Malignant Disease and Cardiovascular Morbidity in Hypopituitary Adults with or without Growth Hormone Replacement Therapy

J. SVENSSON [1]
B.- Å. BENGTSSON [1]
T. ROSÉN [1]
A. ODÉN [2]
G. JOHANNSSON [1]

[1] *Research Centre for Endocrinology and Metabolism (J.S., B.-Å.B., T.R., G.J.), Sahlgrenska University Hospital, SE-413 45 Göteborg, Sweden;*
[2] *consulting statistician (A.O.), SE-44292 Romelanda, Sweden*

Received September 12, 2003.
Accepted April 5, 2004.

Address all correspondence and requests for reprints to: Johan Svensson, M.D., Research Centre for Endocrinology and Metabolism, Gröna Stråket 8, Sahlgrenska University Hospital, SE-413 45 Göteborg, Sweden. E-mail: Johan.Svensson@medic.gu.se.

This study was supported by the chair of Göteborg and the Novo Nordisk Foundation.

Results of this work were presented in part at the 85th Annual Meeting of The Endocrine Society, Philadelphia, Pennsylvania, June 2003.

Abbreviation:

IGFBP-3 - IGF-binding protein-3

A retrospective comparison was performed between 1411 hypopituitary adults without GH replacement [mean age, 56.9 (SD 18.6) yr] and the normal population in terms of fatal and nonfatal morbidity. A similar prospective comparison was then made in 289 hypopituitary patients on long-term GH replacement [mean age, 47.6 (SD 14.8) yr; mean duration of GH treatment, 60 months].

In the 1411 hypopituitary patients without GH replacement, overall mortality ($P < 0.001$), and the rates of myocardial infarctions ($P < 0.01$), cerebrovascular events ($P < 0.001$), and malignancies ($P < 0.001$) were increased compared with the normal population. Colorectal cancer was the most common malignancy in this cohort ($P < 0.001$ *vs.* the background population). In the 289 hypopituitary patients on GH replacement, overall mortality and the rate of malignancies were similar to the

normal population. In the hypopituitary adults on GH therapy, the rate of myocardial infarctions was lower than that in the background population (*P* < 0.05), and there was a tendency toward an increased rate of cerebrovascular events.

In conclusion, overall mortality and the rate of myocardial infarctions were increased in hypopituitary patients without GH replacement. An increased rate of malignancies was observed in the hypopituitary adults without GH therapy, with a predominance of colorectal cancer. GH replacement appeared to provide protection from myocardial infarctions. The rate of cerebrovascular events tended to be increased also in hypopituitary adults on GH therapy. (*J Clin Endocrinol Metab* 89: 3306–3312, 2004)

THREE RETROSPECTIVE STUDIES [1] [2] [3] have revealed an increase in mortality in hypopituitary adults on routine hormone replacement therapy. Two of these studies [1] [2] found that the premature mortality was due to an increase in cardiovascular mortality, whereas there was a small nonsignificant increase in cardiovascular deaths in the third study [3] . In a fourth retrospective study [4] , a small but nonsignificant increase in overall mortality was found, although cardiovascular mortality was decreased. In a recent large prospective study [5] , an increase in overall mortality was observed to a similar degree as that described in the previous retrospective studies [1] [2] [3] . The extent to which the increase in mortality in hypopituitary adults is due to untreated GH deficiency, insufficient replacement of other anterior pituitary hormones, or the treatment of the underlying disease that often involves surgery and radiation therapy is unknown.

Several important cardiovascular risk factors have been observed in adults with untreated GH deficiency such as abdominal obesity and dyslipoproteinemia, which benefit from GH replacement therapy [6] [7] . Moreover, premature atherosclerosis has been found with increased carotid intima media thickness, also suggested to be reduced by GH replacement [8] [9] [10] . The extent to which GH replacement therapy in adults can reduce vascular morbidity and mortality is not known. A report from a large postmarketing surveillance program found that adults on GH replacement therapy had similar overall mortality as the background population [11] . The safety of GH treatment is, however, still under debate as patients included in such studies may be highly selected. In intensive care unit patients, administration of high doses of GH increased overall mortality [12] .

Previous studies have presented conflicting results regarding the incidence of malignancies in patients with pituitary disease. A decreased rate of malignancies in hypopituitary men without GH replacement has been observed in some studies [1] [3] , whereas an increased rate of malignancies was observed in hypopituitary women who did not receive GH therapy [3] . In retrospective studies by Popovic *et al.* [13] and Nilsson *et al.* [14] , the rate of, and the mortality from, neoplasia were increased in patients with pituitary tumors. Studies suggest that high GH/IGF-I levels may be associated with increased incidence of colorectal cancer in acromegalic patients [15] [16] [17] , as well as in young adults who previously had received long-term GH treatment in childhood [18] .

In the present study, a retrospective comparison was made between 1411 hypopituitary adults identified from the National Board of Health and Welfare in Sweden and the normal population in terms of fatal and nonfatal morbidity from cardiovascular disease and malignancies. The rates of vascular disease and malignancy were then determined prospectively in 289 hypopituitary patients being treated with GH at a single center (1443 patient years; mean duration of treatment, 5 yr). Patients with a history of previous acromegaly or Cushing's disease were excluded from both studies.

