EFFECTS OF HUMAN GROWTH HORMONE IN MEN OVER 60 YEARS OLD

Daniel Rudman, M.D., Axel G. Feller, M.D., Hoskote S. Nagraj, M.D., Gregory A. Gergans, M.D.,
Pardee Y. Lalitha, M.D., Allen F. Goldberg, D.D.S., Robert A. Schlenker, Ph.D.,
Lester Cohn, M.D., Inge W. Rudman, B.S., and Dale E. Mattson, Ph.D.

Abstract *Background.* The declining activity of the growth hormone–insulin-like growth factor I (IGF-I) axis with advancing age may contribute to the decrease in lean body mass and the increase in mass of adipose tissue that occur with aging.

Methods. To test this hypothesis, we studied 21 healthy men from 61 to 81 years old who had plasma IGF-I concentrations of less than 350 U per liter during a six-month base-line period and a six-month treatment period that followed. During the treatment period, 12 men (group 1) received approximately 0.03 mg of biosynthetic human growth hormone per kilogram of body weight subcutaneously three times a week, and 9 men (group 2) received no treatment. Plasma IGF-I levels were measured monthly. At the end of each period we measured lean body mass, the mass of adipose tissue, skin thickness (epidermis plus dermis), and bone density at nine skeletal sites.

Results. In group 1, the mean plasma IGF-I level rose into the youthful range of 500 to 1500 U per liter during treatment, whereas in group 2 it remained below 350 U per liter. The administration of human growth hormone for six months in group 1 was accompanied by an 8.8 percent increase in lean body mass, a 14.4 percent decrease in adipose-tissue mass, and a 1.6 percent increase in average lumbar vertebral bone density ($P<0.05$ in each instance). Skin thickness increased 7.1 percent ($P = 0.07$). There was no significant change in the bone density of the radius or proximal femur. In group 2 there was no significant change in lean body mass, the mass of adipose tissue, skin thickness, or bone density during treatment.

Conclusions. Diminished secretion of growth hormone is responsible in part for the decrease of lean body mass, the expansion of adipose-tissue mass, and the thinning of the skin that occur in old age. (N Engl J Med 1990; 323:1-6.)

I N middle and late adulthood all people experience a series of progressive alterations in body composition.[1] The lean body mass shrinks and the mass of adipose tissue expands. The contraction in lean body mass reflects atrophic processes in skeletal muscle, liver, kidney, spleen, skin, and bone.

These structural changes have been considered unavoidable results of aging.[1] It has recently been proposed, however, that reduced availability of growth hormone in late adulthood may contribute to such changes.[1,2] This proposal is based on two lines of evidence. First, after about the age of 30, the secretion of growth hormone by the pituitary gland tends to decline.[1,3,4] Since growth hormone is secreted in pulses, mostly during the early hours of sleep, it is difficult to measure the 24-hour secretion of the substance directly. Growth hormone secretion can be measured indirectly, however, by measuring the plasma concentration of insulin-like growth factor I (IGF-I, also known as somatomedin C), which is produced and released by the liver and perhaps other tissues in response to growth hormone.[5] There is little diurnal variation in the plasma IGF-I concentration, and measurements of it are therefore a convenient indicator of growth hormone secretion.[5] Plasma IGF-I concentrations decline with advancing age in healthy adults.[1,4,6] Less than 5 percent of the healthy men 20 to 40 years old have plasma IGF-I values of less than 350 U per liter, but the values are below this figure in 30 percent of the healthy men over 60.[4] Likewise, the nocturnal pulses of growth hormone secretion become smaller or disappear with advanced age. If the plasma concentration of IGF-I falls below 350 U per liter in older adults, no spontaneous circulating pulses of growth hormone can be detected by currently available radioimmunoassay methods.[4] The concomitant decline in plasma concentrations of both hormones supports the view that the decrease in IGF-I results from diminished growth hormone secretion.[4,6] Second, diminished secretion of growth hor-

