Increased fracture frequency in adult patients with hypopituitarism and GH deficiency

Thord Rosén, Lars Wilhelmsen¹, Kerstin Landin-Wilhelmsen, Georg Lappas¹ and Bengt-Ake Bengtsson

Research Centre for Endocrinology and Metabolism, Sahlgrenska University Hospital, Göteborg, Sweden and ¹Department of Medicine, Östra University Hospital, Göteborg, Sweden

(Correspondence should be addressed to T Rosén, Endocrine Division, Department of Medicine, Sahlgrenska University Hospital, S-41345 Göteborg, Sweden)

Abstract

Fracture frequency was studied in 107 hypopituitary patients with GH deficiency (GHD) (69 men, mean age 53 years, range 18–74 and 38 women, mean age 54 years, range 31–73). Routine hormonal replacement therapy was given, except GH. Five male patients and 15 female patients with untreated hypogonadism were allocated to a separate group. The mean duration of hypopituitarism was 13.4 years. The prevalence of a history of fractures was assessed using questionnaires. A subsample of the Göteborg WHO MONICA Project was used as a reference population (n = 323).

The total fracture frequency was threefold higher (P<0.001) in patients (24.1%) compared with controls (8.7%) (odds ratio 3.49) (1.85–6.56; 95% confidence intervals). In men (n = 64) the fracture frequency was 25.0%, compared with 7.8% among the controls (P<0.001). In women (n = 23) the fracture frequency was 21.7%, compared with 9.5% among the controls (P = 0.08).

The odds ratios for fracture frequency were 3.97 (1.81–8.40; 95% confidence intervals) and 2.64 (0.89–7.81; 95% confidence intervals) in men and women respectively.

In conclusion, adult hypopituitary patients with GHD had a threefold increased fracture frequency compared with controls. Further studies are needed to ascertain whether long-term recombinant human GH treatment can reduce the fracture rate in hypopituitary patients with GHD.

European Journal of Endocrinology 137 240–245

Introduction

Adult hypopituitary patients with growth hormone deficiency (GHD) of both childhood (1) and adult onset (2) have a reduced bone mineral content. A reduced peak bone mass might explain the low bone mineral density among the patients with childhood-onset GHD, but the cause of the osteopenia in the adult-onset GHD is not fully understood. Furthermore, the incidence rate of fractures in hypopituitary patients with adult-onset GHD is not known, although a previous study has indicated an increased risk for osteoporotic vertebral fractures in hypopituitary patients compared with normals (3). We have studied the prevalence of a history of fractures in 107 patients with adult-onset hypopituitarism including GHD with conventional hormonal replacement therapy, except growth hormone (GH). These patients have been studied in a previous work, and were then found to have a reduced bone mineral content compared with normals (2). A subsample of the Göteborg WHO MONICA Study was used as a reference population.

Materials and subjects

Patients

Patients with pituitary disease diagnosed between 1956 and 1990 were investigated for a possible GHD. Each patient had been investigated as an in-patient at the Endocrine Unit, Sahlgrenska Hospital on at least one occasion between 1956 and 1990. All patients lived in the catchment area of the Endocrine Unit, including the city of Göteborg, in total 1.5 million inhabitants.

One hundred and forty-seven adult patients with a maximum age of 75 years were invited to participate in the study; 130 of them accepted the invitation. One hundred and eleven of them (71 males and 40 females) fulfilled the inclusion criteria for GHD described below. Four patients with GHD of childhood onset were excluded. Thus, 107 patients remained; 69 men (mean age 53 years; range 18–74 years) and 38 women (mean age 54 years; range 31–73 years). Routine replacement therapy was given with cortisone.

© 1997 Society of the European Journal of Endocrinology
acacetate (mean dose 25.5 mg/day), l-thyroxine (T4; mean dose 0.12 mg/day) and testosterone (mean dose 247 mg i.m. every fourth week) or estradiol (mean dose 1.8 mg/day). Complete pituitary deficiency (in terms of the thyroid, adrenal and gonadal function) was found in 82 patients and partial deficiency in 22 (Table 1). Three patients suffered from isolated GH deficiency.

Men with normal gonadal function (n = 9) and men with gonadal deficiency on testosterone replacement therapy (n = 55) were allocated to one group (group A), while men with untreated gonadal deficiency (n = 5) were allocated to another group (group B). Women were considered to be gonadal deficient in cases of long-standing amenorrhea before the age of 50 years. Women with normal gonadal function (n = 6) and females on estrogen replacement therapy (n = 17) were allocated to group A. While women with a previous or current history of untreated gonadal deficiency (n = 15) were allocated to group B.

