0021-972X/96/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 81, No. 2
Printed in U.S.A.

Beyond the Somatopause: Growth Hormone Deficiency in Adults Over the Age of 60 Years

ANDREW A. TOOGOOD, PAUL A. O'NEILL, AND STEPHEN M. SHALET

Department of Endocrinology, Christie Hospital National Health Service Trust, Manchester, United Kingdom M20 4BX; and the University Department of Geriatric Medicine, South Manchester University Hospital Trust (P.A.O.), Manchester, United Kingdom M20 8LR

ABSTRACT

GH secretion declines by 14%/decade of adult life, leading to the suggestion that people over the age of 60 yr are functionally GH deficient. If this is the case, one might not be able to detect a difference in GH secretion between the elderly with documented hypothalamic-pituitary disease and an age-matched control group. We studied GH secretion in 24 patients with hypothalamic-pituitary disease and 24 controls matched for body mass index and age using 24-h GH profiles, arginine stimulation tests, and serum insulin-like growth factor I (IGF-I) levels.

The median (range) area under the curve of the GH profile [<9.6 (<9.6–20) *vs.* 18.5 (10.7–74.4) μg/L·24 h; $P < 0.0001$], the median stimulated peak GH response to arginine [<0.4 (<0.4–7.7) *vs.* 8.0 (1.6–37.0) μg/L; $P < 0.0001$], and the median serum IGF-I concentration [102 (<14–162) *vs.* 147 (65–255) ng/mL; $P = 0.0002$] were significantly lower in the patients than in the controls. Fifteen patients showed no evidence of spontaneous or stimulated GH secretion, whereas all controls had evidence of both. The area under the GH curve in the 33 subjects with demonstrable GH secretion correlated significantly with the peak GH response to arginine ($r = 0.71$; $P < 0.0001$), but not with serum IGF-I concentration.

This study suggests that organic GH deficiency in the elderly is distinct from the decline in GH secretion associated with the aging process. These patients may benefit from GH replacement therapy. (*J Clin Endocrinol Metab* **81:** 460–465, 1996)

GH DEFICIENCY is a common finding in adults with pituitary disease. It is characterized clinically by changes in body composition, reduced strength and exercise tolerance, impaired psychological well-being, a reduction in bone mineral density, and changes in renal and cardiac function (1). The serum level of insulin-like growth factor I (IGF-I) is often, but not always, reduced in adults with GH deficiency (2–5). The increase in fat mass and reduction in lean body mass seen in GH-deficient adults are reversed when GH replacement therapy is given (6, 7). There are also improvements in psychological well-being (8), glomerular filtration rate (9), and bone mineral density (10) with GH replacement therapy.

GH secretion in healthy elderly adults is reduced compared with that in young adults (11–21). GH secretion declines by approximately 14%/decade from young adult life (20), and some studies suggest that GH secretion may eventually cease in certain elderly subjects (11). Normal aging is associated with changes in body composition similar to those in patients with GH deficiency, a reduction in bone mass, osteoporosis in severe cases, and a reduction in renal and cardiac function. The similarity of the changes in adults with GH deficiency and those that are part of the normal aging process has led some researchers to suggest that aging may be due to GH deficiency (22). The decline in GH secretion and the physiological changes seen with aging have been grouped together and termed the somatopause.

Received April 25, 1995. Revision received August 3, 1995. Accepted August 28, 1995.

Address all correspondence and requests for reprints to: Prof. S. M. Shalet, Department of Endocrinology, Christie Hospital National Health Service Trust, Wilmslow Road, Manchester, United Kingdom M20 4BX.

GH secretion in the elderly with organic disease of the hypothalamic-pituitary axis has not been studied in detail. Therefore, it is not known whether it differs from that accompanying the somatopause. We have studied GH secretion in a group of patients with pituitary disease over the age of 60 yr and in a normal age- and body mass index (BMI)-matched control group.

Subjects and Methods

Patients and controls

Twenty-four patients with nonacromegalic pituitary disease were studied, 16 men and 8 women between 61.0–85.7 yr of age. All patients were recruited from our out-patient population. We surveyed all our patients with known hypothalamic-pituitary disease who were over 60 yr old and approached all those who had previously had a peak GH response to a provocative test of less than 7.5 μg/L. This GH peak was chosen arbitrarily in the absence of a clearly defined threshold for the diagnosis of GH deficiency in this age group. All patients had hypothalamic-pituitary disease that developed in adult life.

