Excess Mortality Associated With Hypopituitarism in Adults: A Meta-Analysis of Observational Studies

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Context: Several previous observational studies showed an association between hypopituitarism and excess mortality. Reports on reduction of standard mortality ratio (SMR) with GH replacement have been published recently.

Objective: This meta-analysis assessed studies reporting SMR to clarify mortality risk in hypopituitary adults and also the potential benefit conferred by GH replacement.

Data Sources: A literature search was performed in Medline, Embase, and Cochrane library up to March 31, 2014.

Eligibility Criteria: Studies with or without GH replacement reporting SMR with 95% confidence intervals (95% CI) were included.

Data Extraction and Analysis: Patient characteristics, SMR data, and treatment outcomes were independently assessed by two authors, and with consensus from third author, studies were selected for analysis. Meta-analysis was performed in all studies together, and those without and with GH replacement separately, using the statistical package metafor in R.

Results: Six studies reporting a total of 19 153 hypopituiatary adults with a follow-up duration of more than 99 000 person years were analyzed. Hypopituitarism was associated with an overall excess mortality (weighted SMR, 1.99; 95% CI, 1.21–2.76) in adults. Female hypopituitary adults showed higher SMR compared with males (2.53 vs 1.71). Onset of hypopituitarism at a younger age was associated with higher SMR. GH replacement improved the mortality risk in hypopituitary adults that is comparable to the background population (SMR with GH replacement, 1.15; 95% CI, 1.05–1.24 vs SMR without GH, 2.40; 95% CI, 1.46–3.34). GH replacement conferred lower mortality benefit in hypopituitary women compared with men (SMR, 1.57; 95% CI, 1.38–1.77 vs 0.95; 95% CI, 0.85–1.06).

Limitations: There was a potential selection bias of benefit of GH replacement from a post-marketing data necessitating further evidence from long-term randomized controlled trials.

Conclusions: Hypopituitarism may increase premature mortality in adults. Mortality benefit from GH replacement in hypopituitarism is less pronounced in women than men. **(*J Clin Endocrinol Metab* 100: 1405–1411, 2015)**

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Abbreviations: CI, confidence interval; CV, cardiovascular; NFA, nonfunctioning pituitary adenoma; NOS, Newcastle Ottawa Scale; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SMR, standard mortality ratio.

The pituitary gland regulates the functions of human endocrine system by its control over the other hormone-producing organs, and the biochemical deficiency of one or more of the pituitary hormones is termed hypopituitarism (1, 2). The prevalence of hypopituitarism was reported to be 290–455 cases per million, with an incidence of 42.1 cases per million (1, 3). Although the reported prevalence of pituitary adenomas was 14.4% in postmortem studies and 22.5% in radiological studies respectively, with an overall prevalence of 16.7%, these were most often microadenomas with little clinical significance (1, 4). The incidence and prevalence of hypopituitarism are much lower, as most cases are secondary to large nonfunctioning pituitary adenomas or hormone-secreting tumors and their treatment. However, the actual burden of disease may be higher than that found in published literature as the diagnosis is often difficult because of the complexity of endocrine evaluation necessary in cases with hypopituitarism and the consequent under-reporting.

The increased risk of premature mortality associated with hypopituitarism was first identified by Rosén and Bengtsson (5) more than two decades ago. Excess mortality in pituitary diseases had been confirmed by other workers in subsequent observational studies (6–10) and meta-analyses (11, 12). There were also differences in the sex-specific mortality rates between men and women (12, 13). GH deficiency is the most common hormonal abnormality in patients with pituitary disease. Recent studies showed significant reduction in the mortality among hypopituitary adults on GH replacement therapy (14, 15).

However, there are wide differences in the reported case-specific, sex-specific, and cause-specific mortality rates among hypopituitary patients from different regions of the world. To clarify these uncertainties, a meta-analysis was performed with the available studies reporting the standard mortality ratios (SMR) in adults with hypopituitarism. The study also looked into the differences in SMR between patients with and without GH replacement.

