

Impaired growth hormone secretion in the adult population: relation to age and adiposity.

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Research Article

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Impaired Growth Hormone Secretion in the Adult Population

RELATION TO AGE AND ADIPOSITY

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ABSTRACT Growth hormone (GH) release was studied in adults of normal stature, ages 21–86 yr. The subjects were 85–115% of ideal body weight, between the 5th and 95th percentiles in height, and free of active or progressive disease. 9 to 12 individuals in each decade from third to ninth were evaluated. The following criteria of GH status were measured: serum GH concentration, analyzed by radioimmunoassay at half-hour intervals for 4 h after onset of sleep, and at 1-h intervals from 8 a.m. to 4 p.m. in 52 subjects; daily retention of N, P, and K in response to 0.168 U human (h)GH/kg body wt^{3/4}/day in 18 subjects; and plasma somatomedin C (SmC) level before and during exogenous hGH treatment in 18 subjects.

All 10 individuals, 20–29 yr old, released substantial amounts of endogenous GH during both day and night (average peak serum GH obtained during day and night was 7.3 and 20.3 ng/ml, respectively); average plasma SmC was 1.43 U/ml (95% tolerance limits, 0.64–2.22 U/ml). There was no significant effect of exogenous hGH on elemental balances or on plasma SmC. In contrast, 6 of 12 individuals 60–79 yr old showed the following evidences of impaired GH release: peak waking and sleeping serum GH < 4 ng/ml; plasma SmC < 0.38 U/ml; a significant retention in N, P, and K; and a significant rise in plasma SmC, in response to exogenous hGH.

Plasma SmC, serum GH during sleep, serum GH during the day, retentions of N, P, and K in response to exogenous hGH, and rise in plasma SmC in response to hGH were all intercorrelated ($P < 0.05$). Plasma SmC < 0.38 U/ml corresponded to peak nocturnal serum GH < 4 ng/ml. The prevalence of plasma SmC < 0.38 U/ml

increased progressively from age 20 to 90: third decade, 0%; fourth, 11%; fifth, 20%; sixth, 22%; seventh, 42%; eighth, 55%; and ninth, 55%. Within each decade, plasma SmC was inversely related to adiposity.

INTRODUCTION

In children and adolescents, serum growth hormone (GH)¹ levels rise to peak values of 20–50 ng/ml during the first 4 h of sleep (1–3). In adulthood, the nocturnal peaks of serum GH are less pronounced (4–7). Some individuals over age 40 release little GH (4, 5) during sleep. Two easily measured consequences of impaired GH secretion are subnormal levels of circulating somatomedins (8, 9), and hyperresponsiveness to the anabolic effects of exogenous human (h)GH, reflected by retention of abnormally large amounts of N, P, and K during treatment with a standard dose of hGH (10–12).

The object of this study was to investigate the prevalence of impaired GH release in the adult population of normal stature by measuring waking and sleeping release of endogenous GH, plasma concentration of somatomedin C (SmC), and anabolic responsiveness to exogenous hGH. Because endogenous GH release is influenced by nutritional state (13–19) and by disease (20–23), we confined the study to ambulatory adults who were within 15% of ideal body weight and free of progressive or active disease.

METHODS

Subjects. 94 ambulatory individuals, 21–86 yr old, of average height and without overt obesity, were recruited by a

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¹ Abbreviations used in this paper: BW, body weight; GH, growth hormone; h, human; RIA, radioimmunoassay; SmC, somatomedin C; T₃, triiodothyronine; T₄, thyroxine.

TABLE I
Summary of the Subjects

	Age (yr)						
	20-29	30-39	40-49	50-59	60-69	70-79	80-89
	Number of subjects						
Phase of study							
A	3/3*				3/2	4/3	
B	2/2	6/3	4/6	5/4	3/4	3/1	6/5
BW, % of ideal	99 (7)†	100 (9)	107 (8)	101 (8)	102 (8)	104 (8)	101 (5)
Clinical diagnosis							
None	10	8	8	4			
Inguinal hernia		1			1	2	2
Cataracts (present or removed)					1	5	7
Loss of hearing					2	4	5
Edentulous				1	2	3	5
Gall stones				1	2	1	1
Benign prostatic hypertrophy				1	3	4	3
Diaphragmatic hernia					2		
History of peptic ulcer		1		1		1	
Abnormal EKG				1	3	5	10
Inactive pulmonary tuberculosis				1	1		
Osteoarthritis			1	1	4	9	11
Varicose veins		1	2	2	2		
History of myocardial infarction				1	1	2	3
History of cerebrovascular accident						1	2
Diverticulosis					1	1	2
Kidney stone				1	1		

* Data are expressed as male/female.

