ance, hyperinsulinemia, and insulin resistance and raised NEFA levels at 1 wk; modest hyperinsulinemia persisted for 3 months in iv glucose tolerance test. The result of OGTT in the present study showed that five patients in each group had an IGT, although no one developed overt diabetes. This might indicate that 20K-hGH has a similar potency to 22K-hGH in inducing insulin resistance in adult GHD. We previously showed that the diabetic activity of recombinant 20K-hGH is much weaker than 22K-hGH in rats (15). The reason for the difference between rats and humans remains to be determined. It is known that there is a difference in the distribution of GH receptors in major target organs of GH, especially in the liver, between rats and humans. This may be responsible for the discrepancy. Although it has been reported that 20K-hGH has less affinity to GHBP when compared with 22K-hGH, the binding to circulating GHBPs was not investigated in this study. Furthermore, it has been shown that 20K-hGH is likely to form an active 1:2 complex (hGH:hGHR) in a way similar to 22K-hGH but has difficulty in forming an inactive 1:1 complex. The reason 20K-hGH does not show the characteristics that are revealed in cells and animal models has to be clarified in connection with the above molecular biological knowledge in further studies.

We found in this study that serum AST, ALT, or γ-GTP increased in some patients treated with 20K-hGH. None of them was alcoholic, and the liver enzyme values were in normal range in the test carried out immediately before the present study. In another series of studies using 52 patients, we have found that approximately 50% of the patients with GHD have fatty liver as judged by ultrasonographic findings, associated with slight and transient elevation in liver enzymes (our unpublished observation). We presume that the elevated liver enzymes may be due to the fatty liver. It appears that 20K-hGH is not involved in the liver dysfunction because these abnormalities normalized despite continuous treatment with GH. Therefore, these changes should be monitored carefully in the further studies, although all abnormal values returned to normal range without any medical treatment in this study.

Taken together, the results presented here have demonstrated for the first time that recombinant 20K-hGH has metabolic effects comparable to 22K-hGH in human GHD subjects. The biological potency appears to be equal to that of 22K-hGH. 20K-hGH was able to normalize serum IGF-I levels at a dose as low as 0.006 mg/kg·d. Incidence of unfavorable effects was also similar to that reported for 22K-hGH. We suggest that recombinant 20K-hGH could be used in the treatment of patients with GHD. However, further studies are required to investigate the optimum dose and superiority of 20K-hGH over 22K-hGH. This should be clarified in a comparative study.

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Address all correspondence and reprint requests to: Mr. Masakane Hayakawa, Project Management Department, R&D Operations, Nihon Schering K.K., 6-64, Nishimiyahara 2-chome, Yodogawa-ku, Osaka 532-0004, Japan. E-mail: mahayakawa@schering.co.jp.

References

1. **DeNoto FM, Moore DD, Goodman HM** 1981 Human growth hormone DNA sequence and mRNA structure: possible alternative splicing. Nucleic Acids Res 9:3719–3730
2. **Tsushima T, Katoh Y, Miyachi Y, Chihara K, Teramoto A, Irie M, Hashimoto Y** 1999 Serum concentration of 20K human growth hormone (20K hGH) measured by a specific enzyme-linked immunosorbent assay. Study Group of 20K hGH. J Clin Endocrinol Metab 84:317–322
3. **Ishikawa M, Yokoya S, Tachibana K, Hasegawa Y, Yasuda T, Tokuhiro E, Hashimoto Y, Tanaka T** 1999 Serum levels of 20-kilodalton human growth hormone (GH) are parallel those of 22-kilodalton human GH in normal and short children. J Clin Endocrinol Metab 84:98–104
4. **Uchida H, Naito N, Asada N, Wada M, Ikeda M, Kobayashi H, Asanagi M, Mori K, Fujita Y, Konda K, Kusuhara N, Kamioka T, Nakashima K, Honjo M** 1997 Secretion of authentic 20-kDa human growth hormone (20K hGH) in *Escherichia coli* and properties of the purified product. J Biotechnol 55:101–112
5. **Wada M, Ikeda M, Takahashi Y, Asada N, Chang KT, Takahashi M, Honjo M** 1997 The full agonistic effect of recombinant 20 kDa human growth hormone (hGH) on CHO cells stably transfected with hGH receptor cDNA. Mol Cell Endocrinol 133:99–107
6. **Wada M, Uchida H, Ikeda M, Tsunekawa B, Naito N, Banba S, Tanaka E, Hashimoto Y, Honjo M** 1998 The 20-kilodalton (kDa) human growth hormone (hGH) differs from the 22-kDa hGH in the complex formation with cell surface hGH receptor and hGH-binding protein circulating in human plasma. Mol Endocrinol 12:146–156
7. **Tsunekawa B, Wada M, Ikeda M, Uchida H, Naito N, Honjo M** 1999 The 20-kilodalton (kDa) human growth hormone (hGH) differs from the 22-kDa hGH in the effect on the human prolactin receptor. Endocrinology 140:3909–3918
8. **Ishikawa M, Tachibana T, Kamioka T, Horikawa R, Katsumata N, Honjo M, Tanaka T** 2000 Comparison of the somatogenic action of 20 kDa- and 22 kDa-human growth hormones in spontaneous dwarf rats. Growth Horm IGF Res 10:199–206
9. **Asada N, Takahashi Y, Wada M, Naito N, Uchida H, Ikeda M, Honjo M** 2000 GH induced lipolysis stimulation in 3T3–L1 adipocytes stably expressing hGHR: analysis on signaling pathway and activity of 20K hGH. Mol Cell Endocrinol 162:121–129
10. **Wang DS, Sato K, Demura H, Kato Y, Maruo N, Miyachi Y** 1999 Osteoanabolic effects of human growth hormone with 22K- and 20K Daltons on human osteoblast-like cells. Endocr J 46:125–132
11. **Salomon F, Cuneo RC, Hesp R, Sonksen PH** 1989 The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. N Engl J Med 321:1797–1803
12. **Whitehead HM, Boreham C, McIlrath EM, Scheridan B, Kennedy L, Atkinson AB, Hadden DR** 1992 Growth hormone treatment of adults with growth hormone deficiency: results of a 13-month placebo controlled cross-over study. Clin Endocrinol (Oxf) 36:45–52
13. **Bengtsson BA, Eden S, Lohn L, Kvist H, Stokland A, Lindstedt G, Bosaeus I, Tolli J, Sjostrom L, Isaksson OG** 1993 Treatment of adults with growth hormone (GH) deficiency with recombinant human GH. J Clin Endocrinol Metab 76:309–317
14. **Satozawa N, Takezawa K, Miwa T, Takahashi S, Hayakawa M, Ooka H** 2000 Differences in the effects of 20 K- and 22 K-hGH on water retention in rats. Growth Horm IGF Res 10:187–192
15. **Takahashi S, Shiga Y, Satozawa N, Hayakawa M** 2001 Diabetogenic activity of 20 kDa human growth hormone (20K-hGH) and 22K-hGH in rats. Growth Horm IGF Res 11:110–116
16. **Hashimoto Y, Kamioka T, Hosaka M, Mabuchi K, Mizuchi A, Shimazaki Y, Tsunoo M, Tanaka T** 2000 Exogenous 20K growth hormone (GH) suppresses endogenous 22K GH secretion in normal men. J Clin Endocrinol Metab 85: 601–606
17. **Kuzuya T, Nakagawa S, Satoh J, Kanazawa Y, Iwamoto Y, Kobayashi M, Nanjo K, Sasaki A, Seino Y, Ito C, Shima K, Nonaka K, Kadowaki T** 1999 Report of the Committee of Japan Diabetes Society of the classification and diagnostic criteria of diabetes mellitus. J Jpn Diabet Soc 42:385–404
18. **Tanaka K, Nakadomo F, Watanabe K, Inagaki A, Kim HK, Matsuura Y** 1992 Body composition prediction equations based on bioelectrical impedance and anthropometric variables for Japanese obese women. Am J Hum Biol 4:739–745
19. **Teichholz LE, Kreulen T, Herman MV, Gorlin R** 1976 Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence of absence of asynergy. Am J Cardiol 37:7–11
20. **Devereux RB, Reichek N** 1977 Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation 55:613–618
21. **Fukuhara S, Bito S, Green J, Hsiao A, Kurokawa K** 1998 Translation, adap-