Materials and Methods

Literature search was performed in three major databases: Medline, Embase, and Cochrane central library using "medical subject headings" descriptors for Medline and Cochrane library, and "Ovid Tree" terms for Embase up to March 31, 2014. The medical subject headings terms applied were "hypopituitarism," "pituitary neoplasms," "pituitary diseases," "prolactinoma," "chromophobe adenoma," "empty sella syndrome," and "growth hormone (GH)." The Ovid tree terms used were "hypopituitarism," "hypophysis disease," hypopituitary dwarfism," "hypophysoma," "hypophysis tumor," "prolactinomas," "empty sella syndrome," "empty sella turcica syndrome," and "GH." Free-text searches were also performed in the Medline and Embase databases using terms "hypopituitarism," "prolactinoma," and "empty sella syndrome." These key words were combined with the operator "OR" in both databases. We then combined the hypopituitary terms with the operator for mortality terms "mortality" OR "death" using the operator "AND." The searches were limited to human studies and those in English language. The Cochrane library search terms used were "hypopituitarism" "pituitary neoplasms," "pituitary diseases," "prolactinoma," "empty sella syndrome," and "GH."

Additional searches were performed in the recent review articles and original studies on the topics hypopituitarism, pituitary disease, prolactinoma, and pituitary tumors. The first author carried out the literature search with the help of a trained librarian. The titles of all the articles were read and relevant abstracts were assessed by two authors independently to see whether they could be included in the analysis. After extraction of the relevant titles and abstracts by consensus, a third author independently assessed the data, and the articles to be included in the final analysis were selected with the consensus from the first two authors.

Full text articles of the studies selected were read and after reaching consensus regarding the inclusion, the meta-analysis was performed. Studies with more than 10% cases of Cushing's disease and acromegaly were excluded because these diseases as such can increase mortality. Similarly, studies with more than 50% of craniopharyngiomas were also excluded. If there was an overlap between the study populations in two articles, only the larger study was included. Studies reporting the SMR with 95% confidence intervals (95% CI) were only selected for the final analysis. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for reporting the meta-analysis (16). A PRISMA data flow chart of the literature search and a checklist are also provided (Supplemental Appendix).

Quality assessment of the included articles was performed using the Newcastle Ottawa Scale (NOS) for cohort studies (17), modified for this meta-analysis. The studies were evaluated based on the selection, comparability, and outcome. The parameters evaluated in selection of each study were: representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of the study, and a star point was allocated to each of these parameters. A maximum of two star points were allocated to comparability of the exposed and nonexposed cohorts. For outcome, one star point each was allocated for the assessment of outcome, whether follow-up duration was long enough ($\geq$5 y in this study) for the outcome to occur, and the adequacy of the followup of cohorts.

The total average NOS score from 0–9 depending of the number of star points obtained during evaluation of individual studies is conventionally used for the quality assessment of individual cohort studies in meta-analysis. A study with an average total NOS score of at least 5 (of 9) has good quality. It is ideal to include only good quality studies in a meta-analysis because the outcome can be negatively influenced by inclusion of poor quality studies. All the included studies in our meta-analysis scored at least 5, indicating good quality. Details of the NOS score assessment of individual studies is provided (Supplemental Appendix).

Table 1. Demographic Characteristics of Hypopituitray Adult Cases

Study, Publication Year	n	Percent Males	Age, y	Follow-Up Duration, y	Pan-Hypopituitarism, n (%)	Partial Hypopituitarism, n (%)
Bates et al, 1996 (6)	172	59.3	Median: 53 M; 51F	N/A	56 (31)	119 (69)
Bülow et al, 1997 (7)	344	62.2	Mean: 52 (all M/F)	Median: 11.9	73 (21.2)	271 (78.8)
Tomlinson et al, 2001 (9)	1014	50.69	Median: 46.2 M; 45.3 F	Median: 12.1 M; 12.7 F	345 (34.02)	669 (65.98)
Svensson et al, 2004 (10)	1411	52.94	Mean: 56.9 (all M/F)	N/A	N/A	N/A
van Bunderen et al, 2011 (14)	2229	52.0	Mean: 43.5 (all M/F)	Median: 6.1	N/A	N/A
Gaillard et al, 2012 (15)	13 983	51.3	Mean: 43.8 (all M/F)	Mean: 4.9	N/A	N/A

F, female; M, male; N/A, not available because data regarding the number of cases not mentioned in the articles.