mone is accompanied not only by a fall in the plasma IGF-I concentration, but also by atrophy of the lean body mass and expansion of the mass of adipose tissue.[1] These alterations in body composition caused by growth hormone deficiency can be reversed by replacement doses of the hormone, as experiments in rodents,[7] children,[8,9] and adults 20 to 50 years old[10-13] have shown. These findings suggest that the atrophy of the lean body mass and its component organs and the enlargement of the mass of adipose tissue that are characteristic of the elderly result at least in part from diminished secretion of growth hormone.[1,2] If so, the age-related changes in body composition should be correctable in part by the administration of human growth hormone, now readily available as a biosynthetic product.[14]

In this study we administered biosynthetic human growth hormone for six months to 12 healthy men from 61 to 81 years old whose plasma IGF-I concentrations were below 350 U per liter, and we measured the effects on plasma IGF-I concentration, lean body mass, adipose-tissue mass, skin (dermal plus epidermal) thickness, regional bone density, and mandibular-height ratio (the height of the alveolar ridge divided by the total height of the mandible). The measurement of the mandible was included to test the hypothesis that the age-related involution of dental bone results in part from the loss of stimulation by growth hormone.[1] In addition, the men were monitored for possible adverse effects of the hormone by means of interviews, physical examinations, and standard laboratory tests. Nine men matched for age and with similar plasma IGF-I concentrations served as controls.

METHODS

Subjects

Healthy men who were 61 or older and living in the community were recruited through newspaper advertisements followed by an interview. Entry criteria (available from the authors on request) included body weight of 90 to 120 percent of the standard for age, the ability to administer growth hormone to oneself subcutaneously, and the absence of indications of major disease. Ninety-five men who answered the advertisements met criteria that could be ascertained by interview. Their plasma IGF-I concentrations were then determined twice at an interval of four weeks. Consistent with the results of a previous study,[13] the plasma IGF-I values in these men ranged from 100 to 2400 U per liter, with an average of 500 U per liter. Thirty-three of the men had plasma IGF-I values of less than 350 U per liter on both occasions. These 33 men were then further evaluated by a medical-history taking, physical examination, differential blood count, urinalysis, blood-chemistry tests, chest radiography, and electrocardiography. Twenty-six subjects (1 black and 25 white) met all the entry criteria and were enrolled in the 12-month protocol summarized in Table 1.

Study Periods

The men were seen at regular intervals and tested as shown in Table 1 during the first week of the first, third, and sixth months of the base-line period. Five men dropped out of the study during these six months (four for personal reasons and one because carcinoma of the prostate was detected).

At the beginning of the seventh month, the 21 men who had completed the base-line period were randomly assigned to group 1 (growth hormone group) or group 2 (control group) in a ratio of 3 to 2. The randomization table was generated by a computer program

Table 1. Schedule of Tests during the Base-Line and Treatment Periods.

Test	Base-Line Period			Treatment Period					
	MO 1	MO 3	MO 6	MO 7	MO 8	MO 9	MO 10	MO 11	MO 12
Physical examination	x	x	x	x	x	x	x	x	x
Hematology*	x	x	x	x	x	x	x	x	x
Urinalysis*	x	x	x	x	x	x	x	x	x
Blood chemistry*	x	x	x	x	x	x	x	x	x
Chest radiography	x		x						x
Electrocardiography	x		x						x
Echocardiography	x		x						x
Total body potassium†			x						x
Skin thickness‡			x						x
Bone density*§			x						x
Mandibular-height ratio*¶			x						x
Plasma IGF-I‖	x	x	x	x	x	x	x	x	x
Biosynthetic growth hormone**				x	x	x	x	x	x

*Tests included a complete blood count, hematocrit, blood indexes, and the measurement after an overnight fast of plasma glucose, urea nitrogen, creatinine, uric acid, sodium, potassium, chloride, carbon dioxide, phosphate, calcium, total protein, albumin, alkaline phosphatase, aspartate aminotransferase, lactic dehydrogenase, bilirubin, cholesterol, triglyceride high-density lipoprotein cholesterol, and glycosylated hemoglobin levels. Tests were performed at the North Chicago Veterans Affairs Medical Center laboratories.