† BW data are averages. SD in parentheses.

newspaper advertisement offering a free medical evaluation and a small honorarium. Each respondent underwent the following evaluation: history, physical examination, complete blood count, urinalysis, urine culture (clean catch), fasting SMA-14, and 2-h postprandial blood glucose. This evaluation showed that 72 individuals had body weight (BW) 85-115% of ideal, height within the 5-95th percentiles, and either no detectable disease or the nonmetabolic, nonendocrine, non-progressive abnormalities shown in Table I. These subjects, who form the basis of this report, met the following additional criteria: average resting systolic and diastolic blood pressures < 160 and < 90 mm Hg, respectively; blood urea N, serum creatinine, serum albumin, fasting and 2-h postprandial blood sugars within normal ranges; hematocrit 37-50%; clear sensorium; no urinary or fecal incontinence; normal urinalysis and sterile urine culture.

We began by measuring serum GH levels and plasma SmC concentration during the waking and sleeping hours in 12 ambulatory adults, aged 60 to 79. The effects of exogenous hGH on balances of N, P, and K ("elemental balances") and on plasma SmC were then determined. For comparison, the same analyses were made in six normals aged 20-29. These data indicated that 6 of the 12 individuals over 60 yr old had impaired GH release. To learn more about the relationship between defective GH secretion and age, we then measured the plasma SmC level in 54 additional adults and monitored endogenous GH release in a convenient sample of 34 cases.

Experimental design. Phase A involved 18 subjects: 6 in the third decade of life and 12 in the seventh or eighth decade.

There were two inpatient studies. In the first study, serum GH was measured throughout eight waking and four sleeping hours, and plasma SmC was measured at 3 p.m. The latter time was selected for plasma SmC measurements on the basis of preliminary studies on the diurnal variation of this factor, which are described in Results. Within the next 4 mo, during a second inpatient study, we measured the effect of exogenous hGH on elemental balances and on plasma SmC in all of these patients. The experimental details were as follows. The first inpatient admission lasted 7 d. Subjects ate ad lib a general hospital diet at 8 a.m., noon, and 5 p.m.; activity was unrestricted. Blood was removed via an indwelling venous catheter at hourly intervals 8 a.m.-4 p.m. on days 2 and 4, and at half-hour intervals for 4 h after the subject fell asleep on nights 3 and 5; these samples were used for serum GH measurement by radioimmunoassay (RIA) (24). Blood was collected in EDTA for determination of plasma SmC by RIA at 3 p.m. on days 2 and 4 (25). The blood was spun immediately at room temperature for 10 min; the plasma was stored at -20°C until assayed at Nichols Institute, Los Angeles, Calif. Other hormones measured in serum of selected cases were thyroxine (T₄) (26), free T₄ (27), triiodothyronine (T₃) (28), cortisol (29), and (in males) testosterone (30). The latter hormones were determined in blood obtained at 8 a.m. For the RIA of GH, intra-assay and inter-assay coefficients of variation were 5 and 7%, respectively, sensitivity was 0.4 ng/ml, and cross-reaction of human prolactin was <0.01%. For the RIA of SmC, intra- and inter-assay coefficients of variation were 6 and 10%, sensitivity was 0.1 U/ml, and cross-reaction with SmA was 3%. The second

inpatient study lasted 17 d. Subjects ate a constant diet designed for metabolic balance studies of N, P, and K as described (12). Activity was unrestricted. The first 3 d were for adaptation to the diet. The next 7 d represented a control period; during the final 7 d, the subjects were treated with 0.168 U hGH/kg BW^{3/4} per d, given as a single intramuscular injection at 10 p.m. Urine was collected in 24-h pools at 0°C during both periods, and the stools were collected in two 7-d pools. Elemental balances of N, P, and K during control and experimental periods were calculated as described (12). The anabolic response to hGH was calculated as the balance during hGH period minus the balance during control period: $\Delta N = (\text{g/kg BW}^{3/4} \times 10^{-1} \text{ per d})$; $\Delta P = (\text{g/kg BW}^{3/4} \times 10^{-1} \text{ per d})$; and $\Delta K = (\text{meq/kg BW}^{3/4} \times 10^{-1} \text{ per d})$. Balances were also expressed per 70 kg BW/d. Plasma SmC level was measured at 3 p.m. on the last 2 d of both periods.