Only patient 20 had previously received GH replacement, and he had taken it for 6 months, but had stopped it 6 months before taking part in this study. The clinical details of the patients are given in Table 1. Twenty-one patients had additional anterior pituitary hormone deficiencies. All had gonadotropin deficiency, 16 had ACTH deficiency, and 13 had TSH deficiency. Eleven of the 15 men with gonadotropin deficiency were receiving testosterone replacement. Two had received the most recent testosterone implant 3 months before entering the study, the remaining 9 had received an im injection of testosterone esters within the 2 weeks preceding the study. None of the women had received sex steroid replacement therapy during the 5-yr period preceding the study. All patients with ACTH deficiency were receiving replacement therapy with hydrocortisone (n = 9), cortisone acetate (n = 5), or prednisolone (n = 2), and those with TSH deficiency were receiving T_4.

Twenty-four control subjects, 17 men between 60.8–87.5 yr of age, were recruited from a panel of normal volunteers (Table 2). Exclusion criteria consisted of a history of diabetes mellitus, current treatment with psychotropic medication, treatment for thyroid disease, or abnormal

TABLE 1. Clinical characteristics of the 24 patients studied

Patient no.	Age (yr)	Sex	BMI	Diagnosis	Treatment	No. of additional defs	Sex steroid replacement	Additional medication
1	70.8	M	29.1	Nonfunctioning adenoma	S, XRT	FSH, LH, ACTH, TSH	Y	Bendrofluazide, ranitidine
2	66.7	M	23.8	Nonfunctioning adenoma	S, XRT	FSH, LH, ACTH, TSH	Y	Nil
3	63.8	M	28.5	Nonfunctioning adenoma	S, XRT	FSH, LH, ACTH	Y	Coproxamol
4	69.0	M	26.5	Nonfunctioning adenoma	S, XRT	FSH, LH	N	Nil
5	85.8	M	27	Craniopharyngioma	S, XRT	FSH, LH, ACTH, TSH, ADH	N	Nil
6	66.0	M	31	Nonfunctioning adenoma	S, XRT	FSH, LH, ACTH, TSH	Y	Nil
7	69.1	F	23.7	Nonfunctioning adenoma	S, XRT	FSH, LH, ACTH, TSH	N	Coamilozide, slow K, ranitidine
8	64.9	F	22.6	Cushing's disease	XRT		N	Nifedipine, atenolol, bendrofluazide, aspirin
9	66.6	M	30.9	Nonfunctioning adenoma	S, XRT	FSH, LH, ACTH, TSH	Y	Nil
10	65.9	F	33.1	Meningioma	XRT	FSH, LH	N	
11	61.7	F	37.3	Nonfunctioning adenoma	S, XRT	FSH, LH, ACTH	N	Atenolol
12	62.9	M	31.8	Nonfunctioning adenoma	S, XRT	FSH, LH, ACTH, TSH	N	Enalapril
13	63.0	M	27.8	Nonfunctioning adenoma	S	FSH, LH, ACTH, TSH, ADH	Y	Nil
14	64.2	M	29.7	FSH-secreting adenoma	S, XRT	FSH, LH, ACTH, TSH	Y	Nil
15	73.3	M	31.5	Prolactinoma			N	Aspirin, nicoumalone, bromocriptine[a]
16	68.0	F	25.6	Meningioma	XRT		N	Nil
17	83.4	M	25.7	Nonfunctioning adenoma	S, XRT	FSH, LH, ACTH, TSH	N	Sandocal
18	78.5	F	27.3	Nonfunctioning adenoma	S, XRT	FSH, LH	N	Amiloride, voltarol, coproxamol, hydrochlorothiazide
19	60.0	F	26.8	Nonfunctioning adenoma		FSH, LH	N	Isosorbide, mononitrate, aspirin, coamilofruse, bezafibrate
20	61.1	M	29.5	FSH-secreting adenoma	S, XRT	LH, ACTH	Y	Nil
21	65.8	M	29.7	Prolactinoma	S, XRT	FSH, LH, ACTH, TSH	Y	Nifedipine, aspirin, simvastatin, aspirin, bromocriptine[a]
22	64.3	F	22.7	Nonfunctioning adenoma	S, XRT	FSH, LH	N	Ranitidine, bisoprolol, gaviscon, coproxamol
23	64.6	M	31.2	Nonfunctioning adenoma	S, XRT	FSH, LH, ACTH, TSH	Y	Nifedipine
24	68.8	M	25.6	Nonfunctioning adenoma	S, XRT	FSH, LH, ACTH, TSH	Y	Nil