†Total body potassium levels (lean body mass and adipose-tissue mass) were measured according to the method of Flynn et al.[15]

‡Calculated as the sum of the skin thicknesses of the right and left dorsal hand and right and left volar forearm measured with a Harpenden caliper according to the method of Lawrence and Shuster.[16]

§Measured according to the method of Nagraj et al.[17]

¶Measured according to the method of Goldberg et al.[18]

‖Measured at Nichols Laboratory, Los Angeles, according to the method of Furlanetto et al.[19]

**Administered to group 1 only.

such that in each group of five men, three would be assigned to the growth hormone group and two to the control group. All 21 men (12 in group 1 and 9 in group 2) completed the treatment period and constitute the study group for this report. Their clinical characteristics are summarized in Table 2. During the first week of the seventh month, the men in group 1 were instructed in the subcutaneous administration of recombinant biosynthetic human growth hormone (2.6 IU per milligram of hormone; Eli Lilly). The initial dose was 0.03 mg per kilogram of body weight, injected three times a week at 8 a.m., the interval between injections being either one or two days. A sample of venous blood for plasma IGF-I assay was obtained each month 24 hours after a growth hormone injection. If the IGF-I level was below 500 U per liter, the dose of hormone was increased by 25 percent; if the IGF-I level was above 1500 U per liter, the dose was reduced by 25 percent. The men in group 2 received no injections. The schedule of tests for both groups during the treatment period is shown in Table 1.

At the start of the base-line period, the project dietitian instructed each man to follow a diet that furnished 25 to 30 kcal per kilogram. The distribution of kilocalories among protein, carbohydrate, and fat was approximately 15 percent, 50 percent, and 35 percent, respectively. At each scheduled visit shown in Table 1, the dietitian analyzed each man's diet on the basis of a 24-hour dietary recall and instructed the subjects again about the standard diet. The men were told not to alter their lifestyles (including their use of tobacco or alcohol and their level of physical activity) during the 12-month study period.

The study protocol was carried out with the informed consent of each subject and with the approval of the human-research committees of the Medical College of Wisconsin, the Chicago Medical School, and the Veterans Affairs Medical Centers in North Chicago and Milwaukee.

Statistical Analysis

The methods used to measure each response variable and the locations where the tests were performed are described in Table 1.

Table 2. Clinical Characteristics of the Study Subjects.

CHARACTERISTIC	GROUP 1 (N = 12)	GROUP 2 (N = 9)
Median age (range)	67 (61–73)	68 (65–81)
Percent of ideal body weight — median (range)	103 (94–120)	105 (99–117)
Medical conditions (no. of subjects)		
Degenerative joint disease	5	2
Benign prostatic hypertrophy	3	1
Glaucoma	1	1
Cataract	2	1
Arteriosclerotic heart disease*	3	1
Gallstones	0	1
Kidney stone	1	1
Hiatus hernia	0	1
Medications (no. of subjects)		
Nonsteroidal antiinflammatory drug	3	1
Pilocarpine eyedrops	1	1
Cimetidine	0	1

*Defined as a history of myocardial infarction or electrocardiographic abnormality ascribed to coronary artery disease.

The interassay coefficients of variation for the response variables were as follows: plasma IGF-I, 7.2 percent; lean body mass, 3.6 percent; adipose-tissue mass, 6.9 percent; skin thickness, 5.4 percent; and bone density, 2.3 percent (average of nine measured sites).

P values based on two-tailed, matched-pair t-tests were calculated for the comparisons between the 6-month and 12-month values in group 1 and group 2. In addition, for each response variable the 6-month value was subtracted from the 12-month value to represent the change in each subject. P values based on two-tailed, unequal-variance, independent-sample t-tests were then calculated for the comparison of the changes in response variables between groups 1 and 2.

