Safety aspects of GH replacement

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Abstract
In adults, GH replacement therapy will often be maintained for decades. Owing to the long duration of GH replacement in many adults, it is essential to establish the long-term safety aspects of the treatment. In this review, studies that have investigated the safety profile of long-term GH replacement will be reviewed with an emphasis on studies based on data from the Pfizer International Metabolic Database (KIMS). These studies show that long-term GH replacement in adults is safe and that long-term GH replacement may even improve cardiovascular mortality and morbidity in GH-deficient adults.

European Journal of Endocrinology 161 S65–S74

Introduction
In the late 1950s, the profound importance of GH to increase linear bone growth was demonstrated in GH-deficient (GHD) children (1). Not until the late 1980s, when recombinant human GH was introduced, were the effects of GH in adult life studied in detail. During the last 20 years, several studies have shown that long-term GH replacement therapy in adults improves quality of life, bone mass and cardiovascular risk factors (2–6). Safety studies have also been performed; however, single centres most often have access only to relatively small number of hypopituitary patients. Therefore, studies based on data from the Pfizer International Metabolic Database (KIMS) have been of great importance to determine the safety profile of long-term GH replacement. Available safety studies will be reviewed with the emphasis on type 2 diabetes mellitus (DM), mortality, cardiovascular morbidity, reoccurrence of pituitary tumour and risk of malignancies.

Insulin sensitivity
Several studies show that untreated GHD in adults is associated with insulin resistance (7, 8). The effect of GH replacement therapy on insulin sensitivity appears to be biphasic. After an initial deterioration during the first months of therapy, insulin sensitivity then improves and returns towards baseline values as seen in several studies (9, 10). This improvement and return towards baseline values is probably due to the improved body composition by GH replacement with reduced total body fat and increased lean body mass (10). However, all short-term studies have not displayed a return of insulin sensitivity towards baseline values (11), and in a meta-analysis, mainly including the studies of relatively short duration, circulating glucose and insulin values were found to be significantly increased after GH replacement (12).

During prolonged GH replacement, some studies report still impaired (13–15) glucose tolerance, whereas other studies report unchanged (16, 17) glucose tolerance as compared with baseline. The results of one study, using the hyperinsulinaemic, euglycaemic clamp technique, suggest that the decreased baseline insulin sensitivity persists for at least up to 2 years of GH treatment (18). However, in a study by Hwu et al., 1 year of GH treatment normalized insulin sensitivity as measured by a modified insulin suppression test (19). In a study by Jørgensen et al., insulin sensitivity (M-value) was similar in GHD patients to that in controls after 5 years of GH replacement (20). In a study by Svensson et al., insulin sensitivity was unchanged during 7-year GH replacement, and there was even a tendency that the GH replacement provided protection from the age-related decline in insulin sensitivity that was observed in the matched control subjects (21).

In two studies with treatment durations of 7 and 10 years respectively, GH replacement did not affect glucose homeostasis (22, 23); whereas in another study, circulating HbA1c and fasting glucose were increased as compared with baseline after 10 years (24). In a 5-year and a 10-year GH treatment trial, there was a discrepancy in fasting blood levels of glucose and HbA1c, as fasting glucose levels were increased and fasting HbA1c levels were reduced (5, 25). The meaning of an increase in fasting blood glucose combined with

This paper forms part of a special issue on KIMS® and ACROSTUDY™. Pfizer Inc. has supported the publication of this special issue.

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DOI: 10.1530/EJE-09-0287
Online version via www.eje-online.org