Sex steroid replacement in the men consisted of a depot preparation of testosterone esters every 3 weeks apart from patient 3, who took testosterone undecanoate orally, and patients 2 and 20, who received testosterone implants (800 and 600 mg, respectively) every 6 months. All patients with ACTH deficiency were receiving standard steroid replacement.

[a] Bromocriptine was stopped 4 weeks before the patient was studied. Treatment was either surgery (S) or radiotherapy (XRT).

TABLE 2. Clinical characteristics of the controls

Control	Sex	Age	BMI	Medication
1	M	75.9	28.4	Aspirin
2	M	74.6	25.4	Nil
3	M	65.6	21.8	Nil
4	F	62.4	33	Nil
5	F	63.9	20.9	Aspirin
6	M	70.6	28.7	Nil
7	M	66.0	24.9	Nil
8	M	82.0	23.8	Nil
9	M	73.1	24.3	Aspirin, atenolol, nifedipine
10	M	76.6	25.5	Aspirin, oxybutynin
11	M	65.0	27.9	Nil
12	M	68.2	29.4	Nil
13	M	65.4	26.5	Nil
14	M	69.4	30.3	Atenolol, bendrofluazide, aspirin
15	M	70.6	28.6	Nil
16	F	74.8	26.4	Nifedipine
17	F	71.6	21.8	Quinine
18	M	71.1	21.8	Ranitidine
19	F	65.9	37	Warfarin, enalapril, digoxin
20	M	61.8	25.9	Ranitidine
21	F	87.4	20.1	Omeprazole, calcium carbonate
22	M	75.2	33.9	Nifedipine, digoxin, dipyridamole, warfarin
23	M	68.1	25.7	Nil
24	F	71.3	26.2	Diclofenac sodium

thyroid function tests. The controls were matched with the patients for age and BMI. None of the women had received estrogen replacement therapy within a year of entering the study.

Study protocol

The study was approved by the South Manchester Area Health Authority ethics committee. All subjects gave written consent before entering the study.

Patients and controls were admitted to the ward at 0800 h on day 1 after having eaten their normal breakfast. A cannula was inserted into a forearm vein and kept patent with heparinized saline. Blood samples were drawn every 20 min for 24 h. There was no restriction on activity within the ward. A standard hospital diet was consumed until midnight on day 1, when oral intake was restricted to water only. Meal times were midday, 1730 h, and 2200 h on day 1. At 0900 h on day 2, blood was drawn for serum GH and IGF-I estimation. Arginine hydrochloride was given iv over 30 min. The dose of arginine used was 20 g/m^2 (23). Blood was drawn at 30-min intervals for a total of 150 min for measurement of serum GH. The arginine stimulation test was chosen for two reasons. Firstly, we were not prepared to perform an insulin tolerance test in the controls, and secondly, it has been stated that the GH response to arginine does not decline with age (24).

All samples were separated, and serum was kept at −20 C until the assays were performed.

GH and IGF-I assays

The serum GH measurement was performed using an in-house two-site immunoradiometric assay. The samples were assayed in duplicate. The reference preparation used was NIBSC 80/505. The interassay coefficients of variation were 8.8%, 5.5%, and 6.5% for mean GH concentrations of 3.5, 9.6, and 25 μg/L; the intraassay coefficient of variation for a mean GH of 13.5 μg/L was 3%. The limit of detection for this assay was 0.4 μg/L.

Serum IGF-I was measured, after acid-alcohol extraction, by an in-house RIA. The samples were assayed in duplicate as a single batch. The reference preparation used was NIBSC 87/518. The intraassay coefficients of variation for mean IGF-I concentrations of 46, 246, and 706 ng/mL were 11.3%, 6.5%, and 4.7%, respectively. The sensitivity of this assay was 14 ng/mL.

Statistics

Results are quoted as medians (range). The area under the curve of each GH profile (AUC) was calculated using a trapezoidal method, recording serum GH values below the limit of the assay as 0.4 μg/L. Comparisons of individual parameters were made between groups using the Mann-Whitney U test.