Statistical analysis

Statistical analyses were performed using the software R version 3.0.3 (R Core Team (2014). (A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. http://www.r-project.org). The package, metafor for doing meta-analysis was used within the R environment. Graphs were also created using the package, metafor (18).

Forest plots for SMRs were constructed using the data included and the statistical significance was assessed. Random effect models were used to calculate weighted SMRs and 95% CIs. I^2 statistic was used to calculate percentage variation/heterogeneity. The average follow-up period for the total study population and the total number of person years of follow up were calculated. Separate analyses for males and females and those with and without GH replacement were also performed.

Results

A total of 2355 articles were identified by literature search. Fifty two relevant articles were identified and their full texts were reviewed. After discarding irrelevant studies using exclusion criteria mentioned in the methods, six articles were finally selected for the meta-analysis.

A total of 19 153 hypopituitary adults with a follow-up duration of more than 99 000 person years were analyzed. The demographic characteristics such as mean/median age, sex distribution of the cases, duration of followup, and the type of hypopituitarism (partial/pan-hypopituitarism) are shown in Table 1, the probable causes for hypopituitarism in Supplemental Table 1, and mortality statistics in Supplemental Table 2 (with available SMR data from causes such as cerebrovascular disease, cardiovascular disease, respiratory diseases and cancer).

The forest plot depicting the meta-analysis of all the studies is shown in Figure 1. Studies with male and female separation of the analysis are shown in Figure 2, A and B. Separate forest plots for studies with and without GH therapy and that for males and females separately are shown in the Figures 3 and 4, A and B, respectively.

Onset of hypopituitarism at a younger age was reported to be associated with excess mortality in five of the studies [no data in the study by Svensson et al (10)]. The age-specific SMR (95% CI) reported by Tomlinson et al (9) for age-groups <20 years, 20–40 years, 40–60 years, and >60 years were: 11.86 (5.25–26.82); 2.96 (1.61–5.44); 2.17 (1.60–2.95); and 1.22 (0.92–1.62), respectively ($P <$ .0001 for linear trend). The age-specific SMR (95% CI) reported by van Bunderen et al (14) for age-groups <30 years, 30–45 years, 45–60 years, and >60 years were: 8.54 (5.15–14.17); 1.83 (1.02–3.31); 1.19 (0.83–1.72); and 0.94 (0.69–1.28), respectively ($P < .001$ for intergroup comparison). Childhood-onset hypopituitarism was associated with an SMR (95% CI) of 2.92 (2.25–3.72) whereas adult-onset disease with an SMR (95% CI) 1.04 (0.95–1.14) as reported by Gaillard et al (15). Bülow et al (7) reported significantly higher cerebrovascular mortality risk in the age-group <55 years compared with those >55 years (SMR [95% CI], 6.67 [3.38–12.1] vs 2.52 [1.47–4.26]; $P < .001$).