Phase B involved 54 individuals, 4–11 in each decade from the fourth to the ninth. If both phases A and B are combined, there were from 9 to 12 subjects in each decade from third to ninth. An outpatient study was followed by an inpatient study. In the outpatient aspect of phase B, we measured plasma SmC in all 54 individuals twice at 2–3-wk intervals. Diet was not controlled. 34 of these individuals, selected at random from the phase B outpatient population, were hospitalized for monitoring of nocturnal serum GH levels for one night as in phase A (two nights were monitored in 7 subjects).

28 individuals of phases A and B, selected at random from the entire study population, were recalled 6–9 mo after the initial SmC measurement. The history, physical examination, and laboratory evaluation showed that in 20 patients the BW had not changed by more than 2.5 kg, and clinical status was unchanged. In these 20 patients, SmC level was measured again twice, at 1–2-wk intervals, in sera obtained at 3 p.m.

The subjects took no medications during the studies described above, or during the week preceding each test. The investigation was carried out with approval of Emory University's Clinical Trials committee and with informed consent of the subjects.

RESULTS

Diurnal variation of plasma SmC. In three third-decade individuals and three seventh-decade individuals, plasmas were obtained at 7 a.m., 11 a.m., 3 p.m., and 7 p.m. on 2 separate d within the same week. Between 7 a.m. and 7 p.m. no statistically significant ($P > 0.05$) diurnal variation of plasma SmC concentration was found by a repeated measures analysis of variance. Accordingly, 3 p.m. was chosen as the standard time to measure plasma SmC during the remainder of the investigation.

Phase A: 20–29 yr olds. Average serum GH concentration curves for these six subjects in both the waking and sleeping state are shown in Fig. 1a. For patients in the third decade, the peaks of serum averaged 7.3 (day) and 20.4 ng/ml (night); the average areas per hour were 2.84 (day) and 8.64 ng/ml (night). The average level of plasma SmC concentration was 1.38 U/ml. Basal balances of N, P, and K were close to zero. Anabolic responses to the standard dose of hGH were only slight: measured per kilogram BW^{3/4} $\times 10^{-1}$ per day, ΔN was 0.13 g, ΔP was 0.060 g, and ΔK was 1.90 meq. Expressed per 70 kilograms BW per day, these values

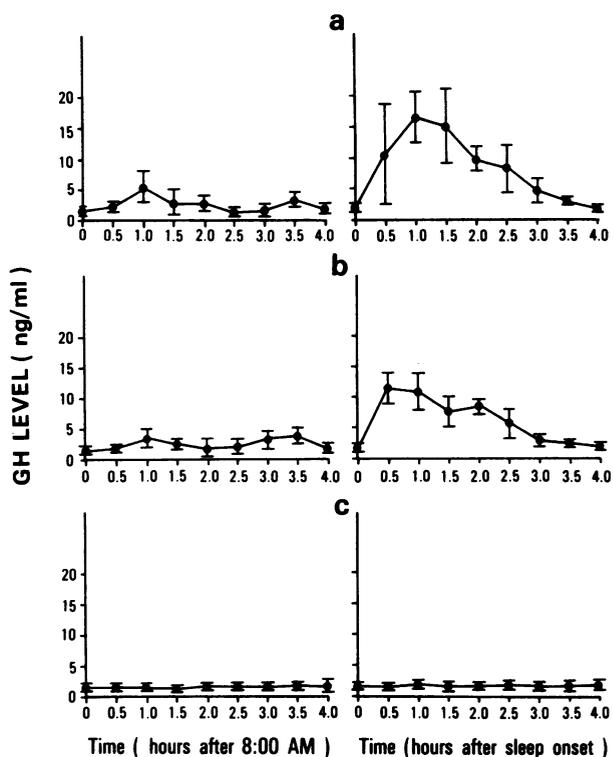


FIGURE 1 (a) Average serum GH concentration curves for six subjects ages 20–29 in both the waking (left) and sleeping (right) state. (b) Average serum GH concentration curves for six subjects ages 60–79 with SmC ≤ 0.64 U/ml in both the waking (diurnal) and sleeping (nocturnal) state. (c) Average serum GH concentration curves for six subjects ages 60–79 with SmC > 0.64 U/ml in both the waking (diurnal) and sleeping (nocturnal) state. Bars represent \pm SD.

were ΔN , 0.31 g; ΔP , 0.15 g; ΔK , 4.60 meq. In addition, hGH had no significant effect on plasma SmC. These data are summarized in Table II.