tation, and validation of the SF-36 Health Survey for use in Japan. J Clin Epidemiol 51:1037–1044
22. **Krauss RM, Burke DJ** 1982 Identification of multiple subclasses of plasma low density lipoproteins in normal humans. J Lipid Res 23:97–104
23. **Austin MA, Breslow JL, Hennekens CH, Buring JE, Willett WC, Krauss RM** 1988 Low-density lipoprotein subclass patterns and risk of myocardial infarction. JAMA 260:1917–1921
24. **Degerblad M, Bengtsson BA, Bramnert M, Johnell O, Manhem P, Rosen T, Thoren M** 1995 Reduced bone mineral density in adults with growth hormone (GH) deficiency: increased bone turnover during 12 months of GH substitution therapy. Eur J Endocrinol 133:180–188
25. **Hansen TB, Brixen K, Vahl N, Jorgensen JO, Christiansen JS, Mosekilde L, Hagen C** 1996 Effects of 12 months of growth hormone (GH) treatment on calciotropic hormones, calcium homeostasis, and bone metabolism in adults with acquired GH deficiency: a double blind, randomized, placebo-controlled study. J Clin Endocrinol Metab 81:3352–3359
26. **Amato G, Carella C, Frazio S, La Montagna G, Cittadini A, Sabatini D, Marciano-Mone C, Sacca L, Bellastella A** 1993 Body composition, bone metabolism, and heart structure and function in growth hormone (GH)-deficient adults before and after GH replacement therapy at low doses. J Clin Endocrinol Metab 77:1671–1676
27. **Jorgensen JO, Pedersen SA, Thuesen L, Jorgensen J, Ingemann-Hansen T, Skakkebaek NE, Christiansen JS** 1989 Beneficial effects of growth hormone treatment in GH-deficient adults. Lancet 1:1221–1225
28. **Holmes SJ, Whitehouse RW, Seindell R, Economou G, Adams JE, Shalet SM** 1995 Effect of growth hormone replacement on bone mass in adults with adult-onset growth hormone deficiency. Clin Endocrinol (Oxf) 42:627–633
29. **O'Neal DN, Kalfas A, Dunning PL, Christopher MJ, Sawyer SD, Ward GM, Alford FP** 1994 The effect of 3 months of recombinant human growth hormone (GH) therapy on insulin and glucose-mediated glucose disposal and insulin secretion in GH-deficient adults: a minimal model analysis. J Clin Endocrinol Metab 79:975–983
30. **Attanasio AF, Lamberts SW, Matranga AM, Birkett MA, Bates PC, Valk NK, Hilsted J, Bengtsson BA, Strasburger CJ** 1997 Adult growth hormone (GH)-deficient patients demonstrate heterogeneity between childhood onset and adult onset before and during human GH treatment. Adult Growth Hormone Deficiency Study Group. J Clin Endocrinol Metab 82:82–88
31. **Merola B, Cittadini A, Colao A, Longobardi S, Fazio S, Sabatini D, Sacca L, Lombardi G** 1993 Cardiac structural and functional abnormalities in adult patients with growth hormone deficiency. J Clin Endocrinol Metab 77:1658–1661
32. **Colao A, Cuocolo A, Di Somma C, Cerbone G, Della Morte AM, Nicolai E, Lucci R, Salvatore M, Lombardi G** 1999 Impaired cardiac performance in elderly patients with growth hormone deficiency. J Clin Endocrinol Metab 84:3950–3955
33. **Colao A, di Somma C, Pivonello R, Cuocolo A, Spinelli L, Bonaduce D, Salvatore M, Lombardi G** 2002 The cardiovascular risk of adult GH deficiency (GHD) improved after GH replacement and worsened in untreated GHD: a 12-month prospective study. J Clin Endocrinol Metab 87:1088–1093
34. **Jorgensen JO, Thuesen L, Muller J, Ovesen P, Skakkebaek NE, Christiansen JS** 1994 Three years of growth hormone treatment in growth hormone-deficient adults: near normalization of body composition and physical performance. Eur J Endocrinol 130:224–228
35. **McGauley GA** 1989 Quality of life assessment before and after growth hormone treatment in adults with growth hormone deficiency. Acta Paediatr Scand Suppl 356:70–72
36. **Moller J, Jorgensen JO, Moller N, Hansen KW, Pedersen EB, Christiansen JS** 1991 Expansion of extracellular volume and suppression of atrial natriuretic peptide after growth hormone administration in normal man. J Clin Endocrinol Metab 72:768–772
37. **Hoffman DM, Crampton L, Sernia C, Nguyen TV, Ho KK** 1996 Short-term growth hormone (GH) treatment of GH-deficient adults increases body sodium and extracellular water, but not blood pressure. J Clin Endocrinol Metab 81:1123–1128
38. **Shimomura Y, Lee M, Oku J, Bray GA, Glick Z** 1982 Sodium potassium dependent ATPase in hypophysectomized rats: response to growth hormone, triiodothyronine, and cortisone. Metabolism 31:213–216
39. **Davidson MB** 1987 Effect of growth hormone on carbohydrate and lipid metabolism. Endocr Rev 8:115–131

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CLINICAL STUDY

Adult GH deficiency in Japanese patients: effects of GH treatment in a randomised, placebo-controlled trial

Kazuo Chihara, Ekaterina Koledova[1], Akira Shimatsu[2], Yuzuru Kato[3], Hitoshi Kohno[4], Toshiaki Tanaka[5], Akira Teramoto[6], Peter C Bates[7] and Andrea F Attanasio[8]

Department of Clinical Molecular Medicine, Kobe University Graduate School of Medicine, Kobe, Japan, [1]Eli Lilly Japan K.K., Kobe, Japan, [2]Clinical Research Centre for Endocrine and Metabolic Disease, Kyoto Medical Centre, Kyoto, Japan, [3]Division of Endocrinology, Metabolism, Hematology and Oncology, Shimane University, Izumo, Japan, [4]Department of Endocrinology and Metabolism, Fukuoka Children's Hospital, Fukuoka, Japan, [5]Division of Endocrinology and Metabolism, National Centre for Child Health and Development, Tokyo, Japan, [6]Department of Neurosurgery, Nippon Medical School, Tokyo, Japan, [7]Cambridge Medical Writing Services, Ickleton, CB10 1SH, UK and [8]Cascina del Rosone, Agliano Terme, Italy

(Correspondence should be addressed to K Chihara; Email: chiharak@med.kobe-u.ac.jp)

Abstract

Objective: To evaluate the influence of factors intrinsic to the Japanese population on consequences of growth hormone deficiency (GHD) and effects of GH treatment in adult Japanese hypopituitary patients with GHD.

Study design: A 24-week, randomised, placebo-controlled, double-blind study in 64 patients in Japan, with GHD onset during adulthood (AO; $n = 27$) or childhood (CO; $n = 37$). Body composition measured by dual-energy X-ray absorptiometry (DXA) was evaluated centrally. Serum IGF-I, IGF binding protein-3 (IGFBP-3) and lipid levels were determined centrally.

Results: In contrast to Caucasian patients, there were no significant differences before treatment between AO and CO patients for body mass index (BMI), lean body mass (LBM) and fat mass (FM). Baseline BMI was $\geq 25\,kg/m^2$ for 32.8% of patients. For all patients combined, a significant increase in LBM and decrease in FM ($P < 0.001$ for each) was seen with GH treatment. Serum IGF-I and IGFBP-3 were significantly lower at baseline in CO compared with AO patients, similar to Caucasian patients, and were increased in both onsets following GH treatment. Serum total and low-density lipoprotein (LDL)-cholesterol concentrations did not differ between AO and CO patients at baseline and were elevated compared with normal ranges. GH-induced decreases were significant compared with placebo for both total ($P = 0.036$) and LDL-cholesterol ($P = 0.040$). Glycosylated haemoglobin was increased with GH compared with placebo treatment ($P = 0.016$) but remained within the upper limit of normal for all patients at endpoint.

Conclusions: Adult Japanese hypopituitary patients with GHD demonstrated obesity relative to healthy Japanese subjects but the clinical presentation differed from that of Caucasian patients. GH treatment improved body composition and serum cholesterol profiles of adult Japanese hypopituitary patients with GHD.

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Introduction

The clinical features of adult hypopituitarism and growth hormone deficiency (GHD) and its long-term consequences have been thoroughly described in Caucasian subjects (1), and the efficacy of growth hormone (GH) replacement is now well established in Western countries (2, 3). In Japanese subjects, the assessment of the adult GHD syndrome and its implications should take into account their different genetic and environmental backgrounds; for example, the overall incidence of atherosclerosis, one of the major postulated consequences of adult GHD, is considerably lower in Japan than in Western countries (4).

The clinical relevance of the adult GHD syndrome and its complications in Japan has recently been investigated by epidemiological surveys sponsored by the Japanese government. According to the 2001 Annual Report of the Study Group on the Epidemiology of Pituitary Diseases (5), it was estimated that in the year 2000 there were approximately 7000 adult patients with hypopituitarism who had been referred to clinicians for treatment. It was also estimated (6) that up to 1995 there were nearly 29 000 Japanese short stature children registered for paediatric GH treatment, some of whom will require further GH replacement as adults.

In a study of adult Japanese patients with hypopituitarism, the 507 patients established to be GHD had higher prevalence of angina pectoris, myocardial infarction, hypertension and hyperlipidaemia compared with the 362 who had non-GHD hypopituitarism (7). Although there was no significant difference between

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the two groups in number and cause of death, the mean age at death of patients with GHD was a decade younger than that of non-GHD patients (7). One very recent study showed that Japanese patients with childhood onset (CO) or adult onset (AO) GHD had an increased intima-media thickness of the carotid artery (8), a finding consistent with data reported in adult Caucasians with GHD (9).

These reports indicate that the adult GHD syndrome is a relevant clinical entity in Japanese subjects and, similar to Caucasians, its consequences have a significant impact on health outcomes and public health consumption. On the other hand, few studies of GH treatment in adult Japanese GHD subjects have been performed (10). In the present paper we report the results of a study carried out in Japanese patients suffering from the adult GHD syndrome. An interpretation of the baseline clinical data of the patients using criteria validated for the Japanese population is presented in addition to efficacy data under GH replacement.

