THERAPY OF ENDOCRINE DISEASE

Growth hormone replacement therapy in adults: 30 years of personal clinical experience

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Abstract

The acute metabolic actions of purified human growth hormone (GH) were first documented in adult hypopituitary patients more than 50 years ago, and placebo-controlled long-term GH trials in GH-deficient adults (GHDA) surfaced in 1989 with the availability of biosynthetic human GH. Untreated GHDA is associated with excess morbidity and mortality from cardiovascular disease and the phenotype includes fatigue, reduced aerobic exercise capacity, abdominal obesity, reduced lean body mass, osteopenia and elevated levels of circulating cardiovascular biomarkers. Several of these features reverse and normalize with GH replacement. It remains controversial whether quality of life, assessed by questionnaires, improves. The known side effects are fluid retention and insulin resistance, which are reversible and dose dependent. The dose requirement declines markedly with age and is higher in women. Continuation of GH replacement into adulthood in patients with childhood-onset disease is indicated, if the diagnosis is reconfirmed. GH treatment of frail elderly subjects without documented pituitary disease remains unwarranted. Observational data show that mortality in GH-replaced patients is reduced compared to untreated patients. Even though this reduced mortality could be due to selection bias, GH replacement in GHDA has proven beneficial and safe.

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Introduction

A growth-promoting activity of anterior pituitary extracts was discovered almost a 100 years ago by Evans and Long, and growth hormone (GH) was isolated in 1944 and tested in human subjects by several groups (1). It became evident that species-specific differences existed

and that only human and – to some extent – simian GH are active in man. The protein anabolic and lipid catabolic effects of GH were comprehensively tested by Maurice Raben and summarized in two seminal publications in 1962, which are recommendable readings owing to their

Invited Author's profile

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clarity and prophetic strengths (2, 3). He was the first to hypothesize that GH replacement therapy in adults with hypopituitarism could be beneficial (3). Subsequently, GH extracted from human cadaveric pituitaries was used therapeutically to promote longitudinal growth in children with hypopituitarism and severe growth retardation, but the limited supply precluded the exploration of other indications. The use of pituitary human GH was halted in several countries in 1985 since it was associated with transmission of Creutzfeld-Jakob disease (4), which accelerated the approval of biosynthetic human GH, that first proved efficacious in GH-deficient children (5). This radically changed the scene by providing a potentially unlimited supply of pure and uncontaminated GH. In response to this, James Tanner, a leading expert in pediatric growth disorders and auxology, stated 'We are now moving from an era in which there were too many patients chasing too little GH to an era in which there will be too much GH chasing too few patients.'

One of the first potential indications to be pursued was GH replacement in adult patients with GH deficiency (GHD) in two investigator-initiated trials (6, 7). This narrative review provides a personal account on the history of GH replacement in adults with a focus on the pivotal trials and the authors' own contributions.

The pivotal trials

The first placebo-controlled trial was performed in Denmark as a collaboration between adult and pediatric endocrinologists and published in 1989 (6). The patients ($n=22$) all had childhood-onset GHD verified by at least two GH stimulation tests and had received GH replacement for a mean period of ≈ 7 years, which was discontinued at least 6 months before study entry (mean duration of discontinuation ≈ 6 years). The diagnosis was reconfirmed prior to the study by a clonidine stimulation test, and the mean age at study start was ≈ 24 years. The study had a double-blind, placebo-controlled crossover design with 4-month treatment periods separated by a 4-month washout period and with the patients being studied at the end of each study period. The daily GH dose was 4 IU/m^2 body surface ($\approx 1.1 \text{ mg/day}$). The major outcomes included body composition in terms of muscle and fat volume of the thigh region assessed by CT scan, isometric muscle strength and aerobic exercise capacity assessed on a bicycle ergometer. In addition, glomerular filtration rate (GFR) and renal plasma flow (RPF) were measured isotopically. A significant increase in muscle

volume ($P<0.01$) and a significant reduction in fat volume ($P<0.05$) were recorded together with a reduction in subscapular skinfold thickness ($P<0.01$). This was accompanied by a significant increase in exercise capacity ($P<0.05$), and an insignificant increase in muscle strength ($P=0.08$). Both GFR and RPF increased ($P<0.01$), which represented a normalization from subnormal levels. As expected, a treatment-induced increase in serum insulin-like growth factor 1 (IGF1) levels ($\mu\text{g/L}$) occurred (96 ± 9 (placebo) vs 224 ± 28 (GH), $P<0.001$).