To estimate the 95% tolerance limits for plasma SmC in the third decade, we included the four subjects of this decade studied under phase B; in the total of 10 individuals aged 20–29, the estimated 95% tolerance limits were 0.64–2.22 U/ml. Results of other endocrine tests (T_4 , free T_3 , cortisol, and testosterone) were within normal limits.

Phase A: 60–79 yr olds. Table II summarizes results of the 60–79 yr olds. Average SmC level was significantly lower than in the 20–29 yr olds ($P < 0.001$). In 6 of 12 subjects, SmC level was below the lower 2.5% tolerance limit for the third decade (< 0.64 U/ml). The 60–79-yr group was now divided into two subgroups based on whether SmC was greater or less than 0.64 U/ml. Subjects with SmC > 0.64 U/ml resembled the 20–29-yr olds in that they had substantial release of GH during the day and night, and an unresponsiveness of elemental balances and SmC to exogenous hGH. Fig.

TABLE II
Data of Phase A: Comparison of Plasma SmC, Diurnal and Nocturnal Release of Endogenous GH, and Response to Exogenous hGH in Subjects of Third, Seventh, and Eighth Decades

	Age group (yr)		
	20–29 (n = 6)†	60–79* (n = 12)	
		(n = 6) SmC < 0.64	(n = 6) SmC ≥ 0.64
SmC, U/ml	1.38 (0.42)	0.27 (0.04)	0.98 (0.15)
GH release‡			
Peak day, ng/ml	7.27 (1.48)	3.25 (0.57)	5.39 (1.09)
Peak night, ng/ml	20.38 (5.51)	3.18 (0.47)	14.10 (3.31)
Ave area/h day, ng/ml	2.84 (0.37)	1.55 (0.13)	2.49 (0.35)
Ave area/h night, ng/ml	8.64 (1.48)	1.57 (0.11)	6.45 (1.00)
Elemental balances			
ΔN, g/kg BW ^{3/4} × 10 ⁻¹ /d	0.13 (0.21)	1.31 (0.21)	0.10 (0.12)
ΔP, g/kg BW ^{3/4} × 10 ⁻¹ /d	0.060 (0.078)	1.15 (0.17)	0.066 (0.080)
ΔK, meq/kg BW ^{3/4} × 10 ⁻¹ /d	1.90 (1.06)	4.68 (2.45)	1.03 (1.58)
ΔSmC, U/ml	0.100 (0.153)	0.642 (0.112)	0.096 (0.085)

* For the 60–79-yr group, average (±SD) SmC was 0.62 (±0.39) U/ml. This group was subdivided on the basis of SmC level above or below 0.64 units/ml because this value represents the lower 2.5% limit for SmC in the 20–29 yr group.

† Phase A; combined SmC for phases A + B (n = 10) averaged 1.43 U/ml (0.34) in the 20–29-yr group.

^{||} P < 0.001 when compared with age 20–29.

‡ GH concentration by time curves were quantitated by (i) measuring the peak serum GH value, and (ii) calculating the area under the serum GH concentration curve and dividing it by the length of the time interval to obtain the ave/hr.

1b displays the average serum GH concentration curves for these six subjects in both the waking and sleeping state. Their average peak day and night serum GH levels were 5.4 and 14.1 ng/ml. Their average values for ΔN, ΔP, and ΔK were 0.10 g, 0.066 g, and 1.03 meq per kg BW^{3/4} × 10⁻¹ per d. Expressed per 70 kilograms BW per day, these responses were only the following: ΔN, 0.27 g, ΔP, 0.160 g, ΔK, 2.52 meq. Not only elemental balances, but also SmC levels were virtually unresponsive to exogenous hGH. In contrast, the geriatric subjects with SmC < 0.64 U/ml differed from the 20–29-yr olds in the following respects: waking and sleeping release of GH were both significantly less, and responsiveness of elemental balances and SmC to exogenous hGH was significantly greater. Fig. 1c displays the average serum GH concentration curves for these six subjects in both the waking and sleeping state. Average day and night peak serum GH levels were only 3.3 and 3.2 ng/ml. Treatment with hGH raised the plasma SmC concentration from the initial average value of 0.27 U/ml to the post-treatment average value of 0.92 U/ml, which was within the normal range for the third decade. hGH treatment simultaneously caused retentions per kilogram BW^{3/4} × 10⁻¹ per day of 1.31 g N, 1.15 g P, and 4.68 meq K (per 70 kilograms BW per day: ΔN, 3.15 g; ΔP, 2.78 g; ΔK, 11.33 meq).