Patients and methods

This was a 24-week, randomised, placebo-controlled, double-blind study performed in 25 Japanese study centres. All patients gave informed consent and the study was performed with appropriate ethical approval and according to the Declaration of Helsinki. Japanese patients aged 18–64 years, with organic or idiopathic, isolated or multiple, CO as well as AO GHD were recruited. AO patients were defined as having onset of GHD at 18 years or older and CO patients as having onset before 18 years of age; 29 of the 37 CO patients enrolled in the study had been treated with GH during childhood. For diagnosis of GHD, patients had to have a serum GH peak $<3.0\,\mu g/l$ in a GH stimulation test (insulin tolerance, arginine or glucagon test). Replacement therapy for other missing hormones was stable and adequate for thyroid, vasopressin, and glucocorticoid during the 3 months prior to entering the study and throughout the study. In hypogonadal females, oestrogen replacement had to be adequate for at least 3 months and was continued during the study if they were younger than 40 years of age; if between 40 and 55 years of age no change in previous oestrogen replacement was permitted for 3 months prior to commencing the study and for those of 55 years or more oestrogen was discontinued at least 3 months before starting the study. Androgen replacement in males was stable throughout the study and was performed according to the physician's judgement and patients' acceptance, conforming to current medical practice in Japan; two males (CO 39 years, AO 59 years) in the GH group and five males in the placebo group (CO 18 years, CO 32 years, AO 48 years, AO 59 years, AO 63 years) were not on androgen replacement during the study. Malignancy, diabetes, severe organ dysfunction and severe hypertension were major exclusion criteria.

A total of 64 eligible patients were enrolled and baseline assessments were carried out during the following 4 weeks. Patients were then assigned to treatment with either recombinant human GH (Humatrope, Eli Lilly and Company, Indianapolis, IN, USA) or placebo by a randomly stratified method using onset of GHD as the stratifying factor, and was further balanced by gender and age with a minimisation method (11). The GH was administered by cartridge pens and placebo was matched by giving excipient solution using the same number of clicks of the pen. By this means, both the investigating physician and the patients were blinded to study treatment. GH was started at 0.021 mg/kg/week (3.0 μg/kg/day) for the first 4 weeks and then increased stepwise to 0.042 mg/kg/week for 8 weeks and a final dose of 0.084 mg/kg/week (12.0 μg/kg/day) for the last 12 weeks. In the event of GH-induced side effects, dose reduction by 25–50% was permitted at the physician's discretion.

Patients attended for clinic visits at the time of starting GH treatment and then at weeks 4, 8, 12 and 24. At the baseline and 24-week visits, lean body mass (LBM) and fat mass (FM) were measured by dual-energy X-ray absorptiometry (DXA). All DXA measurements performed in each investigative centre were evaluated centrally in a blinded fashion (Dept. of Radiology, Kawasaki Medical School, Kurashiki-city, Okayama, Japan). Serum insulin-like growth factor (IGF)-I and IGF binding protein (IGFBP)-3 concentrations as well as triglycerides and total, high- and low-density lipoprotein (HDL and LDL)-cholesterol levels were measured centrally (BML Inc., Shibuya-ku, Tokyo, Japan). IGF-I and IGFBP-3 were determined by standard immunoradiometric assays; cholesterol concentrations were determined by enzymatic methods.

Safety was assessed by the recording of treatment-emergent adverse events (TEAE), coded according to the MedDRA system, and by evaluation of laboratory test values and blood pressure. Laboratory determinations were performed centrally and included measurements of liver and kidney function, thyroid hormones and glycosylated haemoglobin concentrations.

Standard deviation scores (S.D. scores) were calculated from serum IGF-I and IGFBP-3 concentrations by comparison with age- and gender-matched subjects, and from height at baseline by comparison with 18-year-old gender-matched subjects, from a Japanese healthy reference population (12). All results were analysed on an intent-to-treat basis and assessed at a 2-sided significance level of 5%. Baseline comparisons between placebo and GH treatment were carried out using Wilcoxon tests or chi-square tests. A paired *t*-test or Wilcoxon signed-rank test was used to assess the difference between baseline and the end of the study for each treatment group. Student's *t*-test or Wilcoxon rank sum

test was used to test differences between the two groups. Examinations of gender and onset effects and interaction with treatment were carried out using ANOVA. SAS version 8.2 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

Results

Baseline data

The baseline demographic, anthropometric, diagnostic and body composition data of the patients is presented in Table 1. AO patients were older than CO patients and the duration of GHD was longer in CO than in AO patients. All except one AO patient had multiple pituitary hormone deficiencies. Hypopituitarism was due to tumours for most of the patients and an idiopathic cause only occurred in the CO patients. Height S.D. scores were comparable between AO and CO patients. The AO and CO patients were also similar in terms of body composition, with no significant difference between onsets for body mass index (BMI) (23.9±3.7 and 24.1±4.9 kg/m^2 for AO and CO respectively; $P = 0.683$), FM (21.2±6.6 and 21.1±7.9 kg; $P = 0.654$) and LBM (38.2±9.1 and 40.9±10.4 kg; $P = 0.348$). A baseline BMI value of 25 kg/m^2 or greater was recorded for 32.8% of the study population (AO 29.6% (8/27 patients), CO 35.1% (13/37 patients)).

In contrast to body composition, significantly lower values were observed in CO than in AO patients for IGF-I and IGFBP-3 concentrations and S.D. scores. Baseline IGF-I S.D. scores were within ±1.96 for 77.8% of AO patients but only 13.5% of CO patients. The IGF-I and IGFBP-3 S.D. scores were also lower in females than males (Table 2). The mean peak GH values in the stimulation tests ranged from 0.1 to 2.7 μg/l and overall were slightly higher in the AO (0.5±0.7 μg/l) compared with the CO (0.3±0.3 μg/l; P=0.053) group. The GH and placebo groups were well balanced within both AO and CO patients for all parameters.

Baseline values for serum total cholesterol and LDL-cholesterol concentrations were similar in the AO and CO patients (Table 3) and mean values were close to or above the upper limits of the normal ranges. Serum total cholesterol values were >240 mg/dl for 10 (37.0%) AO patients and 8 (21.6%) CO patients.

Efficacy data

The average GH doses at 4 weeks and 8 weeks were as described in the methodology, at 0.021 and 0.042 mg/kg/week respectively. At the end of the 24-week study period, the mean dose in the GH-treated patients was 0.078±0.015 mg/kg/week (range 0.021–0.085). The median doses were the same for AO and CO patients at endpoint although the mean was slightly lower in AO patients (0.071± 0.022 mg/kg/week) owing to dose reductions due to adverse events in four patients.

For all patients combined, a statistically significant ($P < 0.001$) increase in LBM was seen after 24 weeks in the GH-treated patients compared with almost no change in the placebo-treated group (4.7±3.9% versus −0.5±4.1%; $P < 0.001$; Fig. 1). In parallel, a significant decrease in FM was observed for GH compared

Table 1 Baseline characteristics of Japanese adult onset (AO) and childhood onset (CO) GH deficient patients, by assigned treatment group (means±S.D.).

	AO patients		CO patients		
	GH ($n = 14$)	Placebo ($n = 13$)	GH ($n = 19$)	Placebo ($n = 18$)	*P*-value[a]
Age (years)	48.7±11.5	53.0±7.2	28.6±8.1	28.9±6.7	<0.001
Age at onset (years)	33.9±10.0	43.4±10.8	12.2±7.7	10.7±4.8	<0.001
Male/female	5/9	4/9	11/8	11/7	—
Isolated/multiple[b]	0/14	1/12	0/19	0/18	—
Diagnosis					
Idiopathic	—	—	6	9	—
Tumour[c]	12	10	11	9	
Sheehan syndrome	2	2	—	—	
Empty sella	—	1	1	—	
Trauma	—	—	1	—	
Height S.D. score	−0.25±0.89	−0.46±1.25	−0.17±1.21	−0.45±0.85	0.870
BMI (kg/m^2)	24.3±3.6	23.6±3.8	24.9±5.1	23.2±4.7	0.683
LBM (kg)	39.4±10.0	36.9±8.3	41.4±9.7	40.5±11.3	0.348
FM (kg)	21.5±7.4	20.9±6.0	22.9±8.0	19.1±7.7	0.654
Peak GH (μg/l)[d]	0.5±0.7	0.5±0.8	0.2±0.2	0.3±0.4	0.053
IGF-I (μg/l)	89±54	95±47	48±30	58±45	<0.001
IGF-I S.D. score	−1.12±1.15	−0.73±0.93	−3.37±1.69	−2.98±1.24	<0.001
IGFBP-3 (mg/l)	2.5±1.1	2.5±1.0	1.6±0.7	1.7±0.9	<0.001
IGFBP-3 S.D. score	−1.84±2.83	−1.58±2.73	−5.15±3.16	−4.52±3.21	<0.001

[a] *P*-value for AO vs CO patients for combined treatment groups; [b] isolated GHD or mutiple pituitary deficiencies; [c] includes pituitary adenoma, craniopharyngioma, glioma, germ cell cencer; [d] in standard stimulation tests.