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Type 2 diabetes mellitus

In children, data from the Pfizer International Growth Database (KIGS) reported that GH treatment in children might induce a very modest increase in the incidence of type 2 DM (26). The effect of GH on glucose metabolism is, however, considerably different in adults compared with that seen in children. Although there are few data, there is no evidence that GH replacement increases the risk of DM in GHD adults. An analysis was performed in 5120 (2706 men) patients included in KIMS (27). Each patient had at least one return visit corresponding to a total of 11 049 years of GH replacement. Twenty-six men and 17 women developed de novo DM during the follow-up (16 of these during the first year of GH replacement; Table 1). Mean age and body mass index (BMI) of the patients that developed DM were 44.0 years and 34.0 kg/m² in women and 49.2 years and 32.8 kg/m² in men. The standard incidence ratio was calculated using a Swedish cohort of 138 000 of the general population above 18 years of age followed prospectively for 3 years as reference (27) (Table 1). No significant sex difference was found. The conclusion was that the incidence of type 2 DM in GH-treated hypopituitary patients with normal BMI is not increased as compared with that in the background population (27). Furthermore, it was concluded that a high BMI is a risk factor for the development of DM in GHD adults (27).

In a Swedish retrospective multi-centre study by Holmer et al. (28), 750 adult hypopituitary patients with confirmed GHD and 2314 matched population-based controls were included (28). Most of the GHD patients received GH replacement with a mean duration of 6 years. The prevalence of DM was not statistically different from that in the controls in GHD men (28). In GHD women, the prevalence of DM was increased, partly attributed to higher BMI and lower physical activity (28).

In conclusion, there are at present only a few studies that have determined the incidence or prevalence of DM during GH replacement in adults. The scarce data available give at present no evidence that GH replacement increases the risk of DM in GHD patients with normal BMI. The risk of developing DM type 2 in adult GHD patients with high BMI and low physical activity needs to be determined in further studies. It is recommended that GH replacement is initiated with a low dose in GHD adults with high BMI, and also in other groups of GHD patients predisposed to type 2 DM, such as GHD patients with a positive family history or who are older. Furthermore, in GHD patients predisposed to type 2 DM, the dose of GH should be slowly increased based on the clinical response, and careful monitoring of glucose homeostasis is needed.

The heart

Short-term placebo-controlled studies have demonstrated that GH replacement in adults improves diastolic (29) and systolic (30–33) functions. The long-term effects of GH replacement on the heart have been investigated in a few open studies. During 38 months of GH replacement therapy, cardiac structure was normalized, whereas heart rate and cardiac index increased to supernormal levels (34). In 38 young men with childhood-onset GHD followed openly for 55 (range 39–69) months, GH replacement increased stroke volume and maximal exercise capacity without any long-term increase in left ventricular mass (35). In seven adults with adult-onset GHD, 42 months of GH replacement increased left ventricular mass and decreased the atrial emptying index, which reflects diastolic function, as compared with healthy matched controls (36). This last study might suggest, although a higher dose of GH was given than that used today, that increased age might increase the susceptibility to develop inappropriate increment in left ventricular mass during long-term GH replacement. Therefore, in conclusion, low dose, individualized GH replacement therapy improves cardiac function, which may partly

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explain the increased exercise capacity observed in some studies after GH replacement (30, 37–40) including a recent meta-analysis of placebo-controlled, randomized GH treatment trials (41). However, if a too high dose of GH is given, there is a risk of inappropriate increment in left ventricular mass in elderly GHD adults during long-term treatment.

**Mortality**

A retrospective study by Rosén et al. showed doubled overall mortality in hypopituitary adults with routine hormonal replacement therapy, but without GH replacement therapy, as compared with the normal population (42). Four additional retrospective studies (43–46), and one prospective study (47), have confirmed that total mortality is increased in hypopituitary adults without GH replacement therapy. Most of the studies showed that the increased overall mortality in hypopituitary adults without GH replacement therapy was mainly due to an almost doubled cardiovascular mortality (42–44, 47).

A study by Bengtsson et al. included 1903 hypopituitary patients enrolled in KIMS that had received GH for altogether 2334 patient years (48). Expected mortality was obtained from sex- and age-specific death rates in each country. The calculated standardized mortality rate (SMR) was similar to that in the normal population and, furthermore, the mortality rate was significantly lower than that previously observed by Rosén et al., in hypopituitary patients without GH replacement therapy (42, 48). In a study by Svensson et al., increased overall mortality was observed in a cohort of 1411 hypopituitary patients without GH replacement, whereas in another cohort (n=289) of hypopituitary patients receiving GH replacement therapy, overall mortality was similar to that in the background population (45). Therefore, it appears that GH replacement may even reduce the increased mortality observed in hypopituitary patients without GH replacement therapy.