Patients and Methods

Retrospective study

A total of 1411 adult patients (747 men and 664 women) was included in a retrospective study. The mean age at inclusion was 56.9 (SD 18.6) years, the minimum age for inclusion was 18 yr. The patients were selected on the basis of inpatient care in the years 1987–1992 with a primary or secondary medical diagnosis of hypopituitary disease recorded by the National Board of Health and Welfare in Sweden (a governmental institution in Sweden that supervises the health care system) [19] [20] . Patients with a diagnosis of previous acromegaly or Cushing's disease were excluded from the analysis. Only medical diagnoses for inpatient stays are available using the data supplied by the National Board of Health and Welfare in Sweden. Baseline descriptive data such as number of anterior pituitary hormonal deficiencies, estrogen treatment in women, previous surgery or radiotherapy, duration of hypopituitarism, multiple endocrine neoplasia, and other similar baseline data are not given. Therefore, in the retrospective study, the included 1411 patients are presented as hypopituitary patients without giving any further baseline characteristics.

After inclusion of the 1411 hypopituitary patients, the number of these patients who had received inpatient care up to the end of year 1994 (if not dead before) with a primary or secondary diagnosis of a stroke, myocardial infarction, or malignancy (recorded by the National Board of Health and Welfare in Sweden) was determined. A total of 5593 patient years were studied. Fatal as well as nonfatal events were included. Subsequently, the number of these hypopituitary patients who had received inpatient care with a primary or secondary diagnosis of stroke, myocardial infarction, or malignancy was compared with that in the normal population during the same time period. A maximum of one inpatient stay for stroke, myocardial infarction, and malignancy, respectively, for each patient was permitted in the calculation to exclude the possibility of there having been several hospitalizations for the same event.

Before the end of 1994, the use of GH replacement therapy in GH-deficient adults was limited to research in Sweden. It can therefore be assumed that a large majority of the hypopituitary patients included in this retrospective analysis did not have GH replacement therapy. The number of patients with childhood or adult-onset hypopituitary disease and the number of patients who had received GH replacement therapy during

childhood could not be determined from the National Board of Health and Welfare. As stated above, the mean age of the 1411 hypopituitary patients at inclusion in 1987–1992 was 56.9 (SD 18.6) yr. GH replacement therapy in children was introduced in the early 1960s in Sweden. Most of the included patients were therefore older than 18 yr of age when GH replacement therapy in children became available in Sweden. A small portion may, however, have received GH therapy during childhood.

In addition to medical diagnoses for inpatient stays, data were also available from the National Board of Health and Welfare in Sweden relating to fatal myocardial infarctions occurring outside a hospital. Fatal coronary events occurring outside a hospital are obviously the most serious ones with very rapid time courses; death most frequently occurs during transport to hospital [21] . Data regarding myocardial infarctions are therefore presented as myocardial infarctions (including fatal events occurring outside a hospital) or myocardial infarctions (excluding fatal events occurring outside a hospital). Data relating to fatal cerebrovascular events occurring outside a hospital were not available, but fatal cerebrovascular events generally have a slower time course than fatal myocardial infarctions [21] .

Mortality data for the 1411 hypopituitary patients as well as the background population were available from the Swedish Cause of Death Registry (for instance, see Ref. [22]). The reporting rate is 99.6% [22] . The Swedish Cause of Death Registry contains information of all deaths in Sweden and underlying as well as contributing causes of death [22] . Overall mortality in malignant diseases as well as mortality in colorectal cancer could also be calculated in the 1411 hypopituitary patients without GH replacement therapy and in the background population using the Swedish Cause of Death Registry.

The morbidity in malignant diseases (fatal as well as nonfatal) was, in the 1411 hypopituitary patients without GH replacement therapy, as stated above, determined based on inpatient stays with a primary or secondary diagnosis of a malignancy recorded by the National Board of Health and Welfare in Sweden. A maximum of one inpatient stay for malignancy for each patient was permitted in the calculation to exclude the possibility of there having been several hospitalizations for the same event. For the background population, the number of expected malignancies was calculated based on data from the Swedish Cancer Registry (for instance, see Ref. [23]). According to the law in Sweden, all physicians must report all malignancies to the Swedish Cancer Registry. Ninety-eight percent of all diagnosed tumors are reported to the Swedish Cancer Registry [23] . Also, malignancies that are treated without any inpatient stays, for instance some skin cancers, are also included in the Swedish Cancer Registry. Therefore, in the hypopituitary patients, the number of malignancies was based on inpatient stays with a primary or secondary diagnosis of a malignancy, whereas in the normal population, the expected number of malignancies was calculated based on both outpatient and inpatient medical care reported to the Swedish Cancer Registry.

Prospective study

The prospective study is an ongoing, prospective, open-label treatment trial of the replacement of recombinant human GH in adult patients with GH deficiency. The database was started on October 8, 1990 and was closed for analysis on August 15, 2000. Two hundred eighty-nine adults with pituitary deficiency (186 men and 103 women) and with a mean age of 47.6 (SD 14.8; range, 17–75) yr were included. At analysis, the mean duration of GH replacement therapy was 59.9 (SEM 1.9; range, 2–118.5) months; a total of 1443 patient years. Patients with previous acromegaly or Cushing's disease were excluded from the analysis. Sixty-four of the patients had previously received GH treatment during childhood. The diagnosis of GH deficiency was based on known pituitary disease combined with a GH stimulation test in 268 of the patients. In 21 patients with multiple anterior pituitary hormonal deficiencies, the diagnosis was based on measurements of the GH secretory pattern or serum IGF-I concentration. The pituitary deficiency was mainly caused by pituitary tumors or their treatment (Table 1). One hundred one patients (35%) had been treated with transfrontal surgery, and 97 (34%) had previously had transsphenoidal surgery. Ninety-two (32%) of the patients had previously received radiotherapy. Most patients had multiple anterior pituitary deficiencies (Table 1). When required, patients received replacement therapy with glucocorticoids, thyroid hormone, gonadal steroids, and desmopressin throughout the study period. At entry in the study, 70% (62 of 89) of the hypogonadal women received