Table 2 Changes in IGF-I and IGFBP-3 S.D. score values after 24 weeks of GH or placebo in Japanese GHD patients (means±S.D.).

		AO patients		CO patients	
		Male ($n = 9$)	Female ($n = 18$)	Male ($n = 22$)	Female ($n = 15$)
IGF-I S.D. score					
GH	Baseline	−0.68±1.04	−1.37±1.20	−2.59±0.81	−4.43±2.04
	Change	4.56±0.47	2.59±2.15	2.75±1.56	3.93±2.01
Placebo	Baseline	−0.00±0.51	−1.05±0.91	−2.51±1.38	−3.71±0.44
	Change	−0.98±0.78	−0.19±0.54	−0.00±0.40	0.02±0.59
IGFBP-3 S.D. score					
GH	Baseline	−0.77±1.64	−2.43±3.25	−4.57±2.71	−5.96±3.73
	Change	2.21±1.19	2.50±1.84	4.00±2.94	4.67±2.48
Placebo	Baseline	0.38±1.48	−2.46±2.75	−4.37±3.93	−4.75±1.82
	Change	−0.06±0.27	−0.28±1.28	−0.20±1.68	−0.65±1.66

Table 3 Serum total and LDL-cholesterol concentrations at baseline and after 24 weeks of GH or placebo treatment in Japanese GHD patients (means±S.D.).

		AO patients		CO patients	
		Male ($n = 9$)	Female ($n = 18$)	Male ($n = 22$)	Female ($n = 15$)
Total cholesterol (mg/dl)					
GH	Baseline	207±34	237±37	221±54	209±37
	24-weeks	171±16	215±28	210±43	212±43
	Change	−36±30	−22±22	−11±40	4±31
Placebo	Baseline	229±18	226±40	190±47	203±15
	24-weeks	235±19	226±56	205±46	209±36
	Change	7±21	−0±39	15±53	6±27
LDL-cholesterol (mg/dl)					
GH	Baseline	121±31	142±49	130±35	112±31
	24-weeks	97±20	125±41	126±30	122±36
	Change	−24±26	−17±16	−4±29	11±27
Placebo	Baseline	147±46	138±37	116±39	99±29
	24-weeks	153±31	146±44	123±24	112±34
	Change	6±23	8±33	7±31	13±20

Normal ranges: total cholesterol 150–219 mg/dl; LDL-cholesterol 70–139 mg/dl.

with little change with placebo treatment (−9.2±11.8% versus 1.1±6.9%; $P < 0.001$; Fig. 1). The increases in LBM and decreases in FM were significantly greater with GH treatment compared with placebo treatment for both AO and CO patients (Table 4).

Serum IGF-I levels increased significantly ($P < 0.001$) in the GH-treated group from 65±46 μg/l to 240±115 μg/l after 24 weeks, with very little change (−8±25 μg/l) in the placebo group. Expressed as S.D. score, the average change with GH treatment for all patients was 3.26±1.85 S.D., which resulted in a normalisation of the mean IGF-I S.D. score (from −2.42±1.85 S.D. to 0.85±2.29 S.D.; $P < 0.001$). When analysed by subgroup, there was no significant effect of time of onset or gender on the changes in IGF-I S.D. score (Table 2). However, the change was greatest in AO male patients and the mean endpoint value in AO males was well above the normal population. All five GH-treated AO male patients had IGF-I S.D. scores greater than +1.96 either at endpoint or at some period during the study;

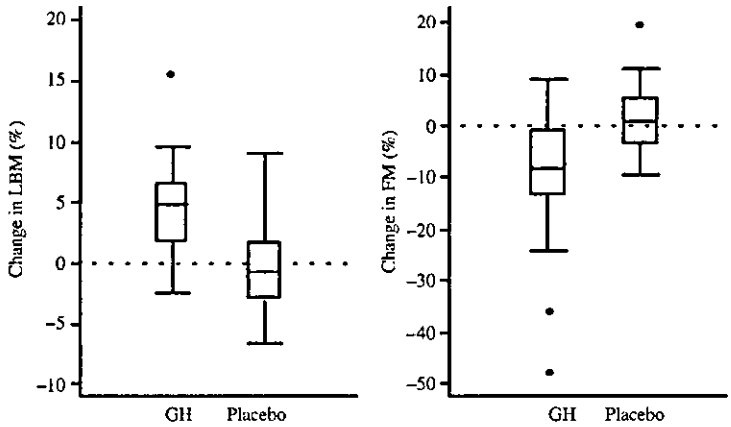

Figure 1 Percentage changes from baseline in lean body mass (LBM) and fat mass (FM) determined by dual-energy X-ray absorptiometry, in Japanese GHD patient treated for 24 weeks with either GH or placebo. The bottom and top edges of the boxes indicate the 25th and 75th percentiles respectively and the horizontal line shows the 50th percentile (median); the vertical lines, or whiskers, extend from the box as far as the data extend, to a distance of at most 1.5 interquartile ranges; values more extreme than this are marked with plot symbols.

Table 4 Changes from baseline in lean body mass (LBM) and fat mass (FM) after 24 weeks of treatment with GH or placebo; *P*-values are for treatment differences within onsets (means±S.D.).

	AO patients			CO patients		
	GH ($n = 13$)	Placebo ($n = 12$)	*P*-value	GH ($n = 19$)	Placebo ($n = 17$)	*P*-value
LBM change (%)	5.5±3.2	−2.0±3.8	<0.001	4.2±4.3	0.6±4.1	0.014
FM change (%)	−7.2±7.1	2.2±8.1	0.005	−10.5±14.2	0.4±6.0	0.006

in addition, three of the nine female AO patients had an IGF-I S.D. score greater than +1.96 during GH treatment. On the other hand, there were no patients who had a combination of an IGF-I exceeding +1.96 S.D. score and an IGFBP-3 below −1.96 S.D. score at any time during treatment (data not shown).

Serum total cholesterol significantly decreased from 220±43 mg/dl to 206±38 mg/dl ($P = 0.025$) in the GH-treated group and the difference between the groups for the change after 24 weeks was significant (GH: −14±34 versus placebo: 7±39 mg/dl; $P = 0.036$). Similar and parallel changes were seen in LDL-cholesterol concentrations and, although the decrease in the GH-treated group did not reach significance, the difference between the groups for the change after 24 weeks was significant (GH: −7±27 versus placebo: 9±27 mg/dl; $P = 0.040$). There were no significant within-group changes or between-group differences for HDL-cholesterol or triglyceride concentrations (data not shown). In a separate analysis, the GH-treatment effect was examined in patients who had serum total cholesterol values either below the upper limit of the normal range or higher than normal at baseline. This analysis (Fig. 2), showed that the GH-treatment effect occurred essentially in patients with high cholesterol levels at baseline and there was almost no change in those who had a baseline value within or below the normal range. The same trends were seen for LDL-cholesterol concentrations (data not shown).

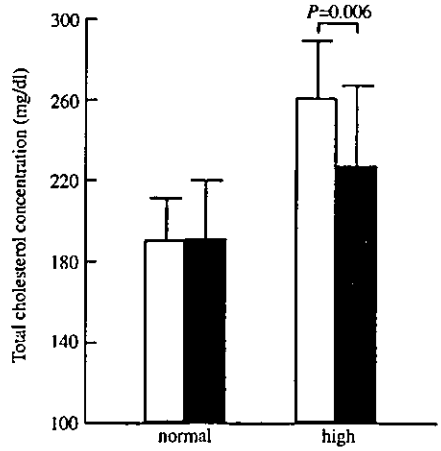

Figure 2 Serum total cholesterol levels at baseline (open bars) and after 24 weeks of GH treatment (solid bars) in Japanese GHD patients with a baseline value either below (normal) or greater than (high) the upper limit of the normal range; values are means ±S.D.; the *P*-value is for the difference between baseline and the 24-week endpoint using the Wilcoxon signed-rank test.

Safety

For TEAEs occurring at a frequency of ≥5%, musculoskeletal and connective tissue disorders (including arthralgia, myalgia, back pain and limb pain) were reported at a significantly higher rate in the GH-treated group compared with the placebo group (39.4% versus 12.9%; $P = 0.016$). Oedema was reported at higher frequency in the GH-treated than in the placebo-treated patients, but the difference was not statistically significant (12.1% versus 6.5%; $P = 0.437$). There was no clinically significant change in systolic or diastolic blood pressure and no difference between treatment groups for changes from baseline.

Levels of free thyroxine (T_4) decreased significanly in the GH-treated group (baseline: 1.5±0.4 ng/dl, 24 weeks: 1.2±0.3 ng/dl; $P < 0.001$) but not the placebo group (baseline: 1.5±0.6 ng/dl, 24 weeks: 1.4±0.3 ng/dl; $P = 0.586$); the difference in the change from baseline was of borderline significance ($P = 0.058$). Glycosylated haemoglobin significantly increased in the GH group (baseline: 4.6±0.4%, endpoint: 4.8±0.4%; $P < 0.001$) and the difference between groups for the change from baseline to 24 weeks was statistically significant (GH: 0.2±0.3% versus placebo: 0.0±0.2%; $P = 0.016$). However, the maximum values remained below the upper limit of normal (5.8%) for all patients at the end of GH treatment.