Phase B. Plasma SmC level declined with age in the third to ninth decade as shown in Fig. 2b (which includes the values of phase A). Nocturnal release of GH correlated closely with SmC level in phase B, as in phase A (Table III and Fig. 3). For example, when SmC was low (high), the area under the nocturnal curve was also low (high).

Other endocrine tests for the 70–89 yr olds indicated that average T₄, free T₄, cortisol, and testosterone (males) were within the normal range but were significantly less (P < 0.05) than in the third decade. Nevertheless, there were no differences between the subjects with serum SmC < 0.64 U/ml and those with SmC ≥ 0.64 U/ml.

Follow-up. Follow-up of SmC values in 20 subjects 6–9 mo later showed a significant decrease in average value (0.96 vs. 0.87 U/ml, P < 0.05). This change was larger than would be predicted due to the increase in age alone. The percent change ranged from 0 to 28% and averaged 15%. The coefficients of variation for the two SmC measurements taken within 1–2 wk were 6.9% in the first series, and 7.0% in the series 6–9 mo later. The coefficient of variation between the initial and follow-up SmC values was 11.8%.

Correlational analysis. Correlations were sought between age, sex, height, BW as percent of ideal, weight/(height)² (a commonly used index of obesity),

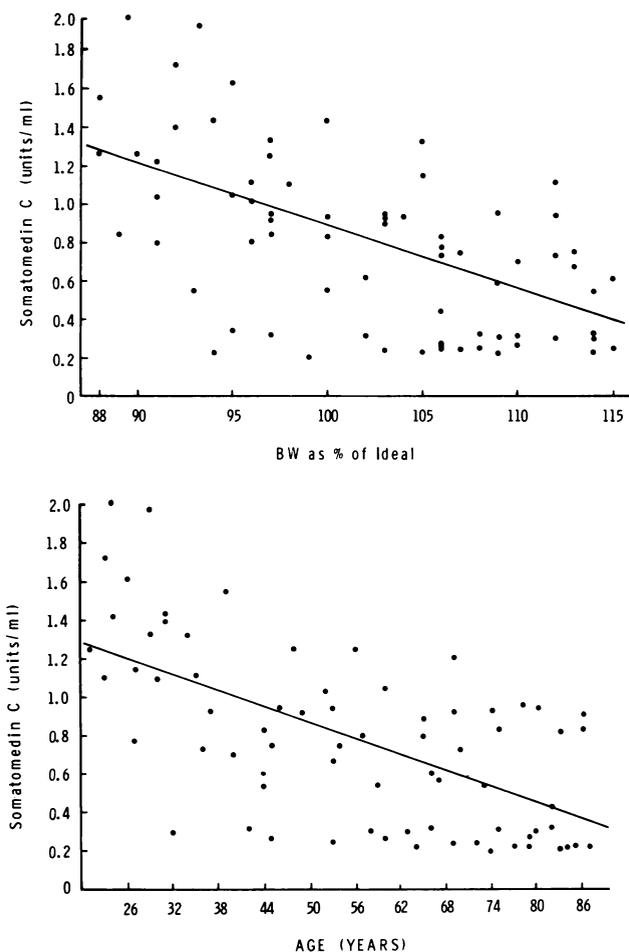


FIGURE 2 (Top) Scatter plot of SmC level vs. BW as a percent of ideal. $r = -0.58$. (Bottom) Scatter plot of SmC level vs. age. $r = -0.63$.

nocturnal GH, waking GH, plasma SmC, and the effect of exogenous hGH on elemental balances and on SmC (Table III). In phase A, nocturnal release, daytime release, anabolic responses (ΔN , ΔP , ΔK), SmC responses, and pretreatment SmC values were a network of closely intercorrelated descriptors (Table III). Therefore, SmC, the variable that was studied in the largest number of patients, could be used to represent the entire system of seven variables reflecting endogenous GH status for the combined analysis of phases A and B (Table III). For example, when nocturnal peak serum GH was regressed on plasma SmC level, a nocturnal peak < 4 ng/ml corresponded to SmC < 0.38 U/ml. Neither height nor sex significantly correlated with this system of indicators. The ratio weight/(height)² and BW as a percent of ideal correlated closely; these variables were independent of height. Both age and the obesity indicators (BW as percent of ideal and weight/(height)²) correlated significantly with all seven indicators of GH status (31).