TABLE 1 -- Causes of pituitary deficiency and the type of pituitary deficiency in 289 GH-deficient adults

	Men	**Women**	**Total**
Nonsecreting pituitary adenoma	89	44	133
Secreting pituitary adenoma	20	6	26
Craniopharyngioma	18	13	31
Empty sella	5	7	12
Meningioma	3	4	7
Sheehan's syndrome	0	4	4
Pituitary apoplexy	3	1	4
Sarcoidosis	4	2	6
Trauma	5	1	6
Previous brain tumor (other than pituitary adenoma/craniopharyngioma/meningioma)	11	3	14
Idiopathic	14	10	24
Other pathology	14	8	22
No. of deficiencies			
Isolated GH deficiency	20	9	29

TABLE 1 -- Causes of pituitary deficiency and the type of pituitary deficiency in 289 GH-deficient adults

	Men	Women	Total
1 Additional deficiency	20	13	33
2 Additional deficiencies	29	17	46
3 Additional deficiencies	117	64	181
Diabetes insipidus	19	13	32

estrogen **replacement** therapy. All the hypogonadal men received testosterone **replacement** therapy.

In five subjects (2%), GH treatment was discontinued due to adverse events other than those listed in *Results* [reoccurrence of pituitary tumor (n = 1), angina pectoris without myocardial infarction (n = 1), intermittent claudication (n = 1), epileptic seizures (n = 1), and excessive weight loss without any malignant disease being found (n = 1)]. Treatment was discontinued in 10 patients (3%) due to lack of compliance. Six patients (2%) were lost to follow-up because they moved to other parts of Sweden or abroad.

The initial target dose of GH in the first 80 patients was 11.9 μg/kg•d (0.25 IU/kg•wk). The dose was gradually lowered and individualized when the weight-based dose regimen was abandoned [24] . In the remaining 209 patients, the GH dose was individualized from the start [24] . The dose of GH was individualized with the aim of normalizing IGF-I SD score and body composition [24] . Dose titration, safety monitoring, and determinations of serum IGF-I concentrations were performed on visits every 3 months during the first year and every 6 months thereafter. Mortality, arthrosclerotic vascular disease, and malignancy were evaluated. Overall mortality, cardiovascular and cerebrovascular morbidity, and the rate of malignancies were compared with those in the normal population (based on data relating to the normal population in Sweden obtained from the National Board of Health and Welfare in Sweden in a similar way as in the retrospective study).

Ethical considerations

Informed consent was obtained from all the patients in the prospective part of the study. The present study was approved by the Ethics Committee at the University of Göteborg and the Swedish Medical Products Agency (Uppsala, Sweden).

Biochemical assays

Serum IGF-I concentration was determined by a hydrochloric acid-ethanol extraction RIA using authentic IGF-I for labeling (Nichols Institute Diagnostics, San Juan Capistrano, CA). Interassay and intraassay coefficients of variation were less than 7%. The individual serum IGF-I values were compared with age- and sex-adjusted values

obtained from a reference population [25] . The individual IGF-I SD scores could then be calculated [26] .

Statistical methods

For serum IGF-I concentration and IGF-I SD score, all the descriptive statistical results are presented as the mean (SEM). The statistical analyses

TABLE 2 -- Overall mortality and incidence of, and mortality in, malignancies in 1411 hypopituitary adults (747 men and 664 women) without GH therapy

	Observed	**Expected**	**Risk ratio**	**95% Confidence interval**	***P* value**
Deaths					
Men	222	66.1	3.36	2.93, 3.83	<0.001
Women	177	39.0	4.54	3.89, 5.26	<0.001
All	399	105.1	3.80	3.43, 4.19	<0.001
All malignancies (fatal as well as nonfatal)					
Men	66	44.0	1.50	1.16, 1.91	<0.01
Women	67	28.6	2.34	1.82, 2.98	<0.001
All	133	72.6	1.83	1.53, 2.17	<0.001
All malignancies (deaths)					
Men	60	16.7	3.59	2.74, 4.63	<0.001
Women	44	9.8	4.49	3.26, 6.03	<0.001
All	104	26.5	3.92	3.21, 4.76	<0.001
Cancer of colon and rectum (fatal as well as nonfatal)					
Men	18	3.98	4.52	2.68, 7.15	<0.001
Women	13	2.46	5.28	2.81, 9.04	<0.001
All	31	6.44	4.81	3.27, 6.83	<0.001
Cancer of colon and rectum (deaths)					
Men	10	1.8	5.56	2.66, 10.22	<0.001
Women	6	1.2	5.00	1.83, 10.88	0.003
All	16	3.0	5.33	3.05, 8.66	<0.001

P values are *vs.* the normal population in Sweden.

for IGF-I values are based on a one-way ANOVA with time as the independent variable, followed by Student-Newman-Keuls *post hoc* test.

The expected number of deaths provided that the death hazard function coincided with that of the general population was calculated taking the current age, gender, and current calendar time into account. In a similar way, the expected number was calculated for other events. Confidence intervals were calculated using Poisson distributions.