Discussion

The adult GHD syndrome and its response to GH replacement are well characterised in Caucasians. In Japanese subjects the clinical presentation and the response to GH treatment is likely to be influenced by factors intrinsic to the Japanese population; for example, the prevalence of obesity, one major consequence of adult GHD in Caucasians, has been reported to be lower in Japan than in Western countries. Using the World Health Organisation criteria for obesity, i.e. a BMI value >30 kg/m^2, only 2–3% of the Japanese

population would be considered obese, which is about 10-fold less than for Western populations (13). On the other hand, it has recently been recognised that the frequency of obesity-related complications such as hyperglycaemia, dyslipidaemia and hypertension are already increased in Japanese subjects with a BMI value $\geq 25\,kg/m^2$ (14, 15). Since almost a third of the GHD patients in the present study had a BMI value greater than $25\,kg/m^2$, it follows that risk-associated obesity was a relatively common feature in these patients.

The obesity of the patients was confirmed by the DXA FM values, which were on average 19 to 23 kg at baseline. For both genders, mean values were higher than the average DXA FM values reported in the normal adult Japanese population, which were 14.6 kg in males and 17.3 kg in females for the age range of 20–79 years (16). The mean FM in the present study was also somewhat higher than the baseline bioelectrical impedance FM values of 14–18 kg reported for GHD patients in a previous study of GH replacement therapy in Japanese patients (10).

The baseline serum cholesterol values were consistent with the body composition findings in showing elevated total and LDL-cholesterol concentrations. The Framingham risk model has recently been validated in the Japanese population (17) and epidemiological studies have reported a total cholesterol value >240 mg/dl in 7.6% of the general population. About 30% of the subjects in the present study had a total cholesterol value higher than the Framingham threshold for cardiovascular risk; this would indicate an approximately fourfold increase in risk compared with the general population and confirms our interpretation of the BMI and FM data. High total cholesterol concentrations were reported for hypopituitary patients in a national survey in Japan (18). However, it was reported that the hypercholesterolaemia was associated with untreated gonadotrophin and thyrotrophin deficiencies and not with GHD. The GH status was equivocal since more than half of the patients did not have a stimulation test and this conflicts with published data on Caucasian patients where elevated total and LDL-cholesterol levels were associated specifically with GHD in patients who either had isolated GHD (19) or were adequately replaced with other pituitary hormones (20), similar to the patients in the present study.

Significant differences at presentation in AO compared with CO GHD have been described in Caucasian patients (1, 21). These differences were essentially related to body mass, body composition and IGF-I and IGFBP-3 levels. Interestingly, body mass and composition did not differ between the AO and CO Japanese patients in the present study; this discrepancy may be accounted for by aspects such as modalities of paediatric GH treatment and racial differences in stature and body shape. However, similar to results in Caucasians, IGF-I and IGFBP-3 were lower in CO than in AO patients, confirming that in Japanese subjects the inherent heterogeneity between the two entities also exists.

To date, results from one other double-blind, placebo-controlled study have been published on the effect of GH replacement in Japanese adult GHD patients (10). The duration of GH administration in that study was 4 months and significant changes in body composition, measured by bioelectrical impedance, and in lipid concentrations were observed with treatment. The present study, in which body composition was measured by DXA methodology, confirmed the efficacy of GH replacement in adult Japanese patients in increasing LBM and decreasing FM. The net changes seen in LBM and FM were quantitatively comparable to those reported in adult GHD patients of Caucasian origin (22).

With the fixed dosage regimen used in this study, IGF-I and IGFBP-3 levels were normalised for most patients. Similar to the baseline comparisons, GH-stimulated levels were higher in males than in females and in AO compared with CO patients, consistent with results in Caucasians (21, 22). The increases by gender and time of onset were similar but because CO patients started with lower S.D. scores than AO patients, and females started lower than males, the IGF-I level was elevated in the AO males and this finding may indicate higher sensitivity to GH in males as has been seen in Caucasians (23).

The response seen in serum lipids was in line with findings in Caucasians (1, 21), although the magnitude of the changes seen in total and LDL-cholesterol was limited. On the other hand, mean baseline total and LDL-cholesterol levels in the patients were within the normal range, which may explain the limited response to GH. When analysed by initial status of total cholesterol it was demonstrated that those patients with the highest baseline levels responded most to GH treatment. Because the effect of GH on lipid status has been considered critical to reduce the increased cardio- and cerebrovascular risk associated with adult GHD, it is important to confirm in Japanese patients similar GH effects on lipids as those seen in Caucasians. However, the Japanese population is not fully comparable to the Caucasian population with respect to lipid status; serum cholesterol levels are relatively low in Japan and hypercholesterolaemia as a risk factor is similarly predictive but at a lower level than in Caucasians. Recent studies have indicated that other lipid fractions, such as the very-low-density lipoprotein particles, may be better risk predictors in the Japanese population than total or LDL-cholesterol (24). This aspect should be analysed in future studies with GH replacement in Japanese adult GHD subjects.

The safety profile for the 6 months of GH treatment in these Japanese adult GHD subjects did not reveal any uncommon or unexpected event. The increase in glycosylated haemoglobin seen in the GH-treated group was within the normal range and in line with the known insulin antagonistic effects of GH.

In summary, this study has confirmed that the short term efficacy of GH replacement in Japanese patients, specifically on body composition changes, is comparable to that seen in Caucasians and has a similar safety profile. However, the study has also indicated that adequate clinical assessment of Japanese adult GHD patients requires slightly different evaluation criteria than in Caucasians. Being less obese, the thresholds for cardiovascular risk factors are lower, although still present and responsive to GH replacement.

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References

1 Attanasio AF, Lamberts SWJ, Matranga AMC, Birkett MA, Bates PC, Valk NK, Hilsted J, Bengtsson BA & Strasburger CJ. Adult growth hormone (GH)-deficient patients demonstrate heterogeneity between childhood onset and adult onset before and during human GH treatment. *Journal of Clinical Endocrinology and Metabolism* 1997 **82** 82–88.

2 Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of adults with growth hormone deficiency: summary statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 379–381.

3 Gibney J, Wallace JD, Spinks T, Schnorr L, Ranicar A, Cuneo RC, Lockhart S, Burnand KG, Salomon F, Sonksen PH & Russell-Jones D. The effects of 10 years of recombinant human growth hormone (GH) in adult GH-deficient patients. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 2596–2602.

4 Assmann G, Cullen P, Jossa F, Lewis B & Mancini M. Coronary heart disease: reducing the risk: the scientific background to primary and secondary prevention of coronary heart disease. A worldwide view. International Task Force for the Prevention of Coronary Heart Disease. *Arteriosclerosis, Thrombosis and Vascular Biology* 1999 **19** 1819–1824.

5 Murakami Y, Yokoyama T, Oiso Y & Kato Y. Clinical features of adult hypopituitary patients in a national survey. In *Annual Report of the Japan Study Group on Hypothalamo-Pituitary Disorders*, pp 170–176. Ed. Y Kato. Ministry of Health, Labour and Welfare: Tokyo, 2002 (In Japanese).

6 Tanaka T, Takano K, Hanew K, Nishi Y, Igarashi Y, Hirano T, Saito T, Tachibana K, Yokoya S, Fujieda K, Shimatsu A, Hizuka N, Tsushima T & Irie M. Registration system for growth hormone (GH) treatment with standardized immunoreactive GH values in Japan. *Endocrine Journal* 1998 **45** 459–465.

7 Irie M, Ito Y, Miyashita H & Shirai K. Complications in Japanese adult patients with growth hormone deficiency. In *Annual Report of the Japan Study Group on Hypothalamo-Pituitary Disorders*, pp 37–40. Ed. M Irie. Ministry of Health, Labour and Welfare: Tokyo, 1994 (In Japanese).

8 Murata M, Kaji H, Mizuno I, Sakurai T, Iida K, Okimura Y & Chihara K. A study of carotid intima-media thickness in GH-deficient Japanese adults during onset among adults and children. *European Journal of Endocrinology* 2003 **148** 333–338.

9 Pfeifer M, Verhovec R, Zizek B, Prezelj J, Poredos P & Clayton RN. Growth hormone (GH) treatment reverses early atherosclerotic changes in GH-deficient adults. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 453–457.

10 Irie M, Shizume K, Takano K, Kato Y, Tanaka T & Chihara K. Growth hormone replacement therapy in adults with growth hormone deficiency: a double-blind, placebo-controlled crossover trial in Japan. *Endocrinology and Metabolism* 1995 **2** (Suppl B) 17–23.

11 Pocock SJ & Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975 **31** 103–115.

12 Shimatsu A. Recent progress in the diagnosis of growth hormone (GH) disorders. *Rinsho Byori* 1997 **45** 837–843 (In Japanese).

13 Yoshiike N, Matsumura Y, Zaman MM & Yamaguchi M. Descriptive epidemiology of body mass index in Japanese adults in a representative sample from the National Nutrition Survey 1990–1994. *International Journal of Obesity* 1998 **22** 684–687.