Multiple linear regression analysis. To further explore the relationships among age, obesity, and SmC as the index of GH status, a multiple linear regression analysis was performed for the combined data of phases A and B (Fig. 4). We used weight/(height)² as our index of adiposity. Regression of SmC onto weight/(height)² and age gave the following equation: $\text{SmC} = 4.55 - 0.0135 \text{ age} - 0.132 (\text{wt}/\text{ht}^2)$ ($R^2 = 0.67$). This equation is represented graphically by Fig. 4b. The estimated partial regression coefficient, -0.0135 , is a measure of the rate at which SmC changes with respect to age when adiposity [weight/(height)²] remains constant. The coefficient -0.132 is a measure of the rate at which SmC changes with respect to adiposity when age remains constant. In the subjects studied, SmC was inversely proportional to adiposity and age, but age and adiposity were independent of each other. The estimated partial correlation coefficients were -0.72 ($P < 0.01$) between SmC and age for a given weight/(height)² ratio, and -0.66 ($P < 0.01$) between SmC and weight/(height)² for a given age. Thus, for a given age, SmC level tended to fall with increasing adiposity; and for a given adiposity, SmC level declined with increasing age. This is illustrated in Fig. 4. Therefore, given age and adiposity, SmC can be predicted from the above equation. For example, in a subject age 37 with height = 1.77 m and weight = 73 kg ($\text{wt}/\text{ht}^2 = 23.3$), the plasma SmC would be predicted to be 0.97 U/ml. The 95% tolerance limits for this prediction are 0.44–1.52. Similar results were obtained if adiposity was measured using either body weight as a percent of ideal or the weight/height ratio, instead of weight/(height)² (32).

DISCUSSION

The data show a progressive decline in GH secretion and plasma SmC level from the third to the ninth decade. Within each decade, however, endogenous GH status showed considerable variability. For example, in 55% of the subjects over 69, we measured little day or night release of GH (< 4 ng/ml in any serum sample), whereas in the remainder, hormone release was readily detected. Associated with the failure to release GH was a hyperresponsiveness to the anabolic action of exogenous hGH, and a subnormal plasma level of SmC, in comparison with the corresponding features in adults of the third decade. Because of the strong correlation between GH release and plasma SmC concentration in the adult population studied, the latter level could be used as an indicator of endogenous GH status in these individuals. In subjects with undernutrition (13–19), liver disease (20, 21), renal insufficiency (22, 23), or hypothyroidism (33), however, SmC is not a reliable indicator of GH release.

Daughaday et al. (34) recently reported that extraction of serum with acid ethanol increases the amount

TABLE III
Correlation Matrix for SmC, Nocturnal and Diurnal Serum GH, Anabolic and SmC Responses to Exogenous hGH, Sex, Height, Age, and Two Indices of Obesity

	Nocturnal GH	Diurnal GH	ΔN	ΔP	ΔK	ΔSmC	Sex	Height	Age	%IBW	wt/(ht) ²
Phase A (18)											
SmC	0.94*	0.93*	-0.83*	-0.82*	-0.45	-0.82*	0.12	0.23	-0.72*	-0.82*	-0.80*
Nocturnal GH		0.94*	-0.87*	-0.83*	-0.56‡	-0.84*	0.001	0.27	-0.64*	-0.78*	-0.74*
Diurnal GH			-0.77*	-0.69*	-0.38	-0.75*	0.07	0.28	-0.71*	-0.75*	-0.73*
ΔN				0.94*	0.73*	0.93‡	0.05	-0.28	-0.48‡	0.85*	0.68*
ΔP					0.70*	0.89*	0.06	-0.25	0.54‡	0.70*	0.62*
ΔK						0.55‡	-0.09	-0.05	0.21	0.66*	0.59*
ΔSmC							-0.002	-0.16	0.49	0.64*	0.61*
Sex								-0.63*	0.01	-0.15	-0.36
Height									-0.22	-0.25	-0.10
Age										0.47	0.44
%IBW											0.97*
Phase A and B (72)											
SmC	0.88*						0.02	0.11	-0.63*	-0.58*	-0.55*
Nocturnal GH§							-0.04	0.17	-0.49*	-0.60*	-0.52*
Sex								-0.61	0.01	-0.02	-0.21
Height									-0.12	0.09	0.04
Age										0.09	0.06
%IBW											0.96*

Number of subjects in parentheses. %IBW, body weight as a percentage of ideal.