Results

Retrospective analysis of hypopituitary adults without GH therapy

In the 1411 hypopituitary patients identified from the National Board of Health and Welfare in Sweden, overall mortality and the incidence of and mortality in malignant diseases were increased in both sexes as compared with the normal population (Table 2). The mean age of the patients in whom a malignancy was diagnosed was 64.7 (SD 14.8; range, 20–92) yr. The most common malignancy was cancer of the colon and rectum (Table 2). The mean age of the patients with colorectal cancer was 70.0 (SD 14.1; range, 32–92) yr. Both the incidence of and mortality in colorectal cancer were increased in the hypopituitary adults without GH therapy as compared with the background population (Table 2). The malignancies (apart from cancer of the colon and rectum) in the 1411 hypopituitary patients were as follows: malignant head/neck tumor (n = 18), malignant brain tumor (n = 16), malignant tumor in other endocrine organs (n = 15), lymphoma (n = 12), malignant breast tumor (n = 7), malignant primary liver tumor (n = 7), malignant gynecologic tumor (n = 5), myeloid leukemia (n = 5), malignant prostate tumor (n = 4), malignant tumor in the urinary bladder (n = 4), malignant tumor in the kidney (n = 4), malignant tumor in the thymus (n = 2), malignant esophageal tumor (n = 1), malignant bile bladder tumor (n = 1), and malignant meningeal tumor (n = 1).

An increase in the rate of all myocardial infarctions was found in the 1411 hypopituitary adults. This was mainly explained by an increase in the relative risk among the hypopituitary women (Table 3). However, if fatal myocardial infarctions occurring outside a hospital were excluded, the rate of myocardial infarctions was similar in both hypopituitary men and women to that observed in the normal population (Table 3). The rate of cerebrovascular events was increased in both sexes as compared with the normal population (Table 3).

Prospective study of GH-treated hypopituitary adults

Serum IGF-I concentrations and IGF-I SD scores in the 289 GH-deficient adults are given in Table 4 . In patients in whom a malignant disease was diagnosed during the study period (n = 7), mean IGF-I SD score before the diagnosis of the malignant disease was statistically similar to that in the total study population: −0.56 (0.46) at baseline, 2.60

(0.98) at 1 yr, 1.66 (0.63) at 3 yr, and 1.41 (0.58) at 5 yr. At the actual time point of the diagnosis of the malignant disease, IGF-I SD was 1.61 (0.44) in these patients. Serum IGF-binding protein-3 (IGFBP-3) concentration was not measured in the present study.

Eight deaths occurred during GH replacement in the 289 GH-deficient adults (1 death in 180 patient years; *P* = non-significant *vs.* the normal population; Table 5). The causes of death were radiation-induced encephalitis (n = 1; after 1.3 yr of GH replacement), malignant brainstem tumor (n = 1; 2.9 yr), cerebral hemorrhage (n = 1; 3.1 yr), renal carcinoma (n = 1; 3.3 yr), pulmonary edema due to suspected myocardial infarction (n = 1; 8.3 yr), cerebral infarction (n = 1; 8.6 yr), and unknown cause of death (n = 2; 1.0 and 3.9 yr, respectively).

A malignant disease was observed in seven patients [prostate cancer (n = 1; diagnosed after 0.2 yr of GH replacement), colonic cancer (n = 2; 0.8 and 5.4 yr, respectively), malignant brainstem tumor (n = 1; 2.9 yr), renal carcinoma (n = 1; 3.3 yr), pulmonary adenocarcinoma (n = 1; 3.7 yr), and malignant tumor in the urinary bladder (n = 1; 6.1 yr)]. This rate (incidence) of malignancies was similar to that in the normal population (Table 5).

Two myocardial infarctions occurred after 5.7 and 8.3 yr of GH replacement therapy, respectively. This rate of myocardial infarctions (including out-of-hospital deaths from myocardial infarctions) was lower than that in the normal population (Table 5). However, if fatal myocardial infarctions occurring outside a hospital were excluded, the rate of

TABLE 3 -- The number of cardiovascular events in 1411 hypopituitary adults (747 men and 664 women) without GH therapy

	Observed	**Expected**	**Risk ratio**	**95% Confidence interval**	***P* value**
Myocardial infarctions (including fatal events outside hospital)					
Men	46	38.3	1.20	0.88, 1.60	0.25
Women	31	16.6	1.87	1.27, 2.65	<0.01
All	77	54.9	1.40	1.10, 1.75	<0.01
Myocardial infarctions (excluding fatal events outside hospital)					
Men	21	24.4	0.86	0.53, 1.32	>0.30
Women	12	10.1	1.19	0.61, 2.08	>0.30
All	33	34.5	0.96	0.66, 1.34	>0.30
Cerebrovascular events (no. of events)					

TABLE 3 -- The number of cardiovascular events in 1411 hypopituitary adults (747 men and 664 women) without GH therapy

	Observed	Expected	Risk ratio	95% Confidence interval	*P* value
Men	47	20.7	2.27	1.71, 3.02	<0.001
Women	46	13.3	3.46	2.53, 4.61	<0.001
All	93	34.0	2.74	2.21, 3.35	<0.001

P values are *vs.* the normal population in Sweden.

myocardial infarctions in the 289 patients was similar to that in the normal population.

The rate of cerebrovascular events was statistically similar to that in the normal population (Table 5). The cerebrovascular events consisted of six cerebral infarctions (diagnosed after 0.6, 0.7, 2.3, 2.4, 7.6, and 8.6 yr, respectively) and one hemorrhage after 3.1 yr of GH replacement therapy. Four of the six patients with cerebral infarctions had previously received radiotherapy.