$P < 0.05$ was considered statistically significant.

Results

The two groups were matched for BMI [median (range), 28.2 (22.6–37.3) in the patients *vs.* 26.1 (20.1–37.0) in the controls]. The controls were slightly, but significantly, older than the patients [70.6 (60.8–87.5) *vs.* 66.0 (61.0–85.7) yr; $P = 0.04$; Table 2].

Fifteen of the subjects with pituitary disease had no evidence of stimulated or spontaneous GH secretion (Figs. 1 and 2). Severe hypopituitarism (GH deficiency plus 2 or 3 additional anterior pituitary hormone deficiencies) was present in 14 of the 15 subjects with undetectable GH secretion compared with 2 of 9 subjects with detectable GH secretion ($\chi^2 = 9.8$; $P = 0.0017$). One patient had detectable GH during the 24-h profile, but not during the arginine stimulation test, and 1 subject had a minimal GH response to arginine of 0.5 μg/L but no evidence of spontaneous GH secretion. All 24 controls showed detectable levels of GH spontaneously and in response to arginine (Fig. 2).

The median (range) AUC of the GH profile (AUC_{GH}) was less than 9.6 (<9.6–20.0) μg/L·24 h and 18.5 (10.7–74.4) μg/L·24 h in the patients and controls, respectively ($P < 0.0001$; Fig. 2a). The median peak serum GH after arginine stimulation (Fig. 2b) was less than 0.4 (<0.4–7.7) μg/L in the patients and 8.0 (1.6–37.0) μg/L in the controls ($P < 0.0001$). Median serum IGF-I concentrations (Fig. 2c) in the patients were 102 ng/mL (<14–162) and 147 ng/mL (65–255) in the controls ($P = 0.0002$).

There was a highly significant correlation between the AUC_{GH} and the peak GH response to arginine ($r = 0.71$; $P < 0.0001$) in the 33 subjects who had demonstrable GH secretion in the 24-h profile or the arginine stimulation test (Fig. 3). Serum IGF-I levels in these 33 subjects did not correlate with the AUC_{GH} curve or with the stimulated peak GH response to arginine.

Discussion

This study has shown that adults over the age of 60 yr with hypothalamic-pituitary disease are markedly GH deficient compared with normal individuals matched for BMI. Despite careful attempts at matching the controls with the patients for age, the controls were slightly, but significantly, older than the patients. The latter adds further weight to our finding of reduced GH secretion in the patients. The biological significance of this difference in GH secretion is demonstrated by the lower serum IGF-I levels found in the patients.

Fifteen members of the patient group had no evidence of detectable GH secretion during the 24-h profile or the arginine stimulation test; all of the controls had detectable GH secretion during both. Although our study used a conventional immunoradiometric assay rather than an ultrasensitive assay for GH estimation, the results demonstrate a considerable and significant difference in GH secretion between elderly patients with