RESULTS

Clinical Observations

All the men remained healthy, and none had any changes in the results of differential blood count, urinalysis, blood-chemistry profile, chest radiography, electrocardiography, or echocardiography during the 12-month protocol. Specifically, none had edema, fasting hyperglycemia (>6.6 mmol of glucose per liter), an increase in blood pressure to more than 160/90 mm Hg, ventricular hypertrophy, or a local reaction to human growth hormone, nor did their serum cholesterol or triglyceride concentrations change significantly. In group 1, however, both the mean (±SE) systolic blood pressure and fasting plasma glucose concentration

were significantly higher (P<0.05 by matched-pair t-test) at the end of the experimental period than at the end of the base-line period (127.2±5.2 vs. 119.1±3.6 mm Hg and 5.8±0.2 vs. 5.4±0.2 mmol per liter, respectively).

Plasma IGF-I Concentration

In group 1, the mean plasma IGF-I concentration ranged from 200 to 250 U per liter throughout the base-line period (Table 3). Within one month after the administration of growth hormone had been initiated, the mean IGF-I level rose to 830 U per liter (P<0.05), and it remained near this value for the next five months. Eight of the 12 men in group 1 required no adjustment in their initial dose of growth hormone. Two required an upward adjustment of 25 percent, and two required a downward adjustment of 25 percent. The mean plasma IGF-I concentration in group 2 remained in the range of 180 to 300 U per liter throughout the base-line and treatment periods.

Lean Body Mass, Adipose-Tissue Mass, Skin Thickness, Bone Density, and Mandibular-Height Ratio

Table 4 shows the mean values for the other response variables at the end of the base-line period (6 months) and the end of the treatment period (12 months). There was no significant change in weight in either group. In group 1, several response variables had changed significantly after 12 months. Lean body mass and the average density of the lumbar vertebrae increased by 8.8 percent (P<0.0005) and 1.6 percent (P<0.04), respectively, and adipose-tissue mass decreased by 14.4 percent (P<0.005). The sum of skin thicknesses at four sites increased 7.1 percent (P = 0.07). The small average change in lumbar vertebral bone density (only 0.02 g per square centimeter) was statistically significant because of very little variability in individual results. The bone density of the radius and proximal femur and the ratio of the height of the alveolar ridge to total mandibular height did not change significantly. In group 2 none of these variables changed significantly. The change in the lean body mass was significantly greater in group 1 than in group 2 (P<0.018), but the differences in changes in skin thickness and adipose-tissue mass between groups did not reach statistical significance in this small series (P = 0.10 and 0.13, respectively).

Table 3. Effect of the Administration of Human Growth Hormone on Plasma IGF-I Concentrations in Healthy Older Men.*

GROUP	PLASMA IGF-I								
	BASE-LINE PERIOD			TREATMENT PERIOD					
	mo 1	mo 3	mo 6	mo 7	mo 8	mo 9	mo 10	mo 11	mo 12
				units per liter					
Group 1	240±86	230±97	230±66	830±339†	680±180†	720±350†	810±305†	810±192†	910±312†
Group 2	240±69	240±126	240±108	200±126	220±123	240±177	180±126	240±186	300±201

*Values are means ±SD.   †P<0.05 for the comparison between groups.

Table 4. Effect of the Administration of Human Growth Hormone on Weight, Lean Body Mass, Adipose-Tissue Mass, Skin Thickness, and Bone Density in Healthy Older Men.*