Hypopituitarism following transcranial surgery for pituitary disease was found to be associated with significantly higher SMR (95% CI) compared with that following transphenoidal surgery (2.17 [1.59–2.86] vs 1.49; $P = .006$) (9). Tomlinson et al (9) reported significantly higher

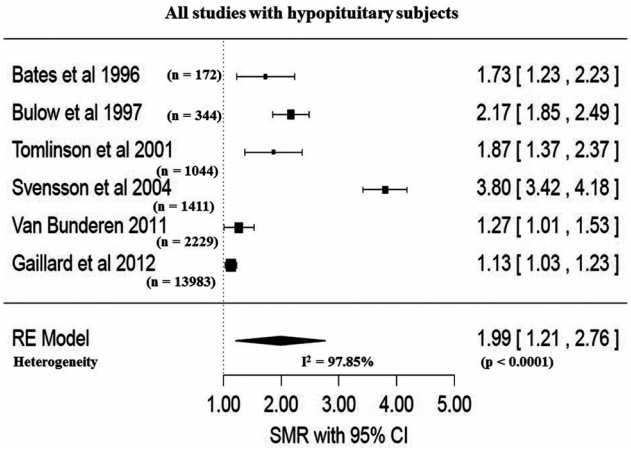

Figure 1. Forest plot showing SMR in hypopituitary adults with all the studies included in the meta-analysis.

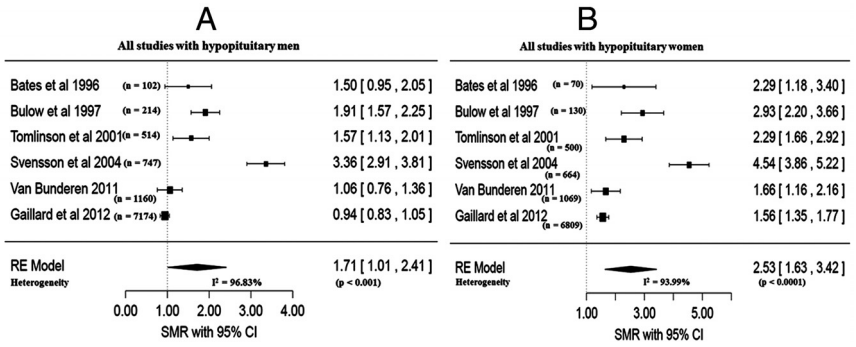

Figure 2. Forest plots to show the sex difference in SMR in hypopituitarism. A, Adult men with hypopituitarism. B, Adult women with hypopituitarism.

SMR in hypopituitary adults who received cranial radiotherapy compared with those who did not (2.11 [1.56–2.86] vs 1.50 [1.17–1.92]; $P = .004$). Gaillard et al (15) also reported higher SMR in those who received cranial irradiation (2.58 [1.89–3.44]). However, van Bunderen et al (14) did not find statistically significant increase in the SMR between patients who received or did not receive cranial radiotherapy (1.39 [1.05–1.83] vs 1.17 [0.87–1.57]; $P = .35$).

Interestingly, GH replacement was associated with significantly lower mortality benefit among hypopituitary women compared with hypopituitary men (SMR [95% CI]: 1.57 [1.38–1.77] vs 0.95 [0.85–1.06]; $P < .01$).

It should be acknowledged that the study by Gaillard et al (15) is based on the postmarketing surveillance data from the KIMS (Pfizer International Metabolic Database) registry, and therefore likely to be influenced by publication bias.