Discussion

This is the first large study that has determined not only mortality but also morbidity in hypopituitary adults with and without GH replacement therapy. Our data demonstrate an increase in overall mortality and in morbidity from myocardial infarctions and malignancies in a large cohort of hypopituitary adults without GH replacement therapy. In the younger and smaller cohort of hypopituitary adults who received GH replacement, overall mortality and the rate of malignancies were similar and the rate of myocardial infarctions was lower than that observed in the background population. The rate of cerebrovascular events was increased in hypopituitary adults without GH therapy and also tended to be increased in the hypopituitary adults undergoing GH replacement therapy.

The study cohort in the retrospective study is not comparable with the study cohort in the prospective study. The study cohort in the retrospective study was older [mean age, 56.9 (SD 18.6) yr] and larger (n = 1411) than that in the prospective study [mean age, 47.6 (SD 14.8) yr; n = 289]. Although comparisons with the background population were corrected for age, sex, and calendar time, differences in the outcome of the patients in the retrospective and the prospective study could be an effect of factors other than GH replacement therapy.

The retrospective study of 1411 hypopituitary adults without GH replacement revealed an increase in cardiovascular and cerebrovascular morbidity. These data on both fatal and

nonfatal morbidity are in line with and confirm previous observations of an increase in the relative risk of total and vascular mortality in hypopituitary patients [1] [2] [5] . The 3.8-times increase in the relative risk for total mortality in the 1411 hypopituitary patients in this study is larger than that observed in previous publications [1] [2] [3] [4] [5] .

TABLE 4 -- Serum IGF-I concentration and IGF-I SD score in 289 GH-deficient adults (186 men and 103 women) on GH **replacement** therapy

	Baseline (n = 289)	**1 yr (n = 259)**	**3 yr (n = 205)**	**5 yr (n = 166)**	**7 yr (n = 68)**	**9 yr (n = 26)**	**Study end (August 15, 2000; n = 260)**
Serum IGF-I (men; μg/liter)	125 (6)	322 (11)[a]	308 (11)[a]	283 (11)[a]	275 (16)[a]	260 (22)[a]	239 (8)[a]
Serum IGF-I (women; μg/liter)	83 (6)	224 (11)[b]	226 (12)[a]	229 (15)[b]	231 (21)[c]	151 (34)[c]	210 (10)[a]
IGF-I SD score (men)	−1.39 (0.12)	2.74 (0.21)[a]	2.54 (0.22)[a]	2.06 (0.22)[a]	1.88 (0.34)[a]	1.46 (0.50)[a]	1.38 (0.17)[a]
IGF-I SD score (women)	−2.12 (0.13)	0.51 (0.22)[a]	0.70 (0.23)[a]	0.83 (0.29)[a]	0.87 (0.43)[a]	−0.17 (0.77)[b]	0.81 (0.18)[a]

[a] $P < 0.001$ (*vs.* baseline);
[b] $P < 0.01$;
[c] $P < 0.05$.

TABLE 5 -- Overall mortality and the number of malignancies and cardiovascular events in 289 GH-deficient adults (186 men and 103 women) on GH **replacement** therapy

	Observed	**Expected**	**Risk ratio**	**95% Confidence interval**	***P* value**
Deaths					
Men	8	7.2	1.11	0.48, 2.20	>0.30
Women	0	2.3	0.00	0.00, 1.62	0.20
All	8	9.5	0.84	0.36, 1.66	0.78
All observed malignancies					
Men	6	5.1	1.17	0.43, 2.56	>0.30

TABLE 5 -- Overall mortality and the number of malignancies and cardiovascular events in 289 GH-deficient adults (186 men and 103 women) on GH **replacement** therapy

	Observed	**Expected**	**Risk ratio**	**95% Confidence interval**	***P* value**
Women	1	2.9	0.34	0.01, 1.92	>0.30
All	7	8.0	0.88	0.35, 1.80	0.91
Cancer of colon and rectum					
Men	2	0.63	3.17	0.38, 11.48	0.26
Women	0	0.27	0.00	0.00, 13.67	0.47
All	2	0.90	2.22	0.27, 8.03	0.46
Myocardial infarctions (including fatal events outside hospital)					
Men	2	6.12	0.33	0.04, 1.18	0.25
Women	0	1.17	0.00	0.00, 3.15	>0.30
All	2	7.29	0.27	0.03, 0.99	<0.05
Myocardial infarctions (excluding fatal events outside hospital)					
Men	2	4.51	0.44	0.05, 1.60	>0.30
Women	0	0.84	0.00	0.00, 4.39	>0.30
All	2	5.35	0.37	0.04, 1.35	0.20
Cerebrovascular events					
Men	6	2.77	2.17	0.79, 4.71	0.13
Women	1	0.82	1.22	0.02, 6.80	>0.30
All	7	3.59	1.95	0.78, 4.02	0.15

P values are *vs.* the normal population in Sweden.

If the prevalence of hypopituitarism was similar to that estimated in Spain in 1992 [27] , the total number of hypopituitary adults in Sweden would be 2500. We cannot therefore exclude the possibility that some selection bias may have occurred, because the age of our patients was higher than that reported in previous mortality studies and our patients might have a more severe hypothalamic-pituitary disease. On the other hand, some patients may not have been included in previous reports that mainly included patients from referral centers.