* $P < 0.05$.

‡ $P < 0.05$.

§ $n = 52$.

of radioimmunoassayable SmC threefold. Evidently a portion of the serum SmC is not detected by RIA unless the peptide is first released from its complex with binding protein. Therefore we cannot exclude the possibility that the age- and adiposity-related decline in plasma SmC in our adults resulted in part from a reduced concentration of binding protein. In addition, it should be noted that other types of somatomedin may show a different relation to age and adiposity in adults than does SmC.

At what age did the secretion of endogenous GH begin to decline in our adult study group? GH release must have been adequate during the growing years, because the study population was of normal height (within 5-95 percentile). Secretion of GH continued at a substantial rate until age 30, and then began to diminish. The decline of plasma SmC with age for a fixed weight/(height)² was described by the partial regression coefficient associated with age (-0.0135). The rate of this decline was augmented by obesity, this influence being described by the partial regression coefficient associated with weight/(height)² for a fixed age (-0.132). However, other factors were also operating, because age and obesity together accounted for only 67% of the SmC variability in the study population. These presently undetermined factors account

for the wide tolerance limits developed to predict plasma SmC from age, weight, and height.

In the adults studied, peak nocturnal serum GH <4 ng/ml corresponded to SmC <0.38 U/ml by regression analysis. The prevalence of SmC below this level in

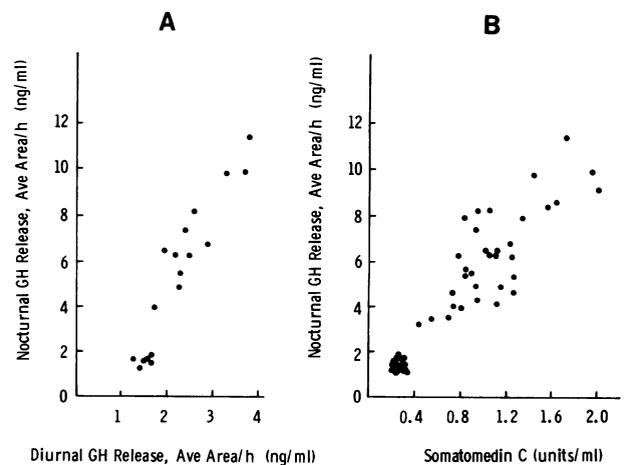


FIGURE 3 (A) Scatter plot of average nocturnal GH release. $r = 0.94$. (B) Scatter plot of average nocturnal GH release vs. average diurnal GH release. $r = 0.94$. (B) Scatter plot of average nocturnal GH release vs. SmC level. $r = 0.88$.