GH deficiency was defined as follows: (a) an i.v. insulin or glucagon tolerance test (performed previously or within 6 months after the follow-up), showing a maximum GH response of less than 5 mU/l (n = 76) or (b) at follow-up, low concentration of EDTA plasma insulin-like growth factor-I (IGF-I) <0.34 kU/l (males) and <0.45 kU/l (females), and serum GH concentration less than 1 mU/l in all of three consecutive morning blood samples drawn at an interval of 1 h (n = 31).

The causes of pituitary deficiency are listed in Table 2. Pituitary deficiency secondary to pituitary adenoma was found in 71 patients; there were 22 patients with prolactinoma and 49 with non-secreting adenoma. Of these patients, 37 had been operated on by the transcranial route and 22 by the trans-sphenoidal route.

Hypopituitarism was attributable to extrapituitary tumor in 27 patients, 25 of whom had undergone transcranial (16 subjects) or trans-sphenoidal (nine) operations. In nine patients, the cause of hypopituitarism was unknown. Of the patients who were not operated on, five received pituitary irradiation, two were treated with bromocriptine only, one patient had combined irradiation and bromocriptine therapy and, finally, six patients received no active treatment for their pituitary tumor.

The mean duration of disease at diagnosis was estimated from patient history according to the medical records. It averaged 3.9 years (0–33 years) for all the patients (n = 107). 3.7 years (0–28 years) for the men (n = 69) and 4.3 years (0–33 years) for the women (n = 38).

The mean duration from the diagnosis of hypopituitarism or pituitary disease to the present follow-up was 13.4 years for all 107 patients (range 0–44 years). The duration was 11.1 years (range 0–37 years) for the male patients (n = 69) and 15.1 years (range 0–44 years) for the female patients (n = 38).

Reference population

A random population sample of the WHO MONICA Project (MONICA = MONItorin affluent trends and determinants in CArdiovasculaRe diseases) in Göteborg was used as a reference population. The MONICA study is designed to measure the trends in mortality and morbidity from coronary heart disease and stroke, and their relation to changes in known risk factors (4). Populations in 38 countries are studied. The sample was divided into four groups according to age: 25–34 years, 35–44 years, 45–54 years and 55–64 years. In total 1421 subjects (691 men and 730 women) were included, with a participation rate of 69.1% (range 61.2–76.5) in men and 73.0% (range 64.9–80.5) in women. For the questionnaires concerning fracture frequency 50 samples from each age group (400 subjects in total) were selected at random. In total 323 subjects (155 men and 168 women) participated, giving a participation rate of 80.8%.

Table 1 Deficiency in adrenal (A), thyroid (T) and gonadal (G) function in 107 patients with GHD.

<table>
<thead>
<tr>
<th>Type of deficiency</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated GHD</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>G</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>T</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>A</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>G + T</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>G + A</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>T + A</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>G + T + A</td>
<td>52</td>
<td>30</td>
<td>82</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>38</td>
<td>107</td>
</tr>
</tbody>
</table>

Table 2 Causes of GHD in 107 patients.

<table>
<thead>
<tr>
<th>Cause</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic (no tumor)</td>
<td>9</td>
</tr>
<tr>
<td>Non-secreting adenoma</td>
<td>49</td>
</tr>
<tr>
<td>Prolactinoma</td>
<td>22</td>
</tr>
<tr>
<td>Cranioophyrgioma</td>
<td>17</td>
</tr>
<tr>
<td>Meningioma</td>
<td>3</td>
</tr>
<tr>
<td>Dysgerminoma</td>
<td>1</td>
</tr>
<tr>
<td>Cholesteatoma</td>
<td>1</td>
</tr>
<tr>
<td>Gangliocytoma</td>
<td>1</td>
</tr>
<tr>
<td>Astrocytoma grade I</td>
<td>1</td>
</tr>
<tr>
<td>Pylocytic optic nerve glioma</td>
<td>1</td>
</tr>
<tr>
<td>Undifferentiated tumor</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>107</td>
</tr>
</tbody>
</table>
Prevalence of fractures

A questionnaire was used in both patients and controls regarding fractures (yes/no) in the upper and lower arm, wrist, vertebrae, rib, femur including cervical neck, lower limb, or at any other location. Minor fractures in fingers and toes, considered not to be of osteoporotic origin were excluded. The number and date (year) of each fracture were also registered. The patients filled in the questionnaires at the follow-up visit and the subjects in the reference population filled in the answers at home.

The number of fractures in the patients from the time of diagnosis of hypopituitarism to follow-up was registered, and likewise the number of fractures in the controls during the corresponding time-period. The frequency of both patients and controls who had a history of one fracture or more was calculated.