Additional publications derived from the original trial revealed that GH replacement was associated with marked and concerted elevations (two- to five-fold) in the levels of serum osteocalcin and urinary excretion of deoxypyridinoline, indicative of increased bone remodeling (8, 9). Compelling evidence that GH promotes the extrathyroidal conversion of T4 to T3 was demonstrated for the first time in a placebo-controlled design (10). The patients also exhibited decreased sweating, which was reversed by GH (11). Finally, the original study was extended with an open phase of uninterrupted GH therapy, which documented continued improvement in body composition, exercise capacity, muscle strength and forearm bone mineral content (12, 13).

The second placebo-controlled trial was published 7 months later and differed in several respects (7). First, it mainly comprised patients with adult-onset GHD due to a pituitary tumor and its treatment. Second, it had a parallel design with a 6 months treatment period where each patient was examined before and after. The daily GH dose was $\approx 1.9 \text{ mg}$ and the mean age of the patients was ≈ 39 years. The main outcomes were body composition assessed by conventional anthropometric measurements and total body potassium, and resting energy expenditure using indirect calorimetry. Lean body mass (LBM) increased significantly and was accompanied by a significant reduction in fat mass. This was associated with an increase in resting energy expenditure (REE) also after correction for LBM. In addition, evidence of GH-induced insulin resistance, as judged by increased fasting levels of glucose and insulin, was reported. Beneficial effects of GH replacement on exercise capacity and hyperlipidemia were also reported from the original study (14, 15, 16).

The syndrome of GH deficiency in adults

In a review of the literature in 1992, Cuneo *et al.* introduced 'syndrome' as a term to describe the emerging clinical picture of GH deficiency in adults (GHDA) and

the effects and side effects of GH replacement. (17) This concept was substantiated by studies from Sweden focusing on the phenotypical features of untreated GHDA (18, 19, 20), and new data regarding the impact of GH replacement (21, 22, 23, 24). The syndrome overlaps with the metabolic syndrome as regards visceral obesity, hyperlipidemia and atherosclerosis. Moreover, evidence of premature cardiovascular morbidity and mortality was reported in GH-untreated hypopituitary adults (25, 26). Echocardiographic studies documented a stimulatory effect of GH on diastolic volume, stroke volume and myocardial contractility (27, 28, 29, 30). It was also observed that untreated GHDA was accompanied by reduced total body water and extracellular fluid volume (18), which reverses by GH replacement (31, 32). Indeed, fluid retention was noted as a frequent and dose-dependent side effect of GH treatment in adults. The mechanism involves sodium retention, but it is uncertain if it is mediated by activation of the renin angiotensin aldosterone system (32, 33), suppression of atrial natriuretic peptide (34) or a direct renal effect of GH or IGF1 (35, 36). Of note, this increase in hydration accounts for a limited part of the GH-induced changes in body composition (36). Impaired thermoregulation in response to the ambient outside temperature (37) and during strenuous exercise (38, 39) was also documented and partly attributed to reduced sweating capacity (11).