In an evaluation based on KIMS data, 4486 GHD patients receiving GH replacement were followed from their 1 year visit, representing 17 573 patient years of follow-up (49). Rates in KIMS were compared with age–gender–country-stratified external rates using the SMR (49). In terms of overall mortality, there were 136 observed cases and 130 expected corresponding to a SMR of 1.05 (95% confidence interval, CI: 0.88–1.24) (49). Forty-three deaths in cardiovascular diseases were reported (SMR 0.98; 95% CI: 0.7–1.3) (49). Taken into account that total mortality is increased in hypopituitary patients not receiving GH replacement, the results give further support for the notion that GH replacement may reduce overall and cardiovascular mortality. There are, however, possibilities other than the GH replacement to explain why there is a trend towards lower mortality in more recent studies using GH replacement than in older studies, in which the hypopituitary patients did not receive GH replacement. First, treatment with radiotherapy of pituitary tumours may contribute to the increased mortality observed in hypopituitary patients not receiving GH replacement (43, 47), and possible lower use of irradiation in more recent studies may be one reason for the trend towards lower mortality observed in these studies. Furthermore, more frequent use of lipid-lowering drugs and anti-hypertensive medication may at least to some extent explain the more beneficial results observed in more recent studies (28). Large prospective, randomized and controlled studies would provide definite conclusions on these issues, but practically this is not feasible and unlikely to be undertaken.

Although the above given data clearly show that overall mortality is increased in hypopituitary patients not receiving GH replacement and that GH replacement appears to reduce overall mortality in these patients, it should be noted that transgenic mice with low activity of the GH/insulin-like growth factor-1 (IGF1) axis have increased life expectancy. Mice with low GH secretion due to mutations of Prop-1 (Ames dwarf mice) (50) or Pit-1 (51) have impaired pituitary gland development resulting in low circulating GH levels and a life span extension of around 50% as compared with control mice. Furthermore, mice with global inactivation of the GHRH receptor (51) or the GH receptor (52) have long lives. Although mice completely lacking the IGF1 receptor have low viability and do not usually survive the postnatal period (53), mice with heterozygous inactivation (~50% reduction) of the IGF1 receptor in total body or the central nervous system including the hypothalamus survive the postnatal period and then have long lives (54, 55). An elongation of life span was also observed in mice with reduced local bioavailability of IGF1 (56) and in mice strains with defect IGF1-signalling downstream of the IGF1 receptor (57, 58).

The reason for the discrepancy between the transgenic mice and the hypopituitary humans with increased life span in GH/IGF1-deficient mice versus decreased life span in hypopituitary patients with untreated GHD is unclear. One reason could be that the increased mortality in hypopituitary adults is not due to the severe GHD, but that previous treatment with surgery or radiation therapy, or inadequate treatment of the deficiency of other pituitary hormones, is of most importance. There may also be species differences as mice have very low cardiovascular mortality, whereas this is the major cause of death in hypopituitary patients with severe GH deficiency. Finally, it is unclear whether life in a cage is representative of how mice survive in real life, and the possibility can not be excluded that transgenic mice with low activity of the GH/IGF1 axis would not be very successful in real life. However, further research is needed to clarify why the consequences of GHD are so different in transgenic mice versus hypopituitary humans in terms of overall mortality.
Cardiovascular morbidity

It is well known that GHD adults without GH replacement have premature atherosclerosis (59), and that GH replacement can improve measures of atherosclerosis such as carotid intima-media thickness (60, 61). However, little is known of cardiovascular morbidity in GHD adults with or without GH replacement. In a study based on data recorded by the Board of Health and Welfare in Sweden, cerebrovascular and cardiovascular morbidities were determined in 1411 hypopituitary patients not receiving GH replacement (45). In these patients without GH replacement, cerebrovascular morbidity was increased compared with that in the background population. The increase in the total number of myocardial infarctions (fatal and non-fatal) was less marked than the increase in cerebrovascular events (45). The risk ratio for myocardial infarction in the hypopituitary patients without GH replacement was 1.40, 95% CI: 1.10–1.75. This increased risk of myocardial infarction was mainly due to an increased risk of very severe myocardial infarctions with rapid time courses. Also, in a later study from Denmark by Stochholm et al., an increased morbidity in circulatory diseases was observed in GHD adults (62).