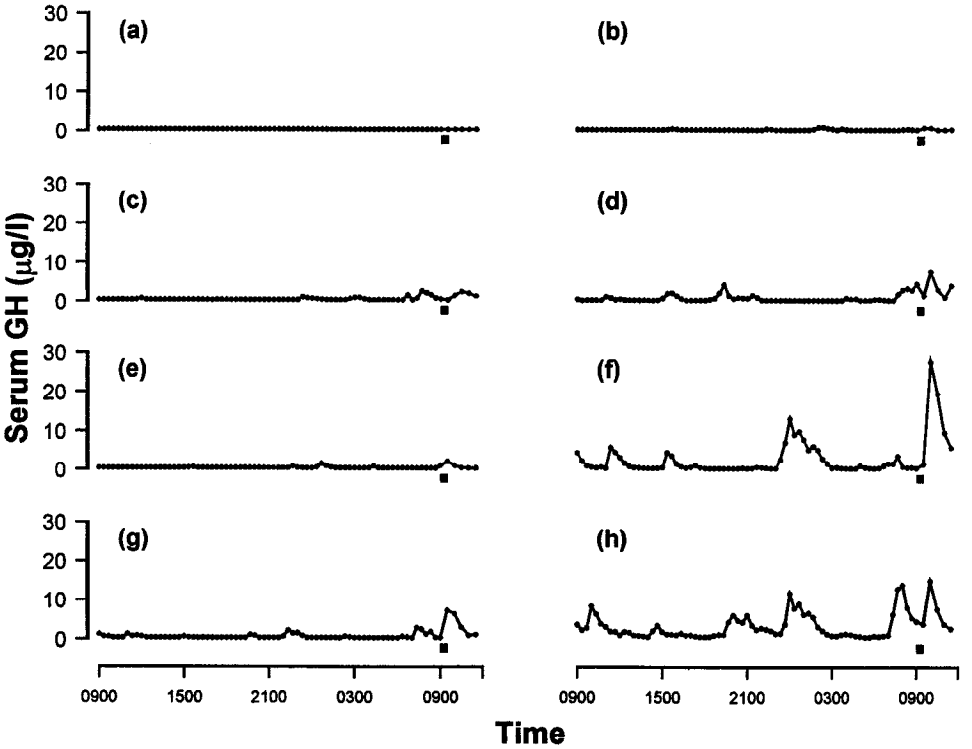

FIG. 1. Twenty-four-hour GH profiles and arginine stimulation tests. ■, The 30-min arginine infusion. a, The profile from 15 patients; b, patient 15; c, patient 16; d, patient 8; e, 68-yr-old male control, BMI 29.4; f, 65-yr-old male control, BMI 21.8; g, 62-yr-old female control, BMI 33; h, 63-yr-old female control, BMI 20.9.

hypothalamic-pituitary disease and normal elderly controls. The use of an ultrasensitive GH assay, however, would allow us to determine with greater detail differences in GH levels between the patients and the controls and provide information that might help in the diagnosis of GH deficiency for an individual in this age group.

There is a degree of overlap for both the AUC_{GH} and the peak GH response to arginine between the patient and control groups. Those patients who had some evidence of residual GH secretion were less likely to have panhypopituitarism, in keeping with our previous finding that the severity of GH deficiency is related to the severity of hypopituitarism (25). Three of the eight patients who demonstrated spontaneous GH secretion exhibited no additional pituitary hormone deficit. Patient 8 is of particular interest. Despite receiving hypothalamic-pituitary irradiation (20 Gy in eight fractions over 11 days) for the treatment, and ultimately the cure, of Cushing's disease 10 yr previously, she has maintained normal pituitary function, including apparently normal GH secretion. Whether the other two patients with spontaneous GH secretion and no other pituitary hormone deficit are truly GH deficient or whether the low circulating GH levels reflect the age-related decline is not certain at the present time. These patients do, however, have undisputed hypothalamic-pituitary disease, and their results highlight the difficult dilemma of diagnosing organic GH deficiency in an elderly individual.

The reduction in GH secretion that occurs with age has been quantified as approximately 14%/decade from the age of 20 yr on (20). The first change that occurs is in the reduction of GH secretion during the day; the majority is produced during sleep (11). With increasing age, the amount of GH secreted during sleep declines (15); the number of GH secretory bursts (20) and the amplitude and the duration of the GH pulses also decrease (19). It has been reported that the spontaneous nocturnal GH peak is absent in the elderly (12) and that there is no significant GH secretion over 24 h in a proportion of the elderly subjects studied (11). The concentration of circulating IGF-I declines with age (26), which reflects the age-related fall in GH secretion.

Whether stimulated GH secretion declines with age is less clear. Kalk *et al.* (27) reported that there was no difference between the peak GH response to an insulin tolerance test (ITT) in a group of healthy old people and a group of young people. Other studies have shown that the GH response to hypoglycemia is reduced in the elderly (28, 29). In one study, 52% of subjects were found to have a reduced peak GH response during an ITT compared with young controls, and 20% had a response consistent with a diagnosis of GH deficiency (28). Similar confusion exists when other GH secretagogues are used in the elderly, for example GH-releasing hormone (GHRH). Some researchers found no relationship between the GH response to GHRH and age (30), whereas others reported a reduction in the GH response to GHRH with increasing age (16, 30, 31).