14 The Examination Committee of Criteria for 'Obesity Disease' in Japan, Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. *Circulation Journal* 2002 **66** 987–992.

15 Ito H, Nakasuga K, Ohshima A, Maruyama T, Kaji Y, Harada M, Fukunaga M, Jingu S & Sakamoto M. Detection of cardiovascular risk factors by indices of obesity obtained from anthropometry and dual-energy X-ray absorptiometry in Japanese individuals. *International Journal of Obesity* 2003 **27** 232–237.

16 Ito H, Ohshima A, Ohto N, Ogasawara M, Tsuzuki M, Takeo K, Hijii C, Tanaka H & Nishioka K. Relation between body composition and age in healthy Japanese subjects. *European Journal of Clinical Nutrition* 2001 **55** 462–470.

17 Suka M, Sugimori H & Yoshida K. Validity of the Framingham risk model applied to Japanese men. *Methods In Informatic Medicine* 2002 **41** 213–215.

18 Murakami Y & Kato Y. Hypercholesteremia and obesity in adult patients with hypopituitarism: a report of a nation-wide survey in Japan. *Endocrine Journal* 2003 **50** 759–765.

19 Gleeson HK, Souza AHO, Gill MS, Wieringa GE, Barretto ES, Barretto-Filho JA, Shalet SM, Aguiar-Oliveira MH & Clayton PE. Lipid profiles in untreated severe congenital isolated growth hormone deficiency through the lifespan. *Clinical Endocrinology* 2002 **57** 89–95.

20 Murray RD, Wieringa GE, Lissett CA, Darzy KH, Smethurst LE & Shalet SM. Low-dose replacement improves the adverse lipid profile associated with the adult GH deficiency syndrome. *Clinical Endocrinology* 2002 **56** 525–532.

21 Attanasio AF, Bates PC, Ho KKY, Webb SM, Ross RJ, Strasburger CJ, Bouillon R, Crowe B, Selander K, Valle D & Lamberts SW. Hypopituitary control and complications study international advisory board. Human growth hormone replacement in adult hypopituitary patients: long-term effects on body composition and lipid status – 3-year results from the HypoCCS database. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 1600–1606.

22 Kehely A, Bates PC, Frewer P, Birkett M, Blum WF, Mamessier P, Ezzat S, Ho KK, Lombardi G, Luger A, Marek J, Russell-Jones D, Sonksen P & Attanasio AF. Short-term safety and efficacy of human GH replacement therapy in 595 adults with GH deficiency: a comparison of two dosage algorithms. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 1974–1979.

23 Span JP, Pieters GF, Sweep FG, Hermus AR & Smals AG. Gender differences in rhGH-induced changes in body composition in GH-deficient adults. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 4161–4165.

24 Koba S, Hirano T, Sakaue T, Takeuchi H, Adachi M & Katagiri T. An increased number of very-low-density lipoprotein particles is strongly associated with coronary heart disease in Japanese men, independently of intermediate-density lipoprotein or low-density lipoprotein. *Coronary Artery Disease* 2002 **13** 255–262.

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特集

アンチエイジングの新しい動向②
ーホルモン補充療法を中心にー

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成人における成長ホルモンの生体作用

飯田　啓二*　　千原　和夫*

KEY WORD

成長ホルモン
ソマトポーズ
体脂肪量
除脂肪体重
骨粗鬆症

POINT

■成長ホルモン(GH)は小児期の成長に重要であるだけでなく，成人になってからも脂質代謝，蛋白代謝，糖質代謝などの調節に多彩な生物効果を発揮する．
■成人GH欠乏症では，体脂肪量が増加するとともに筋肉量，骨量の減少によって筋力や運動能力が低下し，また精神心理的健康感も得られなくなる．
■加齢とともにGH分泌は生理的に減少することから，アンチエイジング薬としてのGH補充療法に期待が寄せられている．
■高齢者に対するGH補充療法の臨床試験では，必ずしも好ましい成績ばかりは出ておらず，さらなるエビデンスを積み重ねる必要がある．

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成人成長ホルモン分泌不全症(欠乏症)の病態

成長ホルモン(GH)は，下垂体前葉から分泌されるペプチドで，小児期には軟骨内骨形成促進による長管骨の長軸方向への身長や骨量増加を促し，この時期にGHが欠乏すると成長障害を来し低身長を呈することはよく知られている．GHは骨，軟骨のほかに肝，脂肪組織，骨格筋，心筋などへも作用して，糖質代謝，脂質代謝，蛋白代謝などの調節に多彩な生物効果を発揮するホルモンである．これらGHの作用の多くはインスリン様成長因子(IGF)-Iを介して発揮される．このようなGHの代謝面での作用は小児から成人，高齢者まで一生を通じて発揮されるが，成人になってから特に大切であることが明らかとなってきた．GH欠乏(GHD)症では，体組成が変化し，体脂肪量が増加するとともに除脂肪体重(主として筋肉量)が減少，筋力や運動能力が低下し，また精神心理的健康感も得られなくなる．この体脂肪の増加は特に内臓脂肪の増加であり，インスリン抵抗性，糖尿病，高脂血症などの病態(内臓脂肪症候群)と密接に関連し，生命予後に深く関わる．

GHDが小児における低身長の問題にとどまらず，成人において代謝面での異常や体組成の変化をもたらし，患者のQOLを損ない色々な合併症を来すことが明らかになるにつれ，欧州

*いいだ　けいじ，ちはら　かずお：神戸大学大学院医学系研究科応用分子医学講座内分泌代謝・神経・血液腫瘍内科

を中心にして成人GHD患者(AGHD)にGH補充療法が試みられてきた．その結果，GH投与によってAGHD患者にみられる症候が改善されるという報告が相次ぎ，すでに多くの国でAGHDに対するGH補充療法が承認されている．本邦においても，いくつかの臨床試験が最終ステップにさしかかっているので早晩使用できるようになるものと思われる．

加齢によるGHの生理的分泌減少

GH分泌は思春期から青年期に最大となり，以後加齢に伴って10歳ごとに約14%ずつ低下する[1]．この加齢によるGH分泌低下はソマトポーズと呼ばれ，脈動的GH分泌パルスの振幅と継続時間の減少が主たる原因でありパルス頻度の低下ではない．すなわち高齢者では全員がGHD類似の状態になる．実際，AGHD症の患者で観察される身体的症候は，老化に伴って出現する諸症候，例えば内臓脂肪蓄積型の肥満，筋肉量の減少と筋力低下，骨塩量の低下と骨粗鬆症など，かなりよく類似している．例えば，老化に伴い男性では平均して12 kg除脂肪体重が減少し(女性では5 kg)，12 kg脂肪量が増加する(女性では15 kg)[2]．一方，加齢による変化は単純にGH分泌減少だけにとどまらず，様々な要素が混在していることも明らかであり，ソマトポーズがどの程度老化に伴って出現する諸症候の原因になっているかは不明である．

青壮年期に疾病のためにGHDに陥った患者は，上記のような高齢者で出現する身体的特徴を示し，さらにこれらの変化がGH補充療法で改善されるというエビデンスから，ソマトポーズに対するGH補充療法に多くの期待が寄せられた．特に高齢者で深刻な問題となるいくつかの点，特に，筋力低下に基づく虚弱fraility，骨粗鬆症を基礎に転倒で誘発される骨折，精神心理的不活発さ，あるいは不健康感がソマトポーズと関連しているかどうか，またこれらがGH補充療法で改善するかどうかは大きな課題である．1990年にRudmanらが最初に報告した高齢者に対するGH療法の成績[3]，すなわち除脂肪体重の増加，脂肪量の減少，そして腰椎骨密度の増加がGH投与群で確認されたことが，GHが「アンチエイジング」薬として期待される基盤になっている．しかし，これに追随して現在までに得られている高齢者に対するGH療法の報告結果は均一でなく，むしろ効果を疑問視する成績も多い．詳細については後述する．

AGHD症に対するGH治療

上記のように，ソマトポーズに対するGH補充療法という概念の基礎にあるのはAGHD症に対するGH治療成績であるので，まずその成績を紹介したい．

1．補充量

投与量は，小児GHDの補充量よりは少量で十分であり，小児に対する補充量をAGHDに投与すると高率に副作用が出現する．欧米におけるAGHDに対するGHの承認用量は，0.006 mg/kg体重/日(0.042 mg/kg体重/週)を開始時の投薬量，0.012 mg/kg体重/日(0.084 mg/kg体重/週，米国では0.0125 mg/kg体重/日)を最大用量として血中IGF-Iレベルを指標に用量を調節することとされている．さらに臨床データが蓄積されるにつれ，本療法に対する感受性は個々の患者で大きく異なることが明らかになってきており，現行の承認用量のほぼ半量の3～6 μg/kg体重/日の量で，有効性が確認され，またこの量であれば副作用の発現もかなり低く抑えることが知られている．

2．補充療法の効果

前述のようにGHは全身の諸臓器に作用するため，様々な面でGH補充の効果が認められる．すでにこれまでにその効果は数多く報告されている[4]．

1）体組成

AGHDの患者では脂肪の増加，除脂肪体重の減少，細胞外液量の減少がみられる．欧米での報告によると，0.1～0.5 IU/kg体重/週(5～25 μg/kg体重/日)のGHを7日から36カ月投