In the study by Svensson et al., there was also a prospective study of 289 hypopituitary patients that received GH replacement (mean duration of GH treatment 60 months, range 2–118 months) (45). In the 289 patients receiving GH replacement, the risk ratio for cerebrovascular events tended to be higher than that in the background population. Radiation-induced angiopathy has been suggested as a risk factor for stroke (63, 64), and radiotherapy is a predictor of stroke in hypopituitary patients (43, 47). A possible interpretation of the tendency to an increased risk ratio for cerebrovascular events also during GH replacement therapy is therefore that GH replacement does not provide protection from strokes that are caused by radiation angiopathy. Furthermore, the relative risk for myocardial infarctions was even lower in the 289 hypopituitary patients on GH replacement therapy than that in the background population (45). Taken into account that the relative risk of myocardial infarctions was increased in hypopituitary patients without GH replacement, the reduced rate of myocardial infarctions in hypopituitary adults receiving GH replacement suggests that GH replacement in adults is a safe procedure and that GH replacement may even reduce the risk of myocardial infarctions in hypopituitary patients.

In a Swedish retrospective multi-centre study by Holmer et al. (28), the incidence of non-fatal stroke (ischemic or hemorrhagic) and non-fatal cardiac events (defined as myocardial infarction, percutaneous transluminal coronary angioplasty or bypass surgery) was investigated in 750 adult hypopituitary patients with confirmed GHD and 2314 matched population-based controls (28). Most of the GHD patients received GH replacement with a mean duration of 6 years. The results of this study suggested that the GH replacement combined with increased prescription of cardioprotective drugs resulted in a reduced risk for non-fatal stroke, particularly noted in women, and in a decline in non-fatal cardiac events in GHD men (28). Thus, the results of this study give further support for a beneficial effect of modern treatment of hypopituitary adults including increased use of GH replacement and cardioprotective drugs. Further studies are needed to investigate how much of this improvement is due to the GH replacement and how much is due to the increased prescription of lipid-lowering and antihypertensive medications.

Hypothalamic–pituitary tumours

It is, during long-term GH replacement, important to consider the risk of regrowth or recurrence of the hypothalamic–pituitary tumour responsible for most of the hypopituitarism seen in patients with adult-onset GHD. In a study of GHD adults, no increase in pituitary tumour recurrence rate was found during an average of 3.6 years of GH replacement as compared with controls not receiving GH treatment (65). In a prospective study of 100 adult-onset GHD patients with pituitary and peripituitary tumours receiving GH replacement therapy, only one case of slight intrasellar tissue enlargement was noted after 1–4 years of follow-up (66). The majority of these patients had received external radiotherapy (66). In a prospective study of 60 childhood brain tumour survivors receiving adult GH replacement therapy over a mean period of 6.7 years, only one incurable ependymoma and one residual meningioma progressed in size (67). Secondary neoplasias were detected both before and after commencing GH replacement (67). Finally, in 130 patients with non-functioning pituitary adenoma treated with surgery alone, treatment with GH for a mean period of 6.8 years was not associated with increased recurrence of the pituitary tumour (68). Therefore, these relatively small studies do not suggest that GH replacement increases the recurrence or regrowth of hypothalamic–pituitary tumours.