The biochemical definition of GH deficiency in adults is controversial at the present time. The ITT is considered the gold standard investigation for the diagnosis of GH deficiency in adults (5). The ITT is, however, unpleasant for the patient and carries a considerable risk, especially in an elderly group, in which ischemic heart disease is more common. In our institute we have opted to use an alternative stimulation test to assess GH secretion in subjects over 60 yr of age. In this study we chose the arginine stimulation test, which has provided a reliable assessment of GH secretion in this age group. In the 16 patients with undetectable spontaneous GH

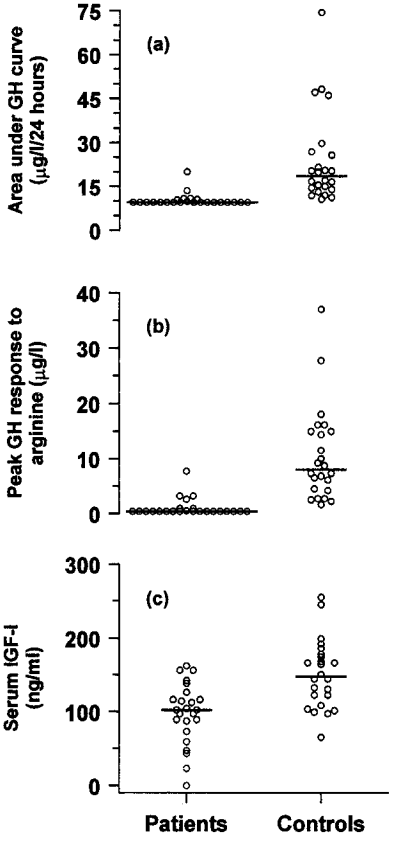

FIG. 2. a, AUC_{GH}; b, peak serum GH attained during the arginine stimulation test; c, serum IGF-I levels in patients and controls. *Bars* represent medians.

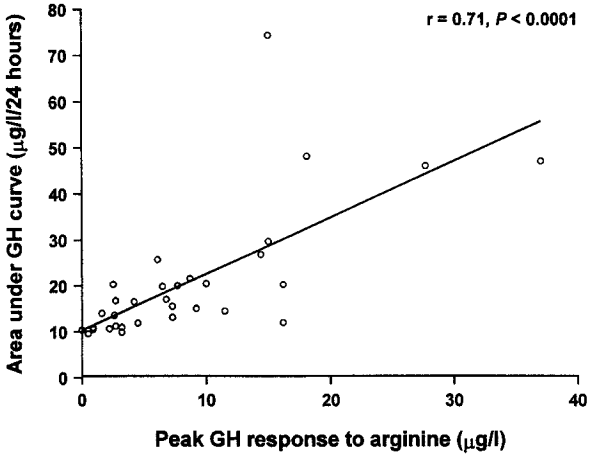

FIG. 3. The relationship between AUC_{GH} and the peak GH response to arginine in 33 patients and controls who had evidence of either spontaneous GH secretion, a response to arginine stimulation, or both.

secretion, only 1 had a GH response to arginine; in the other 32 patients and the controls, there was a good correlation between the stimulated GH peak response to arginine and spontaneous GH secretion.

In this study of the elderly, serum IGF-I levels were lower in the patients with GH deficiency than in the normal controls. In adults between the ages of 20–60 yr with GH deficiency, however, the usefulness of IGF-I to reflect GH deficiency appears to vary with the severity of GH deficiency and the age of the patients (2–5). In a group of young adults (mean age, 26.5 yr) with childhood-onset GH deficiency, serum IGF-I was below the age-related normal range in 96% (2). In an older set of patients, however, Hoffman *et al.* (5) reported that only 30% of the GH-deficient patients (mean age, 45 yr) had an IGF-I concentration below the range found in age- and BMI-matched controls. In our own center, 69% of 65 patients with GH deficiency (mean age, 35.1 yr) had a serum IGF-I concentration more than 2 SD below the age-related mean (4), whereas in the present study, only 21% of elderly patients had a serum IGF-I level below the range found in the elderly controls. Thus, it would appear that with increasing age, IGF-I estimation becomes less reliable for diagnosing GH deficiency in adults. The loss of sensitivity with the use of IGF-I estimation for detecting GH deficiency in the elderly is similar to that seen in the very young child (32); both ends of the age spectrum are associated with low IGF-I levels in normal subjects.