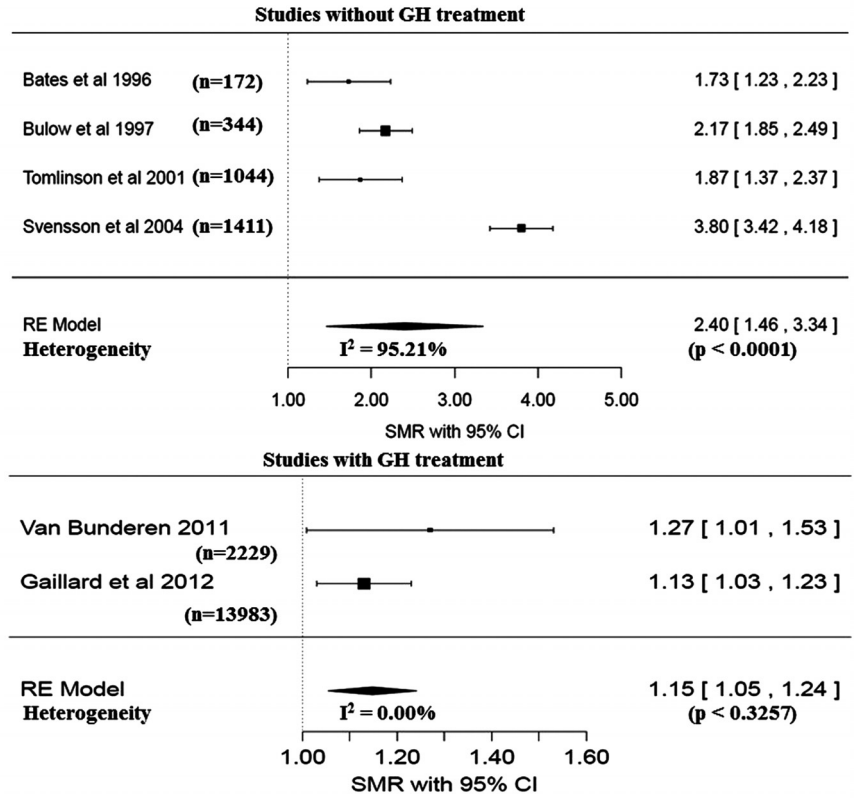

Figure 3. Forest plots showing the difference in SMR among hypopituitary adults without and with GH treatment.

Discussion

The meta-analysis from these observational studies suggests an overall likely risk of premature mortality in patients with hypopituitarism. Similar to the observation made by Nielsen et al in their meta-analysis in patients with pituitary disease (12), we also observed higher SMR in hypopituitary women compared with men. Hypopituitarism, by some obscure reasons, removes the natural survival advantage of women over men in the general population. However, there are no prospective randomized trials to confirm this, nor are there likely to be in future, given that all patients with hypopituitarism will get treated for hormone deficiencies.

The sex ratio was comparable with the male-female proportion almost similar in four of the studies (9, 10, 14, 15) although two studies showed a male preponderance (6, 7). However, the mean/median age of cases in different studies were not comparable. Details regarding the individual hormone deficiencies and the degree of hypopituitarism (pan-/partial hypopituitarism) were available in only three of the studies (nonsimilar and unmatched) and therefore, the effect of degree of hypopituitarism on mortality could not be compared.

Nonfunctioning pituitary adenoma (NFA) was the most common cause of hypopituitaism in three studies accounting for more than 50% of the total number of cases (6, 7, 9). However, NFA was the cause of hypopituitarism in only 29.8% of cases in the study by van Bunderen et al (14). Because the reported incidence of pituitary adenoma is increasing (1, 8), the prevalence of hypopituituitarism is expected to increase in the future. Similarly, as the age of the population is increasing worldwide, the incidence of hypopituitarism is also expected to increase in the future, because older people with NFA tend to have lower recovery rates even after successful treatment of the tumors (19).

