malignancy for patients without GHRT, whereas incidence for malignancy in patients with GHRT did not differ from that in the normal population (38). Furthermore, to date, an increased risk of de novo malignancies associated with GHRT in adults has not been demonstrated (15, 40), however, with the limitation that post-marketing studies are associated with a selection bias. In addition, the follow-up time in the previously conducted studies have often been too short to exclude the risk of malignancies (40). We did not find increased incidence rates of malignancies in either patients with or without GHRT, which is supported by some studies (40) but not others (38). Our study included both colorectal and prostate cancer, thus not lending support to the hypothesis that long-term treatment with GH increases the risk of new or recurrent malignancies.

Multiple pituitary deficiencies are common among patients receiving GHRT (41), and patients with secondary adrenal insufficiency receiving overly high GC doses have been shown to have excess mortality (42). A recent study, including 8818 patients with secondary adrenal insufficiency, showed an increased incidence of comorbidities including diabetes mellitus (OR 1.87; CI: 1.72–2.04; P < 0.001) and infections requiring admission to hospitals (43). Accordingly, an increased incidence of sepsis requiring hospitalization for patients receiving GC replacement was seen in our cohort and may be a consequence of inadequate GC treatment during intercurrent illness and stressful events or due to increased susceptibility to develop severe infections (26, 41, 44).

Previous studies have shown reduced bone mineral density and increased fracture risk in patients with hypopituitarism and adult GHD (8, 45). The reduced bone mass in these patients is positively influenced by GHRT, particularly in men (11). However, prospective studies assessing the efficacy of GHRT on fracture risk are not available to date. The previously shown association between adult GHD and increased fracture risk (45) was not seen in this study and was not influenced by GHRT. Nor was the risk of fracture influenced by GC replacement, which is in line with another large study conducted on patients with pituitary insufficiency (45).

The limitations of this study include the retrospective and non-randomized design with risk of a selection bias. In fact, more men than women were treated with GHRT and the non-treated group were older at diagnosis and had less severe hypopituitarism, all factors that may have influenced the decision of initiating GH replacement therapy. However, the method we used to estimate the incidence, SIR, takes age, gender and calendar year into account when calculating the estimated number of cases. In other words, older patients with higher risk of having T2DM were compared to incidence rates for patients with the same age and gender during the same time period. Furthermore, since the GHRT group had worse metabolic profile and more severe hypopituitarism at baseline, it can be argued that this group of patients would be more prone to develop other comorbidities, i.e., the positive effect of GHRT on the outcome would be underestimated. Also, the GHRT group may have been more thoroughly followed, which can explain the more extensive follow-up time for those patients. Patients in both groups did, however, receive antihypertensive medication to the same extent, which would indicate similar surveillance in both groups. Lastly, adherence to daily GH injections during long-term treatment must be taken into account when interpreting the outcome. A previous study formally assessing adherence found a reduction in adherence from 85% during the first year of treatment to 74% during the 3rd year of treatment (46). We have not objectively measured adherence to GH replacement, but the large majority of patients are treated at a specially dedicated outpatient clinic for GHRT where adherence is discussed at each visit. A major strength of this study is the unselected cohort of patients with only one underlying cause of hypopituitarism, i.e. NFPA, within the same geographical area, and the extensive follow-up period with a median observation time of more than 10 years.

In conclusion, this study demonstrates an excessive morbidity due to cerebral infarction and sepsis requiring hospitalization in patients with NFPA. In addition, NFPA patients without GHRT had an increased risk of T2DM, whereas patients with GHRT, despite higher BMI and more severe hypopituitarism, had a normal incidence of T2DM. Finally, GHRT was not associated with an increased incidence of malignant tumors. This supports that long-term GHRT is a safe treatment with regard to the studied comorbidities in hypopituitary patients.

Supplementary data
This is linked to the online version of the paper at https://doi.org/10.1530/EJE-18-0370.
Declaration of interest

C H, O R, O B and I-L B have nothing to disclose. G J has served as a consultant to Viropharma/Shire and Astra Zeneca, and has received lecture fees from Pfizer, NovoNordisk and Otsuka. D S O has served as a consultant to Pfizer, Sandoz and Ipsen.

Funding

This study was supported in part by the Swedish government under an ALF agreement, and the Gothenburg Growth Hormone database has been partly supported through unrestricted grants from Sandoz, NovoNordisk and Pfizer.

Acknowledgements

The authors would like to express our gratitude to the staff at the Centre for Endocrinology and Metabolism at the Department of Endocrinology at Sahlgrenska University Hospital and to The National Board of Health and Welfare for their excellent collaboration. They would also like to thank Professor Bengt-Åke Bengtsson for his valuable comments on the manuscript.

References