Blood sampling and biochemical methods

Blood samples were drawn after one night’s fasting, and before the intake of the routine replacement therapy. Serum GH and EDTA plasma IGF-I, and serum-free T₄ concentrations in patients were determined using the vacutainer system. Another two blood samples for serum GH concentration were drawn after 2 and 3 h.

GH concentration (mU/l) was determined by an immunoradiometric assay according to the manufacturer’s protocol (Pharmacia, Uppsala, Sweden), with the modification using sera from patients with pituitary deficiency as 0 calibrator. The total correlations of variation (C.V.) were 30%, 4.0% and 7.1% at GH concentrations of 0.26, 13.3 and 32.7 mU/l respectively.

IGF-I concentration in EDTA plasma was determined by a non-extraction RIA (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). This method determines 'low-affinity bound' analyte, i.e. that concentration in non-extracted plasma which is available for a known amount of antiserum to IGF-I under defined conditions. The normal reference intervals for adults are: men 0.34–1.9 kU/l; women 0.45–2.2 kU/l (U = arbitrary unit defined by the manufacturer). The total C.V. values were 8.4%, 6.7% and 5.9% at IGF-I concentrations of 0.26, 1.33 and 6.8 kU/l respectively.

Serum-free T₄ concentration was determined by a ligand-analog RIA (Amerlex M; Amersham International plc, Amersham, Bucks, UK). The normal reference interval for adults is 9–23 pmol/l. The total C.V. values were 6.5%, 4.8% and 5.3% at free T₄ concentrations of 8.3, 15.9 and 46.1 pmol/l respectively.

The patients received both written and verbal information about the study and their written consent was obtained. The study was approved by the Ethics Committee of the Medical Faculty at Göteborg University.

Statistics

Conventional statistical methods were used to calculate means, standard deviations and standard errors. Differences between groups were tested with Student’s test. The Mantel–Haenszel method was used for the calculation of the odds ratio risk for fractures.

Results

Twenty-eight of the 107 patients and 28 of the 323 controls reported one or more fractures during the study period. The number and types of fractures are listed in Table 3.

The total fracture frequency was higher (P<0.001) among male and female patients in group A (n = 87) (24.1%), compared with the controls (8.7%) (Fig. 1).

Table 3 The main fracture type in the 28 patients with GHD and the 28 controls (one per GHD patient and control respectively) who had a history of one fracture or more.

<table>
<thead>
<tr>
<th>Fracture type</th>
<th>Patients (n = 107)</th>
<th>Controls (n = 323)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Upper arm</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Femur</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Tibia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Ankle</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Foot</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Vertebra</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Pelvis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Rib</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Clavicle</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>28</td>
</tr>
</tbody>
</table>

Figure 1 Total fracture frequency in patients with GHD (solid bar) and in controls (open bar). The total fracture frequency was higher in the patients compared with controls (P<0.001).
The total odds ratio for a fracture was 3.49 (1.85–6.56; 95% confidence intervals) in the patients.

Male patients in group A (normal gonadal function and treated hypogonadism) \( (n = 64) \) had a fracture frequency of 25.0%, compared with 7.7% among the control men \( (P < 0.001) \) (Fig. 2). The odds ratio for fracture was 3.97 (1.81–8.40; 95% confidence intervals) in the male patients. There was one fracture in the men with untreated hypogonadism \( (n = 5) \).

Female patients in group A (normal gonadal function and treated hypogonadism) \( (n = 23) \) had a fracture frequency of 21.7%, compared with 9.5% among the controls \( (P = 0.08) \) (Fig. 3a). The odds ratio was 2.64 (0.89–7.81; 95% confidence intervals) for the patients.

The fracture incidence in female patients in group B (untreated hypogonadism) \( (n = 15) \) was 40.0%, compared with 9.5% among the control women \( (P < 0.001) \) (Fig. 3b). The odds ratio was 6.33 (2.23–17.98; 95% confidence intervals) for the patients. The fracture rate for all female patients (groups A plus B; \( n = 38 \)) was 29.0%, compared with 9.5% among the controls \( (P < 0.001) \). The odds ratio for all the female patients was 3.87 (1.69–8.88; 95% confidence intervals).

The mean concentration of plasma IGF-I in the male patients was 0.28 (±0.11) kU/l and in the female patients it was 0.27 (±0.08) kU/l. The mean concentration of serum-free T4 was 13.1 (±4.3) pmol/l in male patients and 15.4 (±4.8) pmol/l in female patients.

**Discussion**

In a previous study comprising 95 hypopituitary patients with GHD, we found these patients to have a reduced bone mineral density (2). The present study clearly shows that these patients have, in addition, three times the risk of fractures compared with a randomly selected reference population.