Insulin resistance, which is a hallmark of the metabolic syndrome, is not part of the GHDA syndrome, rather the opposite. GH antagonizes the effects of insulin on glucose metabolism in both the liver and skeletal muscle, which is causally linked to the lipolytic effects of GH (40). Indeed, increased insulin sensitivity and reactive hypoglycemia are characteristic of children and adolescents with GHD (41, 42, 43), whereas the opposite is true for active acromegaly (44). Treatment-naïve adult-onset GHD may, however, also exhibit insulin resistance (45), which likely represents the long-term consequences of obesity, reduced LBM and physical inactivity. The direct insulin antagonistic effect of GH is rapidly reversible (46, 47), and in normal physiology, it operates in the fasting state, where insulin activity is low (48, 49). However, daily subcutaneous GH injections in the evening are unable to fully imitate the endogenous GH pattern (50); therefore, GH replacement therapy invariably induces a certain degree of insulin resistance (49). Consequently, moderate elevations in the fasting levels of glucose and insulin are recorded in GHDA after GH replacement despite favorable changes in body composition (51).

The annual number of publications in the field of GHDA increased almost exponentially from two in 1989 to >200 in 1999, which, in addition to corroborating the observations from the pivotal trials, added several original contributions (52). Dose-finding studies in different age groups were performed (53, 54, 55), and it was confirmed that adult patients are highly sensitive to GH in terms of serum IGF1 generation and side effects (56), and that male patients are more responsive to GH as compared to females (57, 58). These and other data translated into guidelines for the diagnosis and management of GHDA issued by the Growth Hormone Research Society, which had been established in 1993 (59). The indication for GH replacement in GHDA was approved by the European Union in 1994 alongside with several other countries. In the same year, KIMS, an international outcomes research database with longitudinal data about GH therapy in adults, was initiated by Pharmacia and Upjohn and continued by Pfizer until 2012 with the inclusion of more than 16 000 patients from 31 countries (<https://medicaloutcomes.pfizer.com/kims>). This resource has generated numerous peer-reviewed publications, also recently (60), and similar surveillance programs have been initiated by other providers of biosynthetic GH. In addition to this, several meta-analyses of published data on adult GH replacement have been published on outcomes such as cardiovascular risk factors (51), muscle strength and exercise capacity (61, 62), bone mineral density (63, 64), body composition (65) and cardiac function (66) (Fig. 1). In short, the meta-analyses confirmed and substantiated both the beneficial effects of GH replacement on body composition, bone mineral density, cardiac function and exercise capacity, as well as the side effects attributable to fluid retention and insulin resistance (51, 65) (Fig. 1).

It remains an open question whether GH replacement therapy improves patient-reported outcomes such as quality of life (QoL) or cognitive function in the adult patient, since neither original studies nor meta-analyses provide unambiguous answers (65, 67, 68, 69). There is little doubt that QoL is reduced in the treatment-naïve patients, but it has proven difficult to document significant positive GH effects in placebo-controlled trials, and improvements in open trials are prone to bias and regression toward the means. Most QoL studies have utilized generic or disease-specific questionnaires, which mainly record and depend on the respondents' remembrance and may fail to detect day-to-day experiences in real time; along the same line, it is possible that improvements in remembered QoL cease to provide increased satisfaction, a phenomenon coined hedonic adaptation (70). In this regard, it is interesting

Figure 1

Results of meta-analysis of GH effects on cardiovascular risk factors from Maison *et al.* (51). (Copyright 2004, Oxford University Press). Chol., cholesterol; D.B.P., diastolic blood pressure; Lean B mass, Lean body mass; ns, nonsignificant; S.B.P., systolic blood pressure; TG, triglycerides.

that the most compelling – and beneficial – effects of adult GH replacement on QoL was recorded in a placebo-controlled crossover study, in which the spouse of the patient was asked to score the patient (71). Somewhat ironically, the National Institute for Health and Care Excellence in the United Kingdom (<http://nice.org.uk/guidance/ta64>) requires impaired pretreatment QoL in order to initiate adult GH replacement, and it also demands discontinuation of treatment in case of a lack of QoL improvement after 9-month treatment (72).