Data from KIMS, including 1034 hypopituitary adults treated with GH for a total of 818 patient years, reported four patients with recurrent pituitary adenoma, one with recurrent gonadotrophinoma and one with pituitary dysgerminoma (3). These results were compared with data from 43 clinical trials involving a total of 1145 hypopituitary adults with a similar geographic distribution. This selection included eight cases of central nervous system or pituitary tumours, four during administration of placebo and four during administration of GH. In a later case–control study, the treatment group comprised patients from the German
In the study by Frajese et al., larger studies are still needed. Analysis of the British General Practice Research Database (GPRD) did not suggest that GH replacement increases tumour recurrence in adults. In 23 cases of childhood craniopharyngioma treated with surgery or without radiotherapy, which were assessed up to the age of completed growth (mean follow-up 6.3 years), no significant difference was found in the recurrence rates before and after commencing GH treatment (70). In children with craniopharyngioma who received GH (National Cooperative Growth Study, 1985–1999), there was a recurrence rate of 6.4%, which was considered lower than the previously reported rate in the general paediatric population (71). In two studies based on KIGS data, the recurrence rate of craniopharyngiomas did not appear to be increased compared with other reports (72, 73). In the OZGROW database (a database collecting information on children receiving GH in Australia and New Zealand), the percentage of recurrence/patient year was 3.8% and not different from the recurrence in individuals not treated with GH (74). In a series of 60 children treated with GH, there was no difference in the number of recurrences between patients on GH and those who had not received such treatment (75). Abs et al. reported no recurrence in 127 GH-treated adult patients with craniopharyngioma enrolled in KIMS 1994–1996 (3). In the study by Frajese et al., no recurrence was detected in a series of 13 adults with craniopharyngioma treated with GH (66). In a study reporting the results of prospective imaging in 28 consecutive patients with craniopharyngioma and adult-onset GHD, an apparent increase in tumour volume was found in one subject 6 years after the commencement of GH (76). In another study, 32 patients with a mean age of 17.6 years at diagnosis of craniopharyngioma and with GH replacement for a mean period of 6.3 years were compared with 53 patients who had not received GH but otherwise with a similar tumour and treatment characteristics and follow-up period (77). During the period of observation, 4 patients treated with GH and 22 not receiving GH developed tumour recurrence (77). Thus, in conclusion, data published so far are reassuring and there is, to date, no evidence that GH replacement increases the recurrence rate of craniopharyngiomas in children or adults.

### Risk of malignant disease

In retrospective trials, patients with acromegaly and GH excess have increased the frequency of malignant diseases (78, 79). The most frequently found cancer is mammary cancer and colorectal cancer, and the overall observed/expected ratio for cancer in these studies is between 1.27 and 2.5. In prospective trials, the rate of patients with tubular adenomas and hyperplastic colon polyps is increased with some studies also showing more than expected numbers of colon cancer (78, 79). In a retrospective survey from the UK including 1362 patients with acromegaly, a lower overall cancer incidence rate in the patients than in the general population was found (80). The colon cancer mortality rate was, however, higher than expected with a SMR of 2.47 (CI: 1.31–4.22) (80). Furthermore, an association between serum IGF1 levels in the upper quartile and the risk of prostate, breast and colonic cancer has been demonstrated in the general population in prospective trials (81–84).

In the retrospective study by Rosén et al. (42), the mortality from malignant diseases was reduced in the hypopituitary patients not receiving GH replacement. In a number of other studies of hypopituitary patients not receiving GH replacement, an unchanged or even increased risk of malignancies has been found. Bates et al. observed an increased mortality from malignancies in hypopituitary women (44), whereas the risk of death in a malignant disease was unaffected in the prospective study by Tomlinson et al. (47). In the retrospective study by Popovic et al., the rate of neoplasia in non-functional and GH-producing pituitary adenoma was compared with that in the general population (85). They found increased frequency of cancer both in patients with non-functional pituitary adenoma and in acromegalic patients as compared with the expected incidence in the general population (85). In a large retrospective Swedish study including all individuals with pituitary tumours included in the Swedish Cancer Registry between 1958 and 1991, an excessive mortality from all tumours (pituitary excluded) and malignant tumours of the brain was found (86). Finally, in nationwide studies from Sweden and Denmark, an increased mortality in malignant disease was observed in adults not receiving GH replacement (45, 46). Therefore, the results of some studies suggest that other forms of cancer may be associated with pituitary tumours and/or its treatment independent of GH status. Furthermore, there is also evidence that surgery of pituitary tumours followed by radiotherapy can increase the risk of secondary brain tumours independent of GH status (87, 88).