Studies of GH therapy are currently being carried out in normal elderly people to determine whether GH therapy can reverse the effects of aging. For example, GH supplementation in the normal elderly causes a reduction in fat mass and an increase in lean body mass (33, 34). The dose of GH used in these studies has been similar to that used in younger adults with GH deficiency and has been associated with a considerable number of side-effects, including hyperglycemia, carpal tunnel syndrome, and gynecomastia. It is worth noting that the dose of GH replacement therapy used in young adults with GH deficiency is less than half of that used in GH-deficient children. It is, therefore, likely that adults over the age of 60 yr with hypothalamic-pituitary disease will require a further reduction in GH dose if physiological replacement is desired.

This study provides strong evidence that adults over 60 yr of age with hypothalamic-pituitary disease have GH deficiency, which is distinct from the decline in GH secretion associated with aging. The benefits of GH therapy in these patients need to be determined.

Acknowledgments

We thank Prof. Mike Horan from the University Department of Geriatric Medicine, South Manchester University Hospitals Trust, for allowing us access to the health status defined panel to recruit controls, and Mrs. Morag Caine for secretarial support. We would also like to thank Pharmacia for their support of this study.

References

1. **Cuneo RC, Salomon F, McGauley GA, Sönksen PH.** 1992 The growth hormone deficiency syndrome in adults. Clin Endocrinol. 37:387–397.
2. **de Boer H, Blok G-J, Popp-Snijders C, van der Veen E.** 1994 Diagnosis of growth hormone deficiency in adults [Letter]. Lancet. 343:1645–1646.
3. **Weissberger AJ, Verikiou K, Sönksen PH.** 1994 Diagnosis of growth hormone deficiency in adults. Lancet. 344:483.
4. **Holmes SJ.** 1995 Growth hormone replacement in adults with growth hormone deficiency. MD Thesis. London: University of London; 141–152.
5. **Hoffman DM, O'Sullivan AJ, Baxter RC, Ho KKY.** 1994 Diagnosis of growth hormone deficiency in adults. Lancet. 343:1064–1068.
6. **Salomon F, Cuneo RC, Hesp R, Sönksen PH.** 1989 The effects of treatment with recombinant human growth hormone on body composition in adults with growth hormone deficiency. N Engl J Med. 321:1797–1803.
7. **Bengtsson B-Å, Edén S, Lönn L, et al.** 1993 Treatment of adults with growth hormone deficiency with recombinant human GH. J Clin Endocrinol Metab. 76:309–317.