与すると，除脂肪体重は2～5.5 kg増加し，脂肪量は4～6 kg減少した．この脂肪量の減少は主に内臓脂肪の減少によるものであった．さらにGH補充は減少した細胞外液量を増加させた．

2）骨塩量

AGHDでは骨塩量が低下していることが報告されている．GH補充量の効果については，3～6カ月という短期間の補充では6～12カ月後の骨塩量は減少するが，12カ月以上の長期の補充療法後は基礎値から4～10%程度増加すると報告されている．骨代謝マーカーに関しては，骨形成および骨吸収マーカーともに増加し，骨のリモデリングが活発になっていることが示唆される．

3）筋力

AGHDにおいて，大腿四頭筋の筋力および筋の断面積ともに正常コントロールに比べて減少していることが示されている．GH補充の効果は，6カ月の投与では肢帯の筋力は増加するが，大腿四頭筋は断面積が増えるにも関わらず筋力増加は明らかではなく，12カ月の投与でようやく筋力が増加したと報告されている．

4）心血管系

臨床データでは，AGHDでbody mass index (BMI)が高く，高LDL血症，低HDL血症，血中PAI-1(plasminogen activator inhibitor-1)高値，フィブリノーゲンの増加，頸動脈エコーにおける内膜中膜複合体厚(IMT)の肥厚，プラーク形成などが認められる．心機能に関しては，AGHDで左室の心筋量や収縮能の低下が認められ，GH補充にてこれらの異常は改善するとされる．

5）代謝

糖代謝に関しては，AGHDではインスリン抵抗性を示唆する高インスリン血症がみられる．これらは体脂肪量の増加，特に内臓脂肪の増加の結果だと考えられている．さらに肝のグリコーゲン貯蔵量も減少しているとされる．GH補充療法は，1～6週ぐらいの間はさらにインスリン抵抗性を増大させるが，3カ月の治療でほぼ正常に回復してくる．

6）Quality of life

AGHDでは，精神的活力の低下や情緒不安定のために，生活の質も低下する．多くの大規模研究で，GH補充がこれらの精神面でのQOLを高めることを報告している．

わが国におけるAGHDの臨床像

わが国においてもAGHD患者の合併症について，厚生省間脳下垂体機能障害調査研究班のアンケート結果に基づき入江らがまとめて報告している[5]．AGHDと対照群で比較すると，AGHDで血管障害の保有率が高く，特に狭心症は有意に高かった．次に代謝異常症として高血圧，糖尿病，高脂血症，および肝障害をみてみると，これら合併症の保有率はすべてAGHDで高く，特に高脂血症，肝障害(脂肪肝)で有意な差が認められた．さらに高血圧，糖尿病，高脂血症の重複合併状態を両群間で比較すると，GHDで重複合併が多い結果であった．さらに動脈硬化の指標としての頸動脈内膜中膜複合体厚(IMT)もAGHDでは健常人に比べて肥厚し，しかも小児期発症のAGHDの方が成人期発症のAGHDに比べてIMT肥厚が進行していることが示されている[6]．しかしながら，欧米のAGHDに比してわが国のAGHDは心血管系疾患のリスクはそれほど高くなく，人種による差が示唆される[7]．

高齢者に対するGH補充療法

1．補充量およびその効果

1990年，Rudmanら[3]は，血中IGF-I値が低下した21名の健常高齢者(61～81歳)に0.030 mg/kg体重/週(GH分泌不全性低身長症の治療に使うGH量の約1/6量)のGHを週3回に分けて6カ月間にわたって皮下注射し，無治療群と比較した．前述のように，GH投与群では血中IGF-I値の上昇とともに除脂肪体重が8.8%増加，体脂肪量が14.4%減少，腰椎骨密度が1.6%増加した．しかしながら，GH投与群では収縮期血圧，空腹時血糖が有意に上昇していた点

表1　健常高齢者に対する26週間GH投与の効果(文献8から引用，一部改変)

		女性		男性	
		プラセボ(n=14)	GH(n=13)	プラセボ(n=17)	GH(n=17)
除脂肪体重(kg)	投与前	35.7	36.8	57.0	54.4
	投与後	36.1	37.8	57.0	57.5
	p値(投与前後)	—	0.001	—	<0.001
総脂肪量(kg)	投与前	28.4	27.8	25.0	24.4
	投与後	28.1	25.3	25.0	21.1
	p値(投与前後)	—	0.001	—	<0.001
筋力(kg)	投与前	108.0	107.1	209.8	202.4
	投与後	104.9	109.2	212.8	212.5
	p値(投与前後)	—	0.29	—	0.28
最大酸素取込量(mL/min/kg体重)	投与前	21.4	23.1	28.1	28.2
	投与後	21.1	24.4	26.8	28.4
	p値(投与前後)	—	0.07	—	0.3

など好ましくない成績も示されており，さらには二重盲検試験ではなかった点(治療を受けていない群を対照群としている)，筋肉量の増加は示されているが，筋力や持久力，QOLの変化については示されていないなどの点も忘れてはならない．Blackmanらの最近の報告[8]では，68～88歳の健常高齢者(女性27人，男性34人)に対し，6.5カ月にわたってGHを投与し，プラセボ投与群と二重盲検試験を行ったところ，GHの体組成変化に対する影響は確認されたものの，筋力や運動中における最大酸素取り込み量に関してはGH投与群とプラセボ投与群とで差は確認できなかった(表1)．この成績は1996年に報告されたPapadakisら[9]の報告と一致する．Taaffeら[10]は，65～82歳の18人の健常男性に対し14週間にわたって筋力トレーニングを行い，それに引き続き10週間にわたって，一方のグループは筋力トレーニングプラスGH投与，もう一方のグループは筋力トレーニングプラスプラセボ投与を行い，筋量について評価したところ，筋力トレーニングは有意に筋量を増加するが，GH投与はそれ以上の筋量増加には寄与しない，と結論づけている．Munzerら[11]は，腹部の皮下および内臓脂肪に対するGH治療の効果をみるために，110名の高齢者に0.020 mg/kg体重/週のGHを週3回に分けて6カ月間投与しプラセボ群と比較したところ，女性ではGH治療は腹部の皮下および内臓脂肪量に何の影響も及ぼさなかった．一方，男性では皮下脂肪量が有意に減少したが内臓脂肪量には明らかな変化がなかった．

高齢者へのGH投与は，骨代謝にも影響を与える．前述のようにGHは，骨形成および骨吸収をともに刺激し骨代謝回転を促進する．GH投与6カ月頃は骨吸収が骨形成を上回るため骨塩量はむしろやや減少するがその後増加し1年後には対照群と比べて有意に増加する．Sugimotoら[12]は，骨塩量の低下した高齢女性(平均年齢71歳)に対し，最初の4週間は0.125 U(6.25 μg)/kg体重/週，その後0.25 U(12.5 μg)/kg体重/週のリコンビナントヒトGHを48週にわたって合計1年間投与したところ，投与前に比べ骨密度はわずかではあったが有意に上昇し，興味深いことに，その効果はGH投与中止後1

年後にも持続していた．しかし，GHによる骨塩量増加の程度は，ビスフォスフォネートに比べると明らかに弱い．

2．副作用および安全性

GH治療をはじめてすぐに高頻度にみられる副作用は，GHによる塩分および体液の貯留によるものである．浮腫，関節痛，筋肉痛などが多く，その他，体重増加，手のこわばり感，手根管症候群，まれなものとしては頭痛，耳鳴り，鬱血乳頭，血圧上昇，心房細動などが認められている．また女性化乳房も副作用として報告されている．

長期的にGH治療を続けるときの安全面での問題は，腫瘍の発症および進展である．疫学研究で，血中IGF-I値が正常範囲であってもその中で高め（さらに血中IGFBP-3値が低め）の人は前立腺癌[13]，大腸癌[14]，乳癌[15]になるリスクが高いことが知られている．若者に比べて，癌が発症しやすい高齢者にGHを投与することによってIGF-I系を賦活化することが，発癌を促進する，あるいは潜在的に存在していた癌の増大を促してしまう危険性については，まだ明確な結論は得られていない．

3．高齢者に対するGH治療の問題点

上記のように，高齢でないAGHD患者に対してGH補充療法を行ったときに得られる効果と，高齢者のソマトポーズに対するGH治療の効果には，かなり差があることが明らかになってきている．高齢者に対するGH治療で，共通して得られる成績は，体脂肪の減少と除脂肪体重の増加である．しかし体脂肪の減少も詳細に調べると，Munzerら[11]の報告のように，女性ではほとんどGH投与によって影響されず，男性においても内臓脂肪は減らず皮下脂肪が減少するように，AGHD患者におけるGH投与の効果とは異なっている．さらに期待はずれなのは，GH投与が高齢者の筋力増強に明らかな効果を示さないことである．また，筋力以外にも，高齢者で低下した身体機能に関する検査，最大酸素消費量など，それらほとんどにおいてGH投与は明らかな効果を示さなかった．これらの成績から，高齢者で起こる様々な身体の変化は，単にGH－IGF-I系が減弱したことのみによるのではなく，様々な要因が複雑に関与していることが明らかとなった．さらに考慮すべきエビデンスとしては，種の違いはあるとはいえ，GHDあるいはGH受容体ノックアウトマウスでは皮下脂肪量の増加と筋肉量の減少を示すものの[16]，正常マウスに比較してインスリン感受性はむしろ亢進しているし[17]，明らかに長寿である[18]ことである．もちろんマウスの成績をそのままヒトにあてはめることはできないし，マウスではQOLを評価することはできない．しかしながら，ヒトでのソマトポーズが本当に生体に害なのかどうか，さらにエビデンスを重ね慎重に判断すべきだと思われる．

