Growth Hormone (GH) Status and Body Composition in Normal Ageing and in Elderly Adults with GH Deficiency

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Key Words

Growth hormone · Growth hormone deficiency · Body composition · Elderly adults · Ageing

Abstract

Similarities have been observed between the changes associated with ageing and the symptoms of growth hormone (GH) deficiency. Changes such as increased fat mass and decreased muscle mass occur both in GH-deficient patients and in otherwise healthy elderly individuals. Moreover, ageing is associated with decreasing GH and insulin-like growth factor I (IGF-I) levels. It has been suggested, therefore, that hypothalamic-pituitary disease leading to GH deficiency (GHD) in elderly patients would have less impact than in younger adults. Studies suggest that healthy elderly individuals have normal pituitary reserves of GH, but that spontaneous GH secretion falls by around 14% per decade of adult life, leading to a state of functional GH insufficiency. Despite this, elderly patients with GHD experience reductions in GH secretion and IGF-I levels, compared with controls, which are of similar magnitude to those seen in younger GH-deficient adults. The metabolic changes associated with GHD are also seen in elderly patients compared with healthy elderly controls. Fat mass, particularly in

the abdominal region, is significantly increased, with a strong correlation between fat mass and body mass index. Markers of bone formation and resorption are significantly reduced in the GH-deficient patients. Elderly adults who have hypothalamic-pituitary disease have a degree of GHD that can be distinguished from the decline in GH and IGF-I levels that is seen with normal ageing. GHD in elderly patients leads to significant changes in body composition and bone. Thus, these patients are likely to benefit from GH replacement therapy.

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Introduction

Severe growth hormone (GH) deficiency in adults with hypothalamic-pituitary disease is characterized by adverse changes in body composition (increased fat mass and decreased lean mass), osteopaenia, reduced exercise tolerance, decreased strength and an impaired quality of life [1]. In addition, patients with multiple anterior pituitary hormone deficits, receiving ‘conventional’ replacement therapy but not GH replacement therapy, exhibit an adverse cardiovascular risk profile [2] and have an almost twofold increase in mortality [3].

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Fig. 1. GH secretion in 24 patients with hypothalamic-pituitary disease and 24 control participants. **a** Area under the curve of the 24-hour GH profile (20-min sampling) and **b** peak GH response to arginine. Serum concentrations of GH were measured using an ultrasensitive chemiluminescence assay (sensitivity 0.002 µg/l). Median values are indicated by horizontal bars. Reproduced, with permission, from Toogood et al. [10]; © Blackwell.

Similar changes occur as a result of ageing. For example, during adult life, a man will, on average, lose 12 kg of lean tissue (5 kg in women) and gain 12 kg of fat mass (15 kg in women) [4]. In addition, bone mass is reduced and there is a deterioration in markers of cardiovascular risk associated with increased mortality. These changes occur against a background of declining GH secretion and serum levels of insulin-like growth factor I (IGF-I). The similarity between the pathophysiology of ageing and GH deficiency (GHD) has been reported, and it has also been suggested that GH may be used to improve strength, exercise capacity and functional ability in older individuals, reversing some of the effects of ageing [5]. On a less realistic note, it has been suggested that GH treatment may restore youth and prolong life, but there are no data to support this outcome [6].

GH Status in Healthy Elderly Individuals

It is often stated that old age is a GH-deficient state. The GH Research Society consensus statement on the diagnosis of GHD, however, states that in adults, hypothalamic-pituitary disease must be present before the

diagnosis of GHD can be considered and that the peak GH response during an insulin tolerance test (ITT) should be less than 3 µg/l [7]. The GH response during an ITT has been reported to fall with increasing age in one study [8], but was unaffected in another [9]. The GH response to arginine alone [10], arginine + GH-releasing hormone (GHRH) [11] or GHRH + GH-releasing peptide 6 [12] is sustained across the adult lifespan, suggesting that the releasable reserve of GH in the pituitary gland is not affected by age. Spontaneous GH secretion falls by an estimated 14% per decade of adult life [13], an alteration caused by changes in hypothalamic release of GHRH and somatostatin [14]. These data suggest that ageing results in a state of functional GH insufficiency.

GH Status in Elderly Patients with Hypothalamic-Pituitary Disease

If the hyposomatotropism associated with an increase in age was severe enough to be labelled as GHD, one would not expect hypothalamic-pituitary disease to have a significant impact on spontaneous GH secretion in adults over 60 years of age. To address this question,

Fig. 2. Serum concentrations of IGF-I (a) and IGFBP-3 (b) in 24 patients with hypothalamic-pituitary disease compared with data from 125 control individuals aged over 60 years. Median values are indicated by horizontal bars. Adapted, with permission, from Toogood et al. [10]: © Blackwell.

spontaneous and stimulated GH secretion was studied in 24 patients with hypothalamic-pituitary disease and 24 controls aged over 60 years. The groups did not differ significantly in terms of body mass index (BMI), but the patients with hypothalamic-pituitary disease were slightly younger than the controls (66.0 years [range, 61.0–85.7 years] vs. 70.6 years [60.8–87.5 years], respectively; $p = 0.04$). Each participant underwent a 24-hour GH profile, when a sample was taken every 20 min, and an arginine stimulation test performed immediately after the profile. Blood was also taken for an estimation of serum concentrations of IGF-I and IGF-binding protein 3 (IGFBP-3) following an overnight fast.