Variable	Group	End of Base-Line Period	End of Treatment Period	P Value†	Difference in Changes‡
Weight (kg)	1	77.2±11.4	78.2±12.1	0.26	+1.0 (−1.4 to +3.4)
	2	83.3±11.1	83.3±9.7	0.97	
Lean body mass (kg)	1	53.0±7.4	57.7±9.1	0.0005	+3.7 (+0.7 to +6.6)
	2	54.2±7.1	55.2±7.3	0.17	
Adipose-tissue mass (kg)	1	24.1±5.0	20.6±5.6	0.05	−2.4 (−5.7 to +0.8)
	2	29.0±6.4	28.0±4.0	0.43	
Sum of skin thickness at four sites (mm)	1	9.9±1.2	10.6±1.5	0.07	+0.8 (−0.1 to +1.7)
	2	9.3±0.9	9.23±0.80	0.69	
Bone density (g/cm²)					
Mid-shaft radius	1	0.74±0.10	0.74±0.12	0.85	+0.04 (−0.02 to +0.10)
	2	0.76±0.10	0.71±0.07	0.09	
Distal radius	1	0.37±0.07	0.36±0.08	0.12	−0.004 (−0.03 to +0.02)
	2	0.34±0.04	0.33±0.05	0.26	
Average, lumbar vertebrae 1–4	1	1.23±0.12	1.25±0.13	0.04	+0.006 (−0.04 to +0.05)
	2	1.29±0.25	1.29±0.26	0.64	
Ward's triangle	1	0.70±0.14	0.69±0.13	0.15	−0.018 (−0.08 to +0.05)
	2	0.70±0.17	0.70±0.17	0.69	
Greater trochanter	1	0.85±0.13	0.85±0.13	0.72	+0.007 (−0.05 to +0.03)
	2	0.81±0.15	0.81±0.13	0.55	
Femoral neck	1	0.92±0.15	0.91±0.14	0.53	−0.029 (−0.08 to +0.03)
	2	0.89±0.14	0.85±0.14	0.14	
Mandibular-height ratio	1	0.45±0.15	0.46±0.11	0.87	−0.003 (−0.07 to +0.06)
	2	0.47±0.12	0.47±0.12	0.98	

*Plus–minus values are means ±SD.

†P values are for the change from base line, by matched-pair t-test.

‡The difference in changes (12-month value minus 6-month value) is the average change in group 1 minus the average change in group 2. Values in parentheses are 95 percent confidence intervals, calculated by independent-sample, unequal-variance t-tests.

DISCUSSION

The 21 men studied were representative of the approximately one third of all men 60 to 80 years old who have plasma IGF-I concentrations of less than 350 U per liter (as compared with a range of 500 to 1500 U per liter in healthy men 20 to 40 years old).[4] Our findings cannot be generalized to the approximately two thirds of all men over 60 who have plasma IGF-I concentrations of more than 350 U per liter or to women of a similar age. Furthermore, our entry criteria focused the study on an overtly healthy subgroup of older men.

In the absence of obesity,[4] below-normal weight,[20] or liver disease,[21] a plasma IGF-I concentration of less than 350 U per liter in older men generally signifies that they secrete very little growth hormone.[4] To verify this explanation for the low plasma IGF-I concentration in these men, it would be necessary to measure serum growth hormone levels at frequent intervals for 24 hours or to determine the 24-hour urinary excretion of growth hormone. We did not do this, but Ho et al. found that the 24-hour integrated serum growth hormone level was markedly lower in the men over 55 than in men 18 to 33 years old.[22] An alternative explanation for a low plasma IGF-I concentration is decreased production of plasma IGF-I binding proteins. Most of the IGF-I plasma is bound to these proteins, but their concentrations vary little in healthy people who eat a normal diet.

In the 12 men in group 1, initially low plasma IGF-I concentrations were raised to the normal range for young adult men by the dose of growth hormone administered, with no evidence of tachyphylaxis or hormone resistance. The dose, approximately 0.03 mg per kilogram three times a week, was based on published estimates of the rate of growth hormone secretion in young men[23] and was comparable to or smaller than doses given previously to children with growth hormone deficiency[24,25] and young adults.[10-13] The plasma IGF-I responses to this dose in these older men were similar in magnitude to those in younger people. That "replacement" rather than pharmacologic doses were being administered was confirmed by the plasma IGF-I measurements, which remained within the range for healthy young adults (500 to 1500 U per liter) throughout the treatment period (Table 3). We conclude that in aging men with low plasma IGF-I concentrations hepatic responsiveness to human growth hormone is not impaired, and the decline in plasma IGF-I concentrations in such men results from growth hormone deficiency rather than growth hormone resistance. The increase in plasma IGF-I levels that occurs when growth hormone is administered to children with growth hormone deficiency reflects not only augmented hepatic production of IGF-I, but also increased production of one of the binding proteins that transport IGF-I.[26] The extent to which the production of IGF-I binding protein is increased by the administration of growth hormone has not yet been studied in adults.