The Göteborg sample of the WHO MONICA Study comprising randomly selected individuals was used as a reference population for the fracture frequency rate, which was assessed with questionnaires concerning the type, number and date (year) of specific fractures. Thus, no X-ray diagnosis of fracture was registered. There were no difficulties filling in the questionnaires properly, and we have no reason to believe that there was any discrepancy in the registration of the fracture rates between the patient group and the reference group. We consider that the questionnaire method is a proper method with which to measure fracture incidence rate (5). However, the frequency of vertebral fractures might
be underestimated, as these fractures in higher age groups might be asymptomatic and thus unrevealed unless X-ray is performed (6). Furthermore, the total fracture prevalence of the controls in this study does not seem to be underestimated, as it is similar to that observed in previous Swedish studies (7). The type of fractures seems to be of mainly osteoporotic origin in both patients and controls.

Several factors influence the bone mineral content and thus the fracture incidence. However, the patients’ tobacco consumption was lower and body weight higher than in the controls, as shown in a previous study (8). Smoking and low body weight are both known risk factors for osteopenia. Food habits or alcohol consumption were not evaluated in the patients, but we have no reason to believe that the patients differed in this respect from the controls. Physical inactivity is a risk factor for osteoporosis (9) but this was not specifically measured in the patients. They had, however, to a major extent, retired from work at younger ages and were known to have a low energy level, according to quality of life questionnaires (10), which may indicate a lower degree of physical activity than that in the general population. The low muscle mass, secondary to GHD and/or inactivity noted in the patients (11), might also render a higher risk of fractures. Moreover, balance problems due to disturbed visual capacity and decreased perception ability secondary to the underlying pituitary tumor might also contribute.

Adequate substitution therapy with corticosteroids and T₄ was given to the patients. No continuous or inactivity noted in the patients (11), might also render a higher risk of fractures. Moreover, balance problems due to disturbed visual capacity and decreased perception ability secondary to the underlying pituitary tumor might also contribute.

The relationship between hypogonadism and its treatment and fracture frequency is more complicated. In summary, we found that patients with normal gonadal function and hypogonadal patients with substitution therapy with testosterone or estrogen had an increased fracture rate. This might be interpreted as indicating that ‘routine’ replacement is not sufficient to optimize bone mineral content and prevent fractures. However, the impact of the years of untreated hypogonadism on the fracture frequency must be considered, as it is well known that untreated hypogonadism is a major reason for osteopenia and fractures in both men (14, 15) and women (16, 17). On average, the patients had about 4 years of untreated hypogonadism, which might contribute to some osteopenia. The fracture frequency was increased per se in both male and female patients, although it did not reach statistical significance among the females (P = 0.08). This is probably explained by the low number of female patients (n = 23), compared with the male patients (n = 64).

The role of GH on bone mineral content and bone mineral density is not fully understood. GH exerts both direct and indirect effects on bone metabolism. Longitudinal bone growth is stimulated directly by GH via an effect on chondrocyte proliferation within the growth plate (18). GH also has effects on minerals: it increases the availability of calcium and phosphate and furthermore increases the renal absorption of phosphate (19). In addition, GH enhances local osteoblastic production and responsiveness to IGF-I (20, 21), which, in turn, have stimulatory effects on bone metabolism. However, the osteoblastic IGF-I synthesis is also influenced by stimulatory agents such as estrogen (22), prostaglandin E₂ (23) and parathyroid hormone (24), and by inhibitory agents such as cortisol (25).

Recently, long-term studies with recombinant human GH (rGH) treatment of adult patients with GHD have shown an increase of both trabecular and cortical bone density (assessed with dual energy X-ray absorptiometry; DEXA Scan) by about 5% after 2 years of treatment (26). There was a simultaneous increase in markers for both bone formation and bone resorption, indicating that bone turnover was augmented (26). The increase in bone mineral density implies that bone formation is enhanced preferentially to bone resorption. These results of rGH treatment on bone density are promising, and further on-going studies will tell us whether rGH treatment will reduce the fracture incidence rate in patients with GHD.

In summary, this study shows that adult hypopituitary patients with GHD, in addition to a decreased bone mineral density, have a threefold increased fracture frequency compared with the general population. It is tempting to speculate that long-term GH treatment might improve the fracture rate in these patients.

Acknowledgements
This work was supported by grants from the Swedish Medical Research Council (11621), (B94–27X-10879–01) and the Lundberg Research Fund. It was presented in part at the 77th Annual Meeting of the Endocrine Society, Washington DC, June 1995.

References
5 Beard CM, Melton LJ, Cedel SL, Richelsen LS & Riggs BL. Ascertainment of risk factors for osteoporosis: comparison of


Received 6 November 1996
Accepted 12 May 1997