With the use of a standard GH immunoradiometric analysis (sensitivity, 0.4 µg/l), it was shown that 16 of the 24 patients had no detectable release of GH. In contrast, all of the control participants had detectable GH secretion at some point during the 24-hour profile [15]. When re-evaluated using an ultrasensitive chemiluminescence assay (sensitivity, 0.002 µg/l), GH was measurable in all of the samples obtained during the 24-hour profiles from the controls and the patients [16]. The area under the curve of the GH profile (AUC_{GH}) was significantly lower in the patients with hypothalamic-pituitary disease than in the

control participants, 119.3 µg/l·min (range, 7.3–843.6 µg/l·min) compared with 968.5 µg/l·min (range, 227.2–4,625.0 µg/l·min) ($p < 0.00001$) (fig. 1). Thus, GH secretion in the patients with hypothalamic-pituitary disease was only 12% of that observed in the controls, a reduction similar in size to that observed in younger adults with hypothalamic-pituitary disease [17]. A similar reduction was observed in the peak GH response to arginine stimulation (fig. 1) [10]. Serum levels of IGF-I and IGFBP-3 were significantly lower in the patients than in the controls (102 µg/l [range, 14–162 µg/l] vs. 142 µg/l [59–298 µg/l] [$p < 0.0001$] and 2.29 mg/l [0.81–3.75 mg/l] vs. 2.59 mg/l [1.00–3.52 mg/l] [$p = 0.009$], respectively), but there was a significant degree of overlap between the two groups (fig. 2).

The Impact of GHD on Body Composition and Bone in Adults over 60 Years of Age

Hypothalamic-pituitary disease in adults over 60 years of age causes a reduction in GH secretion beyond that associated with an increase of age. The magnitude of the decrease is similar to the decrease observed in younger

adults with pituitary disease [17] and is severe enough to cause a reduction in serum levels of IGF-I and IGFBP-3. To determine whether GHD in elderly individuals had a significant impact upon body composition and bone, 21 patients and 24 controls of similar age, height, weight and BMI underwent dual-energy X-ray absorptiometry scanning of the hip, spine and total body. In addition, a 24-hour urine collection was performed and serum was analysed for an estimation of deoxypyridinoline excretion and osteocalcin, respectively.

Body Composition

Fat mass was significantly increased in the patients with hypothalamic-pituitary disease (27.8 kg [range, 19.2–50.2 kg]), compared with the control group (21.2 kg [8.8–49.2 kg]; $p < 0.005$). Estimation of regional fat mass showed that these patients had a greater fat mass in the trunk, in the arms and in the legs than the control participants (table 1). There was a strong correlation between total fat mass and BMI in the control participants ($r = 0.80$; $p < 0.0001$), but this relationship was not seen in the patients ($r = 0.23$), suggesting that body composition was abnormal in these individuals. The waist:hip ratio was higher in the patients with hypothalamic-pituitary disease (0.93 [0.70–1.17]) than in the control participants (0.89 [0.69–1.02]; $p < 0.05$), suggesting that the degree of central obesity was greater in

the patients. There was a significant negative correlation between total fat mass and GH secretion (AUC_{GH}) in the control participants ($r = -0.542$; $p = 0.006$), but this relationship was not evident in the patients with hypothalamic-pituitary disease ($r = -0.127$; $p = 0.58$).

In contrast to younger patients with GHD, total fat-free mass was not significantly different in elderly patients with GHD compared with their healthy peers (50.87 kg [range, 26.96–69.18 kg] vs. 51.55 kg [32.35–60.53 kg]; $p = 0.8$). The fat-free mass in the arms, legs and trunk were not significantly different between the two groups (table 1) [18].

Bone

Markers of bone formation and resorption were significantly reduced in the patients with hypothalamic-pituitary disease compared with the controls. The median serum concentration of osteocalcin was 11.5 ng/ml (range, 3.6–23.0 ng/ml) versus 15.1 ng/ml (0.7–40.5 ng/ml; $p = 0.019$), and the deoxypyridinoline:creatinine ratio was 3.5 $\mu\text{mol/mol}$ (0.8–8.3 $\mu\text{mol/mol}$) versus 4.9 $\mu\text{mol/mol}$ (3.0–9.7 $\mu\text{mol/mol}$; $p = 0.038$), in the patients and controls, respectively. In the control group, there was a significant correlation between serum levels of osteocalcin and AUC_{GH} ($r = 0.43$; $p = 0.039$) and urinary deoxypyridinoline cross-links and age ($r = 0.64$; $p = 0.002$). These rela-

Table 1. Fat and lean mass measured in elderly patients with hypothalamic-pituitary disease and elderly controls

Mass, kg	Patients (n = 21)	Controls (n = 24)	p
Total fat	27.5 (19.2–50.2)	21.2 (8.8–49.2)	0.0047
Total lean	50.9 (27.0–69.2)	51.6 (32.4–60.5)	0.8
Arms, fat	3.3 (2.0–8.3)	2.4 (0.8–7.1)	0.033
Legs, fat	7.3 (4.2–16.4)	5.6 (2.4–17.1)	0.021
Trunk, fat	15.7 (10.0–24.1)	12.4 (5.1–23.2)	0.009
Arms, lean	6.7 (2.8–8.6)	6.5 (3.5–8.1)	0.9
Legs, lean	16.2 (8.8–22.5)	17.1 (10.6–21.0)	0.4
Trunk, lean	24.4 (12.5–35.2)	24.8 (15.3–29.9)	0.96

Values are expressed as median (range).