The transition phase

Normal puberty marks the transition from childhood to adulthood and represents a period with marked physical changes including a pubertal growth spurt and the development of secondary sexual characteristics leading to attainment of adult reproductive capacity. Muscle and bone mass increase markedly during this period leading to the adult phenotype. These important physical changes depend in part on amplified GH secretion and action resulting in grossly elevated – even acromegalic – IGF1 levels in healthy subjects (73) (Fig. 2). Serum IGF1 levels remain elevated 2–5 years after peak height velocity, suggesting additional physiological actions of GH in this transition period on muscle and bone mass accrual. The

transition phase starts in late puberty when final adult height is attained (mean age ≈15–17 years) and terminates in early adulthood when peak bone mass is reached (mean age ≈20–23 years).

Before 1985, GH replacement in childhood patients terminated as soon as a certain target height was achieved due to the scarce supply of pituitary GH, but the introduction of biosynthetic GH enabled continuation during the entire transition phase. The early adult GH replacement trials did not capture this important period,

Figure 2

Serum IGF1 levels as a function of chronological age in 3851 healthy subjects of both sexes. The gray area indicates the duration of the transition phase. Modified from Juul *et al.* (13)

but a prospective study reported that discontinuation of GH replacement in childhood-onset patients at the time of transition induced unfavorable changes in lipid profile and body composition (74). Subsequently, a Danish double-blind, placebo-controlled parallel study evaluated the effects of continuation vs discontinuation of GH after cessation of linear growth (75, 76). This study revealed that GH discontinuation resulted in decreased IGF1 as well as increased body fat and insulin sensitivity in the placebo group. After resumption of GH, LBM and IGF1 increased. Likewise, increased muscle volume of the thigh, muscle/fat ratio and glucose oxidation rates increase following resumption of GH. Comparable results were reported in 2004 from an open study of 12-month continuation vs discontinuation of GH replacement (77).

Guidelines as regards management of GHD patients during the transition are available and a few issues merit mention here (78). First, a large proportion of GHD children exhibit normal stimulated GH secretion when retested after completion of GH treatment. Therefore, GH status and the indication for continued GH replacement in adulthood must be evaluated on an individual basis, which requires retesting unless there is strong evidence of either organic panhypopituitarism or a genetic cause of GHD. Second, the pediatric mode of GH dosing according to body size (weight or body surface) translates into high daily doses to achieve the appropriate pubertal growth response and the normal high pubertal IGF1 levels. These high GH doses are usually continued in the transition period even when growth is decelerating due to sex steroid-induced epiphyseal closure. Third, the proper management of transition patients includes patient involvement and a close collaboration between pediatric and adult endocrinologists (78).

The senescence

Endogenous GH production and serum IGF1 levels decline with age (79) in parallel with senescent changes in body composition and physical performance (Fig. 2). Interestingly, in midlife adults, abdominal adiposity is the strongest and negative determinant of endogenous GH secretion (80). Such correlations have led to speculations about a causal link between reduced GH production and the physical frailties of aging, which has been coined 'somatopause' (81). This controversial concept is beyond the scope of our review, but a meta-analysis of GH treatment studies in elderly subjects without overt pituitary disease record only limited positive effects and a high prevalence of GH-related side effects (82).

Despite the age-associated decline GH secretion, elderly patients aged 60–80 years with panhypopituitarism due to well-defined pituitary pathology exhibit distinctly reduced GH and IGF1 levels as compared to age-matched controls (83). Moreover, GHDA patients in this age group seem to respond to GH replacement in the same manner as younger patients (84, 85, 86). However, the GH dose requirement in order not to exceed IGF1 levels above the upper normal range for age and to avoid side effects, declines with chronological age (Fig. 3).