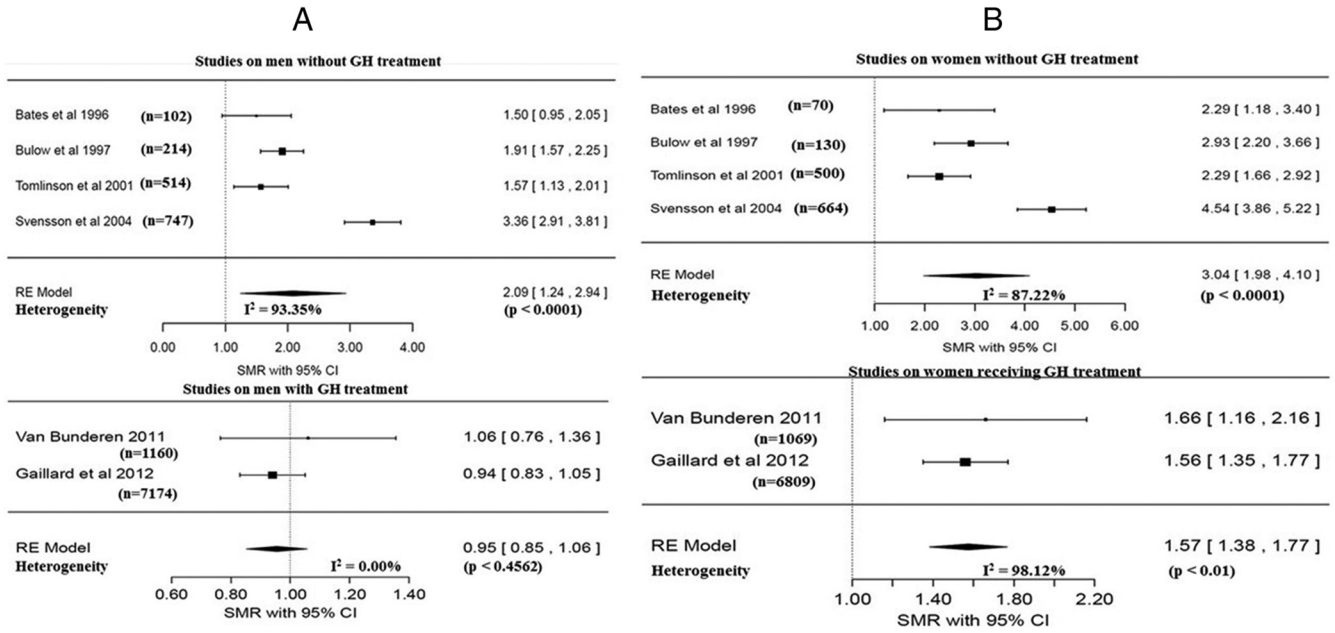

Figure 4. Forest plots showing the sex difference in SMR among hypopituitary adults. A, Men without and with GH replacement. B, Women without and with GH replacement.

Onset of hypopituitarism at a younger age posed significantly higher risk of mortality in most studies. The higher SMR reported in younger patients compared with the background population may reflect an increased risk of vascular disease and malignant disease, and the related mortality associated with hypopituitarism and its treatment (20). Significant increase in malignancy-related deaths were also observed in younger patients with hypopituitarism (6, 8, 10).

The association between higher mortality among hypopituitary subjects following transcranial surgery compared with that following transphenoidal surgery observed by Tomlinson et al (9), may be related to the greater extent of injury to the intracranial structures in the former. Similarly, the higher SMR reported by Tomlinson et al (9) and Gaillard et al (15) in patients who had cranial radiotherapy may be related to the damage to the intracranial structures and worse degrees of pituitary hormone insufficiency caused by radiation. Up to 43% of adult survivors of childhood brain tumors treated with cranial radiotherapy showed pituitary hormone insufficiency (21). New-onset or worsening hypopituitarism was reported in 24% of NFA managed by gamma knife radiosurgery in a recent study (22).

Cerebrovascular mortality was reported to be significantly higher among hypopituitary adults in three of the studies analyzed (7, 9, 15). Carotid artery atheromatous plaques were observed more frequently in hypopituitary subjects than age- and sex-matched controls (59.5% vs 2.5%; $P < .01$) (23). Significantly higher proportion of patients with hypopituitarism also had metabolic syndrome compared with the normal population, making them more prone to develop premature atherosclerosis (23, 24). Increased risk of atherosclerosis and strokes had been demonstrated in patients who had cranial irradiation for other reasons (25, 26). Patients treated with irradiation for pituitary adenomas had strokes near radiation field (27). The vasculopathy related to pituitary irradiation, and the metabolic syndrome and higher prevalence of atherosclerosis related to pituitary insufficiency, are all factors contributing to excess cerebrovascular mortality in hypopituitary adults.