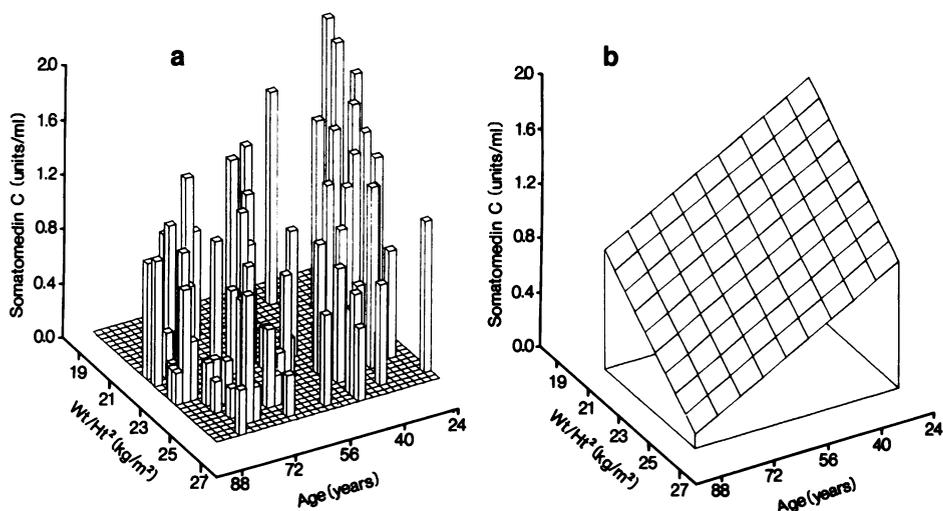


FIGURE 4 (a) Three-dimensional plot of SmC level as a function of $wt/(ht)^2$ and age for 72 subjects. The heights of the vertical columns give the SmC level for each subject. This figure illustrates the high correlations among age, $wt/(ht)^2$, and SmC levels. (b) Three-dimensional representation of the estimated multiple regression equation relating SmC level to age and $wt/(ht)^2$ ($SmC = 4.55 - 0.0135 \text{ age} - 0.132 \text{ wt}/[ht]^2$).

each decade of our study population was as follows: third decade, 0%; fourth decade, 11%; fifth decade, 20%; sixth decade, 22%; seventh decade, 42%; eighth decade, 55%; ninth decade, 55%. Therefore, impairment of GH secretion begins to appear in the fourth decade and thereafter becomes more common with advancing age.

Our data showing that GH secretion declines with age confirm Finkelstein et al. (4), Carlson with co-workers (5), and Bazzarre et al. (6). Our data on the inverse correlation of adiposity with endogenous GH secretion parallel previous observations on pharmacologically provoked GH release in obese vs. lean subjects (13, 14). Our finding that adiposity is inversely related to spontaneous nocturnal GH release throughout the 20–90 yr age span supports the similar conclusion of Othmer et al. in 20–29-yr-old subjects (15).

What mechanisms cause this age-related decrease in the secretion of GH? The mechanisms responsible could be operating at the (a) suprahypothalamic, (b) hypothalamic, (c) hypophyseal, or (d) peripheral level. The cessation of nocturnal GH release in old age could be related to the decline in slow wave sleep that occurs during the same decades (35). GH releasing mechanisms depend on α - and β -adrenergic, dopaminergic, and serotonergic neural circuits (3, 36). Levels of bioactive amines in some brain regions change with advancing age (37–40); such alterations could influence hypothalamic secretion of GH-releasing factor and of somatostatin. The size of the pituitary gland decreased by only 20% in old age (41). The concentration of GH within the adult rat or human

hypophysis does not decline with advancing age (42–45). Nevertheless, the amount of GH released in vitro by the aged rat pituitary gland in response to a hypothalamic GH-releasing factor preparation is markedly less than by the young gland (46). At a given age, endogenous GH release is inversely related to degree of adiposity (15, Fig. 4a). With advancing age, the adipose mass/lean body mass ratio tends to increase (47, 48). Thus, even when BW remains constant, the adipose mass tends to expand with age. Therefore, increasing adiposity may play a role in the decline of GH secretion that occurs with age even when BW remains fixed within the range of 85 to 115% of ideal.

What factors are responsible for the inverse relation between adiposity and GH release shown in Fig. 2a? Normal subjects who have been made obese by forced feeding release subnormal amounts of endogenous GH in response to hypoglycemia (49). The blunted endogenous GH response to hypoglycemia that is characteristic of obesity is often improved by weight reduction (50–54). Thus, expansion of the adipose organ tends to suppress endogenous GH release, but the mechanism for this endocrine effect of obesity remains unknown.

In those older adults who have low plasma SmC, the impairment of GH release is not necessarily permanent. Caloric deprivation or wasting illnesses raise serum GH levels in adults (55). Since the pituitary gland's content of GH does not decline with age (42–45), it is possible that adults with reduced plasma SmC would resume GH secretion if subjected to such stimuli.

Future studies should consider whether the impair-

ment of GH secretion, so prevalent in the adult population, alters the health or physiology of the affected individuals. For example, GH promotes bone formation (56–59), increases renal blood flow (60), and stimulates protein synthesis in the lean body mass (61, 62). The geriatric decline in each of these functions (63–67) could result in part from cessation of GH secretion.

The present findings imply a possible new clinical use for hGH. Those older individuals who have stopped secreting endogenous GH are highly responsive to the anabolic actions of the exogenous hormone at a dose (0.168 U/kg BW^{3/4}/d) similar to those used to treat GH-deficient children (0.125–0.25 U/kg BW^{3/4}/d). In such adults, whose proportion in the population increases progressively with age, hGH provides a new way of accelerating protein synthesis and stimulating positive N balance.

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