In the 289 hypopituitary adults who received GH replacement, 30% percent of the women were not receiving estrogen treatment at baseline. This is a similar percentage than that reported in a prospective trial of survival in hypopituitary patients in whom untreated gonadotropin deficiency was associated with increased mortality [5] . In the 1411 hypo-pituitary patients who did not receive GH replacement, data regarding estrogen replacement were not available. In the general population, however, recent studies have shown an increased risk of breast cancer during estrogen replacement therapy in postmenopausal women [28] , and estrogen replacement did not improve cardiovascular disease outcomes [29] [30] . Therefore, the outcome of estrogen replacement in hypopituitary patients is not yet clear.

Overall mortality in the 289 hypopituitary adults on GH replacement therapy was similar to that in the normal population. The upper limit of the 95% confidence interval for the relative risk was 1.66 in the total study population. As a result, this study does not have the statistical power to exclude a small increase in overall mortality in hypopituitary adults on GH replacement as compared with the normal population. However, as discussed above, the relative risk of overall mortality was 3.8 in the 1411 hypopituitary adults without GH replacement therapy. Although the study cohort in the retrospective study is not fully comparable with the study cohort in the prospective study, the present results could suggest that GH replacement therapy reduces mortality in hypopituitary adults.

The rate of myocardial infarctions was increased in hypopituitary women without GH replacement therapy if fatal out-of-hospital myocardial infarctions were included. Furthermore, the rate of myocardial infarctions (including fatal events occurring outside a hospital) in the hypopituitary patients on GH replacement therapy was even lower than that in the normal population. If fatal myocardial infarctions occurring outside a hospital were excluded, however, no difference was found between hypopituitary adults with or without GH therapy and the background population. The present results therefore suggest that GH may play an important role in providing protection from serious myocardial infarctions with a rapid time course. Furthermore, in the hypopituitary women, no death and only one malignancy (malignant tumor in the urinary bladder) were observed, and only one woman suffered from a cerebrovascular event. The present results could therefore suggest that GH replacement is accompanied by less adverse events in women than in men. One possible explanation for this could be that men were overtreated during the first years of GH replacement, as their mean IGF-I SD score was above +2 SD during yr 1–5 of treatment.

The rate of cerebrovascular events was increased in both hypopituitary men and women without GH replacement therapy. In the 289 hypopituitary adults undergoing GH replacement therapy, there was a tendency toward a higher rate of cerebrovascular disease than predicted. A power analysis revealed that a 3.8-times-larger study cohort was needed in the prospective study to achieve 80% power. Radiation-induced angiopathy has been suggested as a risk factor for stroke [31] [32] , and two previous studies [2] [5] have found that radiotherapy is a predictor of stroke in hypopituitary patients. A possible interpretation of our data is that GH replacement therapy does not provide

protection from strokes that are caused by radiation angiopathy. This is perhaps supported by the fact that four of the six patients treated with GH who suffered cerebral infarctions had previously received radiotherapy. This suggests that the increase in morbidity and mortality that we and others have observed in hypopituitary patients is multifactorial, including untreated hypogonadism, previous radiotherapy, and underlying disease as important contributory factors together with untreated GH deficiency.

In the 1411 hypopituitary adults without GH replacement, the incidence as well as the mortality in malignancies was increased as compared with the normal population. The mean age of the patients in whom a malignancy was diagnosed was 64.7 (SD 14.8; range, 20–92) yr. As discussed above, the patients included in the retrospective study were older than in previous mortality studies [1] [2] [3] [4] [5] . The relatively high age of the patients with malignant disease in the present retrospective study may possibly explain why we, in contrast to most previous studies, found an increased incidence of malignant disease in hypopituitary patients without GH therapy. One cause of the increased incidence of malignancies in hypopituitary patients without GH therapy could be that surgery and radiotherapy on pituitary tumors had caused secondary brain tumors [33] . Furthermore, 15 malignant tumors in other endocrine organs were found in the 1411 hypopituitary adults, which is probably explained by multiple endocrine neoplasia in these patients. It is therefore plausible that the increased rate of malignancies in the hypopituitary patients can be partly explained by factors other than their hypopituitarism.

Studies of acromegalic patients suggest that high GH/IGF-I levels are associated with an increased risk of colorectal cancer [15] [16] [17] . In mice with deficiency of liver-derived IGF-I, the onset and development of colon cancer and mammary tumors are delayed [34] [35] . *In vitro* data suggest that functional IGF-I receptors on the tumor cells may be needed for tumor formation and progression [36] [37] . An association between serum IGF-I levels and prostate, breast, and colon cancer risk in the general population has been demonstrated in prospective trials [38] [39] [40] [41] [42] . There appears to be an inverse association between risk of prostate, breast, and colon cancer and serum IGFBP-3 concentration [37] [38] [39] [40] [41] [42] . In the present study, in patients in whom a malignant disease was diagnosed during the study period, serum IGF-I concentration was similar to other patients. Serum IGFBP-3 concentration was not measured in the present study.

The number of the 1411 hypopituitary patients who had childhood- or adult-onset disease as well as the number of patients who had received GH treatment during childhood could not be obtained in the retrospective study. However, GH replacement therapy in children was introduced in the early 1960s in Sweden. Only three of the patients with colorectal cancer could therefore have received GH treatment (born 1947 and later). All other patients with colorectal cancer were too old to have received GH treatment in childhood (born 1937 and earlier). Even if the three patients who could possibly have received GH treatment in childhood were excluded, the increase in colorectal cancer was still highly significant ($P < 0.001$ *vs.* the background population). We can therefore exclude the possibility that the increase in colorectal cancer in the hypopituitary patients without GH treatment in adult life was due to GH treatment in childhood. In contrast, our data suggest that not only increases in GH/IGF-I levels play a causal role in the development of

colorectal cancer in patients with pituitary disease. Two retrospective studies [13] [14] have found increased rate and mortality from neoplasia in patients with pituitary tumors, suggesting an association that may be inherent or due to increased surveillance of this patient population.