Table 2. Age-specific standard deviation scores at each site measured in elderly patients with hypothalamic-pituitary disease and elderly controls

	Patients (n = 21)	Controls (n = 24)	p
Vertebrae L2–L4	0.80 (–2.83 to 2.95)	1.10 (–2.87 to 2.64)	0.68
Femoral neck	0.27 (–1.48 to 3.43)	0.25 (–2.29 to 3.26)	0.89
Femoral trochanter	0.46 (–2.14 to 3.37)	0.50 (–2.4 to 3.8)	0.98
Ward's triangle	0.10 (–1.58 to 3.94)	0.47 (–2.45 to 3.31)	0.96

Values are expressed as median (range).

Fig. 3. Measurement of bone mineral in 21 patients with hypothalamic-pituitary disease and 23 control individuals. **a** Total bone mineral content (BMC), and bone mineral density measured at **b** the lumbar spine and **c** the hip. Median values are indicated by horizontal bars. Adapted, with permission, from Toogood et al. [19]: © The Endocrine Society.

tionships were not seen in the patients with hypothalamic-pituitary disease. Despite this reduction in bone turnover, total body bone mineral content and bone mineral density at the hip and spine were almost identical in both groups (fig. 3, table 2) [19].

Discussion

Adults over the age of 60 years who have hypothalamic-pituitary disease have a degree of GHD that can be distinguished from the hyposomatotropism of ageing; spon-

taneous secretion of GH is only 12% of that observed in healthy controls. This degree of GHD is significant enough to impact on serum markers, body composition and bone. The magnitude of the changes that occur, however, is attenuated compared with those changes observed in younger patients with a similar deficit in GH secretion.

A considerable degree of interest surrounds the use of GH as an anti-ageing compound. There are some 'special clinics' in many countries that offer GH treatment to paying customers on the grounds that the process of ageing will be reversed. Some researchers also claim that GH may extend the human life span. The short-to-medium-term effects of GH treatment, however, as shown through well-designed, randomized, controlled studies are less impressive. Improvements in body composition occur, but improvements in physical function are difficult to demonstrate [20]. Furthermore, many authors report a high incidence of adverse effects including gynaecomastia, carpal tunnel syndrome, peripheral oedema and impaired glucose tolerance. The lack of efficacy demonstrated and the high incidence of side effects reported during GH treatment suggest that older adults are not truly GH deficient, a supposition confirmed by the studies discussed in this review. In addition, the observation that the effects of GHD in older adults are attenuated suggests that changes in body composition, muscle mass and strength are not driven solely by the observed changes in GH status that occur with increasing age. Thus, GH should not be considered as an elixir of youth to be administered to all adults over the age of 60 years. Research efforts should, instead, focus on identifying groups of patients in whom the risk of adverse effects is outweighed by the benefits achieved from GH treatment.

Patients over the age of 60 years who have hypothalamic-pituitary disease, on the other hand, do suffer from

the effects of GHD, which suggests that these patients would benefit from GH replacement therapy. Li Voon Chong et al., who studied the quality of life in these patients, demonstrated that patients had less energy, mobility and personal life fulfilment, and had more problems with emotional reaction, social isolation and mental fatigue. Li Voon Chong and colleagues also reported a greater impairment in some areas of social functioning, general health and mental health compared with healthy controls [21]. Although there are no data from controlled studies, GH replacement therapy appears to be beneficial to adults over the age of 60 years with organic GHD. In an open, dose-finding study, serum IGF-I increased, fat mass fell, lean mass increased and there was a significant improvement in quality of life determined using the Adult GHD Assessment (AGHDA) questionnaire [22]. Data from KIMS (Pharmacia International Metabolic Database) indicate that 6 months of GH replacement therapy in adults over 60 years of age resulted in a reduction of waist circumference, waist:hip ratio, diastolic blood pressure, total and low-density lipoprotein cholesterol, and an improvement in quality of life as determined by the AGHDA score [23]. Thus, there is a strong case for a well-designed, placebo-controlled study to confirm these effects and to determine other benefits that may strengthen the case for treating patients with organic GHD, for example improvements in functional parameters such as exercise capacity.

In conclusion, it is clear that GH continues to have a role in metabolism and bone physiology throughout the human life span and that specific patient groups may benefit from treatment with GH. More work is required to define the effects of GHD in patients over the age of 60 years and to identify other patients who do not have pituitary disease but could potentially benefit from the anabolic effects of GH.

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