At the beginning of our study, adverse reactions to human growth hormone were thought to be unlikely because physiologic doses were being used. Furthermore, similar or larger doses have not caused undesired reactions in children or young adults.[10-14,25] Nevertheless, it remained possible that this dose, when given for six months to older subjects, might cause some manifestation of hypersomatotropism, such as edema, hypertension, diabetes, or cardiomegaly.[27-29] Although none of these conditions developed, there were small increases in the mean systolic blood pressure and fasting plasma glucose concentration of the group of men who received growth hormone.

The magnitude of the increases in lean body mass and the decreases in adipose-tissue mass (8.8 and −14.2 percent above and below base line, respectively) in the aging men who received human growth hormone for six months was similar to the magnitude of these re-

sponses in children[8,9] and young adults[10-13] treated with similar or lower doses for three to six months, a comparison that provides further evidence that tissue responsiveness to growth hormone and IGF-I is not altered in older men. Until now, the evidence for such a conclusion came only from short-term nitrogen-balance experiments.[14,30-32]

Salomon et al. reported that the administration of human growth hormone in a dose of 0.49 unit per kilogram per week (0.19 mg per kilogram per week) for six months to adults 20 to 50 years old who had growth hormone deficiency lowered the serum cholesterol concentration significantly.[13] Serum cholesterol concentrations did not change in our study, in which the dose of growth hormone was about half as large (0.9 mg per kilogram per week). The divergent results could reflect differences in the subjects' ages, the degree of growth hormone deficiency, the dose of hormone, or all three.

In rodents, the increase in lean body mass in response to growth hormone is due to increases in the volume of skeletal muscle, skin, liver, kidney, and spleen.[1,7] In young human subjects, an enlargement of muscle and kidney induced by growth hormone has been documented[8-12]; other organs have not yet been assessed. The reduction in adipose-tissue mass when children with growth hormone deficiency are treated with human growth hormone is associated with a redistribution of adipose tissue from abdominal to peripheral areas.[31] It is not known, however, whether the increase in lean body mass and the decrease in adipose-tissue mass are qualitatively as well as quantitatively similar in old and young human subjects.

Biosynthetic human growth hormone had no detectable effect on the bone density of the radius or proximal femur in the aging men, but it increased the density of the lumbar vertebrae by about 1.6 percent. Although the decrease in bone density with advancing age in men may be due in part to diminished secretion of growth hormone,[1,33] longer periods of administration of human growth hormone will be required before a final conclusion can be drawn regarding its efficacy in reversing that decrease. A similar interpretation applies to the lack of increase in the mandibular-height ratio.

The findings in this study are consistent with the hypothesis that the decrease in lean body mass, the increase in adipose-tissue mass, and the thinning of the skin that occur in older men are caused in part by reduced activity of the growth hormone–IGF-I axis, and can be restored in part by the administration of human growth hormone.[1,2] The effects of six months of human growth hormone on lean body mass and adipose-tissue mass were equivalent in magnitude to the changes incurred during 10 to 20 years of aging.[1,34,35] Among the questions that remain to be addressed are the following: What will be the benefits and what will be the nature and frequency of any adverse effects when larger numbers of elderly subjects and other doses of human growth hormone are studied? What organs are responsible for the increase in lean body mass, and do their functional capacities change as well? Only when such questions are answered can the possible benefits of human growth hormone in the elderly be explored. Since atrophy of muscle and skin contributes to the frailty of older people, the potential benefits of growth hormone merit continuing attention and investigation.

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