8. **McGauley GA.** 1989 Quality of life assessment before and after growth hormone treatment in adults with growth hormone deficiency. Acta Paediatr Scand. 356(Suppl):70–72.
9. **Caidahl K, Eden S, Bengtsson B-Å.** 1994 Cardiovascular and renal effects of growth hormone. Clin Endocrinol (Oxf). 40:393–400.
10. **O'Halloran DJ, Tsatsoulis A, Whitehouse RW, Holmes SJ, Adams JE, Shalet SM.** 1993 Increased bone density after recombinant human growth hormone therapy in adults with isolated GH deficiency. J Clin Endocrinol Metab. 76: 1344–1348.
11. **Finklestein JW, Roffwarg HP, Boyar RM, Kream J, Hellman L.** 1972 Age-related change in the twenty-four-hour spontaneous secretion of growth hormone. J Clin Endocrinol Metab. 35:665–670.
12. **Carlson HE, Gillin JC, Gorden P, Snyder F.** 1972 Absence of sleep related growth hormone peaks in aged normal subjects and in acromegaly. J Clin Endocrinol Metab. 34:1102–1105.
13. **Dudl RJ, Ensinck JW, Palmer HE, Williams RH.** 1973 Effect of age on growth hormone secretion in man. J Clin Endocrinol Metab. 37:11–16.
14. **Rudman D, Kutner MH, Rogers CM, Lubin MF, Fleming GA, Bain RP.** 1981 Impaired growth hormone secretion in the adult population: relation to age and adiposity. J Clin Invest. 67:1361–1369.
15. **Prinz PN, Weitzman ED, Cunningham GR, Karacan I.** 1983 Plasma growth hormone during sleep in young and aged men. J Gerontol. 38:519–524.
16. **Shibasaki T, Shizume K, Nakahara M, et al.** 1984 Age related changes in plasma growth hormone response to growth hormone releasing factor in man. J Clin Endocrinol Metab. 58:212–214.
17. **Florini JR, Prinz PN, Vitiello MV, Hintz RL.** 1985 Somatomedin-C levels in healthy young and old men: relationship to peak and 24-hour integrated levels of growth hormone. J Gerontol. 40:2–7.
18. **Zadik Z, Chalew SA, McCarter RJ, Meistas M, Kowarski AA.** 1985 The influence of age on the 24-hour integrated concentration of growth hormone in normal individuals. J Clin Endocrinol Metab. 60:513–516.
19. **Ho KY, Evans WS, Blizzard RM, et al.** 1987 Effects of sex and age on the 24-hour profile of growth hormone secretion in man: importance of endogenous estradiol concentrations. J Clin Endocrinol Metab. 64:51–58.
20. **Iranmanesh A, Lizarralde G, Veldhuis JD.** 1991 Age and relative obesity are specific negative determinants of the frequency and amplitude of growth hormone (GH) secretory bursts and the half-life of endogenous GH in healthy men. J Clin Endocrinol Metab. 73:1081–1088.
21. **Veldhuis JD, Iranmanesh A, Ho KKY, Waters MJ, Johnson ML, Lizarralde G.** 1991 Dual defects in pulsatile growth hormone secretion and clearance subserve the hyposomatotropism of obesity in man. J Clin Endocrinol Metab. 72:51–59.
22. **Rudman D.** 1985 Growth hormone, body composition and aging. J Am Geriatr Soc. 33:800–807.
23. **Sizonenko PC, Rabinovitch A, Schneider P, Paunier L, Wollheim CB, Zahnd G.** 1975 Plasma growth hormone, insulin and glucagon responses to arginine infusion in children and adolescents with idiopathic short stature, isolated growth hormone deficiency, panhypopituitarism and anorexia nervosa. Pediatr Res. 9:733–738.
24. **Ghigo E, Goffi S, Nicolosi M, et al.** 1990 Growth hormone responsiveness to combined administration of arginine and GH-releasing hormone does not vary with age in man. J Clin Endocrinol Metab. 71:1481–1485.
25. **Toogood AA, Beardwell CG, Shalet SM.** 1994 The severity of growth hormone deficiency in adults with pituitary disease is related to the degree of hypopituitarism. Clin Endocrinol (Oxf). 41:511–516.
26. **Landin-Wilhelmsen K, Wilhelmsen L, Lappas G, et al.** 1994 Serum insulin-like growth factor I in a random population sample of men and women: relation to age, sex, smoking habits, coffee consumption and physical activity, blood pressure and concentrations of plasma lipids, fibrinogen, parathyroid hormone and osteocalcin. Clin Endocrinol (Oxf). 41:351–357.
27. **Kalk WJ, Vinik AI, Pimstone BL, Jackson WP.** 1973 Growth hormone responses to insulin hypoglycaemia in the elderly. J Gerontol. 28:431–433.
28. **Laron Z, Doron M, Amikam B.** 1970 Plasma growth hormone in men and women over 70 years of age. Med Sport. 4:126–131.
29. **Muggeo M, Feddele D, Tiengo A, Molinari M, Crepaldi G.** 1975 Human growth hormone and cortisol responses to insulin stimulation in ageing. J Gerontol. 30:546–551.
30. **Pavlov EP, Harman SM, Merriam GR, Gelato MC, Blackman MR.** 1986 Responses of growth hormone and somatomedin-C to GH-releasing hormone in healthy aging men. J Clin Endocrinol Metab. 62:595–600.
31. **Lang I, Schernthaner G, Pietschmann P, Kurz R, Stephenson JM, Templ H.** 1987 Effects of sex and age on growth hormone response to growth hormone-releasing hormone in healthy individuals. J Clin Endocrinol Metab. 65:535–540.
32. **Zapf J, Walter H, Froesch ER.** 1981 Radioimmunological determination of insulin-like growth factors I and II in normal subjects and in patients with growth disorders and extrapancreatic tumour hypoglycaemia. J Clin Invest. 68:1321–1330.
33. **Rudman D, Feller AG, Nagraj HS, et al.** 1990 Effects of human growth hormone in men over 60 years old [see comments]. N Engl J Med. 323:1–6.
34. **Cohn L, Feller AG, Draper MW, Rudman IW, Rudman D.** 1993 Carpal tunnel syndrome and gynaecomastia during growth hormone treatment of elderly men with low circulating IGF-1 concentrations. Clin Endocrinol (Oxf). 39: 417–425.