Although the CV mortality was reported to be higher in three of the studies (7, 9, 14), the reported CV mortality was lower in one study (largest of the six studies with hypopituitary subjects on GH replacement) (15). The overall improvement of CV mortality seen in patients receiving GH may be related to vascular benefits from the hormone. A significant proportion of CV mortality in the study by van Bunderen et al (14) was from strokes (there was no clear categorization between cerebrovascular/CV mortality in this cohort) which may explain the slightly higher CV mortality in their cohort receiving GH replacement. The improvement of CV mortality in the recent study cohorts with hypopituitarism may also be related to better utilization of new cardiovascular drugs and therapeutic interventions (28).

The SMR data related to respiratory diseases in the reported studies were conflicting. Although Bülow et al (7) and Tomlinson et al (9) reported higher SMR related to respiratory diseases in their cohorts, Gaillard et al (15) reported lower SMR compared with the background pop-

ulation. Lower doses of steroids used in hypopituitary subjects and the improvements in treatment of infections in the recent years might explain this discrepancy. Lower dose of hydrocortisone replacement has shown to improve the quality of life in hypopituitary adults in a recent study (29). The lower SMR from cancer reported in the more recent studies (14, 15) compared with the older ones (6, 7) may be related to the relatively younger age of subjects in the recent studies.

GH replacement in hypopituitary adults showed an overall improvement in the mortality risk that is comparable to the background population. The weighted SMR (95% CI) for studies receiving GH replacement was 1.15 (1.05–1.24); $P = .3257$ whereas the weighted SMR (95% CI) for studies without GH replacement was 2.40 (1.46–3.34); $P < .0001$. The symptomatic beneficial effects of GH replacement in deficient adults were first reported in 1989 (30, 31). Many subsequent studies could reproduce these effects, and GH replacement has now become regular practice in the care of GH-deficient adults showing therapeutic benefit. Although Svensson et al (10) observed an improvement of the incidence of fatal myocardial infarctions in 2004, the study by van Bunderen et al (14) showed convincing reduction in overall mortality in GH-treated hypopituitary adults. Our meta-analysis shows the beneficial effects favoring GH replacement in adult hypopituitarism with reduction of SMR comparable to the background population.

However, GH replacement did not reduce SMR in the female subjects as much as it did in the male hypopituitary adults (0.95 [0.85–1.06] vs 1.57 [1.38–1.77]), although there was a statistically significant reduction in the SMR in GH-treated hypopituitary women compared with women without GH replacement. Multiple factors may cause reduced survival in hypopituitary females such as delay in diagnosis of hypopituitarism in women and increased CV mortality from oral estrogen replacement that increases GH resistance and also elevates levels of circulating cortisol (from increased level of corticosteroid-binding globulin) (1). Though these factors may partly explain the sex-specific discrepancy in the mortality benefit conferred by GH replacement in hypopituitary adults, additional research is warranted to clarify this.

The major limitation of this conclusion (clear beneficial effects of GH replacement) is that it is based on the data from postmarketing surveillance of the effects of GH treatment in hypopituitary subjects. Being an observational study without an untreated control group, the positive results favoring GH replacement should be interpreted with caution because there is likely to have been selection bias in those treated. The large proportion of cases from this study also would have influenced the meta-analysis results in favor of GH replacement. Large, well-designed, randomized, double-blind future clinical trials should address this limitation.

Conclusions

Hypopituitarism tends to increase premature mortality in the affected individuals. Adult females with hypopituitarism seem to have higher SMR compared with the adult males with the disease. Younger adults had higher SMR when compared with the older age groups with hypopituitarism. Cranial irradiation for pituitary disease may worsen the chance of hypopituitarism and the related mortality. Cerebrovascular and CV mortality seems to be higher in hypopituitary adults.

GH replacement seems to improve the overall mortality in hypopituitary adult subjects. Male adults with hypopituitarism on GH replacement have SMR similar to that of the background population. However, the mortality benefit from GH replacement in the female subjects is less pronounced compared with the males. Further research is necessary for finding the exact reasons for this discrepancy. Properly designed large randomized controlled trials should look into the exact benefits of GH treatment to avoid potential selection bias from observational studies.

Acknowledgments

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