これまでの高齢者のソマトポーズに対するGH治療成績から，確定的な結論を出すのはまだ早計である．過去の臨床研究を振り返ってみると，いくつもの問題点がある．まず，研究に参加した被験者の多くは，きわめて元気で健康な高齢者でありソマトポーズに起因する諸々の症候を必ずしも示していない方々である．また，今までの成績は3カ月～6カ月の短期間の研究が多く，年単位の研究はまだない．使用されたGHの投与量，投与方法も様々である．そして一番問題なのは，身体機能評価において高齢者の正常値は若者と同じではないにもかかわらず，多くの身体機能検査において高齢者の年代別正常値が設定されていないことであろう．高齢者の身体機能検査でGH治療がほとんど効果を示さないという成績は，被験者になった元気で健康な高齢者は，若者と比べれば劣るもののその年代としては最大の身体機能を発揮していて（頭打ち現象あるいは天井効果），それ以上の成績は望めない可能性も考えられる．長期のGH補充成績も含め，今後の結果に期待したい．

文　献

1) Iranmanesh A et al：Age and relative adiposity 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, 1991.
2) Forbes GB and Reina JC：Adult lean body mass declines with age：some longitudinal observations. Metabolism 19：653-663, 1970.
3) Rudman D et al：Effects of human growth hormone in men over 60 years old. N Engl J Med 323：1-6, 1990.
4) Carroll PV et al：Growth hormone deficiency in adulthood and the effects of growth hormone replacement：a review. J Clin Endocrinol Metab 82：82-88, 1997.
5) 入江　實：本邦における成人GH欠損症例の合併症に関する検討(厚生省間脳下垂体機能障害調査研究班アンケートから)，厚生省特定疾患間脳下垂体機能障害調査研究班，平成6年度総括研究事業報告書，pp37-40, 1994.
6) Murata M et al：A study of carotid intima-media thickness in GH-deficient Japanese adults during onset among adults and children. Eur J Endocrinol 148：333-338, 2003.
7) Kaji H et al：Adult growth hormone deficiency in Japan：results of investigation by questionnaire. Endocr J 49：597-604, 2002.
8) Blackman MR et al：Growth hormone and sex steroid administration in healthy aged women and men：a randomized controlled trial. JAMA 288：2282-2292, 2002.
9) Papadakis MA et al：Growth hormone replacement in healthy older men improves body composition but not functional ability. Ann Intern Med 124：708-716, 1996.
10) Taaffe DR et al：Effect of recombinant human growth hormone on the muscle strength response to resistance exercise in elderly men. J Clin Endocrinol Metab 79：1361-1366, 1994.
11) Munzer T et al：Effects of GH and/or sex steroid administration on abdominal subcutaneous and visceral fat in healthy aged women and men. J Clin Endocrinol Metab 86：3604-3610, 2001.
12) Sugimoto T et al：Effect of low-dose of recombinant human growth hormone on bone metabolism in elderly women with osteoporosis. Eur J Endocrinol 147：339-348, 2002.
13) Chan JM et al：Plasma insulin-like growth factor-I and prostate cancer risk：a prospective study. Science 279：563-566, 1998.
14) Giovannucci E：Insulin-like growth factor-I and binding protein-3 and risk of cancer. Horm Res 51：34-41, 1999.
15) Hankinson SE et al：Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. Lancet 351：1393-1396, 1998.
16) Donahue LR and Beamer WG：Growth hormone deficiency in 'little' mice results in aberrant body composition, reduced insulin-like growth factor-I and insulin-like growth factor-binding protein-3(IGFBP-3), but does not affect IGFBP-2, -1 or -4. J Endocrinol 136：91-104, 1993.
17) Dominici FP et al：Compensatory alterations of insulin signal transduction in liver of growth hormone receptor knockout mice. J Endocrinol 166：579-590, 2000.
18) Coschigano KT et al：Assessment of growth parameters and life span of GHR/BP gene-disrupted mice. Endocrinology 141：2608-2613, 2000.

(執筆者連絡先)　飯田啓二　〒650-0017　神戸市中央区楠町7-5-1　神戸大学大学院医学系研究科応用分子医学講座
内分泌代謝・神経・血液腫瘍内科

Ⅲ．研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Yoshioka S, Y Okimura, Y Takahashi, K Iida, H Kaji, M Matsuo, K Chihara	Up-reguration of mitochondrial transcription factor 1 mRNA levels by GH in VSMC	Life Sciences	74	2097-2109	2004
Iida K, Y Okimura, K Takahashi, S Inomata, G Iguchi, H Kaji, K Chihara	A variety of phenotype with R161Q germline mutation of the von Hippel-Lindau tumor suppressor gene in Japanese kindred	International Journal of Molecular Medicine	13	401-404	2004
Kaji H and K Chihara	Direct causes of death in Japanese patients with hypopituitarism as analyzed from a nation-wide autopsy database	Eur J Endocrinol	150	149-152	2004
Sowa H, H kaji, R Kitazawa, S Kitazawa, T Tsukamoto, S Yano, T Tsukada, L Canaff, N Hendy, T Sugimoto and K Chihara	Menin inactivation leads to loss of transforming growth factor β inhibition of parathyroid cell proliferation and parathyroid hormone secretion	Cancer Research	64	2222-2228	2004
Myriam R, W F.Blum, D J. Edwards, E P.Shavrikova, D valle, S W. J. Lamberts, E M Erfurth, S M. Webb, R J. Ross, K Chihara, G Henrich P Herschbach and A F. Attanasio	Long-term improvement of quality of life during growth hormone (GH) replacement therapy in adults with GH deficiency, as measured by questions on life satisfaction-hypopituitarism (QLS-H)	The Journal of Clinical Endocrinology & Metabolism	89	1684-1693	2004

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Hayakawa M, Y Shimazaki, T Tsushima, Y Kato, K Takano, K Chihara, A Shimatsu and M Irie	Metabolic effects of 20-kilodalton human growth hormone (20K-hGH) for adult with growth hormone deficiency : results of an exploratory uncontrolled multicenter clinical trial of 20K-hGH	The Journal of Clinical Endocrinology & Metabolism	89	1562-1571	2004
Shimatsu A, M Hayakawa, Y Shimazaki, T Tsushima, Y Kato, K Takano, K Chihara and M Irie	Metabolic effects of human growth hormone Isoform (20K-hGH) in adult with growth hormone deficiency	Clinical Pediatric Endocrinology	13 (Suppl 21)	1-7	2004
Enas Atef Al Naggar, F Kanda, S Okuda, N Maeda, K Nakazawa, K Oishi, K Sekiguchi, H Ishihara, K Chihara	Focal myositis in monozygotic twins	Internal Medicine	43	599-601	2004
Kanatani M, T Sugimoto, H Sowa, T Kobayashi, M Kanzawa and K Chihara	Thyroid Hormone stimulates osteoclast differentiation by a mechanism independent of RANKL-RANK interaction	J Cell Physiol	201	17-25	2004
Chihara K, E Koledova, A Shimatsu, Y Kato, H Kohno, T Tanaka, A Teramoto, P C Bates and A F Attanasio	Adult GH deficiency in Japanese patients:effects of GH treatment in a randomized, placebo-controlled trial	Eur J Endocrinol	151	343-350	2004

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Iida K, M Hanafusa, I Maekawa, T Kudo, K Takahashi, S Yoshioka, M Kishimoto, G Iguchi, T Tsukamoto, Y Okimura, H Kaji and K Chihara	A novel splice site mutation of the thiazide-sensitive NaCl cotransporter gene in a Japanese patients with Gitelman syndrome	Clinical Nephrology	62	180-184	2004
Murata M, A Hashiramoto, T Yamaguchi, C Takabayashi, T Yamane, Y Miura, H Baba, K Chihara, S Shiozawa	A case of central nervous system lipus in succession to lupus peritonitis: a difficulty in the differential diagnosis between lupus psychosis and steroid-induced psychosis	Mod Rheumatol	14	323-326	2004
Takeno R, Y Okimura, G Iguchi, M Kishimoto, T Kudo, K Takahashi, Y Takahashi, H Kaji, M Ohno, H Ikuta, Y Kuroda, T Obara, H Hosoda, K Kangawa and K Chihara	Intravenous administration of ghrelin stimulates growth hormone secretion in vagotomized patients as well as normal subjects	Eur J Endocrinol	151	447-450	2004
Okuda S, F Kanda, K Kawamoto and K Chihara	Subacute bulbar palsy as the initial sign of follicular thyroid cancer	Internal Medicine	43	997-999	2004