In the prospective study, the rate of malignancies was similar to that in the normal population. Two patients had colorectal cancer in the 289 hypopituitary patients who received GH replacement therapy ($P = 0.46$ *vs.* normal population). The risk ratio for malignant disease in hypopituitary adults undergoing GH replacement therapy must, however, be determined in studies with longer follow-up time than that in the present study.

In conclusion, overall mortality and the rate of all observed malignancies were increased in hypopituitary adults before GH replacement therapy in adult life became available. Colorectal cancer was the most frequently found malignancy in these patients. GH replacement appeared to provide protection from fatal myocardial infarctions with rapid time courses. An increased rate of cerebrovascular events was also present in hypopituitary adults who received long-term GH replacement therapy, demonstrating that factors other than GH in the overall treatment have an important effect on the outcome in this patient group.

Acknowledgments

We are indebted to the personnel at the Research Centre for Endocrinology and Metabolism for their skillful technical support.

References

1. **Rosén T, Bengtsson B-Å** 1990 Premature mortality due to cardiovascular diseases in hypopituitarism. Lancet 336:285–288 Abstract

2. **Bülow B, Hagmar L, Mikoczy Z, Nordström C, Erfurth E** 1997 Increased cerebrovascular mortality in patients with hypopituitarism. Clin Endocrinol (Oxf) 46:75–81 Abstract

3. **Bates A, Van't Hoff W, Jones P, Clayton R** 1996 The effect of hypopituitarism on life expectancy. J Clin Endocrinol Metab 81:1169–1172 Full Text

4. **Bates A, Bullivant B, Sheppard M, Stewart P** 1999 Life expectancy following surgery for pituitary tumours. Clin Endocrinol (Oxf) 50:315–319 Abstract

5. **Tomlinson J, Holden N, Hills R, Wheatley K, Clayton R, Bates A, Sheppard M, Stewart P** 2001 Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. Lancet 357: 425–431 Abstract

6. **De Boer H, Blok G-J, Van Der Veen E** 1995 Clinical aspects of **growth hormone** deficiency in adults. Endocr Rev 16:63–86 Citation

7. **Carroll P, Christ E, Bengtsson B-Å, Carlsson L, Christiansen JS, Clemmons D, Hintz R, Ho K, Laron Z, Sizonenko P, Sönksen P, Tanaka T, Thorner M** 1998 **Growth hormone** deficiency in adulthood and the effects of **growth hormone replacement**: a review. J Clin Endocrinol Metab 83:382–395 Full Text

8. **Markussis V, Beshyah S, Fisher C, Sharp P, Nicolaides A, Johnston D** 1992 Detection of premature atherosclerosis by high-resolution ultrasonography in symptom-free hypopituitary adults. Lancet 340:1188–1192 Abstract

9. **Pfeifer M, Verhovec M, Zizek B, Prezelj J, Poredos P, Clayton R** 1999 **Growth hormone** (GH) treatment reverses early atherosclerotic changes in GH-deficient adults. J Clin Endocrinol Metab 84:453–457 Full Text

10. **Borson-Chazot F, Serusclat A, Kalfallah Y, Ducottet X, Sassolas G, Bernard S, Labrousse F, Pastene J, Sassolas A, Roux Y, Berthezene F** 1999 Decrease in carotid intima-media thickness after one year **growth hormone** (GH) treatment in adults with GH deficiency. J Clin Endocrinol Metab 84:1329–1333 Full Text

11. **Bengtsson B-Å, Koppeschaar H, Abs R, Bennmarker H, Hernberg-Stahl E, Westberg B, Wilton P, Monson JP** 1999 **Growth hormone replacement** therapy is not associated with any increase in mortality. KIMS Study Group. J Clin Endocrinol Metab 84:4291–4292 Full Text

12. **Takala J, Ruokonen E, Webster N, Nielsen M, Zandstra D, Vundelinckx H, Hinds C** 1999 Increased mortality associated with **growth hormone** treatment in critically ill patients. N Engl J Med 341:785–792 Abstract

13. **Popovic V, Damjanovic S, Mimic D, Nesovic M, Djurovic M, Petakov M, Obradovic S, Zoric S, Simic M, Penezic Z, Marinkovic J** 1998 Increased incidence of neoplasia in patients with pituitary adenomas. The Pituitary Study Group. Clin Endocrinol (Oxf) 49:441–445 Abstract

14. **Nilsson B, Gustavsson-Kadaka E, Bengtsson B-Å, Jonsson B** 2000 Pituitary adenomas in Sweden between 1958 and 1991: incidence, survival, and mortality. J Clin Endocrinol Metab 85:1420–1425 Full Text

15. **Bengtsson B-Å** 1993 Acromegaly and neoplasia. J Pediatr Endocrinol 6:73–78 Citation

16. **Orme SM, McNally RJ, Cartwright RA, Belchetz PE** 1998 Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab 83:2730–2734 Full Text

17. **Jenkins P, Besser M** 2001 Clinical perspective: acromegaly and cancer: a problem. J Clin Endocrinol Metab 86:2935–2941 Full Text

18. **Swerdlow A, Higgins C, Adlard P, Preece M** 2002 Risk of cancer in patients treated with human pituitary **growth hormone** in the UK, 1959–85: a cohort study. Lancet 360:273–277 Abstract