In a study by Swerdlow et al., young adults who previously had received long-term GH treatment in childhood were studied (89). A small but significant excess of cancer deaths was observed due to colorectal cancer (two cases) and Hodgkin’s disease (two cases) (89). However, as discussed above, the risk of neoplasms in hypopituitary patients may be increased independent
of GH status. Specifically, in the study by Svensson et al. in which 1411 hypopituitary patients without GH replacement therapy were studied retrospectively, the most predominant malignancy in hypopituitary adult patients not receiving GH replacement was colorectal cancer, which was increased compared with the normal population (45). Therefore, with regard to the results of the studies discussed above and specifically the study by Svensson et al. (45), the meaning of the results from the study by Swerdlow et al. (89) is unclear.

Of some concern is the report of a small increase in the number of patients who survived childhood cancer but subsequently developed secondary neoplasms (90). Survivors of childhood cancer treated with GH had a 2.15-fold greater risk of developing a secondary neoplasm, mostly meningiomas, as compared with survivors that had not received GH treatment (90). The investigators concluded that the increased risk associated with GH use appeared to decrease over time because a previous report from the same cohort demonstrated a relative risk of secondary neoplasia of 3.12 (91). The data should, however, be interpreted with caution, given the small number of events. In adults, there is at present no comparable data.

In KIMS, the incidence of neoplasms was evaluated in 6428 patients (3281 men) enrolled in KIMS (92). All patients had at least one baseline visit and one return visit on GH replacement therapy. Median age was 44.4 years and total duration on GH replacement therapy in KIMS was 14073 years. One hundred and eighteen neoplasms were reported in 115 patients, which did not indicate that GH replacement in KIMS increased the risk to develop a malignant neoplasm (92). In another evaluation based on KIMS data, 4486 GHD patients receiving GH replacement were followed from their 1 year visit, representing 17573 patient years of follow-up (49). Thirty-nine observed deaths in malignant neoplasms were reported in 115 patients, which did not indicate that GH replacement in KIMS increased the risk of developing a new or a recurrent malignancy.

In conclusion, for survivors of childhood cancer, there are some data indicating that GH could induce a slight increase in the relative risk of developing a secondary neoplasm. However, the number of events has been very small in the studies of childhood cancer survivors and there are no comparable data in adults. On the contrary, in adults, there is no evidence that GH replacement increases the risk of developing a new or a recurrent malignancy.

Summary and conclusions
A summary of current data of safety aspects of GH replacement in adults and some clinical recommendations are presented in Table 2. Available data suggest
that long-term GH replacement therapy is safe in hypopituitary adult patients in terms of incidence of type 2 DM, although the risk of type 2 DM during GH replacement in obese patients needs to be determined in further studies. There is no evidence that GH replacement in adults increases the reoccurrence of pituitary tumours or the risk of malignancies. Long-term GH replacement therapy is safe in terms of overall mortality, and at least when combined with increased use of cardioprotective medication, GH replacement may reduce the increased cardiovascular mortality and morbidity observed in hypopituitary patients not receiving GH replacement therapy. Long-term monitoring is, however, mandatory in terms of glucose metabolism, cardiovascular measurements and underlying neoplasia.

Declaration of interest

The authors have no potential conflicting relationship with Pfizer. J Svensson has no conflict of interest. B-A Bengtsson was co-founder of Tercica Inc., a company that produced IGF1 for use in children of short stature. Tercica Inc. was acquired by Ipsen June 2008. B-A Bengtsson has no current ownership of stocks or options in Tercica or Ipsen. KIMS is supported by Pfizer Inc. This paper forms part of a European Journal of Endocrinology supplement, supported by Pfizer Inc.

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Received 22 June 2009
Accepted 25 June 2009