GH replacement and mortality

Increased mortality in hypopituitary patients due to cardiovascular disease is well established, and it has been difficult to resist the temptation to attribute this to unsubstituted GHD (26, 87). However, numerous underlying mechanisms may be equally – or more – likely, for example additional features of hypopituitarism including the underlying disease, treatment complications and suboptimal substitution of additional pituitary deficiencies. It is also noteworthy, that mortality and cancer incidence are increased in acromegaly (88, 89), and that a strong inverse relation exists between activation of the IGF/insulin axis and longevity in many species (90, 91). Moreover, epidemiological human studies suggest an U-shaped association between serum IGF1 levels and all-cause mortality in the general population (92). Most importantly, controlled studies of GH replacement therapy with mortality as an endpoint do not exist and

Figure 3

Daily GH dose (mg) in GH-deficient adults employed to ensure a serum IGF1 level within the upper normal range for age as a function of chronological age. The figures are based on the authors own experience and data from the literature (42, 52, 53, 83, 85). In addition to age, the GH dose also depends on gender.

are very unlikely to appear in the future. An undisputable answer to the question whether GH replacement reduces mortality in GHD patients is therefore not available. However, observational studies in GHDA suggest that mortality is reduced in GH-replaced patients as compared to GH-untreated patients (87, 93, 94, 95). A meta-analysis reported that the standardized mortality rate was 2.40 (95% CI: 1.46–3.34) in GH-untreated vs 1.15 (95% CI: 1.05–1.24) in GH-treated patients (87), and an even larger difference was reported recently by Stockholm *et al.* (93).

Discussion

Adult subjects, including hypopituitary patients, were used to investigate the short-term metabolic effects of pituitary-derived human GH more than half a century ago, and it was speculated that GH replacement in GHDA could be beneficial (2, 3). This therapeutic option became feasible 25 years later with the introduction of biosynthetic GH, and a number of positive effects have been reported. Indeed, GH therapy in GHDA is probably the best-documented therapeutic indication in pituitary endocrinology in terms of placebo-controlled trials and observational studies. The change in body composition with reduced fat mass and increased LBM is the most robust effect. Most studies also record improvements in aerobic exercise capacity and cardiac function. As regards bone mass and strength, data from placebo-controlled trials for up to 1 year record increased bone turnover, but unchanged or even reduced bone mass (96), whereas one study of 18 months observed a significant increase in bone mineral density (BMD) of both the lumbar spine and the femoral neck (97). An increase in BMD is also reported in several open trials of prolonged GH replacement therapy, and it is believed by most that GH replacement initially increases bone remodeling, which transiently reduces BMD, followed by a moderate but sustained increase at least in male patients (63). Whether this reduces the risk of osteoporotic fractures is uncertain, but observational studies suggest a reduced fracture risk (98). Whether QoL improves remains uncertain, since the results from placebo-controlled trials are ambiguous, and the results from open and observational studies are likely biased. The level of education is similar among GH-treated adult patients as compared to the background population, but a higher proportion of the patients are unemployed, retire earlier and are less likely to live with a partner (93, 99). These socioeconomic outcomes demonstrate that hypopituitarism remains a clinical challenge. Cancer risk

is not increased with GH treatment, and mortality (100), if anything, is reduced (93, 94). The latter observation is reassuring even though it – to a large extent – is explained by selection bias (healthy user bias).

Side effects in terms of fluid retention and impaired insulin sensitivity are recognized, but they are dose dependent, rapidly reversible and probably of limited concern. Nevertheless, caution and vigilance are mandated to avoid overtreatment not least of the elderly patient. The daily GH dose requirement to avoid supernormal IGF1 levels and side effects may become as low as 0.1 mg in male patients aged ≥ 70 years (personal observation), which is more than ten-fold lower than the doses used in the early adult trials. This raises the question whether lifelong treatment is justified? In this regard, it should be recalled that although serum IGF1 is strictly GH dependent, its performance as a biomarker of GH treatment is far from perfect (101). The need for better biomarkers of GH treatment is accentuated by the recent introduction of long-acting GH preparations, since these compounds in contrast to daily subcutaneous GH therapy result in fluctuating serum IGF1 levels (102).

In conclusion, the first anecdotal report in 1962 of GH replacement in a patient with adult hypopituitarism concluded that ‘observations will be needed in more cases to indicate whether the favorable effect was more than coincidental’ (3). In 2018, it is safe to state that observations from numerous trials confirm the beneficial effects and justify this treatment modality.

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