19. **Hedbäck G, Abrahamsson K, Husberg B, Granholm T, Oden A** 2001 The epidemiology of infantile hypertrophic pyloric stenosis in Sweden 1987–96. Arch Dis Child 85:379–381 Abstract

20. **Kanis J, Odén A, Johnell O, De Laet C, Jonsson B, Oglesby A** 2003 The components of excess mortality after hip fracture. Bone 32:468–473 Abstract

21. **Thomas A, Knapman P, Krikler D, Davies M** 1988 Community study of the causes of "natural" sudden death. BMJ 297:1453–1456 Abstract

22. **Swedish National Board of Health and Welfare, Centre for Epidemiology** 1998 Causes of death. Stockholm: National Board of Health and Welfare

23. **National Board of Health and Welfare. The Cancer Registry** 1996 Cancer incidence in Sweden 1993. Stockholm: Center for Epidemiology 10

24. **Johannsson G, Rosén T, Bengtsson B-Å** 1997 Individualized dose titration of **growth hormone** (GH) during GH **replacement** in hypopituitary adults. Clin Endocrinol (Oxf) 47:571–581 Abstract

25. **Landin-Wilhelmsen K, Wilhelmsen L, Lappas G, Rosén T, Lindstedt G, Lundberg P-A, Bengtsson B-Å** 1994 Serum insulin-like growth factor I in a random population sample of men and women: relation to age, sex, smoking habits, coffee consumption and physical activity, blood pressure and concentrations of plasma lipids, fibrinogen, parathyroid hormone and osteocalcin. Clin Endocrinol (Oxf) 41:351–357 Abstract

26. **Svensson J, Johannsson G, Bengtsson B-Å** 1997 Insulin-like growth factor-I in growth hormone-deficient adults: relationship to population-based normal values, body composition and insulin tolerance test. Clin Endocrinol (Oxf) 46:579–586 Abstract

27. **Regal M, Paramo C, Sierra S, Garcia-Mayor R** 2001 Prevalence and incidence of hypopituitarism in an adult Caucasian population in northwestern Spain. Clin Endocrinol (Oxf) 55:735–740 Abstract

28. **Beral V, Million Women Study Collaborators** 2003 Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet [Erratum (2003) 362:1160] 362:419–427 Abstract

29. **Cherry N, Gilmour K, Hannaford P, Heagerty A, Khan MA, Kitchener H, McNamee R, Elstein M, Kay C, Seif M, Buckley H, ESPRIT team** 2002 Oestrogen therapy for prevention of reinfarction in postmenopausal women: a randomised placebo controlled trial. Lancet 360:2001–2008 Abstract

30. **Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, Hsia J, Hulley S, Herd A, Khan S, Newby LK, Waters D, Vittinghoff E, Wenger N, HERS Research Group** 2002 Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin **Replacement** Study follow-up (HERS II). JAMA [Erratum (2002) 288:1064] 288:49–57

31. **Flickinger J, Nelson P, Taylor F, Robinson A** 1989 Incidence of cerebral infarction after radiotherapy for pituitary adenoma. Cancer 63:2404–2408 Abstract

32. **Murros K, Toole J** 1989 The effect of radiation on carotid arteries. Arch Neurol 46:449–455 Abstract

33. **Erfurth E, Bulow B, Mikoczy Z, Svahn-Tapper G, Hagmar L** 2001 Is there an increase in second brain tumours after surgery and irradiation for a pituitary tumour? Clin Endocrinol (Oxf) 55:613–616 Abstract

34. **Wu Y, Yakar S, Zhao L, Hennighausen L, LeRoith D** 2002 Circulating insulin-like growth factor-I

levels regulate colon cancer growth and metastasis. Cancer Res 62:1030–1035 Abstract

35. **Wu Y, Cui K, Miyoshi K, Hennighausen L, Green J, Setser J, LeRoith D, Yakar S** 2003 Reduced circulating insulin-like growth factor I levels delay the onset of chemically and genetically induced mammary tumors. Cancer Res 63:4384–4388 Abstract

36. **Freier S, Weiss O, Eran M, Flyvberg A, Dahan R, Nepesh I, Safra T, Shiloni E, Raz I** 1999 Expression of the insulin-like growth factors and their receptors in adenocarcinoma of the colon. Gut 44:704–708 Abstract

37. **Khandwala H, McCutcheon I, Flyvberg A, Friend K** 2000 The effects of insulin-like growth factors on tumorigenesis and neoplastic growth. Endocr Rev 21:215–244 Abstract

38. **Chan J, Stampfer M, Giovannuci F, Gann PH, Ma J, Wilkinson, P, Hennekens CH, Pollak M** 1998 Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. Science 279:563–566 Abstract

39. **Hankinson S, Willett W, Colditz G, Hunter DJ, Michaud DS, Deroo B, Rosner B, Speizer FE, Pollak M** 1998 Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 351:1393–1396 Abstract

40. **Shaneyfelt T, Husein R, Bubley G, Mantzoros C** 2000 Hormonal predictors of prostate cancer: a meta-analysis. J Clin Oncol 18:847–853 Abstract

41. **Chan J, Stampfer M, Giovannucci E, Ma J, Pollak M** 2000 Insulin-like growth factor I (IGF-I), IGF-binding protein-3 and prostate cancer risk: epidemiological studies. Growth Horm IGF Res 10(Suppl A):S32–S33 Citation

42. **Juul A** 2003 Serum levels of insulin-like growth factor I and its binding proteins in health and disease. Growth Horm IGF Res 13:113–170 Citation